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HALOGEN BOND: THE ACTIVE ROLE OF HALOGEN ATOMS IN THE BINDING TO BIOMACROMOLECULES

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Halogen atoms are scarce in biomolecules. Most of the biogenic organohalogens are marine-derived, but many have also been found in terrestrial plants, fungi, lichen, bacteria, insects, some higher animals, and humans. Biogenic organofluorine and –iodine derivatives have been isolated, bur are quite rare and more than 90% of naturally occurring organohalogens are chlorine and bromine derivatives, the former being more numerous than the latter [1]. The iodinated thyroid hormones T4 (thyroxine, 3,5,3′,5′-tetraiodothyronine) and T3 (3,5,3′-triiodothyronine) are probably the best known examples of naturally occurring halogenated compounds, and in the context of this lecture it is important to observe that they work as halogen bonding donors when bound to the respective target proteins [2].
In contrast, a large proportion of the drugs used for human therapy are halogen-substituted. According to a search of Thomson Reuters Pharma performed in 2014, the organohalogens content is 34.6%, 36.4%, 29.8%, 36.4%, 33.1%, and 25.5% in drug discovery stage, clinical phase I, clinical phase II, clinical phase III, preregistered and registered, launched stages, respectively. In the drug design process, halogen atoms are often introduced in order to enhance membrane permeability, an ability resulting from their high lipophilicity. Alternatively, they are used with the aim of prolonging the half-life of the drug by delaying the catabolic process that leads to drug degradation and excretion. In fact, fluorine, and to a lesser extent chlorine, for hydrogen substitution on aromatic rings of drugs affords compounds where the carbon–halogen bonds are catabolically more resistant than the corresponding C–H bonds.

Usually, halogen atoms in drugs are expected to be involved in non-directional hydrophobic interactions or just point into relatively empty spaces or cavities which they tend to occupy without being involved in specific stabilizing contacts. But in the last decades experimental results and theoretical calculations have shown that the distribution of the electron density in covalently bound halogens is anisotropic so that these atoms show an amphoteric character,, namely they can attractively interact with both electrophile and nucleophiles. The two resulting interactions are highly directional and are geometrically orthogonal each other.

Due to their high electronegativity, halogen atoms in organic derivatives are typically considered as sites of high electron density. Consistent with this model, it is commonly accepted they can attractively interact with partially positive hydrogen atoms and function as hydrogen bond acceptors. Recently, directional preference in these interactions has become apparent consistent with the fact that halogen atoms in organohalogen derivatives show an anisotropic distribution of their electron density with a belt, perpendicular to the covalent bond formed by the halogen, where the electrostatic potential is most negative. Electrophiles enter this region: If the electrophile is a hydrogen atom, a hydrogen bond is formed and attractive interactions can be developed with other electrophiles, e.g. alkaline and alkaline earth cations [3]. Importantly, a cap of depleted electron density where the electrostatic potential is frequently positive (the so-named σ-hole) is present on the elongation of the covalent bond formed by the halogen. Lone pair possessing atoms, π-systems, and anions can all form short and attractive interactions with this positive region, and the resulting bondings are named halogen bonds, the term being used for any attractive interaction wherein the halogen atom is the electrophile.

Electron-rich sites such as oxygen, nitrogen, and sulfur atoms as well as aromatic □-electron systems are abundant in proteins and the □-hole of halogen atoms in drugs can form, when structurally possible, stabilizing halogen bonds with the amino acids at the walls of the binding site of target proteins and containing these moieties.

In this lecture we will show how the halogen bond frequently plays an active role in small molecule–protein complex formation and this role should not be underestimated. Largely overlooked until a decade ago, the potential for halogen atoms to generate intermolecular stabilizing forces with electron-rich atoms in the form of halogen bonding similar in strength and directionality to hydrogen bonding is now commonly accepted. It will be proven how this type of interaction can critically enhance the overall binding affinity and specificity of the drug, thus providing an often-disregarded viable route to an efficient structure-based drug design. It will be recognized that halogen bond could play an important role during hit identification and lead optimization. Some case histories will be described.

For instance, it will be reported how a series of halogenated compounds targeting phosphodiesterase type 5 (PDE5) were designed and synthesized. The halogen bond between the phenolate oxygen atom of Y612 of PDE5 and the new halogenated inhibitors was validated by X-ray crystal structures (PDB ID: 3SIE) [4]. A series of halogenated compounds were synthesized as human Cathepsin L (hCatL) inhibitors. The introduction of halogen bond between the 4-chlorophenyl moiety of the drug and the backbone carbonyl oxygen of Gly61 in hCatL enhances the binding affinity by a factor of 13 (PDB ID: 2XU1) with respect to the unsubstituted phenyl derivative [5],
The crystal structure of ferritin complexed with the general anesthetic halothane (CF3CHClBr) has been determined at 1.75 Å resolution (PDB code = 1XZ1). Halothane is bound in a hydrophobic cavity at the interface between two ferritin monomers. The bromine atom of halothane forms a halogen bond with the carbonyl oxygen of Leu24 of ferritin [the C–Br···O(Leu24) distance is 3.10 Å, the C–Br···(Leu24) angle is 144.91°], while the chlorine atom forms a halogen–□ contact with the ring of Tyr28 of ferritin, the farthest carbon atom of the ring being at a 4.8 Å distance from the chlorine atom and the closest at 3.3 Å (Cl···centroid = 4.1 Å, C–Cl···centroid angle is 155.51°) [6].
Finally, it will be discussed how important or prevalent the halogen bonds is to play other roles beyond drug-target binding affinity, e.g., in development processes. The examples mentioned above are aimed at improving the drug−target protein binding affinity at the drug discovery stage, but halogen bond can also be used to overcome drug resistance. A halogen bond between the iodine atom of an HIV-1 reverse transcriptase inhibitor and the backbone carbonyl oxygen of Tyr188 of the transcriptase increases the affinity of the small molecule (PDB ID: 2BE2) but it also avoids drug resistance [7].

It is particularly worth observing that halogenated drugs are more common (34%) in clinic trials or at the stage of pre- and registered than in the launched drugs (26%). As the drugs in clinical phases reflect the opinions and interests in drug discovery about ten years ago, while the launched molecules collects the successful drugs over approximately the past one hundred years; the digits mentioned above may imply that halogenations have been much appreciated in recent years. As mentioned at the beginning of this abstract, halogenated natural products are not common. Therefore, halogenation might be a valuable approach for the structural modification of natural products for drug development.

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THE DISCOVERY AND EARLY HISTORY OF PROPOFOL

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Introduction: In 1972 thiopentone remained the gold standard for induction of anaesthesia. The new agent sought was one that would reproduce the quality of anaesthesia provided by thiopentone but would undergo more rapid metabolism such that anaesthesia could be maintained by repeated injections or by continuous infusion without the penalty of delayed recovery. The availability of the surfactant, Cremophor EL, already being used in the solubulisation of propanidid ('Epontol') and the steroid mixture of alphaxalone and alphaxalone ('Althesin'), for laboratory use now allowed poorly water-soluble compounds to be tested for anaesthetic activity in animals.

Methods: All compounds were given in the first place to laboratory mice by i.v. injection. If anaesthetic properties were detected, the test compound entered a cascade of secondary tests in mice and rabbits to determine in greater detail hypnotic potency, speed of onset, duration of effect, speed of recovery and side effect profile. In early 1973 we detected hypnotic activity in ICI 43,117 (2,6- diethylphenol), one of a number of poorly soluble compounds selected by Roger James, a project chemist, from ICI's existing compound collection. Because induction of anaesthesia was slow, this compound was not taken further, but it provided a lead to follow. Related alkyl phenols were then tested and on 23 May 1973 the anaesthetic activity of propofol (ICI 35,868; 2,6-diisopropylphenol) was first observed in mice. A degree of hypnotic activity was observed in many of these compounds [1] but propofol was selected as the only compound with the optimum balance of properties and acceptable effects on respiration and circulation. In comparison with thiopentone, propofol could be given by repeated injection without prolonging recovery time; and full recovery of coordination also occurred much more quickly.

Pure propofol is a highly lipophilic oil and difficulty in finding an acceptable i.v. formulation led to a 13 year delay before the new agent could be marketed. The clinical acceptance of 'Epontol' and 'Althesin' prompted the continuing use of this agent for initial trials with propofol. However, a number of anaphylactoid reactions had been reported with both of these agents and we decided that a non-Cremophor formulation would be sought before marketing propofol.

In parallel with the search for an improved formulation, pharmacology studies continued to examine anaesthetic effects in other animal species, potential drug interactions and alternative routes of administration [2,3]. Oral doses of propofol up to 300mg/kg failed to induce anaesthesia in mice, indicating rapid first pass metabolism. Results in animal models indicated that propofol was unlikely to induce known undesirable effects of other agents such as adrenocortical depression, malignant hyperthermia or porphyria. Cremophor EL induces histamine release and marked hypotension in dogs and studies to examine the haemodynamic and respiratory effects of propofol, thiopentone and 'Althesin' were therefore done in mini-pigs. In the process of this work a suspected anaphylactoid reaction occurred when a second injection of Althesin was given to a pig. This observation led to a systematic evaluation of the effects of Cremophor EL and Cremophor containing agents in this species. This work confirmed that a second administration of Cremophor EL or one of the Cremophor containing agents, given 7 days after an uneventful first exposure, produced a marked anaphylactoid response in the mini- pig [4]. When propanidid was administered in this way in a non-Cremophor solvent (propylene glycol and alcohol) no adverse response was observed. With alphaxalone and alphadolone in this same non-Cremophor solvent some reactions were still seen, suggesting that these steroids could play a contributory role. With this model it was now possible to examine alternative solubilising agents for propofol and a synthetic polyoxyethylene/polyoxypropylene surfactant (Synperonic PE39/70) manufactured by another division of ICI produced no adverse response in the mini-pig. Pharmacology and toxicology studies were repeated with a Synperonic formulation of propofol, but histological changes in liver tissue prevented further progress in this direction.

In the meantime, clinical trials began with a formulation containing 2% propofol in 16% Cremophor EL and 8% ethyl alcohol. The first study by Kay and Rolly in Belgium in 1977 found that in unpremedicated patients induction of anaesthesia was rapid and smooth and recovery rapid [5]. The induction dose at 1 mg/kg was smaller than I had anticipated and several patients reported pain on injection, which had not been seen in animal studies. In view of these results the concentration of propofol was reduced to 1%, alcohol was no longer needed as a co-solvent and the severity of pain on injection was reduced in subsequent studies. In follow on studies a dose of 1mg/kg of propofol was found to be insufficient to induce anaesthesia in

unpremedicated patients and further dose finding studies determined an induction dose closer to my original prediction of 2 mg/kg.
With the demise of the Synperonic formulation, studies continued with propofol in Cremophor and at one stage in 1980, very much against my advice, it was thought that this formulation could be marketed. However, when more than 1000 patients had been studied, a number of anaphylactoid reactions were encountered and clinical studies with this formulation were stopped. Earlier attempts to produce an emulsion formulation had failed but as the clinical results with propofol continued to look promising and emulsion manufacturing technology had recently improved, a decision was made in 1981 to reopen research on an emulsion formulation. A formulation containing soybean oil and purified egg phosphatide was eventually identified and pharmacology and toxicology studies repeated again. These confirmed that the desirable properties observed with the propofol formulation were retained in the emulsion preparation and no adverse response or histamine release was produced by the repeated administration of the emulsion formulation [6]. Behavioural responses in the rat also suggested that the emulsion formulation should produce less discomfort on i.v.injection.

Conclusion: The clinical evaluation of the emulsion formulation began in 1983 and was planned and coordinated by an ICI physician, Ron Stark and his team. At this time I moved to the Medical department to assist with international trials. With the experience gained with the Cremophor formulation, studies proceeded rapidly and the initial program was completed by the end of 1984. Regulatory approval was obtained and first commercial launches, for use in induction of anesthesia and short-term maintenance in adults, occurred in 1986.
Much remained to be done to determine the clinical profile of propofol in a wide range of patients and procedures and to extend its use into maintenance of anaesthesia, sedation and intensive care sedation. This extended clinical programme was very much a collaborative process between the pharmaceutical company and clinicians with expertise in each particular area.

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FRIDAY, SEPTEMBER 29th

SESSION A1 08:30 – 10:45 MONITORING DEPH OF ANAESTHESIA AND CLOSED LOOP ANESTHESIA

TIVA, AWARENESS AND DEPTH OF ANAESTHESIA MONITORING

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- The latest TIVA guidelines in the UK will recommend that all anaesthetists should be competent to deliver a TIVA anaesthetic
- TIVA has many risk factors for inadvertent awareness
    - Most practitioners use set rules to minimise these risks
        - Pumps in a certain order every time
        - Drawing up of drugs in a set way and careful labelling
        - Single concentrations of drugs
        - Spare cannula
        - Running IVI in view
- Much recent evidence points to the fact that TIVA with a muscle relaxant can lead to an increased incidence of awareness
- NAP 5 also concluded that the use of a nerve stimulator decreases the incidence of awareness by 50%
- The isolated forearm technique is the gold standard for detecting awareness
- NICE recommends the use of a processed EEG (pEEG) monitor when TIVA is used for maintenance of anaesthesia with concomitant use of a muscle relaxant
- It is important to understand how pEEG such as BIS works and what information it can (and cannot) give the anaesthetist
- BIS only gives a numerical value corresponding to the risk of recall following anaesthesia; it does not monitor awareness.
    - Studies have shown that >5% of patients can be aware during a standard induction, thankfully very few of these have recall
    - BIS will increase after a painful stimulus (as of course does BP) so BIS must be low (eg less than 40) before allowing airway intervention or painful surgery, depending on adjuvant opiate administration.
- BIS uses the EEG and the EMG to produce a value between 0 and 100
    - EMG is zero in a patient with full NM paralysis.
    - Beware: the scale of BIS is non-linear and studies on volunteers have demonstrated that a patient with NM paralysis who is fully aware may not have a BIS much above 70-80.
    - Interference, movement and diathermy is misinterpreted as EMG by the BIS and will give rise to an elevated BIS.
    - The raw EEG display can be useful if the different EEG waves; delta, beta and alpha waves, can be recognised by the clinician
    - A high dose opiate anaesthetic will give a much smoother BIS trace with fewer trend spikes.
- The suppression ratio can also be displayed. It should rarely be above zero in most balanced anaesthetics, but can be useful if burst suppression is required (eg in neuro) when a value of 50 – 80 corresponds to approximately 3-5 bursts per minute.
    - Alternative montages of BIS can be useful if the forehead is not available (eg in bi-frontal craniotomy)
- BIS can be used during transport, which is a particularly high risk time for awareness especially if the mode of anaesthesia has been changed from volatile to TIVA.

- BIS allows less guesswork when using TIVA in obese patients since the hypnotic can successfully be titrated to the BIS value.
- There is some evidence that BIS can affect outcome, with the avoidance of excess depth of anaesthetic being advocated by some.
- The combination of 'triple low' (low BIS, low BP and low MAC/TIVA) may be marker for poor outcome.
- BIS is no good unless alarms are set to alert the clinician to a problem.

WHAT'S NEW IN CEREBRAL MONITORING DURING CAROTID ENDOARTERECTOMY

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Background. Selective shunting during carotid endarterectomy (CEA) is advocated to reduce shunt-related stroke. Cerebral monitoring is essential for temporary carotid shunting. Many techniques are available for cerebral monitoring; however, none is superior to monitoring the patient's neurological status (awake testing) while performing the procedure under local anesthesia (LA).
Cerebral oximetry (CO) has previously been used to show the adequacy of cerebral circulation in patients undergoing CEA. This investigation was designed to compare the performance of the INVOS-4100 cerebral oximeter and the neurologic functions, by means of detecting cerebral ischemia induced by carotid cross-clamping, in patients undergoing CEA under LA, namely cervical plexus block. Mean while we performed a comparison between blind and echoguided locoregional anesthesia in terms of patient discomfort and volume of anesthetic infused.

Methods. Patients scheduled for CEA under LA were included. Patients converted to general anesthesia (GA) or other types of operations other than CEA were excluded from this study. We enrolled 100 consecutive patients. Bilateral regional cerebrovascular oxygen saturation (rSO2) was monitored in all patients, in addition to the awake testing. Changes in rSO2 following carotid artery clamping were recorded. A drop greater than 20% was considered as an indicator of cerebral ischemia that might predict the need for carotid shunting. Patients were only shunted based on the awake testing. Half of patients underwent to echo-guided anesthesia.

Results. Of the 100 patients undergoing CEA under LA, 9 showed a significant drop in rSO2 (range: 22.6-32.8%, mean: 26.4%): only three of them required shunting, while the remaining 6 had no changes in consciousness after internal carotid artery (ICA) cross-clamping and it was not necessary to place a shunt (false positive). Compared to the preclamping values, a significant decrease in rSO2 was found on the hemisphere of the operated side, while no significant change was observed contralaterally. Ninety-one patients had no significant changes of CO values: in 89 of them there was no consciousness deterioration, so we didn't place a shunt (true negative), but 2 patients showing a non-significant post-clamping decline in CO saturation (1.5% and 18.2%) required shunting based on the awake testing (2 false negative). In the current study, the median drop in rSO2 was 19% (range: 1.5-26.4%) in the 5 patients that required shunting. This represents a sensitivity of 60% and a specificity of 25% for CO in comparison to the awake testing.
The patient underwent to locoregional anesthesia needed a significant reduction of anesthetic volume (10 cc of Lidocaine vs 20 cc in case of blind anesthesia), without need of adjunct by the surgeon during the operation. Neurological stupor related to the anesthesia were significantly reduced.

Conclusion. The results of this study suggest that the usefulness of CO in predicting cerebral ischemia is modest. Cerebral monitoring with INVOS-4100 has a high negative predictive value, but the positive predictive value is low.

CO monitoring provides additional safety for the indication of elective shunt insertion and furthermore allows optimisation of cerebral perfusion by blood pressure manipulation. In case of general anesthesia a combination of two monitoring system were necessary to obtain a valid prediction of shunting necessity. However, a large multicentre prospective trial would be desirable.
Loco-regional anesthesia improved by echo-guided method if applicable represents the best method to provide selective shunting and to reduce patient discomfort.

DESIGN AND IMPLEMENTATION OF A CLOSED-LOOP CONTROL SYSTEM FOR INFUSION OF PROPOFOL GUIDED BY BISPECTRAL INDEX (BIS)

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Introduction. The need for hypnotics varies in different patients and also during surgery for the same patient. The dose adjustment is set according to a balance between the anesthetic and autonomic states and the response to noxious stimuli. Manual infusion of propofol is based on pharmacokinetic (PK) linear models that characterize plasma or effect concentrations and elimination [i]. The bispectral index (BIS) monitor is a passive analyzer of EEG that provides surrogated measures of the hypnotic level. BIS allows hypnotic titration over the complete range of cortical activity [ii]. It is possible to adjust the propofol dose to actual needs [iii] with a reduction in expected consumption. It is accepted that hemodynamic variables are not appropriate to determine whether a patient is unconscious or not [iv].
When anesthesiologists perform manual control for TIVA-TCI, they act like controllers closing the loop, modifying the rate or the target concentration according to patient data. However, it is possible to implement an automatic control to regulate a physiological variable with a closed loop control (CLC). The crucial concept of any CLC system in which a process is automatically regulated is a feedback mechanism (Figure 1).
This study describes the design, implementation and feasibility of a PI (proportional-integral) CLC for propofol infusion guided by the BIS. The performance of the PI controller was compared with a manual control group representing the standard practice.

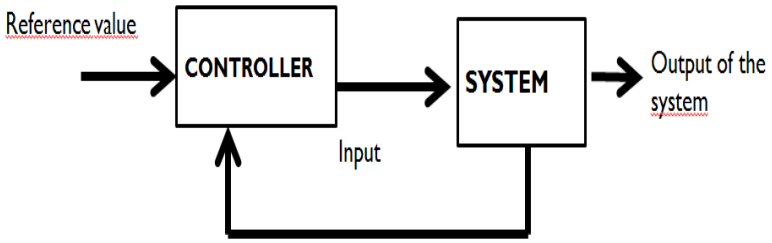

Figure 1: The system output signal (controlled variable) has a direct effect on the control action (control variable).

Material and methods. PI for hypnosis control. CLC was developed in 3 phases: modeling of the system, designing a control strategy and carrying out a clinical evaluation. Models are useful to design the controller and to tune the controller. We obtained an ARX (AutoRegressive with eXogenous input) parametric model using data from 12 patients. PID is an efficient solution widely used in engineering that has been used in CLC for propofol. The PID controller does not have any knowledge of the drug metabolism or of a potentially dangerous concentration.
The control objective was to maintain the BIS within a target range (BISr=50). The measurement and actuation period was 5 sec. The controller was continuously monitoring patient hypnotic state through the BIS. The difference between the measured BIS and BISr is analyzed to adjust the input value for the calculation of the infusion rate. This error results from a sum of 3 terms: proportional to the current error (P), proportional to the sum of the error (I) and to the derivative of the error (D). A derivative action (D) was not implemented. P and I actions (PI) are regulated by gains that were adjusted in an empirical way. The adjustment of constants Kp and Ki was based on simulation after clinical tests with MATLAB. We implemented a security module to alert of different types of errors.

Clinical study. After approval from the Local Research and Ethics Committee, 59 patients (ASA I-II) scheduled for surgery under general anesthesia with propofol and remifentanil were recruited. There were 2 groups, one under closed loop control (CLCG) and a second under manual control (MCG).
A BIS® A-2000 Vista monitor was used. The communication with the computer was through a RS-232 serial interface. The actuator was an infusion pump (Graseby 3500®). A remifentanil infusion at 0.25 mcg kg-1min-1 was started for analgesia. After 3 min of preoxigenation, the system was switched to manual mode and anesthesia was induced by a bolus of 2 mg kg-1 of propofol. Once the patient achieved a BIS value close to 50, the system was switched to automatic and the control algorithm was responsible for the administration of propofol to regulate the BIS around the target. In the MCG, propofol infusion was titrated manually by a skilled anesthesiologist trying to maintain BIS near 50 during the maintenance phase.
The performance of the two groups was compared with the global score (GS) and Varvel's indices[v]: median performance error (MDPE), median absolute performance error (MDAPE), offset and wobble. The percentage of time with BIS values within 20% of target BIS (50), BIS<40 or BIS>65 was also recorded. The doses of propofol and remifentanil and time to eyes opening and to tracheal extubation were registered.

Results. A total of 29 patients in the MCG and 30 in the CLCG completed the study. The automatic control worked properly in all the patients. GS was better ($p<0,001$) in the CLCG (34.9±1) than MCG (50.9±2). The proportion of time with BIS between 40 and 60 during the maintenance of anesthesia was higher ($p<0.01$) in the CLCG (73.7±14%) compared with MCG (61.2±15%). Overshoot (BIS<40) and undershoot (BIS> 65), were significantly less common in the CLCG.
Indices to assess performance were significantly better in the CLCG; MDPE was -2.5 ± 5,1 in the CLCG vs -10 ± 9.1 in MCG ($p<0.001$); MDAPE was 12.1 ± 13.7 in the CLCG vs 16.5 ± 4.7 in the MCG ($p<0.001$); offset was 1,1 ±2,5 in the CLCG vs -3.8±4.7 in the MCG ($p=0.015$); wobble did not differ significantly. There were no significant differences in propofol dose, 4.2± 1.3 vs 4.9 ± 1.6 mg kg-1h-1 in MCG and CLCG respectively. The time to ocular opening was slightly shorter in the CLCG, being the time to tracheal extubation 9.9±5 and 8.2±1 min in the MG ($p=0.053$,. The dose of remifentanil administered was similar in both groups. Hemodynamic severe adverse event was not recorded.

Discussion. The key concept in CLC is to use information on the state of the patient to adjust the control action. The feedback comes directly by a measure of the hypnotic effect, being BIS the controlled variable to calculate propofol infusion rate. Most of the existing CLC use BIS values to adjust a target propofol concentration [vi] [vii]. We propose a simpler method [viii] that does not depend on the use of PK/PD models. The procedure consisted of three stages, obtaining a patient model, designing a controller using the model and finally carrying out a pilot study to adjust the optimal values of the PI controller. A specific method to tune the parameters using real data from patients in a preliminary study was developed.
The CLC has been proved clinically feasible without additional risks for the patients. The results of CLCG compared with an equivalent group under manual control showed significantly better performance in terms of MDPE, MDAPE, offset, global score and percentage of time of optimal control (BIS 40-60). The BIS evolution presented oscillations in four cases of CLCG. One reason is that the nominal PI parameters chosen are not the best choice for all the patients. There is also a delay between infusion and observed effect that may exceed two minutes. The application of specific strategies to affront the delay such as the Smith predictor could be promising. Another type of controller using fuzzy logic tries to transfer the knowledge of an expert to the control system and has been proven with good results [ix].
The implementation of a CLC reduces repetitive tasks and allows the same level of vigilance to be maintained during the entire procedure. The phases of inadequate control during routine practice can be reduced and the quality of anesthesia improves for a more precise control with fewer side effects. It is possible that an adjusted intraoperative drug administration allows faster recovery and decreases post-operative side effects.
In summary, the CLC was able to titrate the rate of propofol infusion to maintain the BIS close to a target in routine surgery. The CLC controller outperforms manual control during maintenance of general anesthesia.

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CLOSED-LOOP IV ANESTHESIA: IMPACT ON ROUTINE ANESTHESIA

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Introduction: The benefit of an automated controller is to obtain precise control of the variables with continuous analysis and frequent changes in anesthetic drug concentrations. Thus, the drug infusion is titrated to the specific needs of each patient, taking into account inter- or intra-individual dynamic variability, specificity of the surgery thus avoiding drug accumulation. Currently, over 4100 surgical patients have been anesthetized with different automated controllers. For automated propofol titration our team has published studies involving 70 % of these patients.

Automated titration of propofol: Since 2006 we have developed different Closed-loop controllers allowing the automated titration of intravenous anesthesia guided by the Bispectral index (BIS). In particular, we have developed the first prototype allowing the automated titration of propofol during the induction period1, the controller modifies the propofol effect concentration using the pharmacokinetic model of Schnider.2 We have combined the induction and the maintenance of general anesthesia (GA) and the controller was evaluated by a randomized controlled study including more than 180 patients with patients ASA II and III in different centers.3 The same controller was used in an observational study in patients undergoing lung transplantation.4 Lung transplantation is a major procedure including patients ASA IV. In this context, the controller appears safe as shown by its use by several physicians for patients presenting high anesthetic risk with or without cardiopulmonary bypass. Finally, these studies demonstrated that the electro-cortical activity measured by the BIS is a measure of the depth of hypnosis allowing the automated titration of propofol.

Multiple controllers: General anesthesia is a dynamic balance between hypnosis, analgesia and muscle relaxation. The clinical relevance of automated administration of neuromuscular blocking agents is limited since the introduction of a specific antidote5. Finally, the ultimate challenge is probably the automated control of analgesia.
The first automated administration of alfentanil guided by electrocortical activity was published 20 years ago6. A study reported that a mixture of propofol and alfentanil in the same syringe can be administered automatically using the BIS7. We have developed a proportional-integral-derivative controller for automated propofol infusion3. After this first controller, we implemented a second controller allowing the automated titration of remifentanil also guided by BIS using the pharmacokinetic model of Minto.8 The principle of this controller is based on the assumption that rapid BIS increase is secondary to noxious stimulation and is related to a deficit of anti-nociception and not to a deficit of the hypnotic component. The controller first administers remifentanil if the error is small and administers remifentanil and propofol when the error is higher. This controller has been validated by a randomized controlled multicenter study including 167 patients ASA II

and III.9 The dual-loop controller outperforms skilled manual control to maintain the BIS in the range 40-60 and decrease the number of episodes of too deep anesthesia.
A similar controller was developed using the M-Entropy monitor® (GE Healthcare, Helsinki, Finland). The monitor calculates two parameters:"State Entropy" which is the measure of the irregularity of frontal cortical electrophysiological activity and "Response Entropy". The difference between "Response Entropy and Entropy State" represents the activity of facial electromyography which is a surrogate measure to quantify the deficit in antinociception. The controller allows the automated titration of propofol and remifentanil during induction and maintenance of general anesthesia. In a randomized controlled study including 61 patients, we reported the feasibility of automated titration of propofol and remifentanil guided by the M-Entropy monitor®.10 However, this controller has not been tested clinically under physiologically challenging conditions during major surgery.
The dual-loop controller of propofol and remifentanil with the BIS was evaluated in different clinical situations and has been studied most extensively. Rigid bronchoscopy is a particularly challenging condition: it involves the management of high-risk patients with central airway obstruction, with co-morbidities, an unpredictable duration and with intense noxious stimuli during rigid bronchoscopy mobilizations. We have reported the use of the dual-loop controller during this procedure and demonstrated that the controller acts similarly to manual control to maintain the BIS in the desired range.11 In an observational study, we have reported with the dual-loop controller the occurrence of suppression ratio related to too deep anesthesia. During 3742 hours of automated titration of propofol and remifentanil or after more than 210000 modifications of target concentrations we found that the occurrence of suppression ratio was 0.5‰ after a decision made by the controller. 12 This study involving 1494 adult patients demonstrated that the dual-loop controller was feasible in routine anesthesia. We have reported the use of the dual-loop controller in a patient who suffered from gigantism with a height of 248 cm13 and in a 9-year-old boy requiring emergency lung volume reduction.14 The dual-loop controller has been evaluated in pediatric and adolescent patients during GA. In a randomized controlled study with 42 pediatric patients the controller outperforms skilled manual control to maintain the BIS in the desired range while the adult pharmacokinetic models were used.15 The dual-loop was used in obese patients while the pharmacokinetic model of propofol was Schnider2 and Minto for the remifentanil.8 Propofol and remifentanil consumptions were evaluated using the dual-loop controller between 30 obese and 29 lean patients.16 The dual-loop controller delivered half as much remifentanil and no propofol overdosing was reported. The controller was based on individual patient responses and was independent of the underlying pharmacokinetic model. We have evaluated the impact of post operative nausea and vomiting in 117 obese patients undergoing sleeve gastrectomy.17 The study demonstrated that the combination of 4 mg of dexamethasone and 4 mg of ondansetron was not effective in prevention of post operative nausea and vomiting in obese patients. The dual loop was also used during orthotopic liver transplantation and propofol requirements were reduced during the anhepatic phase.18
The dual-loop controller of drug delivery is a robust, reproducible and unbiased method for the assessment of anesthetic requirement when an adjunct such as nitrous oxide was used,19 dexmedetomidine20, thoracic epidural analegesia21 or when different propofol formulations22 were evaluated because investigator bias is eliminated.
However, these prototypes have been used only as a research tool and there is currently no dedicated automated controller marketed for anesthesia18.

Conclusion: Published studies have reported the clinical relevance and the technical performance of automated administration of anesthetic agents. But drug administration is only one task of the patient care during anesthesia. The presence of an anesthesiologist remains essential to maintain cardiopulmonary homeostasis during all procedures. However, the introduction of automated systems in the clinical setting will become a reality and will modify anesthesia practice. The next challenge will be to determine whether the introduction of the automated controller in a clinical setting can decrease the cost, morbidity or mortality associated with anesthesia or sedation.

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THE INFLUENCE OF DIFFERENT PHARMACOKINETIC MODELS ON PROPOFOL DELIVERY

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Introduction: Any technique of target controlled drug infusion (TCI) requires the incorporation of a pharmacokinetic model for the drug to be infused to determine the amount of drug delivered at any given target blood concentration. In the case of propofol, the use of different pharmacokinetic models can have a significant effect on the profile of drug delivery. In addition when a TCI system is used to target brain (effect-site) drug concentration, use of different rate constants for effect site equilibration (ke0) can have a marked effect on the early phase of drug delivery. The aim of this work was to determine the influence of different pharmacokinetic models and ke0s on propofol delivery.

Methods: Following validation studies where drug delivery in response to a given input profile, as measured by an electronic balance, was compared with values predicted by computer simulation, the pharmacokinetic simulation program PK-SIM (Specialized Data Systems, Jenkintown, PA, USA) was used to determine the influence of the Marsh and Schnider models for adults and the Paedfusor and Kataria models for children, on the cumulative amount of drug (mg/kg) delivered over the first five minutes and thereafter the infusion rate provided (mg/kg/hr). It is suggested that the comparison of different pharmacokinetic models in this way may be more useful than comparison of information on predictive performance, in providing users with guidance on the likely clinical performance of different models.

The drug delivery profile is influenced by all of the parameters of each model, but by far the most important of these are the volume of the central compartment (V1) and clearance from the central compartment (V1 x k10). The amount of drug delivered as an initial rapid infusion to achieve the target set, with a TCI system controlling blood concentration (CbT), is directly related to V1. On the other hand, clearance is the principal determinant of the infusion rate required to maintain a desired target concentration and the two again are directly related, such that doubling the target setting will double the amount of drug given at induction and the infusion rate at any particular time point.

With the Marsh model, as the central compartment volume of distribution (V1, 228 ml/kg) is related to body weight, all volumes of distribution and clearance are related to body weight and a single set of rate constants can be used for all patients. The consequence is that with body weight being an input parameter, drug delivery in terms of mg/kg or mg/kg/h is the same for all patients, independent of body weight, gender or patient age. In contrast the Schnider model is more complex. In this model V1 is constant at 4.27 L, age is a covariate for V2 and Cl2 (rapid peripheral clearance) and weight, height and lean body mass are all covariates for metabolic clearance (Cl1). Although gender is not a covariate, it has an influence on Cl1, and hence on drug delivery, as the James equation used to calculate lean body mass is gender specific, such that metabolic clearance is 15-30% greater in female subjects. With a propofol target blood concentration (CbT) of 4µg/ml, the Schnider model, with a much smaller V1 than the Marsh model, delivers only 0.7 mg/kg over the first 2 min in a 70 kg, 50 yr old, male patient whereas the Marsh model provides 1.4 mg/kg, independent of patient age. For this reason it has become common practice in centres which use the Schnider model to select an effect control mode of operation (CeT). With a CeT of 4µg/ml with the Schnider model in the same patient the amount of propofol delivered at 2 min is still less than that provided by the Marsh model such that a slower onset of anaesthesia would still be expected [1].

Five minutes after the achievement of an effect site target concentration with the Schnider model there is very little difference between CeT and CbT in the infusion rates delivered to maintain a given target with this model. Whereas with the Marsh model the infusion rate profile at a given target setting, in terms of mg/kg/h, is independent of patient age or weight this is not the case with the Schnider model. With this model, rapid peripheral clearance (Cl2) is increased in younger patients leading to a slightly greater infusion rate while the opposite effect occurs in older patients. While it may be desirable to compensate for age related changes in the pharmacokinetics of propofol, with both models the selection of an appropriate target concentration should also take age related changes in the pharmacodynamics of propofol into account [2]. In relation to adjustments for patient weight with the Schnider model, some undesirable effects occur. As body mass index increases above 35kg/m2 in females and above 42 kg/m2 in male subjects, the James equation [3] used for the calculation of lean body mass (LBM) begins to provide declining values of LBM which results in increased values for clearance and greater infusion rates in patients above these limits. An increase in clearance and

propofol delivery is also seen in underweight patients and this effect persists when alternatives to the James equation are used for the calculation of LBM.
A further complication occurs with the Schnider model in that TCI systems which aim to achieve effect-site concentrations with methodology utilising a fixed time to peak effect of 1.6 min, deliver a much larger initial dose in young, heavy patients than systems which use a fixed ke0 of 0.46 /min.
In children, both the Paedfusor and Kataria models deliver greater initial doses and greater infusion rates during maintenance than the Marsh adult model, with the greatest increase being seen with the Kataria model.

Conclusion: With effect-site TCI, the size of the initial dose delivered is dependent on the PK model, the ke0 and the target concentration. The ke0 has no significant effect on the maintenance infusion rate but does influence the size of supplementary dose required to achieve a higher target and the duration of cessation of infusion when a lower target is requested. The relationship between ke0 and the initial dose delivered is non linear in that small changes in ke0 in the range 0.1- 0.3/min have a marked effect on the size of the initial dose, whereas very little change is seen with ke0s in the range of 0.8 – 1.2 /min [4]. This study proposed that a clinically effective ke0 should deliver an initial dose adequate to induce anaesthesia rapidly at an effect site target likely to be close to that required for maintenance. More detailed information on drug delivery during TCI can be found in a recent publication [5].

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THE ROLE OF PHARMACOKINETHIC MODELS ON THE OPIOIDS DELIVERY

Freddy Del Gaudio

Fentanyl, Alfentanil, Sufentanil and Remifentanil have important pharmacokinethic and pharmacodynamics (PK/PD) differences: Their effects usually parallel the plasma concentrations but with a temporal shift. This temporal shift differs between opioids. It is small with alfentanil or remifentanil andvery long with the active metabolite of morphine, morphine-6-glucuronide (M6G). The mathematical and experimental techniques for modeling these PK/PD relationships were developed in the late 1970s. The delay between plasma concentrations and effects is accounted for by the introduction of a hypothetic effect compartment, which is linked to the plasma compartment by a first-order transfer function with a rate constant ke0. The effects are then linked to the concentrations at effects site by standard pharmacodynamic models such as sigmoid ("Emax") models or power models, depending on the actual effect measure. These principles were first applied to the opioids fentanyl and alfentanil in 1985. Since then, PK/PD of opioids have been repeatedly assessed, using EEG derived parameters, pupil size, and experimental and clinical pain as effect measures. Alfentanil and remifentanil are very fast equilibrating opioids with equilibration half-lives between plasma and effect site of about 1 minute. They are followed by fentanyl and sufentanil, each with equilibration half-lives of about 6 min. Methadone equilibrates with a half-life of about 8 min. Morphine, in contrast, equilibrates with a half-life of 2–3 h. The slowest opioid with respect to plasma-effect site transfer is M6G, with an equilibration half-life of about 7 h. PK/PD modeling has advanced the understanding of the time course of the clinical effects of opioids after various dosing regimens. It may provide a rational basis for the selection of opioids in clinical circumstances. The most important problem of these models is the numerosity of the subjects considered that is very low in all models. So it is possible to perform errors linked to the interindivdual variability.

SESSION A2 11:15 – 13:20 OLD AND NEW IN ANESTHESIA

THE PLACEBO EFFECT: WHAT IT IS, HOW IT WORKS

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The placebo effect is an important component of any therapy, both in modern conventional medicine and in traditional alternative medical practices. Although placebos have long been considered a nuisance in clinical research, today they represent an excellent model to understand how words and therapeutic rituals may affect the patient's brain. Placebo effects, and their evil twins, nocebo effects, are today an active and productive field of research and, because of the involvement of many mechanisms, the study of the placebo effect can actually be viewed as a melting pot of concepts and ideas for neuroscience. Indeed, there exists not a single but many placebo effects, with different mechanisms and in different systems, medical conditions, and therapeutic interventions. For example, brain mechanisms of expectation, anxiety, and reward are all involved, as well as a variety of learning phenomena, such as Pavlovian conditioning, cognitive and social learning. There is also some experimental evidence of different genetic variants in placebo responsiveness. The most productive models to better understand the neurobiology of the placebo effect are pain and Parkinson's disease. In these medical conditions, the neural networks that are involved have been identified: that is, opioid, cannabinoid, cholecystokinin, dopamine modulatory networks in pain and part of the basal ganglia circuitry in Parkinson's disease. Important clinical implications emerge from these recent advances in placebo research. First, as the placebo effect is basically a psychosocial context effect, these data indicate that different social stimuli, such as words and therapeutic rituals, may change the chemistry and circuitry of the patient's brain. Second, the mechanisms that are activated by placebos are the same as those activated by drugs, which suggests a cognitive/affective interference with drug action. Therefore, by taking all these data together, today we can talk of a true pharmacology and toxicology of words and rituals.

POSTOPERATIVE NAUSEA AND VOMITING

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Postoperative nausea and vomiting (PONV) is one of the most frequent postoperative complications, occurring after surgery under general, regional or local anaesthesia. Previous studies have shown that patients

regard vomiting as the most undesirable complication of anaesthesia and qualify it as a more unpleasant sensation than pain (1,2). The incidence of PONV in adult population is 30% (3), and in population with elevated risk such as gynaecologic and laparoscopic surgery, it can be up to 80% (4,5).

The potential risk factors for PONV can be classified into four groups: patient related factors (female gender, age, positive anamnesis for PONV, kinetoses, non-smoking status, the patient's ASA status, positive anamnesis for migraine, menstrual cycle phase), surgery related factors (length of surgery, type of surgery), anaesthesia related factors (inhalation anaesthetics, intravenous anaesthetics, opioids, muscle block reversal, anaesthetic technique and N2O), and early postoperative period related factor (pain, opioid administration, postoperative movement of patients, early fluid and food ingestion and hypotension) (6).

The significance of PONV is reflected not only in its incidence, but also in consequences that it can have on the outcome of surgical treatment in terms of disorders of general condition, reduced fluid intake, discontinuation of regular therapy, compromisation of successfully performed surgery (especially in the areas of aesthetic, ophthalmological and neuro-surgery (7), occurrence of dehiscence, haemorrhage, aspiration of stomach contents and occurrence of asphyxia and/or aspiration pneumonia (8,9,10). In addition to possible medical complications, it reduces patients' satisfaction with provided medical service, and economic consequences are not negligible either, in terms of additional costs due to additional engagement of medical staff, delayed discharge from recovery unit, and extended stay in the hospital (11)

The most used antiemetic drugs used in PONV prevention and therapy include dopamine receptor antagonists, serotonin 5-HT3 receptor antagonists and corticosteroids and later-generation antiemetics, neurokinin-1 (NK-1) antagonists (8,12).

In the therapy and prevention of PONV, anaesthesiologists have the most experience in the application of dopamine antagonist metoclopramide. Due to its short-term action, it should be administered towards the end of the surgery. At the dosage of 0.1 to 0.2 mg/kg, it very rarely causes adverse effects in adult patients (8,12).

From the group of corticosteroids, antiemetic effect is shown in the administration of dexasone. Its exact mechanism of action is unknown, but it is assumed to be based on inhibition of prostaglandin synthesis, decrease of serotonin levels in the brain, local anti-inflammatory action and reduction of brain-blood barrier permeability (8,12). Dexasone potentiates the action of other antiemetics through the stabilisation of receptors on which they act (13). The recommended dose of 2.5 to 5 mg is given at the beginning of the surgery.

One of the most potent selective 5-HT3 antagonists is granisetron, which can provide a 24-hour antiemetic effect at the dose of 1 mg after induction of anaesthesia. The main factor limiting the clinical use of granisetron is its price, rendering the routine prophylaxis with this drug extremely costly (8,12).

There are over 60 randomized controlled studies comparing the effects of antiemetics in comparison with monotherapy, and most showed better results when using two or more agents with different location of receptor action (14,15), which is also in compliance with the multifactorial origin of PONV.

A rational approach when combining antiemetics implies that combined administration of drugs potentiates their positive sides, and reduces adverse effects.

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FINE-TUNING OF NEUROMUSCULAR RELAXATION ACCORDING TO SURGICAL NEEDS

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In the past, we viewed neuro-muscular blockade (NMB) as an on/off-function: the patient had either a blockade or no blockade. Before termination of anesthesia, one had to check whether an apparent diminishing of NMB was sufficient to wake up the patient, and whether reversal was necessary. For the distinction of fitness to extubation we applied the «train of four» (TOF) ratio and viewed a value of >0.7 as sufficient. Meanwhile this threshold has been elevated to 0.9. However, conventional relaxometry equipment only rarely delivered accurate measurements and if so, not all users were familiar with the details and pitfalls of the technique. In many cases, a fine-tuning of neuromuscular blockade during and towards the end of anesthesia was a difficult and insufficiently mastered undertaking. However, by now we have adequate equipment to fine tune the level of NMB. The scope of this presentation is to raise the awareness to this still largely ignored problem and the recent possibilities to solve it.

Before going into the details of NMB fine-tuning, we have to discuss the rational for applying NMB and for which purpose it might be necessary and when it should be avoided. In this respect, anesthetists and surgeons may have partially converging and partially diverging interests. The anesthetist needs or prefers NMB for better intubation conditions, to aim for a lighter anesthetic depth with less undesired hemodynamic responses, a patient who exerts no defense reflexes and does not interfere with ventilation. The surgeon on the other side requires NMB to achieve better viewing conditions during laparoscopies or in interventions when the patient should not move (1). In contrast, there might be good reasons to minimize or even obviate NMB during surgery. The anesthetist wants to avoid unnecessary prolongation of anesthesia and insufficient spontaneous ventilation after surgery. Surgeons want to avoid NMB when they need to use neuro-monitoring they abhor NMB. This dualism between the necessities for a deep NMB vs. its avoidance is no contradiction and may be necessary during the same intervention. This finally means that there is a strong indication for good control of NMB level, which includes both: 1. a reliable and precise monitoring by relaxometry, and 2. an exactly goal directed dosing of NMB and of reversal agents.

In order to adapt to the need of fine-tuning of NMB to the actual requirements during surgery and anesthesia, we need to distinguish two fundamentally different NMB activity patterns. The first one is the „gecko pattern“, in which the NMB agent has been given at induction of anesthesia in a large bolus dose to enable smooth intubation, but subsequently it is left to natural decay during surgery. In contrast, a „dachshound” pattern is indicated if NMB must be maintained on a higher level throughout the whole operation. These two patterns imply different approaches to terminate anesthesia and to return to wakefulness. Longer lasting «gecko» anesthesias are easy to terminate, while often the NMB has dissipated completely towards the end of surgery. Here usually no reversal is necessary. Short «gecko» like anesthesias might necessitate conventional reversal of residual blockade. The termination of anesthesia in «dachshound» patterns is more difficult and usually requires a strong and reliable reversal. This transition from deep blockade to almost no blockade is manageable with sugammadex only. Otherwise, one might wait for a longer period until the natural decay of NMB permits the use of neostigmine. Even more difficult is the emergence from a short time

lasting permanent blockade, where the same rule applies: either one invests sugammadex or time. In clinical routine, there is a multitude of possible combinations for surgery durations (from ultra-short to very long) with suitable NMB patterns („gecko“ vs. „dachshound“). They all need customized choices of NMB agents and reversal strategies.

A particularly specific type of surgery requiring the maintenance of a typical «dachshound» strategy is the robot-assisted endoscopic intervention. During the critical phase of pneumoperitoneum, a deep NMB is necessary to improve operation conditions and to avoid inadvertent moves by the patient. The shape of such an NMB profile is characterized by an initial deep NMB for intubation, a period of deliberate diminishing of NMB during positioning, exposure and disinfection of the operation site, followed by a persistently deep NMB during pneumoperitoneum, and finally a fast recovery during emergence from surgery and anesthesia. It can be achieved either by an intricate combination of NMB-dosing and fast reversal, or in a simpler but more brute way by deliberate overdosing of both, the NMB agent as well as administering a large amount of sugammadex at the end. However, this approach is not only less elegant, but far more costly.

To understand the procedure of NMB fine-tuning, we have to acknowledge the motor response patterns in differently intense NMB levels, which are characterized by a group of 3 motor response categories. After a large initial bolus dose leading to 100% receptor occupancy and full blockade, the patient passes through periods with intense blockade (0 post tetanic count PTC), deep blockade (1-3 PTC), moderate blockade (4 and more PTC to 1 train of four count TOFc), to superficial blockade (2 to 4 TOFc) and increasing positive train of four ratio (TOFr). This is the spectrum in which the NMB level is to be adjusted according to the actual needs of surgery and anesthesia. The problem is that while the receptor occupancy is linear from 0 to 100% and vice versa, the available motor responses are neither linear nor proportional, thus making it difficult to correlate them with the level of NMB. In particular, the ability to move remains for a large proportion of receptor occupancy unaffected and diminishes only above 70% of blocked receptors. On the other hand, the ability to return to spontaneous ventilation and protected airways is only possible if there is almost no NMB blockade at all. These two extremes in the relaxometric spectrum result in the circumstance that a large part of it is in clinical terms useless. Moderate NMB, as represented by motor responses of PTC > 3 to positive TOFc or low TOFr levels may be not profound enough for safe intubation and surgery, but or still too intense for safe emergence from anesthesia. The recognition of this «dilemma» is a first step to understand the necessity of fine-tuning NMB based on suitable monitoring with a sufficient resolution level.

The primary goal of NMB during surgery is actually the controlled maintenance of paralysis during pneumoperitoneum followed by a swift move towards recovery afterwards. Conventional relaxometry based on acceleromyography or mechanomyography has been applied over decades with various degrees of success. The inconsistence from their readings was a consequence of too many artefacts. They also do not display a NMB level course over time, which otherwise would depict the individual dynamics of the patient’s NMB course.

Recently, a novel relaxometry device, the TOFcuff™ has been introduced to the market, which clearly distinguishes the different motor response levels and displays them as a curve over time (2). The stimulation electrodes are incorporated into a non-invasive blood pressure cuff, which senses the motor responses by pressure variations of the slightly pre-inflated cuff. The TOFcuff™ is a high-end relaxometer, device calibrates itself by one TOF measurement before the initial relaxant bolus (but after loss of consciousness), and chooses which stimulation pattern has to be applied at which stage of relaxation.

In a prospective, non-randomized, un-blinded, single center «proof of concept» study, which is still in the phase of including patients, we are checking a simple and straightforward model of fine tuning of deep neuromuscular blockade in robot-assisted urological surgery on 20 patients. By administering small repetition doses of rocuronium in variable time periods according relaxometry, we assess the ability to maintain a NMB level of PTC 1-3 throughout the pneumoperitoneum period, thus avoiding either an intense or a too superficial blockade. The objective is to assess the absolute and relative times of adequate NMB (PTC 1-3) and to describe the necessary dosage patterns of NMB and reversal agents. First results show that even with precise and reliable relaxometry it is not easy to maintain an adequate NMB level. In four consecutive patients, we succeeded to maintain PTC 1-3 in 41% of the relevant time, while a similar fraction (40%) of intense block prevailed. In 10% of the time the block was only borderline (PTC 4 to 5) and needed immediate correction, while during 8% the NMB level was judged moderately deep, which might be considered inacceptable. An important aim during this investigation is to improve these results by further decreasing the time spent in inacceptable conditions and to increase the fraction of adequate NMB time.

Future investigations with a modified dosing pattern are necessary to find the ideal procedure for NMB in robot-assisted surgery. These may comprise continuous infusions of NMB agents, combinations of manual bolus doses with continuous infusion, a target controlled infusion (TCI) model and maybe in a farer future an automated or semi-automated dosing system based on feedback loop-control.

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SCOPE OF 3D PRINTING IN ANESTHESIOLOGY

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3D printing as the name suggests is printing something in 3 dimensions as text or an image is printed on a paper in 2 Dimensions. The inclusion of the 3rd dimension in printing raises questions as what is the 3rd dimension, how can it be printed, what can be printed and most importantly how can it be useful.

3D printing basically rather printing is manufacturing on a miniature scale. This printing additive manufacturing whereby a desired structure is created by addition of layer by layer of a material over and above each layer, giving rise to a 3 dimensional structure which can be a replica of a structure or any other desired entity. The finished structure is highly accurate and the process is very versatile.

The material used for printing can be thermoplastics, carbon fibers, polycarbonates etc. Newer and newer materials with ability to get 3d printed are being discovered.

Just like a printer which prints on paper using ink, a 3D printer uses a suitable material which can be layered by different techniques. The most common technique is extrusion of molten material by nozzles, which gets layered over each other.

The instructions for printing such as size, texture, shape etc are fed into a computer and through it the instructions are delivered to the printer which then acts accordingly.

Using nanotechnology the process can be further intricated.

Since the technique of 3D printing has been invented, it was being used basically for industrial model manufacturing, prototyping, mould construction and engineering of designs. However, recently 3D printing has a newfound use. This technique has recently ventured into the medical field. It can create replicas of body parts, design prostheses, mimic anatomy, and using data from scans can reproduce deeper diseased parts or defects 3 dimensionally.

As far as Anesthesia is concerned, 3D printing has immense scope in the field.

First of all it can be used for planning in anesthesia

Difficult airway is commonly encountered. Mostly it is anticipated and there can be different options of managing it. As 3D printing can replicate body parts, a replica of the airway can be constructed and then the best method of securing that airway can be decided by practical trial on the replica. This would thus save time and damage to patient's airway by singling out the best suited technique.

Such an exercise would also reduce the time for laryngoscopy which can be useful in a particular set of patients such as hypertensives where laryngoscopic response is desired to be minimum.

3D Printing can be useful in construction of airway adjuncts

Many patients have tracheal stenosis, deviation or an asymmetric trachea or even oral anatomy. There can be difficulty in securing the airway with conventionally available airway adjuncts. So tailor made patient specific airways or particularly deviated tubes may be made with this technique.

3D Printing in Anesthesia can also be used for teaching and training purposes.

An exact replica of a difficult airway or a spine with altered anatomy can be made and trainees can be asked to practice on these products. This would enhance the confidence of trainees, make them feel apprehension free and at the same time save the patient from repeated trial and error. By this approach the student would have practically tried many airways and spines before the actual patient.

Often the students are taught on mannikins. But these are costly, require consumables and have limited number of repeated use. With the advent of 3D printing, the use of mannikins can thus be minimised.

Also as 3d structures can be replicated using scans etc of actual patients, over a period of time a bank of models of difficult airway can be created which can give the students a first hand information and exposure of a variety of peculiar cases. Even for examination and evaluation, the examiner can test the actual skill of students using these replicas.

The technique of 3D printing is evolving at a rapid pace and is finding newer uses day by day. With increase in usage and advancement in technology, the process is bound to become cheaper, quicker and more practical.

SESSION A3 15:00 – 16:40 TCI AND SEDATION

TEACHING TIVA TCI WITH FULL SCALE PATIENT SIMULATORS

Wolfgang Heinrichs

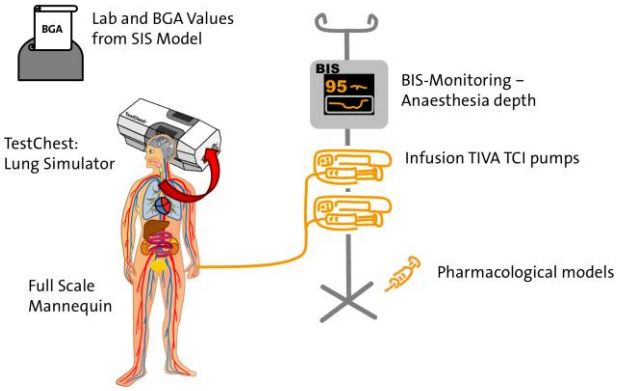
AQAI Simulation Center Mainz, Germany

Target-controlled infusion (TCI) technology is available in most countries worldwide for clinical use in anesthesia. Pharmacokinetic models are used in this infusion mode to calculate infusion rates necessary to reach and maintain the desired drug concentration. The calculated infusion rates during TCI are consistent with manually controlled infusion rates. Nevertheless, there may be unique safety concerns when using this technology under various clinical conditions.
In a recent report Schnider (1) analyzed the available data about safety and complications using TCI. While TCI is reported to be more complex than traditional modes of drug administration, he found no evidence that TCI mode of drug delivery introduces unique safety issues other than selecting the wrong pharmacokinetic model. A look through recent literature shows that selecting the right model and adapting the model to the correct patient data in terms of height, weight and LBM (lean body mass) is very important for the safe use of TCI in the daily practice (2,3,4).

Finally, for every single anesthesiologist the first use of TCI is a new adventure. Although he or she may be experienced in administering TIVA (total intravenous anesthesia), there may be several new approaches and a lot of different steps in the usage of the pumps. Once these learned, TCI is indeed a very safe and elegant method.

How to learn TCI? Traditionally there are classes offered where the theory of TCI and pharmacological models is explained using a traditional class room setting. In a number of these classes, the simulation software TIVA Trainer™ was added to the course settings. With this simulation software participants are able to conduct virtual TCI's. The disadvantage still is that TIVA Trainer does not show any physiological reactions of the patient himself.

To make TCI training as real as possible, we developed a program starting at 2005 as a cooperation between Quirino Piacevoli at the Ospedale San Filippo Neri, Rome, Italy together with the AQAI simulation center in Mainz, Germany. To show the effect of the anesthesia besides cardiovascular reactions the BIS (Bispectral Index by Aspect - today owned by Medtronic) was used. TCI pumps and the BIS monitor were directly connected with the patient simulator using an own development of interface software (SIS = Simulator Interface Software; © AQAI). Laerdal SimMan3G simulators are used in the classes. The following picture gives an overview about the setting:



The SIS software thus has the following functions: Control the mannequin in a physiological manner
Create realistic cardiovascular and respiratory responses
Interact with participant's maneuvers done in the course of the anesthesia
React to the drugs infused by at least 2 TCI pumps (Propofol + Opioid)
Calculate the depth of anesthesia according to the pharmacological concentrations
Generate EEG traces and send these to the BIS monitor
Allow the control of various scenarios like simulating patients of different age, height, weight and gender.
The overall setting is integrated into a real OR atmosphere featuring OR table, anesthesia machine, anesthesia equipment and several more typical devices. As we teach not only the normal TCI application but also some abnormal complications, additional material like difficult airway equipment, defibrillator and other materials for emergencies are available.
Video recordings may be used during the different scenarios to facilitate debriefing session immediately following the scenario. Thus a maximum of learning effect is achieved.
Based on this technology, we developed a basic and an advanced TCI learning curriculum. Originally each of these curricula lasts one day. So, we have plenty of time to do several theoretical lectures followed by praxis exercises in the simulator setting. The detailed content of the 2 curricula is presented in the following tables:

Basic – Seminar (1. Day) (7h excluding breaks): Learning objectives: Participants are able to
understand the basics of TCI, to demonstrate TCI and to use TCI in simulation software
conduct routine anesthesia with TCI safely
name and recognize advantages of TCI compared to conventional application of TIVA drugs
Contents:
Pharmacological basics of TCI (TIVA Trainer „hands on") (60min)
Applications of TCI (TCI pumps) („Introduction into the use of TCI-Pumps") (30 min)
Monitoring – BIS – Other EEG-Parameter (30 min)
Introduction into TIVA/TCI using the patient simulator; Comparison TCI and conventional (BET) application (60 min)
Participants conduct anesthesia using the patient simulator:
Routine, healthy, no complications TCI anesthesia (30 min + 30 min Debriefing)
Titration of induction using TCI (30 min + 30 min Debriefing)
Recovery, prediction of ROC from the models (30 min + 30 min Debriefing)
(Analgo-) sedation with TCI (30 min + 30 min Debriefing)

Advanced – Seminar (2. Day) (7h excluding breaks): Learning objectives: Participants are able to
describe interactions between various TIVA drugs and use this information for the adequate control of TIVA with TCI
select the adequate model for the individual patient and conduct TCI anesthesia in various cases including high risk patients
transfer the experience of various simulated patients into their daily professional practice.
Contents:
Interactions of Propofol and Remifentanil respect. various opioids; theory and demonstration with the patient simulator (60 min)
Various TCI Models (why / how) in theory and practice (TIVA Trainer) (60 min)
Various patients (participants conduct anesthesia with the patient simulator):
ASA IV due to cardiac problems (30 min + 30 min Debriefing)
Extreme low/high body weight (30 min + 30 min Debriefing)
Extreme age (30 min + 30 min Debriefing)
Pediatric TCI applications (30 min + 30 min Debriefing)
Long term TCI, e.g. sedation in intensive care (30 min + 30 min Debriefing)

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Conflict of interest: Wolfgang Heinrichs is CEO and senior developer of AQAI GmbH, Simulation Center, Mainz, Germany. AQAI has developed the models, the SIS interface software and the curriculum presented in this article. AQAI functions as supplier of these products. Wolfgang Heinrichs is also consultant to Laerdal, Norway.

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TCI SEDATION. CLINICAL APPLICATION

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TCI is used to provide anesthesia or sedation for patient undergoing a wide type of diagnostic and therapeutic procedures (1).
TCI sedation offers some advantages versus other sedation techniques, increasing patient safety and allowing for more rapid wake-up times (2). TCI provide an accurate titration of dose administered and consider patient covariates. Depth of sedation can be changed quickly during procedure by simply selecting a new target concentration. TCI offer a better hemodynamic stability, allow spontaneous ventilation (2,3). Also, there are some limitation of TCI sedation such as performance of TCI system (accuracy, outcome) and narrow therapeutic range between adequate sedation and anesthesia.
TCI system used for sedation are commercially available TCI pump (open TCI system), and closed-loop TCI system. Newer generation closed loop TCI system allow real-time patient monitoring and titrate drug dose automatically to maintain optimal depth of sedation (2).
Propofol and remifentanil are the most used drugs for TCI system because of its effect profile. For both drugs, there are pharmacokinetic (PK) and pharmacodynamic (PD) models published that establish the relation between dose, plasma concentration and effect. A combination of propofol and opioid improve the quality of sedation and reduce propofol requirements but increase the risk of apnoea.

TCI sedation is used for diagnostic and therapeutic procedure in or outside the operating room. Perioperative TCI sedation improve patient tolerance and acceptability in performing the neuraxial or peripheral nerve block and facilitation the surgery (4,5). In awake fiberoptic intubation, propofol and remifentanil TCI sedation offer good tolerability and better condition for intubation (3,6). Propofol decrease incidence of recall compared to remifentanil but the risk of oversedation is higher in propofol TCI (6).
Propofol and opioid TCI have been used in a variety of settings, including endoscopy, dental procedures, burn dressing change etc (2,3,7). Propofol TCI for GIE procedures demonstrates better sedation, less adverse effects and higher patient satisfaction than remifentanil TCI (8). The combination of propofol and remifentanil for deep sedation in spontaneously breathing patient offer better condition for colonoscopy (9). The targets concentration for endoscopy procedures depend on the procedure, the physiological variables and the comorbidity (10).
TCI poses many advantages for administering sedative drugs in the ICU. The sedative regime can be tailored to the patient's needs, which may change over time. Difficulties may be encountered because the algorithm incorporated in currently available TCI systems may not be suitable for the population of patients in the ICU. The pharmacokinetic and pharmacodynamics properties of drugs may be different in ICU patients. TCI sedation in ICU has been used for facilitation of mechanical ventilation, for painful procedures and for performing procedures in spontaneous breathing patients such as non-invasive ventilation, fiberoptic bronchoscopy and bronhoalveolar lavage (11,12).
In conclusion, TCI sedation is a safe, attractive and easy to use mode of delivering sedation, provide hemodynamic stability, maintain adequate spontaneous ventilation and can be used in a variety of clinical conditions.

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TARGET CONTROLLED INFUSION (TCI) OF ANTIBIOTICS

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The management of infectious diseases in intensive care is becoming increasingly difficult for the continued rise of
antimicrobial resistance. Given the lack of new antibiotics, the only chance we have to treat multiresistant pathogens is
to maximizing the effectiveness of available drugs [1].
We know little of antibiotics pharmacokinetics and pharmacodynamics in critically ill patients.
Homeostatic disturbance, endothelial dysfunction, altered major organ blood flow, vasopressor medications, drug
interactions, low plasma proteins concentration, organ dysfunctions, augmented renal clearance, use of extracorporeal
circuits contribute to avert critical patients from healthy volunteers or other hospitalized patients, on which antibiotics
pharmacokinetics were studied [2].
For time-dependents agents, such as ß-lactams and glycopeptides, in vitro and animal studies have demonstrated that
the critical factor for bacterial killing is the amount of time in which the free drug concentration exceeds the MIC of the
organism. So that we have to Maintain Sufficient drug Concentrations (>MIC) throughout the dosing interval.
To achieve this we have to tailor the dose to the Pharmacokinetic Characteristics (PK) of the patient, pratically we
need to know the plasma concentration of antibiotic and set infusion programs able to reach the concentrations required.
De Waele et al. reported that Therapeutic Drug Monitoring (TDM)-based dose adaptation of ß-lactams improves
antibiotic exposure in critically ill patients at risk of under dosing [3].
To reach elevated MICs we can administer the medication frequently or use continuous/extended infusions [4].
Recent meta-analysis concluded that continuous/extended infusions of antibiotics in critical patients improve cure rates
and length of stay [4]. Additionally other studies showed that prolonged infusions are cost savings and mitigate the
emergence of resistance.
Unfortunately, the plasma assay of antibiotics is not available in all hospitals and the implementation of TDM requires
pharmacological expertise.
Enhanced knowledge of PK and PD would allow us to build Target Controlled Infusion (TCI)-devices for administering
time-dependent antimicrobial drugs; as it does now for anaesthetics [5].
Target Controlled Infusion (TCI) is a computer-assisted administration of drugs designed to achieve a user defined
concentration in a tissue of interest.
The computer is programmed with a pharmacokinetic model which is describing the distribution and elimination of the
drug within the body. TCI-system calculates the initial loading dose needed to obtain the desired target concentration and
the infusion rate needed to maintain it constant and sends instructions to the infusion device.
The clinician should decide the most appropriate antimicrobial and enter in the computer the desired target concentration
and the clinical parameters of the patient.
The use of TCI-systems for antibiotics would get a target concentration continuously above-MIC, aim difficult to achieve
with intermittent administration in critical patients infected by resistant pathogens.
A computerized system also would consider and weight all the pharmacokinetic changes that affect the critically ill.
Large-size studies on the Pharmacokinetics (PK) and Pharmacodynamics (PD) of time-dependent antibiotics in critically
ill patients are required urgently to use them better and to give us the only weapon available in the short term against

multiresistent pathogens.
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PROPOFOL TARGET CONTROLLED INFUSIONS (TCI) FOR GASTROINTESTINAL SEDATION BY NON-ANESTHESIOLOGISTS. OUR EXPERIENCE IN ALZAHRA HOSPITAL DUBAI (AZHD).

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There is a considerable move from traditional methods for gastrointestinal sedation based on Benzodiazepines +/- Opioids, to Propofol based sedation. This is understandable because compared with traditional sedation, Propofol based sedation have very slightly lower rates of adverse events, provide better sedation and patient cooperation, it also decreases recovery and discharge times, and achieve much better post anesthesia recovery profile of the patients.

In the Middle East region, Propofol based sedation whether as a sole agent or with Opioid is gaining more popularity and can be administered by Non- Anesthesiologists (when the proper pre-procedural evaluation and assessment of the patient indicate that the patient can be sedated by Non-Anesthesiologist)

The only method of administering Propofol based sedation by Non- Anesthesiologists is using repeated Intravenous bolus doses. This practice obviously leads to significant variability of the Propofol level in the patient's blood, in other words patient will experience periods of over sedation with consequent increase in adverse effects, and other periods of under sedation with its unfavorable consequences.

Target Controlled Infusion (TCI) is designed to achieve a preset target blood (or brain) concentration.

It is easy to use, and provides a very high level predictability of the maintenance of the same anesthesia (Sedation) level.

We set a formal theoretical training course for all our endoscopists and endoscopy nurses, then we started to do lists supervised by an anesthesiologist, till every endoscopy team felt very confident in administering the TCI sedation, signed competent by the Anesthesiology team, then they were allowed to do procedures on their own.

Alzahra Hospital in Dubai (AZHD) is one and half years along the way, it is now our standard technique for gastrointestinal endoscopy sedation. All sedation in Endoscopy is done by Propofol TCI administered by Non-Anesthesiologists in patients groups that fulfill the criteria for sedation by Non-Anesthesiologists. Patients who require the presence of anesthesiologists, Propofol TCI was done by an Anesthesiologist. These later cases were also used as refresher and training cases for the Endoscopy teams allowing further interactions, questions and improvements in their TCI sedation performance.

In Conclusion:

Propofol TCI sedation for gastrointestinal endoscopy cases by non-anesthesiologists is a safer technique than repeated IV Propofol boluses technique, provides more optimal sedation depth control, minimal

hemodynamic variability, much less respiratory adverse effects, and much better endoscopists and patients satisfaction.
There is a huge potential for using Propofol TCI sedation whether by Anesthesiologists or Non-anesthesiologists for many other sedation in other areas than endoscopy.

SESSION A4 17:10 – 18:45 PK /PD MODEL

EXTERNAL VALIDATION OF MCT/LCT PROPOFOL TCI WITH THE MODIFIED MARSH AND SCHNIDER MODELS

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Background: Propofol formulated with long-chain triglycerides (Propofol-LCT) has been gradually replaced by propofol formulated with medium- and long-chain triglycerides (Propofol-MCT/LCT) in anesthetic filed. However, the modified Marsh and Schnider models developed using propofol-LCT are still widely used for target-controlled infusion (TCI) of propofol. This study was designed to perform the external validation of the two popular pharmacokinetic models with TCI of propofol-MCT/LCT during general anesthesia.

Method: Forty-eight adult patients, scheduled for elective surgery, were randomly allocated to receive propofol-MCT/LCT with TCI using the modified Marsh or Schnider model. During general anesthesia with propofol and remifentanil, arterial bloods were sequentially sampled at the propofol effect-site concentrations of 3 (or 3.5), 4, 5, 5, 4, 3, 2.5, 2.5 and 2 (or 2.2) ug/ml. Each sampling was performed at least 8 min after achieving pseudo-steady-state, and actual plasma concentration of propofol was determined by high-performance liquid chromatography. The pooled bias, inaccuracy, divergence and wobble of the both propofol models were determined from the performance errors.

Results: A total of 426 propofol plasma samples were analyzed. The pooled median (95% confidence interval) biases and inaccuracies were 16.4% (12.7 to 20.1) and 24.4% (21.8 to 26.9) for the modified Marsh model and 16.6% (13.2 to 20.2) and 26.9% (23.9 to 29.6) for the Schnider model, respectively. The pooled divergence and wobbles (95% confidence interval) were -3.3%/h (-4.7 to -1.8) and 11.7% (9.1 to 14.3) for the modified Marsh model and -7.2%/h (-11.8 to -6.0) and 8.8 (5.9 to 11.4) for the Schnider model, respectively (Fig 1.).

Conclusion: Propofol-MCT/LCT can be administered via TCI using both the modified Marsh and Schnider models with acceptable bias and inaccuracy.

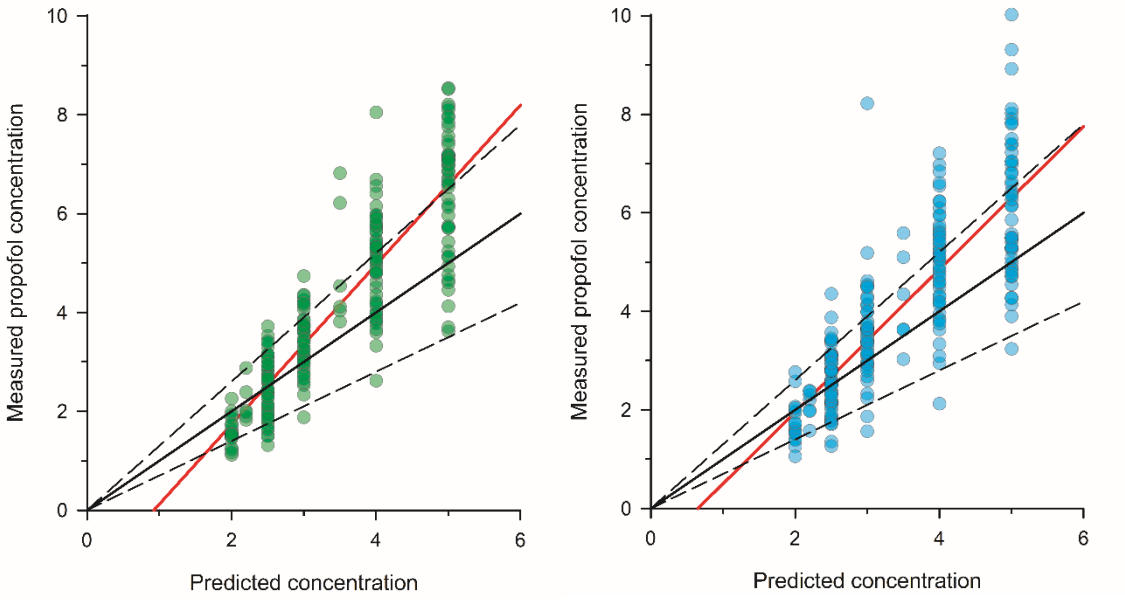

Fig. 1. Measured vs. predicted plasma concentration of propofol for the modified Marsh model (left) and Schnider model(right). The black solid and dashed lines represent the line of identity and biases of ± 30%, respectively. The red solid lines indicate the linear regression between measured and predicted values.

MANAGING ANTINOCICEPTION DURING CLOSED-LOOP BALANCED ANESTHESIA

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Introduction: Giving a balanced anesthesia means to provide the best combination of drugs: hypnotics, analgesics and muscle relaxants in order to be the most efficient and the less harmful to the patient. Better knowledge of the pharmacology of the main anesthetic drugs and the use of new technology -including monitors of drug effects and high-quality syringe pumps for drug delivery, may help the anesthesiologists to reach this goal. Following Target Controlled Infusion systems, closed-loop drug delivery is among the last promising revolution in Anesthesia care.

The issue remains how to optimize the pharmacodynamics interactions, using monitors in order to assess and maintain the desired level of an effect, i.e hypnosis and or analgesia? Are these monitors specific and reliable, so that they may be used in closed-loop systems?

About pharmacodynamics interactions between opioids and hypnotics:

The supra-additive synergy between opioids and hypnotics is well known. B Guignard has shown that rising concentrations of remifentanil in presence of constant concentration of Propofol will blunt the reaction to laryngoscopy and maintain bispectral index of the EEG within the recommended range 40 to 60 (1). Kern S also presented also this synergism with a shift to the left of the concentration-effect curve of remifentanil in presence of rising concentration of Propofol(2). Johnson shown that a pair of remifentanil and Propofol may warrant the lack of reaction to definite noxious stimulation (3). As Sleigh said, we may consider that: "…perhaps it would be more accurate to say that the propofol is increasing the potency of the remifentanil."(4)

These considerations are at the base of some closed-loop anesthesia delivery systems, specially, in dual closed-loop system, which uses data from cortical EEG as surrogate for evaluation of antinociception. However, it makes sense to get information about antinociception directly from a monitor of antinociception in a closed-loop system. Instead, the antinociception is adjusted by the anesthesiologist according to his clinical sense or data from available monitor of nociception.

Monitoring antinociception.

Specific monitors of the level of antinociception would have opened the perspective for closing the loop also on this parameter in a balanced anesthesia protocol. The ideal "nociception" monitor would be simple to use, not require calibration, and function with high specificity and sensitivity in predicting patient response without being influenced by the subject's age, gender, concurrent illness, or use of a specific anesthetic or combination of drugs. Such a device remains the "holy grail" of monitoring for anesthesiologists. Few of them have been used experimentaly in a closed-loop system. Some of them which seem more promising are presented here. They allow at least to optimize the analgesics regimen in a balanced anesthesia.

Skin conductance

Fluctuation of skin conductance at the palm of the hand reflects the activity of sympathetic systems. These fluctuations are well inhibited by remifentatil in the condition of standardized stimuli: The monitor may detect activation of sympathetic tone in response to noxious stimuli or insufficient analgesia. Skin conductance has some limitations due to drugs (high doses of muscarinic agents, clonidine (central action)), or caused by movement artifacts, electromagnetic interferences (5).

Analgesia Nociception Index (ANI)

ANI was developed by Metrodoloris. The ANI is obtained from a computation of RR series of the ECG. After normalization and resampling, the parasympathetic compound of the RR series is obtained by filtering in order to keep only high frequency signals in the RR series. The surface delineated by successive respiratory patterns is directly related to the instantaneous parasympathetic tone: the more parasympathetic tone there is, the bigger the surface. An index between 0 and 100 has been designed and an ANI measure between 50 and 70 during surgery under GA makes a hemodynamic reactivity episode unlikely in the following 10 min and confirm rather good analgesia level. It is a good tool for following the level of antinocecpetion during surgery. This technique has limitation due to electromagnetic interferences and perturbation of the RR series by drugs. It remains a good tool for continuous evaluation of anti-nociception (6)

Pupillometry

Antinociception may be assessed with Algiscan® (IdMed™, Marseille France).

This device evaluates a measure of Pupillary Dilatation Reflex caused by a calibrated noxious stimulation (tetanos with increasing intensity by steps from 10 to 60 mA until response).

It returns a composite index, the pupillary pain index (PPI), from 0 to 10, taking into account both the PDR value and the maximal intensity of stimulation. A PPI < 2 is recommended to prevent response to incision. Maintaining this concentration during the intervention, may provide antinociception for equivalent noxious stimuli (7).

Closed-loop anesthesia

Dual closed-loop system: Liu N developed a closed-loop system based on PID algorithm and capable of delivering Propofol and remifentanil alternatively according to informations coming from the BIS monitor and the trend of these values. The performances of this concept have been evaluated on a large number of patients and confirm the pertinence of their approach. The system is designed to be used with remifentanil as analgesic.(8)

Concert-CL®: Concert-CL® is a syringe pump station for closed-loop on the BIS delivery of Propofol. The device includes one syringe pump devoted to closed-loop delivery of propofol, one syringe pump for the analgesic inTCI mode and a syringe pump for muscle relaxants with possible automatic reinjection.

We have used this commercially available cIosed-loop system and we found similar performances with other experimental closed-loop delivery systems for propofol (9), titration of antinociception being performed before skin incision in our case.

Titration of antinociception was focused on skin incision which is a classical standard of nociceptive stimulation during surgery.

In this context, pupillometry demonstrates a smart way to manage the antinociception. The strong control on hypnotic component of anesthesia as achieved by the Concert-CL® closed-loop system may help remifentanil to face other intense stimulations occuring during surgical intervention. Although the rapid kinetics of remifentanil makes it more suitable for closed-loop anesthesia, we expect that similar results are possible with sufentanil provided that a similar titration will be performed before skin incision.

Conclusion: Till we'll have reliable, well accepted monitor of nociception incorporated in a closed-loop system, the management of antinociception will rely upon clinical judgement and informations coming from the existing monitors when available. Closed-loop on the BIS which reflect actually the level of hypnosis may optimize the interaction between hypnotics and opioids and help to respond to acute noxious stimulation, provided that antinociception have initially calibrated to a standardized high level noxious stimulation.

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FRIDAY, SEPTEMBER 29th

SESSION B1 08:30 – 10:45 WHAT'S NEW IN INTENSIVE CARE

PRECISION MEDICINE AND TCI

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The acronym TCI, standing for Target Controlled Infusion, refers to a system by which a drug is given intravenously with a pump controlled by a computer; a TCI system aims to get a target plasma concentration chosen by the user [1]. The importance of getting a steady plasma concentration of a drug lies in the link between that concentration and the concentration near the effectors, in the assumption that the intensity of the pharmacological effect is proportional to the latter. This tecnich is based on the knowledge of the Pharmacokinetics and Pharmacodynamic.
Many studies have showed that the covariates, like age, BLM, gender are not anymore enough in order to tailored the right dosage of drug, in other terms we also to associate the Pharmacogenomic.
In his 2015 State of the Union address, U.S. President Barack Obama stated his intention to fund a United States national "Precision Medicine Initiative".[18] A short-term goal of the Precision Medicine Initiative is to expand cancer genomics to develop better prevention and treatment methods.[19] In the long-term, the Precision Medicine Initiative aims to build a comprehensive scientific knowledge base by creating a national network of scientists and embarking on a national cohort study of one million Americans to expand our understanding of health and disease.[20] The Mission Statement of the Precision Medicine Initiative reads: "To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments".[21]
Precision medicine (PM) is a medical model that proposes the customization of healthcare, with medical decisions, practices, or products being tailored to the individual patient. In this model, diagnostic testing is often employed for selecting appropriate and optimal therapies based on the context of a patient's genetic content[1] or other molecular or cellular analysis. Tools employed in precision medicine can include molecular diagnostics, imaging, and analytics.[2]

Contents: Relationship to personalized medicine
In explaining the distinction from a similar common term of personalized medicine, the National Research Council explains: Precision Medicine refers to the tailoring of medical treatment to the individual

characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Although the term 'personalized medicine' is also used to convey this meaning, that term is sometimes misinterpreted as implying that unique treatments can be designed for each individual.[2]
On the other hand, use of the term "precision medicine" as well can extend beyond treatment selection to also cover creating unique medical products for particular individuals—for example, "...patient-specific tissue or organs to tailor treatments for different people."[3] Hence, the term in practice has so much overlap with "personalized medicine" that they are often used interchangeably.[4]

Scientific basis: Precision medicine often involves the application of panomic analysis and systems biology to analyze the cause of an individual patient's disease at the molecular level and then to utilize targeted treatments (possibly in combination) to address that individual patient's disease process. The patient's response is then tracked as closely as possible, often using surrogate measures such as tumor load (v. true outcomes, such as 5 year survival rate), and the treatment finely adapted to the patient's response.[5] The branch of precision medicine that addresses cancer is referred to as "precision oncology".[6][7]
Inter-personal difference of molecular pathology is diverse, so as inter-personal difference in the exposome, which influence disease processes through the interactome within the tissue microenvironment, differentially from person to person. As the theoretical basis of precision medicine, the "unique disease principle"[8] emerged to embrace the ubiquitous phenomenon of heterogeneity of disease etiology and pathogenesis. The unique disease principle was first described in neoplastic diseases as the unique tumor principle.[9] As the exposome is a common concept of epidemiology, precision medicine is intertwined with molecular pathological epidemiology, which is capable of identifying potential biomarkers for precision medicine.[10]

Practice: The ability to provide precision medicine to patients in routine clinical settings depends on the availability of molecular profiling tests, e.g. individual germ line DNA sequencing. While precision medicine currently individualizes treatment mainly on the basis of genomic tests (e.g. Oncotype DX[11]), several promising technology modalities are being developed, from techniques combining spectrometry and computational power to real-time imaging of drug effects in the body.[12] Many different aspects of precision medicine are tested in research settings (e.g., proteome, micro biome), but in routine practice not all available inputs are used. The ability to practice precision medicine is also dependent on the knowledge bases available to assist clinicians in taking action based on test results.[13][14]
On the treatment side, PM can involve the use of customized medical products such drug cocktails produced by pharmacy compounding[15] or customized devices.[16] It can also prevent harmful drug interactions, increase overall efficiency when prescribing medications, and reduce costs associated with healthcare.[17]
Inizio modulo
Fine modulo
What is precision medicine?
According to the National Institutes of Health (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is in contrast to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.
Although the term "precision medicine" is relatively new, the concept has been a part of healthcare for many years. For example, a person who needs a blood transfusion is not given blood from a randomly selected donor; instead, the donor’s blood type is matched to the recipient to reduce the risk of complications. Although examples can be found in several areas of medicine, the role of precision medicine in day-to-day healthcare is relatively limited. Researchers hope that this approach will expand to many areas of health in coming years.
Inizio modulo
What is the difference between precision medicine and personalized medicine? What about Pharmacogenomic?
There is a lot of overlap between the terms "precision medicine" and "personalized medicine." According to the National Research Council, "personalized medicine" is an older term with a meaning similar to "precision medicine." However, there was concern that the word "personalized" could be misinterpreted to imply that

treatments and preventions are being developed uniquely for each individual; in precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors. The Council therefore preferred the term "precision medicine" to "personalized medicine." However, some people still use the two terms interchangeably.
Pharmacogenomic is a part of precision medicine.
Pharmacogenomic is the study of how genes affect a person's response to particular drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to variations in a person's genes.
A 2011 report from the National Research Council (PDF) (downloadable as a PDF) provides a detailed overview of precision medicine, including the reasoning behind the Council's preference for the term "precision medicine" over "personalized medicine."

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DELIRIUM IN ICU

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Delirium is an acute organic brain dysfunction characterised by disturbances of attention and cognition with a fluctuating course, as a direct consequence of an underlying medical condition. Delirium occurs frequently in intensive care unit (ICU) patients, and is associated with poor outcome(1, 2). The occurrence of delirium in ICU may also have a long-term impact on cognition and psychosocial function(3).

There is strong evidence that age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation II score, mechanical ventilation, metabolic acidosis, delirium on the prior day and coma, but not gender, are risk factors for delirium(4). There is moderate-quality evidence that Bispectral Index (BIS)-guided anaesthesia reduces the incidence of postoperative delirium compared to BIS-blinded anaesthesia or clinical judgement(5).

Systematic delirium assessment in ICU patients is important to deliver adequate patient care by allowing clinicians to detect and treat delirium at an early stage (6-8). In a large multinational study, we developed and validated an early ICU delirium prediction model that revealed sufficient validity(9). The model enables the clinician to identify those patients likely to develop delirium following ICU admission using only nine predictors: age, history of cognitive impairment, history of alcohol abuse, BUN at time of ICU admission, admission category, urgent admission, MAP at the time of ICU admission, use of corticosteroids, and respiratory failure. Consequently, the model may allow for early delirium preventive interventions in ICU patients with a high risk of delirium.

Several promising interventions to prevent delirium are available that target cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment (5, 10-13). Other modifiable risk factors include minimising the use of benzodiazepines in critically ill patients(14). Surprisingly, the administration of nicotine replacement therapy in critically ill smokers has not shown a reduction in delirium incidence, and several studies including one of our own have suggested possible harm(15-17). Early pharmacological interventions such as the use of prophylactic haloperidol in patients at high risk for delirium may be considered(18). There is currently insufficient evidence to provide a strong recommendation regarding the use of second-generation antipsychotics for the treatment of ICU delirium(19). The use of dexmedetomidine is associated with a lower delirium prevalence(4). In patients with agitated delirium receiving mechanical ventilation in the intensive care unit, we showed that the addition of dexmedetomidine to standard care compared with standard care alone (placebo) resulted in more ventilator-free hours and earlier extubation(20). In addition, dexmedetomidine may be a useful rescue drug for treating agitation due to delirium in non-intubated patients in whom haloperidol has failed, and it seems to have a better effectiveness, safety, and cost-benefit profile than does haloperidol(21).

In conclusion, delirium in critically ill patients is a frequent and significant problem, which requires a multipronged approach with careful attention to prediction, early recognition, prevention and treatment to improve short and long-term patient-centred outcomes.

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HR CONTROL IN ICU

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The incidence of sepsis is increasing in recent years, whereas the mortality is reducing to about seventeen percent.
The guidelines for management of severe sepsis and septic shock are today worldwide applied and the golden hours (three, six hours from the diagnosis of sepsis) are still crucial for survival if we follow the bundles. The Early goal directed therapy, based on the Rivers' protocol, has been the key to the birth of Surviving Sepsis Campaign Bundles.
Recently, many milestones of those bundles are collapsing. The first one is related to Early Goal Directed Therapy that in a multicenter trial in the tertiary care setting failed to improve outcome
Another widely discussed and controversial issue, in the last two years, has been fluid therapy in sepsis. Without entering into the minefield that is the debate about crystalloid or colloid in sepsis, we have accepted the results of Six S trial and everyone has avoided use of synthetic colloids for volume replacement in septic patients.
Albumin utility in septic patients does not demonstrate any advantages and the probability of survival in severe septic patients is not changed by the use of albumin for volume replacement
Mortality in septic shock is very different in the literature and varies from twenty five to eighty percent. Why does this incredible difference exist? Are there different types of septic shock? Maybe. But there is a close relationship between the starting dose of norepinephrine and mortality. So, when we are forced to use a huge dose of norepinephrine we can expect an increase in mortality, especially for a dose of vasopressor above point three microgram per kilogram per minute. This high mortality is related to greater severity of patients but also to high dose of catecholamines. And if we use a second line vasopressor added to norepinephrine, the increase in mortality is even more accelerated.
Critical illness, and overall septic shock, determines a large sympathetic overstimulation and the effect of this adrenergic stress causes myocardial damage and cardiomyocyte death.
Hyperadrenergic status, developed by an increase in sympathetic outflow and catecholamine therapy, determines tachycardia and vasoconstriction which cause left ventricular stretch and release of BNP and serum troponin in relation to myocyte necrosis. These facts associated with others such as microvascular thrombosis, acute lung injury, renal failure, inflammatory cytokines release, cause a sepsis-associated myocardial dysfunction and we can have a stress cardiomyopathy that increases mortality especially in patients suffering from coronary artery disease.
To conclude, sepsis causes an acute and chronic inflammatory response that determines, through a mediators' release and hemodynamic reorganization, heart remodeling, myocite death, beta adrenergic desensitization and hypercontractility, all leading to cardiac dysfunction with cardiomyopathy and arrhythmias.
The final results of sepsis related myocardial dysfunction are clinically demonstrated in systolic and diastolic impairment. Recently, more importance has been given to diastolic dysfunction, because diastole is not easy to treat and the aim is not to worsen diastolic function through incorrect therapy.
Physicians consider heart rate increase in septic shock a compensatory mechanism to maintain stroke volume and that its manipulation is very dangerous.
More than thirty years ago, Parrillo and coauthors considered heart rate an early predictor of bad prognosis in septic shock. A heart rate below one hundred and six beats per minute was considered safe and a reduction of eighteen percent in heart rate suggested survival. Incredible, we were in nineteen eighty-seven!
In 2005, Sander and coauthors registered a different outcome in ICU patients who remained tachycardic for various periods during their hospitalization. The authors concluded that ninety five beats per minute can represent the cut off value for heart rate in ICU patients Generally, heart rate in overall population represents an important cardiovascular risk factor because of the large increase in oxygen consumption, the development

of tachyarrhythmia and especially the impairment in diastolic function that, causing myocardial ischemia, worsens septic myocardial dysfunction.
It is well recognized that tachycardia can induce cardiomyopathy for many reasons related to cardiac remodeling, diastolic dysfunction, oxygen imbalance, but the harmful value of heart rate has not been clearly demonstrated. Authors think that a sustained heart rate greater than one hundred beats per minute may be dangerous.
The use of beta blockers in septic shock patients has been evocated as an interesting option, however the most important concept was the decatecholaminization, which means reduction of endogenous but overall exogenous adrenergic stimulation.
Beta blockers such as esmolol, a selective beta one blocker, allow us to attenuate myocardial dysfunction, as in experimental protocols in septic rats, restoring the adrenoreceptor density thus using lower dose of norepinephrine to maintain mean arterial pressure.
Some authors, again using rats, were able to preserve gut barrier function with the use of beta blockers as demonstrated by histological preservation of gut mucosa and by the difference in survival percentage and survival time.
In an inflammation model of sepsis, induced by lipopolysaccharide, the use of landiolol, a very selective beta one blocker, determines an important reduction of inflammatory mediators as TNF alpha, interleukin six and high mobility group box 1 proteins, with a large reduction in septic markers.
Nowadays, heart rate in sepsis was identified as an independent factor for mortality so we speculated that the heart rate reduction in sepsis might lead to an increase in survival.
But what happens if we use beta blockers in septic patients? Perhaps we have a reduction in cardiac index, peripheral flow, finally drastic hemodynamic consequences. In a pilot study, Morelli and coauthors demonstrated a stable microcirculation flow despite little reduction in cardiac index.
All the discussed issues about decatecholaminization, reduction of adrenergic stress, heart rate control in septic model, have lead us to design a trial, recently published on JAMA.
We have enrolled more than three hundred patients with severe septic shock and finally we have randomized one hundred fifty four patients divided into two groups, the first one received esmolol to control heart rate below ninety five beat per minute and the second one in which heart rate has not been controlled. However, heart rate was controlled only after a phase of resuscitation following the bundles of septic shock treatment and excluding every different cause of tachycardia.
In this recent paper we can observe how high the mortality is in septic shock patients related to SAPS two value, up to seventy percent.
The esmolol group had an important reduction in heart rate, as expected hemodynamics were stable in both the groups.
We had a large reduction in norepinephrine dose in the esmolol group, although we expected the opposite.
The performance of left ventricle was maintained with an increase in stroke volume and stroke work balanced by a small reduction in cardiac index related to the decrease in heart rate.
Then, we had a stable oxygenation parameters in both groups and a better metabolic condition in the esmolol group.
A very surprising result was the large difference in mortality as showed in a univariate and adjusted survival analysis. The mortality was greatly reduced in the esmolol group below fifty percent after twenty eight days.
Heart rate is an important hemodynamic factor that determines stroke volume. Its manipulation can cause large modifications in volume loading, in contractility and in diastolic function, Esmolol, after an adequate fluid resuscitation, lowers heart rate without affecting stroke volume.
In conclusion, in this prospective randomized clinical study, we have demonstrated the safety of esmolol and its efficacy in reducing heart rate. The heart rate control, below ninety five beats per minute, brought a marked improvement in survival in ICU, especially in septic patients.

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PRESEPSIN: A NEW BIOMARKER FOR SEPSIS

Radmila Karan, Quirino Piacevoli

Aim: Sepsis is the main cause of death in the ICUs present day. About 13 million people annually aquire sepsis, and more than 30% dies. Only 50% patients with sepsis receives best standard of care, including western world as well.
Early diagnosis of sepsis and timely initiation of antimicrobial therapy are the keys to improved survival. Although many laboratory biomarkers are available for the diagnosis of sepsis, only few markers have proven to be beneficial in differentiating infectious disease sepsis and sepsis of non-infectious origin. Mainly used biomarkers are Plasma C-reactive protein (CRP) or Procalcitonin (PCT).
Procalcitonin (PCT), as a biomarker in sespis, has limited specificity and can be elevated in other scenarios of systemic inflammatory response syndrome (SIRS).
Presepsin is a soluble fragment of the cluster of differentiation marker protein 14 (CD14) involved in pathogen recognition by innate immunity. Available literature suggests that levels of presepsin are significantly higher in septic patients than in healthy individuals.
Cardiac surgery is very specific because of the use of cardio pulmonary bypass machine (CPB), during which pt are in relative hypotensive state, moderate hypothermia, and the use of CPB leads to moderate systemic inflammatory response. This inflammatory response attenuates quickly after surgery. Presepsin levels are high in pt with acute heart failure and acute coronary syndrome without signs of infection. The use of volatile anesthetics and intravenous anesthetic- propofol, can lead to decreased expression of inflammatory biomarkers, which is important in interpreting results.
The aim of this study is to investigate the diagnostic and prognostic value of presepsin compared to CRP, PCT , White Blood Cell in patients with sepsis or septic shock in intensive care unit and in more specific group of patients-cardiac surgery patients.

Methods: This study was conducted in San Filippo Neri Hospital in Rome, Italy, and consecutively continued at Clinic for Cardiac Surgery, Clinical Center of Serbia, Belgrade, Serbia.
Patients were recruited from three critical areas: a general intensive care unit, mainly interacting with the Emergency Room; a post-operative intensive care unit for general, orthopedic and vascular surgery; a neurosurgical intensive care, and post cardiac surgery intensive care
Inclusion criteria were: age between 18 and 80; hospitalized due to major medical or surgical reasons (abdominal surgery, major vascular surgery, cardiac surgery, ENT major surgery, major orthopedic surgery, neurosurgery, other major surgery), burn victims, patients with exogenous intoxication, all subjects with traumas not mentioned in the exclusion criteria in this list, SAPS II score greater than or equal to 20, hospitalization, even in the in-patient area, for the minimum number of days required for observation (three days).
Female patients who are pregnant women or lactating mothers cannot be enrolled in the trial. Patients with kidney failure, even when treated with CRRT at the beginning of the observation, were eligible to participate.
The assay for biomarkers were performed on whole venous or arterial blood, on days 1, 2, 4, and 7 from the admission of all the patients eligible for the study. Once the hematocrit value is known, the analysis will be performed on the Mitsubishi Compact Immuno-Analyzer unit. Patients enrolled in the trial had to test - on the same day and within six hours after the PSP dosage – also the dosage of PCT, of Creatinine, of PCR and of the complete Blood Count , with or without the formula. The patient's information flow should include the outcome or the possible death, if it occurs within the 7th day (the last day of observation).
Sensitivy, specificity, Positive Predictive Value and Negative Predictive Value were calculated for each biomarker. The diagnostic accuracy of the four biomarkers studied was evaluated using the areas under the curve (AUCs)

Results: The data are showed in table 1.
Table 1. Parameters analyzed of the four biomarkers studied

	DAY	PSP	CRP	PCT	WBC
SENSITIVITY	1	81%	90%	50%	52%
	2	75%	95%	63%	38%
	4	74%	61%	94%	53%
	7	58%	42%	75%	42%
SPECIFICITY	1	51%	46%	69%	57%
	2	51%	46%	64%	61%
	4	35%	70%	37%	63%
	7	42%	81%	41%	67%
PPV	1	49%	49%	45%	42%
	2	45%	49%	48%	44%
	4	52%	55%	47%	48%
	7	32%	50%	36%	36%
NPV	1	83%	89%	73%	67%
	2	79%	94%	77%	71%
	4	58%	75%	92%	68%
	7	69%	76%	79%	72%
AUC	1	0,66	0,68	0,59	0,55
	2	0,77	0,68	0,74	0,65
	4	0,65	0,66	0,66	0,58
	7	0,50	0,62	0,58	0,55

PSP = PRESEPSIN; CRP = C-REACTIVE PROTEIN, PCT = PROCALCITONIN; WBC = WHITE BLOOD CELLS; PPV = POSITIVE PREDICTIVE VALUE; NPV = NEGATIVE PREDICTIVE VALUE; AUC = AREA UNDER CURVE;

Discussion: The accuracy of all the biomarkers decreases with time until they are not more useful.
We found highest predictive values in the first measurements on day 1, with PSP reaching the value AUC of 0.66 (CRP = 0.68 and PCT = 0.59). Being that CRP is increased in patients after surgery, this is a valuable result because using PSP to early detect presence of infection could improve patient's survival.

Conclusion: In our experience, presepsin could be useful in the early diagnosis of infection in patients and distinguishing sepsis from SIRS in intensive care. The early detection of the disease could allow a rapid targeted therapy and an improved outcome.

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SESSION B2 11:15 – 13:20 SPECIAL PATIENT POPULATIONS AND ANAESTHESIA

MATERNAL FETAL AND NEONATAL MEDICINE 2017: WHAT DOES AN ANESTHESIOLOGIST NEED TO KNOW?

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Obstetric anesthesia is considered by many to be a high-risk subspecialty of anesthesia practice that is laden with clinical challenges and medico-legal liability. Anesthesia-related complications are the sixth leading cause of pregnancy-related maternal mortality in the United States. Difficult or failed intubation following induction of general anesthesia for cesarean delivery remains the major contributory factor to anesthesia-related maternal complications.

Obstetric anesthesia has been a major subspecialty of anesthesiology for a long time and is now an integral part of practice of most anesthesiologists. An obstetric anesthesiologist has become an essential member of the obstetric care team, who closely works with the obstetrician, neonatologist and Labor and Delivery nurse to ensure the highest quality care for the parturient and her baby. The anesthesiologist's unique skills in acute resuscitation combined with experience in critical care make members of our specialty particularly valuable in the peripartum care of the high risk patients, extending our role well beyond the routing provision of intrapartum anesthesia or analgesia.

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ENHANCING THE SAFETY OF LABOUR PCIA REMIFENTANIL THROUGH THE INTEGRATED ANALYSIS OF MATERNAL ANALGESIC NEEDS AND VITAL SIGNS

Raymond Goy

Central neuraxial block is currently the gold standard for providing labour analgesia. Of the parturients who are unable or unwilling to receive this form of pain relief, intravenous remifentanil has used less efficaciously, in an attempt to achieve comparable maternal analgesia and satisfaction. In Singapore, the use of intravenous remifentanil is reserved for patients with contraindications to epidural insertions, largely due to concerns with maternal side effects of the drug. In our setting, the three top indications for intravenous remifentanil analgesia include the presence of significant neurological symptoms as a result of spinal pathology, previous lumbar spinal surgery and medical coagulopathy. Remifentanil is an attractive opioid for patient controlled labour analgesia. As it is rapidly metabolized by the plasma esterases, placental transfer to the fetus is very limited. Its short context sensitive half-life of 3-4 minutes and elimination half time of 10-20 minutes confer the

advantage of the rapid decline in plasma concentration after discontinuation of an infusion. However, remifentanil, being an extremely potent μ-agonist, has the propensity to cause maternal respiratory depression, oxygen desaturation, sedation and bradycardia. These side effects are common and have resulted in maternal oxygen desaturations (defined as SpO2< 95%) in 39% to 74% of the patients in previous studies. Serious maternal respiratory arrest, with dire consequences had been reported too.

In order to enhance the safety of PCIA remifentanil for labour analgesia, four interrelated components of a safety strategy are recommended. They include careful patient selection, close collaborations between the professions, optimal dosing regimen and close monitoring. The two latter components constitute the scientific basis of our ongoing studies. For safety, the approach of using incremental bolus doses with the avoidance of a continuous infusion in conjunction with PCA is advocated. Close one-to-one monitoring by a trained anaesthetist is imperative and contingency plans must be in place for airway and respiratory resuscitation. Physiologic monitors, including pulse oximetry is mandatory. However, our current system weaknesses include the closed design of the delivery suite rooms for patient privacy, the lack of remote connections of the physiological monitors to the central monitoring station and potential staff distractions.

In the hope of integrating analgesic goals and physiological outcomes, we developed a novel, interactive system of parturient-assisted intravenous remifentanil analgesia, which was modulated by the vital signs of the parturient (VPIA). Increasing demands by the patient would result in to incremental doses of remifentanil (boluses followed by infusion) for the escalation of pain with the progress of labour. In VPIA, the patient's vital signs, namely pulse rate and SpO2 were continuously monitored and integrated to control and obviate the risk of over-administration. Using present thresholds of SpO2 < 95% for > 15 seconds and heart rate < 60 bpm, for > 15 seconds, any breach in these safety limits would result in the shut-down of the system and the appropriate trigger of the alarm system. Our preliminary results showed that though SpO2 reduction was not uncommon, VPIA could potentially enhance the safety of IV remifentanil in labour. The role of VPIA as an early warning system could be further improved with more reliable respiratory modalities (the end tidal CO2). This may potentially redefine the use of remifentanil for labour analgesia.

UPDATE ON LABOUR ANALGESIA.

Raveenthiran Rasiah

President, Malaysian Society of Anaesthesiologists, Malaysia

“The delivery of the infant into the arms of a conscious and pain free mother is one of the most exciting and rewarding moments in medicine.” Moir.

Labour analgesia has come a long way from the early years of ether and chloroform to the modern- day practice of neuraxial analgesia using computerized medical devices. Introduction of newer drugs like levobupivacaine, ropivacaine and remifentanil as well as combined spinal epidurals (CSE), has revolutionized the practice of pain management in laboring parturient.

Computerized medical devices like the syringe pumps, patient controlled epidural analgesia pumps(PCEA) and devices which can give programmed intermittent bolus of drugs into the epidural space has improved the quality of the analgesia provided. The volume of the drug delivered by using these devices has reduced with a marked improvement in pain management with a gross reduction in side effects. The use of ultrasound in localizing epidural space have helped clinicians to minimize the failure rates. We can now customize various drug regimes to suite individual patients. The overall effect of these new drugs, techniques, medical devices, and the education through antenatal classes has led to a better maternal satisfaction and safety.

The long term back ache and increase in caesarean sections with parturient on epidurals is a myth as evidenced by several controlled trials and Cochrane reviews.

In many developing countries, awareness and pain relief for the laboring parturient does not exist. In some countries, the availability of regional labour analgesia is taken as a marker for the standard of obstetrics care.

PROPOFOL INFLUENCE ON FETOPLACENTAL CIRCULATION-OUTCOMES AND CONSEQUENCES

Kiro Churlinov

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Object of study: Propofol crosses the placenta and is distributed into breast milk. Propofol is 95—99% protein-bound. Propofol is an injectable anesthetic agent that has been widely used in obstetrical anesthesia. It crosses the placenta and induces vasodilatation of isolated vessels and may therefore alter fetal placental vascular resistance. After its administration to the mother during a caesarean section, some neonatal depression may occur. Hypotension is a common side effect associated to propofol due to both vasodilation and negative inotropic effects. Pregnancy results in dramatic changes to the uterine circulation, with a marked increase in blood flow, related to an overall increase in maternal cardiac output and a reduction in resistance of the vascular bed of the uteroplacental circulation.

Materials and methods: Parturients, about 300 of them, were examined during 2 years period . Those with eclampsia, hypertension, diabetes mellitus, Rhesus incompatibility, or other recognized medical conditions were excluded from the study. Demographic profile of parturients is shown. Propofol was administered during cesarean section baby delivery, in general anesthesia one. A standard and additional haemodynamic profile was in use. Vasoactive effects are expressed as an increase or decrease of pressure, primarily systolic pressure (mmHg) on the monitor. Occasionally and intermittently, the 4D ultrasound was used to measure the mean placental flow rate, till baby delivery. Propofol induced a slow and steady decrease in placental perfusion pressure. Propofol at concentrations reduced the perfusion pressure of isolated human placentas due to a direct vasodilator effect on fetal placental vessels. The reduction of fetal placental perfusion pressure observed during constant flow indicates that propofol reduces the fetal vascular resistance. As fetal placental vessels are devoid of autonomic innervations and the vasodilating effect of propofol shown in the present the most likely action is a direct effect on vascular resistance. Propofol has been demonstrated to induce vasodilatation by inhibition of calcium mobilization.

Conclusion: Propofol induced vasodilatation and inhibited the vasoconstrictive effects of some vasoactive agents, like bradykinin (BK), prostaglandin F2a (PGF2a) in the human placenta. These findings suggest that propofol may not reduce fetal placental blood flow. The vasodilatory effect of propofol in the human placenta involves inhibition of Ca2+ channels. Propofol has a dilating effect on fetal
placental blood vessels, probably due to inhibition of calcium influx through the smooth muscle sarcolemma. Thus, the vasodilator effect of propofol may be important in maintaining umbilical blood flow in normal pregnancies.
In addition, the effect of propofol may also be important in some pathological states where there is a reduction of umbilical blood flow, including preeclampsia, which is characterized by an increase in vasoconstrictive prostanoid production.

USE OF BODYWEIGHT AS DOSING SCALAR FOR ANESTHESIA IN CHILDREN AND ADULTS IN THE ERA OF OBESITY?

Professor Catherijne A. J. Knibbe

Clinical pharmacologist-hospital pharmacist
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The incidence of overweight and obesity is rising across the world. In the Netherlands, currently almost half of the population is overweight with a body mass index (BMI) of at least 25 kg/m2. Alarmingly, in the United States two-thirds of adults are overweight, with 36% of adults and 17% of children and adolescents being obese (BMI > 30 kg/m2). If current trends continue, the prediction is that in 2030 there will be 2.16 billion overweight and 1.12 billion obese individuals worldwide as compared to around 400 million obese individuals in 2005.

Despite the large numbers of (morbidly) obese patients, there are very few evidence based dosing guidelines for commonly used drugs in this special patient group. Often, the dose is based on clinical experience of the prescriber rather than on clinical evidence. When aiming for efficacious and safe dosing strategy for obese patients in practice, an important question is whether (total) bodyweight is the best dosing scalar. This is of particular relevance in anaesthetic practice where typically (also in adult patients) drugs are dosed on a mg/kg basis. This question also applies when treating (morbidly) obese adolescents and children. Particularly in case these obese adolescents have the same bodyweight as morbidly obese adults.

In order to address these questions and to get to safe and efficacious dosing in these populations, clinical studies in these patient groups together with non obese control children and adults are needed that include pharmacokinetic and pharmacodynamics measurements and from which the data are analysed using advanced pharmacometric modelling together with physiologically based pharmacokinetic concepts.

In the lecture, results of recent clinical studies on commonly used drugs in morbidly obese adult and adolescent patients are presented from which on the basis of advanced computational modelling, dose adjustments are proposed. For instance for propofol, the influence of both body(over)weight and age could be characterised on the basis of a population pharmacokinetic meta-analysis in morbidly obese and non-obese adults, adolescents in such a way that dosing guidelines for morbidly obese adolescents and adults can be established. The results on propofol however differed substantially from results of studies on midazolam, where morbidly obese adolescents were found to have a higher (instead of lower) clearance than morbidly obese adults, and from results on paracetamol and morphine.

As such, while performing clinical studies on specific drugs in obese adolescents and adults are a prerequisite to get to dosing guidelines for specific drugs, it seems important to know the exact (patho)physiological changes in the human body when weight and age increase. For this, a semi-physiological hybrid between empirical population modelling and physiologically-based pharmacokinetic modelling individualized drug dosing applied to results of studies of specific drugs is proposed. Using this approach, results from specific drugs can be used to learn about physiological changes in the system (i.e. liver blood flow, enzyme activity in the liver etc), that can potentially be used to guide dose adjustments for other drugs. In the lecture this approach will be illustrated.

From the studies that will be presented, it can be concluded that by merging information obtained using the powerful parameter estimation approach of nonlinear mixed effects modelling with the physiological insight of PBPK modelling, predictive models can be developed that can accelerate the development of dosing guidelines for existing and new drugs in each individual with a certain age and weight.

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SESSION B3 15:00 – 16:40 ANAESTHESIA AND SURGERY

A STATE OF THE ART PHARMACOLOGICAL MODEL TO SIMULATE DRUGS AND DRUG INTERACTIONS IN PATIENT SIMULATION

Wolfgang Heinrichs

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To make TCI training as real as possible, we developed a program starting at 2005 as a cooperation between Quirino Piacevoli at the Ospedale San Filippo Neri, Rome, Italy together with the AQAI simulation center in Mainz, Germany. To show the effect of the anesthesia besides cardiovascular reactions the BIS (Bispectral Index by Aspect - today owned by Medtronic) was used. TCI pumps and the BIS monitor were directly connected with the patient simulator using an own development of interface software (SIS = Simulator Interface Software; © AQAI). Laerdal SimMan3G simulators are used in the classes.

SIS – Simulation Interface Software is a flexible software for simulation. Details please see Figure 2. The SIS software combines several modules which are used in the simulations. The most important module is the core physiological and pharmacological model which is designed like a grid, where rows are inputs, column outputs and the cells do the calculations needed for combining inputs to outputs. The system is highly flexible and can serve an almost unlimited number of situations and tasks. Attached to this, several drivers are used to communicate inputs and outputs to external devices. Input drivers include communication to iv-pumps, to maneuvers performed at the mannequin or interventions done by the participants. Output drivers include the full control of the mannequin, the EEG which is represented as BIS values and other displays like special monitors. Special monitors may show the actual plasma- or effect site concentration of the drugs, interactions between Propofol and Opiates and more.

The pharmacokinetic models are open 3-compartment models. If certain models are used in the TCI pumps (like Marsh for Propofol) the corresponding pharmacological model will use the constants and distribution volumes like in the original one. By this the actual plasma or effect site concentration can be calculated to be the same than those calculated by the commercial pumps. Input of height, weight, age and gender supports those models that do adaptions of the exponential exchange constants (like Schnider model for Propofol). Many data for these drugs and models are to be found in TIVA Trainer™ - simulation software for intravenous anesthesia edited by the European society for intravenous anesthesia (Euro-SIVA).

During the simulations the data flows from the TCI pumps into the pharmacological model. This calculates the actual plasma and effect site concentration in parallel to the pumps. The actual effect site concentrations are then used to model the effects of the drugs used. For example, Propofol commonly has a heart rate and blood pressure lowering effect. With some typical nonlinear functions, the concentration of Propofol is used to modulate heart rate and blood pressure.

A special model was necessary to show the effects of Propofol on the depth of anesthesia. There is some data given in the literature [1,2,3,4,5] and some assumptions had to be used that may not be absolutely correct from a scientific point of view, but do it perfectly for the simulation sessions. The following table shows some relations between Propofol target concentration and depth of anesthesia.

Clinical Situation	Dose Propofol (mg/kg)	TCI Effect concentration (µg/ml)	BIS
Awake / Normal Memory	0	< 0.5	100 – 85
Sedation	0.5 – 1.0	0.5 – 2.5	85 – 65
Adequate Anesth	1.0 – 2.0	2.5 – 5.0	65 – 40
Deep Anesth	2.5 – 3.5	5.0 – 8.0	40 – 20
Full depression	> 4.0	> 8.0	20 – 0

Table 1: Relationship between clinical observations, Propofol administration and BIS values. This table is used for procedural sedation cases using Propofol alone.

The principles of BIS EEG monitoring have been selected to represent depth of sedation and anesthesia. The data flow in the model is as follows:

IV-Pump sends drug amount administered every 10 seconds
Pharmacological model calculates plasma- and effect-target concentration
Effects of drugs are modelled to cardiovascular parameters directly
Lookup function similar to the table given above derives BIS value
BIS value is used to represent depth of anesthesia
BIS below 80: Eyes of the simulator will be closed
BIS below 60: Depression of respiration present
BIS below 40: Deep anesthesia, apnea
BIS value is also used to generate a typical EEG trace that is used as input to any real BIS monitor which will then analyze the trace and show the appropriate value

With this setup, it is possible for the participants to work with Propofol in any TIVA mode (repeated boluses, conventional iv-application, TCI) like in a real patient and see and feel the results of the drugs on the mannequin and on the monitoring

What about the typical combination of Propofol together with Opiates, e.g. Remifentanil? Remifentanil on its own does not show major effects on BIS. In combination with Propofol it is a well-known clinical effect that anesthesia is well influenced by the combination of both. The excellent work of Milne and Vuyk [4,6] gives a relation of both concentrations on the resulting clinical effects (like loss of consciousness). The following diagram shows the resulting model that is used. Propofol and Remifentanil effector concentration are entered into a 2-dimensional matrix to find a corresponding BIS value. In the example shown a Propofol effect concentration 3 µg/ml with a Remifentanil concentration around 8 ng/ml will result in a BIS value of 40. The same will be true for Propofol 4.4 µg/ml plus Remifentanil 4 ng/ml. Thus the lines in the model represent lines of equal BIS values. Values between the lines are derived by linear interpolation.

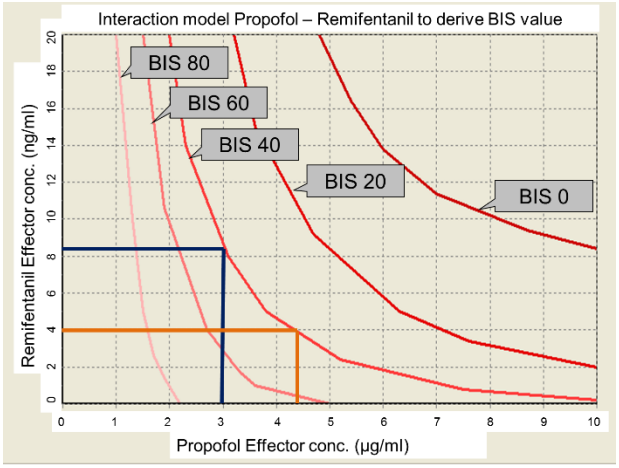

Fig. 1 Interaction diagram used (see text)

Similar models are used for other opioids (e.g. Alfentanil [7]). If additional sedatives (e.g. Midazolam or inhalational anesthetics) are used, the model will calculate additive effects of sedation and analgesia separately and then use an interaction model similar to the one given in the example.

This design has several advantages: it does not limit the application to certain drugs or models. Even the combination between TIVA and inhalational anesthetics can be performed, thus creating the most realistic training environment possible.

Special interest may be directed to procedural sedation with TCI systems. These can be applied very successfully and they also give information about the interactions between Propofol and Remifentanil [8]. Borrat and colleagues looked at the gag reflex in endoscopy and were able to define levels of Remifentanil and Propofol to avoid this reflex during gastroscopy. [9]

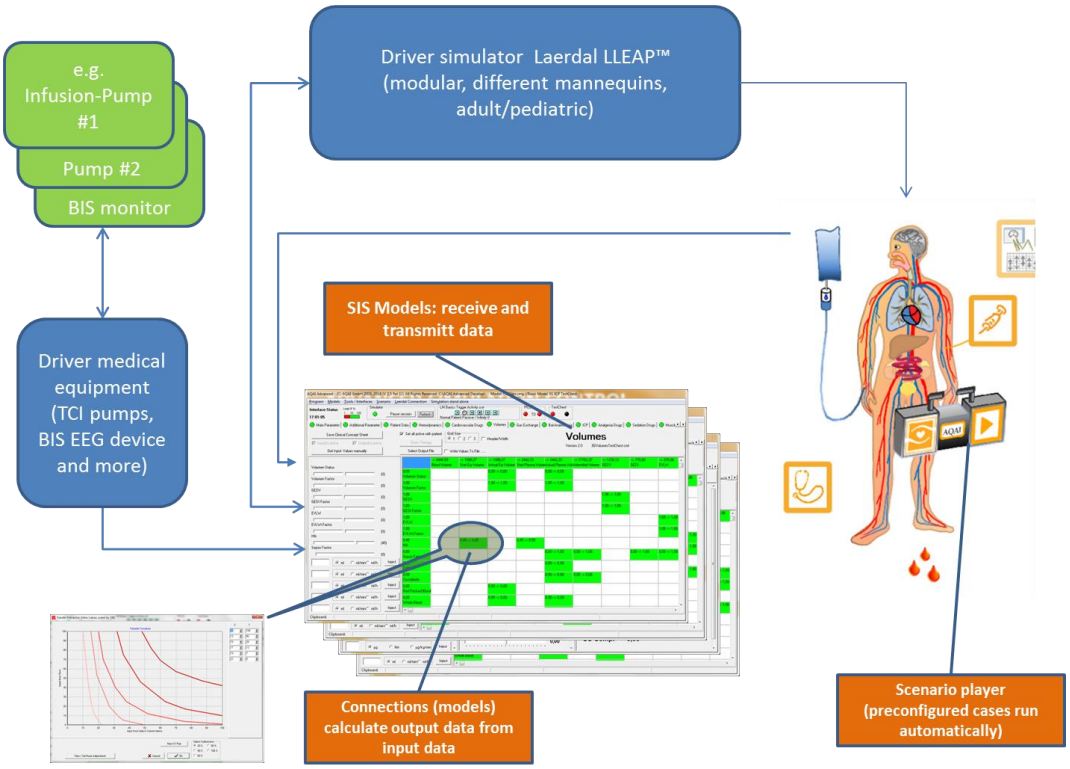

Figure 2: Schematic drawing of the simulator and software setup used for TCI training.

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Conflict of interest: Wolfgang Heinrichs is CEO and senior developer of AQAI GmbH, Simulation Center, Mainz, Germany. AQAI has developed the models, the SIS interface software and the curriculum presented in this article. AQAI functions as supplier of these products. Wolfgang Heinrichs is also consultant to Laerdal, Norway.

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EFFECT OF ADDING DEXAMETHASONE AS A ROPIVACAINE ADJUVANT IN ULTRASOUND-GUIDED TRANSVERSUS ABDOMINIS PLANE BLOCK FOR INGVINAL HERNIA REPEAR

Kartalov A [1], Jankulovski N [3], Kuzmanovska B [1], Zdravkovska M [2], Shosholcheva M [5], Spirovska T [1], Panovska Petrusheva A[1], Tolevska M [1], Srceva M [1], Durnev V [1], Jota G [3], Selmani R [3], Sivevski A [4]

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Background: The transverses abdominals plane block (TAP) is a regional anesthesia technique that provided analgesia to the parietal peritoneum, skin and muscles of the anterior abdominal wall. The aim of this randomized double-blind study was to evaluate postoperative analgesia on patients undergoing open inguinal hernia repair under general anesthesia (GA), (GA + TAP) block preformed with ropivacaine and (GA + TAP-D) block preformed with ropivacaine and 4 mg dexamethasone. TAP block can provided excellent analgesia to the skin and muscules of the anterior abdominal wall following ingvinal hernia repair, appendectomy, radical prostatectomy, abdomionoplasty, renal transplantation, large bowel resection, cesarean section, laparoscopic cholecystectomy and iliac crist bone grafting. (2, 3, 4, 5) A lot of reports suggest that TAP blocks may also be a safe alternative to neuroaxial blockade in patients who are on anti-coagulant therapy or in patients who would not tolerate the hemodynamic instability.
This ultrasound procedure is performed with ultrasound high frequency (5 -13 MHz) probe which is placed on the lateral abdominal wall between the costal margin and the iliac crest at the anterior axillary line. The technique involves injection of local anaesthetic solution into a plane between internal oblique muscle (IO) and transversus abdominis (TA) muscle. This plane contains the thoracolumbar nerves originating from T6 to L1, ilioingvinal and iliohipogastric nerves. They supply sensory blockade of the skin, muscules and parietal peritoneum of the anterolateral abdominal wall.
There is a new strategy to prolong analgesia beyond the pharmacological duration of the local anesthetics. They include itroduction of perineural catheters to allow prolonged infusion of the local anesthetics or co-administration of adjuvants such as epinephrine, α2 agonists (i.e. clonidine), midazolam or corticosteroides - dexamethasone. (8, 9) Perineural catheter techniques can be very effective and provide analgesia for several days, but this technique is limited with difficulties with placement and removal of the catheter or rarely infection. (9, 10)
It is believed that dexamethasone as a supplement improves the quality and duration of local anesthetics. This is thought to be mediated by attenuating the release of inflammatory mediators, reducing ectopic neuronal discharge, and inhibiting potassium channel-mediated discharge of nociceptive C-fibres.
The aim of this randomized controlled double-blind study was to evaluate the effect of dexamethasone added to 0.5% ropivacaine on the quality of TAP block used as a supplement of general anesthesia on patents undergoing elective unilateal inguinal hernia repair.

Methods: 90 (ASA I–II) adult patients for unilateral open inguinal hernia repair were included in this study. In the group I (n=30) patents reseaved only general anesthesia (GA). Patients in group II (n=30) resaved GA and unilateral TAP block with 25ml of 0.5% ropivacaine and the patients in group III (n=30) resaved GA and unilateral TAP-D block with 25ml of 0.5% ropivacaine + 4 mg Dexamethadsone. In this study we assessed pain score - VAS at rest at 2, 4, 6, 12 and 24 hours after operation and total analgesic consumption of morphine over 24-hours.

Results: There were statistically significant differences in VAS scores between group I, group II and group III at all postoperative time points - 2^{hr}, 4^{hr}, 6^{hr}, 12^{hr} and $24^{hr.}$ ($p < 0{,}00001$). The cumulative 24 hours morphine consumption after the operation was significantly lower in the group III ($5{,}53 \pm 1{,}21$mg) than group II ($6{,}16 \pm 2{,}41$mg) and group I ($9{,}26 \pm 2{,}41$mg). This difference is statistically significant ($p < 0{,}00001$).
Acute postoperative pain has different components (e.g. nociceptive, inflammatory, and neuropathic because of direct nerve injury) and all of them are possible targets for postoperative analgesic strategies. The precise mechanism of extend analgetic action of dexamethasone added to local anaesthetics is stell unknown. Some studies described a direct effect of glucocorticoids on nerve conduction while others reported that dexamethasone induced perineural vasoconstriction with concomitant slower absorption of the administered local anesthetics. (15, 16) After intracellular uptake, glucocorticoids will activate cytoplasmatic glucocorticoid receptors which will bind to glucocorticoid response elements in the DNA. This leads to both a decreased production of inflammatory proteins [COX-2, iNOS, cytoplasmatic PLA2, interleukins (ILs), inflammatory chemokines, etc.], and an increased production of anti-inflammatory proteins [lipocortin-1 (IL-1) receptor antagonist].

Conclusion: For ingvinal hernia repair we faund better postoperative pain scores and 24 hours reduction of the morphine consumption in group III (GA and TAP-D block) compared with group I (GA) and group II (GA+TAP block).

Keywords: Unilateral open ingvinal herniotomy, US-TAP block, Ropivacaine, Dexamethasone

ANAESTHESIA & ANALGESIA FOR TOTAL KNEE ARTHROPLASTY

Raveenthiran Rasiah

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The population of many countries in the World is an aging population. One of the most common disease this group of population will have is osteoarthritis. The demand of the population has changed over time. The most common symptom presented for osteoarthritis is pain. Relief of Pain is a basic human right. The technique for total knee arthroplasty(TKA) has evolved over time and is still evolving. Not only the technique has evolved, the quality of the implants used has been improved.

In the past, General Anaesthesia has been the anaesthesia of choice for TKA. Today regional anaesthesia techniques have become the anaesthesia of choice. Regional anaesthesia like peripheral nerve block and periarticular injection of local anaesthetics has now formed part of the multi-modal analgesia applied by Anaesthesiologists to improve postoperative pain relief with less use of narcotics. With better postoperative pain control and better patient rehabilitation new clinical pathways are being developed. With the new clinical pathway of Enhanced Recovery After Surgery (ERAS) and Early Recovery After Anaesthesia (ERAA), these clinical pathways are designed to improve patient outcomes such as decrease length of stay in hospital and patient mortality as well as reduce cost.

In the future, more clinical pathways will be developed to improve the perioperative care and perioperative rehabilitation of patients.

CERVICAL EPIDURAL ANAESTHESIA FOR BREAST, THYROID AND UPPER ARM SURGERIES

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Regional anaesthesia is preferred over general anaesthesia to overcome the side effects of general anaesthesia. Cervical epidural anaesthesia is mainly used for relief of chronic pain in head and neck cancer and degenerative conditions of cervical spine etc.

But recently increased use has been reported for carotid endarterectomy, neck surgeries especially thyroidectomies ,combined neck and arm surgeries,thymectomies ,mastectomies,upper limb and shoulder surgeries,thyroglossal cyst excision surgeries.

Cervical epidural anaesthesia offers safe and reliable anaesthesia in carotid artery surgery, handsurgery,neck ,arm and upper thoracic surgeries .

Advantages of Cervical epidural anaesthesia over general anaesthesia(1,2):

Reduction in stress response ,
stable hemodynamic parameters ,
stablerespiratory rate,
effective control of pain in the post operativeperiod,
reduced blood loss,
reduced perioperative myocardial infarction,
early ambulation and reduced post operative morbidity,
post operative comfort for the patient,
less nausea or vomiting,
no shivering or sorethroat
low cost of analgesia.

As the patient is awake ,reliable and sensitive cerebral monitoring is possible through verbal communication by frequent evaluation of motor strength.
It is a safe alternative to general anaesthesia particularly where selective sensory blockade is required.
It is considered in cases where the operating mass is very large(eg.thyroid) and poses difficulty in intubation.
It is also useful in cases of fluctuating thyroid profile ,orwhere the patient is not medically fit for anticipated complications under general anaesthesia.
It is also useful in patients who are professional singers and orators/public speakers as it avoids intubation.

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SESSION B4 17:10 – 18:45 DEXMEDETOMIDINE

DEXMEDETOMIDINE: RESEARCH FROM LAB BENCH TO CLINICAL APPLICATION

Daqing Ma

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The physiological changes in the perioperative period can precipitate a number of neurological complications, ranging from acute confusion and cognitive dysfunctions, to long lasting cognitive decline and cerebral vascular accidents. Postoperative delirium is an acute confusional state characterised by fluctuation; inattention and altered level of consciousness. It is associated with high incidence of postoperative complications, and lead to adverse outcomes for patients as well as increased health care costs. It is common presentation with incidence as high as 70% in certain patient groups, but due to its broad range of presentations it remains underdiagnosed in the clinical environment. Unfortunately the currently available pharmacotherapies are mostly symptom orientated are associated with a number of side effects. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist with anxiolysis and analgesic properties as well as benefit on neuro-protection. It has been demonstrated to reverse a number of pathological changes associated with postoperative delirium. In my talk, I will review the pharmacological properties of Dexmedetomidine and its effect on pathophysiology of the central nervous system, in particular, focusing on postoperative delirium in a "Research from lab bench to clinical application" manner.

COGNITIVE FUNCTIONS AFTER TIVA WITH DEXMEDETOMIDINE

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Postoperative cognitive dysfunction (POCD) is one of the most common complications affecting the central nervous system after general anaesthesia, especially in elderly patients (1).
Its clinical manifestations include cognitive function disorder, personality change and memory impairment; in severe cases, Alzheimer's disease (AD) may occur (1). For patients over the age of 60 years, POCD can reportedly be identified in 25.8% of cases 1 week after surgery and in 9.9% of cases 3 months after surgery. Recovery is a continuous process, and patients are considered fully recovered only when they return to their preoperative physiological status, which may take days.

Although POCD is common, its pathophysiologic mechanism is poorly understood. Li et al. (2) showed that anesthesia, especially with inhalation drugs, results in cholinergic disturbance and damage to cognitive structures. Other reports demonstrated that cognitive function may be influenced by the duration of anesthesia and the dose of anesthetic drugs (3-5). Previous studies demonstrated that deep anesthesia during surgery [6, 7] and use of high doses opiates and/or sedatives after surgery (8, 9) are important predisposing factors.

Dexmedetomidine is a highly selective α2-adrenoreceptor (α2-AR) agonist. It has been shown to exhibit various properties, including sedative, analgesic and sympatholytic activities, and an ability to stabilize hemodynamics.

We hypothesized that adding dexmedetomidine would reduce the requirement for anesthetic in patients receiving TIVA, decrease the magnitude of postoperative cognitive disruption, and lead to better hemodynamic stability.

After approval from the Ethics Committee, and having obtained informed consent from all participants, we recruited 40 patients scheduled to undergo general anesthesia to repair a prolapsed lumbar disc (Clinical trials.gov ID: NCT02631135, protocol ID: 2007-21/1). All patients were administered the Standardized Mini Mental State Examination (SMMT-E) during the premedication visit. In the operation room, standard and BIS monitoring were applied. Group I (TIVA, n:20) received propofol and remifentanil and group II (TIVA+D, n:20) received the same plus dexmedetomidine. The BIS value was maintained at 40–60 until the end of surgery. The dexmedetomidine infusion rate was 0.5 $\mu g \cdot kg^{-1}$ without a loading dose. Rocuronium (0.5 $mg \cdot kg^{-1}$) was used to facilitate neuromuscular transmission block. The cognitive function tests were performed at 2 and 24 hour postoperatively and 1 week and 1 month later.

Mean arterial blood pressure and mean diastolic arterial blood pressure was significantly lower in the TIVA+D group. Patients receiving dexmedetomidine, total remifentanil usage was lower at the end of surgery in these patients than in those who did not receive dexmedetomidine ($p < 0.05$). No differences in the SMMS-E scores were detected at any of the time points between the groups.

Our results suggest that dexmedetomidine added to TIVA had no negative effects on postoperative recovery or cognitive function.

It is considered a useful adjuvant to general anesthesia, since it is able to decrease the required doses of anesthetics and analgesics, and promote hemodynamic stability (10). Furthermore, α2-ARs have been found to be closely associated with cognitive function (11), which may be affected by increased activity in the dorsal noradrenergic bundles, where α2-AR are located, and in the frontal lobe, where α2-ARs mediate increased attention (12).

In addition, previous studies have demonstrated neuroprotective effects for dexmedetomidine in animal models of stroke, and also it protects neuronal tissue against ischemic cerebral injury (13, 14), and reduces ischemia-induced neuronal apoptosis by upregulating anti-apoptotic proteins and down-regulating pro-apoptotic proteins (15). In neonatal rats, dexmedetomidine attenuates isoflurane induced neurocognitive impairment and neuronal apoptosis by activating the **α**2 –adrenergic receptor, possibly via activation of the PI3K/Akt pathway (16). With regards to molecular mechanisms, a previous study showed that dexmedetomidine could ameliorate neurocognitive impairment induced by repeated propofol exposure via the PI3K/Akt/GSK□3**β** signaling pathway in neonatal rats (17).

Our results suggest that dexmedetomidine added to TIVA had no negative effects on postoperative recovery or cognitive function, and showed that dexmedetomidine had no significant adverse effects on cardiovascular or respiratory systems.

It has been reported that dexmedetomidine appears to reduce significantly the risk of early POCD in elderly patients after general anaesthesia, and improve postoperative MMSE score (1).

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DEXMEDETOMIDINE AND SLEEP DISTURBANCES

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Introduction: Sleep disturbance is commonly encountered amongst intensive care patients and has significant psychophysiological effects, which protract recovery and increases mortality. Bio-physiological monitoring of intensive care patients reveal alterations in sleep architecture, with reduced sleep quality and continuity. The etiological causes of sleep disturbance are considered to be multifactorial, although environmental stressors namely, noise, light and clinical care interactions have been frequently cited in both subjective and objective studies. As a result, interventions are targeted towards modifiable factors to ameliorate their impact.
Sedation is used in many ICU patients, particularly in those requiring mechanical ventilation. Despite their sedative, anxiolytic, and analgesic properties, benzodiazepines and opiates are potentially disruptive to sleep. Benzodiazepines provide sedation through GABAergic pathways but increase stage N2 and reduce N3 sleep at low doses in healthy participants. Opiates such as fentanyl and morphine promote sleep onset in healthy adults, but inhibit REM, profoundly suppress N3, provoke nocturnal awakenings, and can precipitate central apneas. Both benzodiazepines and opiates are associated with delirium in critically ill patients, even at low doses. Propofol, a GABA receptor agonist, is associated with suppressed N3 sleep in human studies. However, in a rat model, a continuous propofol infusion did not result in sleep deprivation and suggested rebound sleep (based on EEG analysis) following prolonged sleep deprivation. Dexmedetomidine, a newer α2-agonist with both sedative and analgesic properties, enhances N3 sleep in a rat model, and is associated with lower incidence of delirium compared to benzodiazepines in ICU patients. Further investigation is needed to examine the effects on sleep architecture in both healthy and ICU populations receiving these sedative agents. The current PAD Guidelines suggest implementing light sedation in intensive care patients. The choice of sedative drug may affect clinical outcomes and the onset of delirium, one of the major post-operative complications also in the cardiovascular field.
In selected critically ill patients, dexmedetomidine infusions at night to achieve light levels of sedation increases sleep efficiency and modifies 24-h sleep patterns by shifting sleep to nights.
In addition, we wanted to evaluate how DEX had a lesser impact on EEG de-structuring and evoked potentials, so as to reduce the negative effects both on sleep and on environmental contact in intensive care.
Study objective: To evaluate the impact of sedation and the type of sedative drug used on the incidence of postoperative delirium through clinical and instrumental monitoring.

Materials and methods: Patients aged between 18 and 80 years of age who underwent postoperative cardiovascular surgery in intensive care were recruited. Subjects with dementia, neurodegenerative neurologic pathology, neoplastic or vascular pathology have been excluded. The study was divided into three times.
T0 (preoperative time) was performed anesthesiologic examination, neurological objective examination, MMSE, and electroencephalographic (EEG) and potential evoked cognitive (ERP) tests.

At T1 (intensive care) patients were randomized into two groups: P group (light sedation with Propofol) and group D (light sedation with Dexmedetomidine). Patients of both groups were evaluated for delirium both clinically (via CAM-ICU) and instrumental examinations (EEG and ERPs).
T2 (48 postoperative hours) were repeated: MMSE, EEG, and ERPs.

Results: Preliminary data showed an incidence of delirium of 18% (3 out of 16 patients).
Of these, two belonged to the Propofol group and one to the Dexmedetomidine group.
Patients with delirium showed characteristic alterations in EEG pathways (reduction in the power of alpha rhythm and increased theta and delta rhythm power) at all study times (starting from baseline T0 monitoring) and alterations of mismatch negativity To potential evoked cognitive ones.
Patients sedated with Propofol showed a destruction of the physiological components of cognitive potential similarly to those in patients with delirium.
However, patients with Dexmedetomidine have maintained the physiological characteristics of both the electroencephalographic tract and potential evoked cognitive ones.

Conclusions: The instrumental EEG and ERPs have proved to be predictors of post-operative delirium, as early as the preoperative time. Light sedation with Dexmedetomidine, preserving the physiological characteristics of electroencephalographic pathways and potentially evoked cognitive potentials, showed a therapeutic and protective effect on delirium.
In view of the pharmacological and pharmacodynamic properties of DEX, we use it at low doses at night time to help patients sleep, stopping infusion in daytime hours so as to have alert and collaborative patients, creating as much as possible a natural circadian rhythm.

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SEDATION AND REGIONAL ANESTHESIA

Mario Bosco[1], Antonio Clemente[2]

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Introduction: Regional anesthesia (RA) is increasingly used for a variety of surgical procedures providing a number of benefits either to anesthesiologists and patients. An earlier family contact than general anesthesia, a shorter post-operative fasting, the chance to stay awake are important advantages from the patients' point of view, while anesthesiologists appreciate the preservation of protective airways reflexes and a steadier cardiovascular stability. 1 Adding a proper sedation regimen increase patients 'satisfaction and acceptance of regional anesthetic techniques. 2
The aim of this paper is to review the role of sedation in RA, the methods for monitoring the degree of sedation and how RA itself can exert an additive sedative effect that can't be ignored in particular in fragile patients.

Role Of Sedation In Regional Anesthesia: Providing some form of sedation during regional anesthesia increases patient's acceptance and satisfaction during these procedures. Different indications highlight the importance of sedation in the context of regional technique3: anxiolysis, it is helpful to have a calm and cooperative patient; reduction of postoperative recall; better global tolerance and comfort, in particular during long surgeries. Sedation/analgesia could also be useful for decreasing the requirements of opioids and as a means of supplementing an incomplete block.

Some drawbacks are linked either to an excessive sedation, such as respiratory depression and cardiovascular instability, and to an insufficient one, causing hypertension, tachycardia and severe discomfort. 4

Sedo-analgesic techniques are complementary to AR procedures because guaranteed comfort and sedation for stressful surgical procedures. Painful position due to patient osteoarthritis, psychological problems, surgeon manoeuvre may be eliminated by an efficacy sedation.

Main drugs used are propofol, midazolam and remifentanil administered by infusion devices (TCI). If sedoanalgesia is deep and the patient is unconsciousness airway control is advisable (by LMA). Sedoanalgesia decrease pain threshold but is not substitute of a nerve block failure. Moreover, an effective drug dosage is variable from patient to patient therefore it is mandatory a titration based on the depth of sedation. Methods of evaluating the degree of sedation are collected in three categories: patient-, observer and machine-based evaluation. 5

Patients can express their perception of sedation through one of several visual analog scales ranging from 0 to 10 or 100 with the end-points corresponding to the two extremes of a sedation. Easiness and quickness in administering are counterbalanced by significant limits such as poor feasibility at higher degrees of sedation or high variety between patients. Observer-based scales were designed to standardize assessment and minimize the inter-observer variation. The most studied are: Ramsey; modified Wilson; Observer's Assessment of Alertness/Sedation (OAA/S). 6 Their main disadvantage is the repeated verbal or even tactile stimulation of patients in administering them. Measurements by electronic devices are perceived as the most objective assessments.

As sedative agents depress the central nervous system, it is expected that changes in the electroencephalogram (EEG) should relate to adequacy of sedation/analgesia. The bispectral analysis derivative of EEG (Bispectral Index Scale) was the first approved. 7 A good correlation between BIS, OAA/S and hypnotic drug concentration for perioperative sedation was demonstrated. BIS values of 65–80 define an acceptable loss in conscious information processing and recall during sedation. 8

The imperfect correlation of electroencephalogram modifications to clinical score is because the former is a passive measure, whereas the latter measures the reaction to an active stimulus. Regardless the new advancement in technology, the use of clinical endpoints remains essential, although promising results deem necessary further well-designed studies.

The Sedative Effects Of Regional Anesthesia: Some regional anesthesia techniques exert a sedative effect, reduce the anesthetic requirement, cause measurable effects on the EEG. Epidural anaesthesia produces block-dependent sedation and sensory block level significantly predicted sedation depth in volunteers, as measured by both objective (impairment of brainstem auditory evoked responses) and subjective methods (OAA/S score).9 Moreover, epidural has been shown to reduce midazolam requirement for sedation.10

A significant relationship was also found between the maximum extent of sensory block in spinal anesthesia and the level of sedation estimated by using the Ramsey scale, with or without administration of midazolam. 11 Caution is needed using these drug in sedating patients under high spinal anesthesia because the latter markedly increases the sensitivity to the midazolam sedative effects. This factor should be taken into consideration for risks of the interaction on respiratory function.

The effects of regional anesthesia on the EEG was studied by Morley et al. 12 In their spinal group an increase in bispectral index, spectral edge frequency and median frequency appeared to be due to a relative increase in power in the beta-wave band occurring at the expense of a decrease in the delta-wave band, a similar pattern is found as effect of sedative drugs such as midazolam or propofol; in the epidural group, all changes occurred in the same direction but did not attain significance. In order to evaluate the effects on BIS of spinal anesthesia, Iida et al. 13 conducted a study under deep sedation avoiding confounding factor on BIS such as movements, noise, cough, etc. A higher spinal anesthesia deepened the level of sedation, mirrored by the BIS, compared with a lower spinal anesthesia and this sedative effect is dependent just on the spread of spinal sensory block with unchanged dose and baricity of the local anesthetic.

Several mechanisms are advocated to explain these effects, such as systemic general anesthetic effects of absorbed local anesthetics, rostral spread of the local anesthetics through cerebrospinal fluid with direct actions on the brain, and decreased facilitatory sensory input to the reticular activating system due to loss of proprioceptive inputs from skin, muscles, or joints. Although all the above factors cannot be excluded entirely,

the most profound physiological effect of spinal anesthesia is sensory deafferentation and it seems to play a major role in the sedative effect.

Conclusion: The increased use of regional anesthesia in recent years has led to an increased need for sedation during surgery in awake patients. Sedation is known to increase patient's acceptance of regional techniques. In order to avoid excessive or inadequate sedation an appropriate evaluation is needed. Regional anesthesia techniques can themselves have a measurable sedative effects. It should be taken in account in administration of intravenous sedation.
An appropriate sedation in conjunction with the right choice of a regional anesthetic technique allow a safer and more comfortable "surgical journey" in particular for our more and more complex patients.

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SATURDAY, SEPTEMBER 30th

SESSION D1 08:30 – 10:45 TIVA/TCI IN MAJOR SURGERY

DOES THE TYPE OF ANAESTHETIC TECHNIQUE AFFECT OUTCOMES AFTER CARDIAC SURGERY?

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In contrast to non-cardiac surgery, myocardial injury is a common complication of cardiac surgery, which can result in delayed recovery, organ failure, increased hospital length of stay, and mortality. Several protective approaches have been postulated, such as ‘‘anaesthetic preconditioning’’ and ‘‘anaestheticpostconditioning’’ when applied before myocardial ischaemia or upon reperfusion, respectively (1).Volatile anaesthetics(VA) have specific cardioprotective properties, independent of the hypnotic properties of the gases, which attenuate apoptosis and necrosis, and reduce myocardial dysfunction after ischaemia and reperfusion (2). The mechanisms involved in the protective effect of VA regimens account for decreased cytosolic and mitochondrial calcium loading with the final objective of maintaining intracellular homeostasis through the preservation of the mitochondria and its normal function (3). There is evidence that sevoflurane provides slightly better protection of the mitochondrial outer membrane than propofol in patients undergoing coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB) (4).

Intravenous (iv.) anaestheticsare also reported to have cardioprotective effects related to antiinflammatory, immuno-modulatory and antioxidant properties (3). For example, propofol may be a preemptive intraoperative cardioprotectant for patients with diabetes mellitus under conditions of normothermic bypass and blood cardioplegic arrest resulting in decreased episodes of low cardiac output (CO) and heart failure events following cardiac surgery (5).VA also have immuno-modulatory qualities which contribute to organ protection, such as the lung (6). As for the cerebral protection, whilst some studies point to a neuroprotective effect, others suggest neurodegeneration, apoptosis and cognitive dysfunction especially when high doses of volatile anesthetics are being given to elderly patients (7). There have been several studies that have reported that propofol appears to be better than VA in terms of renal protection (8).Propofol could also act synergistically with VA and attenuate myocardial ischaemia-reperfusion injury (9), suggesting that the relation between systemic inflammation and myocardial protection may be more complex than commonly thought.Interestingly, genetic susceptibility, age and male sex, can alter the cardioprotective benefits of anaesthesia (3).However, which anesthetic is more favorable in cardiac surgery is controversial.

The cardioprotective potential of various VA applied during cardiac surgery, measured by a reduction in biomarkers of cardiac injury, has been confirmed by clinical studies. A meta-analysis of 30 studies, which included a total of 2578 patients, showed significantly lower postoperative cardiac troponin I levels in patients receiving a VA regimen compared with an iv.anaesthetic regimen (10). The trial sequential analysis indicated that there is no need for new studies looking into markers of myocardial injury and volatile protection in on-pump cardiac surgery (11).

The clinical implications, however, are less obvious. The first meta-analysis showing that the choice of the anaesthetic regimen has an impact on patient outcome, including mortality, was published in 2007 (12). Landoni’s group performed another meta-analysis in 2013 and included 38 cardiac surgery studies with 3966 patients (13). They observed that mortality, at the longest follow-up available, was doubled in patients receiving iv. anaesthesia compared with VA, especially when sevoflurane or desflurane was used.The statistical significance was reached exclusively when combining all volatile agents. The mortality benefit of VA has been confirmed in a recent meta-analysis which also found a lower incidence of pulmonary and other complications (14). In addition to this, another meta-analysis demonstrated a reduction of acute kidney injury and renal failure after cardiac surgery under VA compared to total iv. anaesthesia (TIVA) (15).

Other meta-analyses looked specifically into sevoflurane, in both on- and off pump CABG, and found reduced mortality within 180 to 365 days of surgery andreduced need of inotropic and vasoconstrictor support compared to propofol(16). In contrast, other authors (17) did not find a mortality benefit, but improved CO, inotropic and vasoconstrictor drug use, intensive care unit (ICU) length of stay, and incidence of atrial fibrillation.

More recent large studies in cardiac surgery do not support the improved outcome of volatile cardioprotection. A multicenter randomized controlled trial (RCT) in patients undergoing high risk cardiac surgery has not observed any beneficial effect of anaesthesia with sevoflurane and desflurane compared with propofol based iv. anaesthesia, on the composite end-point of prolonged ICU stay, mortality (30 days and 1 year) or both (18). In a large cohort study of cardiac surgery patients from three university hospitals in Denmark there were no differencesin postoperative short and long outcomes between VA and TIVA (19).

The reasons of the contradictory results from meta-analyses, previous and recent studies may be related to the small sample size of previous studies included in meta-analysis with no blinding in some studies, differences in anaesthesia protocols, surgery types and procedures, differences of patients' conditions, etc. For example, although it has been demonstrated that administration of the VA throughout the entire procedure results in a more pronounced protective effect than when administered intermittently (20), in some previous studies, VA or propofol were administered in any combination of the pre-, during and post-bypass period. Moreover, the least effective 1 MAC concentration at the time of reperfusion, was sometimes difficult to obtain in practice (2).

Owing to the fact that the extent of cardioprotection may vary depending on the protocol used, interpretation of the clinical relevance of cardioprotection with VA in cardiac surgery still remains a point of debate.

In fact, the optimal VA protocol is unknown and molecular interactions interfering with VA-induced cardioprotection are frequent. Advanced age or comorbidities such as hyperglycemia and diabetes mellitus diminish its effectiveness similar to several non-VA;propofoland β1- and β2-adrenergic receptor blockers may cancel the cardioprotective response, whilst the concomitant administration of opioids elicits favorable effects (21). On the other hand, administering the VA throughout the entire operation, including the CPB, requires a dedicated calibrated anaesthetic vaporizer incorporated into the gas supply of the heart–lung-machine oxygenator. While this anaesthetic technique stood the test of time, in many countries, it is now difficult to implement in terms of certification, maintenance costs, and regulatory affairs that may have led many hospitals to switch to propofol-based iv.anaesthesia (22).

Interestingly, the same protective effect of VAwas not evident in off-pump CABG surgery where ischaemia-reperfusion injury is not so prominent (10). The beneficial results reported by some authors (23) could be related to the use of sedation with sevoflurane in the postoperative period which enhanced the intraoperative cardioprotective properties(1).

Epidurals provide excellent analgesia for cardiac surgery and may reduce complications. However, their use has been tempered because of concern with the rare, but serious complication of epidural haematoma in the context of the full-dose anticoagulation required for the CPB. In a meta-analysis 57 trials (randomized and case-matched studies) including 6383 patients the use of epidural analgesia in cardiac surgery was associated with a reduction in mortality, mechanical ventilation and myocardial infarction (24). Twenty-five haematomas have been identified from an estimate of 88 820 positioned epidurals, producing an estimated risk of 1:3552 (24). However, if only RCTs are included, the benefits are less impressive. In a meta-analysis of 25 RCTs enrolling 3,062 participants thoracic epidural anaesthesia with or without general anaesthesia did not show a benefit in reducing the rate of death or the risk of myocardial infarction or stroke but showed significant reduction of pain, supraventricular arrhythmias, time to tracheal extubation, respiratory complications and ICU stay (25).

Therefore, it is still difficult to conclude whether one anesthetic approach is superior to the other in terms of patient outcome and there is no strong recommendation on the use of a specific regimen. However, an updated international web-based consensus conference process identified VA amongst 13 interventions supported by widely agreed evidence suggesting a positive impact on mortality in patients undergoing cardiac surgery (26). Finally, we may speculate on a prolonged active protection of VA because of their effects on cellular genomic expression and that one day there may be a "preconditioning gene panel" that would be performed on every patient preoperatively to customize choice of anesthetic regimen for surgery (27).

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TOTAL INTRAVENOUS ANESTHESIA IN CARDIAC SURGERY

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Introduction: Total Intra venous anaesthesia is a form of balanced anaesthesia where the anaesthetic state is achieved with the help of intravenous administration of a combination of hypnotic and analgesic drugs without the use of inhalational anaesthetic agents including N_2O.

TIVA mandates the establishment of intravenous access, use of syringes and micro-processor controlled infusion pumps for delivery of anaesthetic agents.

TIVA results in rapid and smooth induction, better control of anaesthetic depth, decreased awareness, reduced nausea and vomiting, no atmospheric pollution, prevention of malignant hyperthermia in susceptible patients. However, it requires use of special equipment to infuse drugs at controlled rate to predicted plasma/effect-site concentration, actual drug concentration cannot be monitored, involves higher cost, causes venous irritation and once any drug is given, it cannot be retrieved.

Pharmacokinetic Pharmacodynamic Concepts of TIVA: Like end tidal concentration in case of inhalational anaesthetics, there is no clinically available monitor for real time measurement of plasma concentration of drug, based on which the dose of intravenous anaesthetics can be titrated. These agents are, however, titrated targeting a virtual plasma concentration, calculated based on pharmacokinetic based models.

Correlation Between Infusion Rate and Concentration: Because of presence of considerable lag time between change in infusion rate and actual change of effect site concentration of the drug being infused, quick achievement of a steady plasma or effect site concentration can be done best by using a combination of bolus/high infusion rate followed by decreasing infusion rates.

Onset of Drug Effect: After a bolus dose, plasma concentration of the drug rises, which facilitates its entry to effect site down the concentration gradient. Bigger initial dose of a drug and a drug having higher ke0 (transfer constant) helps in faster achievement of effect site concentration..

Recovery From Drug Effect: After stoppage of infusion of IV anesthetic agent, as the plasma concentration of the drug drops, drug from the effect site comes back to plasma because of the reversal of gradient. Decrease in the effect site concentration of the drug below a certain level, which is different for each drug, leads to recovery from the drug effect.

Context sensitive half time: It is the time taken for plasma concentration of a drug to decline by 50% after stoppage of infusion of different duration. It increases with increase in duration of infusion, as the decrease in plasma concentration of the drug after stoppage of infusion is not linear, but its slope gradually decreases with time due to pooling back of the drug accumulated in the peripheral compartment to plasma compartment. Drugs that are metabolised and eliminated rapidly have short CSHT.

However, the threshold for clinical recovery from drug effect is different for different drugs such that decrease in drug level to 50% of maintenance concentration does not always mean clinical recovery.

History of Drugs used for TIVA in cardiac surgery: Drugs to be used for TIVA should have/be ideally-

Rapid onset of action (Small volume of distribution)

Rapid and predictable recovery (Rapid metabolism with no active metabolites)

High clearance

Short context sensitive half life

Devoid of adverse side effects

Potent and lipid soluble

Relatively cheap

Stable in solution

Various drugs and drug combinations have been used for TIVA till now.

Use of TIVA in cardiac surgery was first heralded by Lowenstein, et al in 1969 when they administered equivalent large doses of morphine as that used for patients requiring mechanical ventilation following cardiac operations[x,xi].

However, due to its inability to produce complete amnesia, diazepam was added as a supplement, which, however, produced significant cardiovascular instability[xii].

The search of alternative opioids led to invention of fentanyl family of opioids, with high dose fentanyl anaesthesia becoming popular mainly due to remarkable hemodynamic stability[xiii]. Sufentanil was introduced in 1979. It was more potent, but, due to its relatively long half-life, it caused more respiratory depression and prolonged mechanical ventilation. Alfentanil was introduced next, its advantage being shorter half life than its previous congeners. Its suitability for use as TIVA in combination with Propofol was soon established[xiv].

Thiopentone was being used during CPB for heart valve surgery to reduce neurologic deficits. However, it led to prolonged sedation due to prolonged elimination half life and increased need for inotropic support.[xv]

Ketamine was first used in pediatric cardiac surgery in 1970 and it is still popular as an induction agent in cyanotic children as it increases systemic vascular resistance, thus decreasing right to left shunting. However, a long recovery time following infusion and emergence phenomena have prevented its scope for use as a TIVA agent. Its role in TIVA has re-emerged due to its NMDA blocking ability preventing the post op hyperalagesia and prevention of postop pain including neuropathic chronic pain.

Use of benzodiazepines was popular by the end of 1980s for use as an IV technique in CPB[xvi], especially with opioid anesthetic techniques. However, they could ensure neither lack of awareness nor intra-operative recall.

Three new agents- Althesin, Etomidate, Propofol- came into being for use in cardiac anesthesia[vii]. Althesin was withdrawn for incidents of anaphylaxis. Etomidate was used for TIVA, but, failed to gain popularity, probably because it was found to cause an increase in mortality when used to sedate patients in ICU[xvii].

Use of Propofol for cardiac anesthesia as TIVA was reported in 1989[xviii].Due to its short-acting nature, along with availability of smart syringe pumps to administer target controlled infusions due to predictable pharmacokinetics even during CPB- led to popularization of TIVA using it in cardiac surgery. Combining Propofol with short acting opioids alfentanil and remifentanil added further momentum to it.

Effect of CPB on the PK-PD of drugs used for TIVA:

Cardio-pulmonary bypass inculcates profound effect on the pharmaco-kinetics as well as dynamics of the drugs used during cardiac surgery. The major factors[xix] responsible for this are-

Hemodilution and plasma protein binding- On initiation of CPB, there is admixture of the CPB circuit prime with patient's blood, leading to acute hemodilution. This leads to a decrease in the total plasma concentration of any drug present in blood.

At the same time, the plasma proteins, e.g, albumin, α1-acid glycoprotein are also diluted, leading to increase in plasma free fraction of the drugs. A drug with high plasma protein binding will have more pronounced effect in this regard.

Administration of heparin leads to hydrolysis of plasma triglycerides to fatty acids via release of hepatic lipase and lipoprotein lipase. The fatty acids bind competitively to the plasma proteins by displacing the bound drugs and thus increasing their concentration.

Hypotension and altered blood flow- Initiation of CPB is associated with hypotension due to acute hemodilution. Moreover, various factors like non-pulsatile perfusion, reduction in pump flow alter hepatic and renal blood flow, thereby reducing clearance of drugs. Again, upon rewarming and restoration of pulsatile perfusion, redistribution of drug from peripheral compartment into plasma leads to increase in plasma level of the drugs. At the same time, drug metabolism also increase with re-warming, thus counteracting the above effect. The actual balance depends upon the characteristics of the individual drug.

Hypothermia- Hypothermia induced on bypass may affect hepatic drug elimination in three ways:(a) A direct effect on metabolism from hypothermia alone,(b) Intra hepatic circulation may be altered by hypothermia, (c) Cooling may reduce binding affinity of opiate receptors for certain opioids.

Lung isolation- Because of exclusion of lungs from the rest of the circulation during CPB, drugs that are sequestered in lung tissue, are trapped in there. On resuming mechanical ventilation, these drugs come back to the circulation, thereby increasing their concentration. Fentanyl and Sufentanil are good examples of such pharmacokinetics.

Sequestration in cardiopulmonary bypassequipment- In vitro experiments have demonstrated that significant amounts of fentanyl and alfentanil can be sequestered in bypass equipment.

Specific Drugs:

Propofol:

Propofol has PK and PD properties that are well suited to the implementation of TIVA, e.g, no active metabolites, short context sensitive half time, rapid onset of action, reasonably rapid decline in concentration despite long infusionsxx and the clear headed, often nausea-free recovery xxi,xxii, xxiii,xxiv.

It has variable effect on heart rate, causes significant reductions in systemic vascular resistance and cardiac index and also causes a dose-dependent decrease in myocardial contractilityxxv,xxvi. Significant depression of cardiac systolic function occurs beyond Propofol effect site concentration of 3 µg/ml, a level which, is rarely used clinicallyxxvii.

It reduces oxygen consumption during hypothermic CPBxxviii. It does not alter the arrhythmogenic myocardial threshold, stabilizing Ca++ homeostasisxxix. As a potent scavenger of oxygen free radicalsxxx, propofol also attenuates ischemia-reperfusion injury, which helps to reduce oxidative stress during the intra- and postoperative phasexxxi,xxxii. All these properties make Propofol a preferred drug for TIVA in cardiac surgery and during CPB.

There is a decrease in total propofol concentration on initiation of CPBxxxiii,xxxiv, with a small increase in free fraction. Clearance decreases during CPBxxxv, resulting in gradual rise in plasma concentration with time. Heparin administration prior to initiation of CPB increases free fraction of Propofol, which, however, reverses on administration of protamine following termination of CPB. All these factors should be kept in mind while adjusting dose of Propofol manually or during developing TCI algorithm for use in cardiac surgery. In spite of this decrease in propofol concentration on CPB , BIS, a representative of drug effect has been shown to decreases with CPB when TCI infusion was kept constant. This may also be due to confounding effect of hypothermia in addition to altered free fraction of drug.

Due to known and predictable pharmacokinetics, propofol is also preferred drug for use via TCI and a number of models are also available for such purpose in both adult and pediatric age group.

Etomidate:

Although it maintains a good cardiopulmonary function and has been used in TIVA, it is expensive, suppresses cortisol production, presence of high concentration of propylene glycol in its preparation causes hemolysis leading to hemoglobinuria- all these disadvantages make it less favourable for use in TIVA during cardiac surgery.

Midazolam:

Despite the fact that the elimination half-life of midazolam is comparatively short, its context-sensitive half-time increases rapidly with increasing durations ofinfusion, probably because of its low clearance rate, thus making this unsuitable for use in TIVA for cardiac surgery. It is, now-a-days, mainly used as supplemental boluses in CPB, especially when no inhalational agent is being used during CPB.Use of midazolam has been associated with deliriumxxxvi,xxxvii.

Dexmedetomedine:

Use of dexmedetomedine for TIVA has been shown to potentiate analgesia and sedationxxxviii. It has also been used successfully in cardiovascular surgeryxxxix, where it has been shown to be effective and also associated with hemodynamic stability, lower mortality rates, lower rates of myocardial ischemia and infarction[xl]. It also decreases inflammatory response to surgery under CPB[xli]. Even in elderly patients

undergoing cardiac surgery, dexmedetomedine use has been found to be associated with decrease in hospital and operative mortality, reduced incidence of stroke and delirium[xlii].

Opioids: Intravenous opioid formulations form important as well as mandatory part of TIVA in cardiac surgery. Since the first report of use of fentanyl in cardiac anaesthesia in 1978[xliii], The fentanyl group of opioids has been proved to be most reliable and effective drugs for anaesthetizing patients undergoing CABG or valvular heart surgeries.

Overall, opioids produce very minimal effect on hemodynamic parameters. Opioid effect on hemodynamics relates mostly to their influence on central sympathetic outflow. Almost all opioids produce bradycardia, which may be advantageous in CAD patients. High doses of opioids can cause decrease in SVR through direct and indirect effects on the vascular smooth muscles.

Fentanyl, Sufentanil and Alfentanil pharmaco-kinetics during CPB has been extensively studied. There is decrease in plasma concentration of all three agents due to hemodilution as well as variable sequestration in CPB equipment. due to deceased hepatic elimination from decreased blood flow and hypothermia, a slow rise in plasma concentration occurs during bypass[xliv,xlv]. Rise of concentration occurs after restarting lung ventilation due to return of sequestered drug[xlvi].

Combined with Propofol, the fentanyl group of opioids exert synergistic effect and requires reduced dosage of both during induction and maintenance of anaesthesia.

Remifentanil:

Remifentanil is frequently the opioid of choice when relying on total intravenous anesthetic (TIVA) protocols. The unique pharmacokinetic properties of remifentanil afford a fast onset of action and a predictable and rapid recovery independent of the infusion duration[xlvii,xlviii]. The high lipid solubility and low ionization of remifentanil at physiological pH allow for its quick transfer from blood to central nervous system binding sites as mirrored by its fast onset of action. The very short elimination half-life and stable context-sensitive half time reflect the exceptionally high clearance of remifentanil by plasma and tissue esterases. Use of smaller dosages of other longer acting opiates are suggested towards the end of anaesthesia to prevent high incidence of hyperalgesia after use of this potent short acting drug.

Fentanyl:

As the first of the fentanyl congeners, the pharmacokinetics and dynamics have been extensively studied, leading to development of suitable delivery models. Moreover, synergistic interaction with Propofol, remarkable hemodynamic stability have also added to its popularity in the past as well as present as a TIVA agent along with Propofol in cardiac surgery.

Alfentanil:

It is less potent and has more rapid onset of effect than fentanyl. Otherwise, its properties are almost similar to fentanyl and also has been used extensively in combination with Propofol for TIVA.

Sufentanil:

It is ten times more potent than fentanyl, have slower onset of action and more rapid recovery. It has also been used in combination with Propofol extensively and safely.

Delivery technologies:

The regulation of dosages of the drugs during the course of the surgery can be manual or by automatic, computer assisted techniques.

Target controlled infusion (TCI) includes the instantaneous calculation of the infusion rates necessary to obtain and maintain a given therapeutic drug blood concentration
based on average pharmacokinetic parameters.

For drugs whose pharmacokinetics are described by a two-compartment model, Kruger-Thiemer[xxxix] described the theoretical infusion regimen required to achieve and maintain a constant plasma drug concentration. Based on the concept of additivity, the required dosage includes a bolus to fill the central compartment, followed by an infusion to compensate for the loss of drug by elimination processes and superimposed as an
exponentially declining infusion to replace drug transfer into the peripheral compartment.

This infusion scheme is commonly referred to as the bolus-elimination-transfer (BET) scheme.Performance of PK model based TCI systems have been found to be satisfactory during cardiac surgeries utilising hypothermic CPB[xlix,l].

However, much criticism has been expressed at the extent of pharmacokinetic variability. The choice of an appropriate pharmacokinetic model has been the concern of many investigators.

Pharmacodynamic feedback based models have been experimented to overcome this inter-individual variations by altering plasma concentration of the drugs according to feedback from measures of hypnotic drug effects.

Closed-loop drug delivery systems have used the median electroencephalographic frequency, bispectral index (BIS), or auditory-evoked potentials to control intravenous anesthetic delivery, mainly incorporating PID (Proportional, Integral, Derivative) algorithm.
PD feedback model based closed loop delivery of propofol adjusted to BIS is feasible and may be useful in open heart surgery under hypothermic CPB[li,lii] and even in pediatric cardiac surgery[liii].
As the PK-PD properties of anesthetic drugs change during pathophysiological states, like low cardiac output, reduced EF, etc and as hemodynamic parameters are poor markers of anaesthetic depth under these circumstances, an objective monitor of anaesthetic depth should preferably be used for controlling TIVA in cardiac surgery. At the same time, feedback controlled automated anesthesia delivery systems reduce the burden of work on the cardiovascular anaesthesiologists, who are usually subjected to multitasking in cardiac OR. Feasibility, safety and superiority of such systems over manual control has been demonstrated in contemporary literature [xliii,xliv]. With the hope of end tidal propofol concentration monitoring becoming more practical in future TIVA titration may become more versatile in complimentary to effect site clinical drug effect monitoring.

Current Role: For cardiac anesthesia, TIVA obviates the problem of adding inhalational agents into or scavenging waste gases from the oxygenator, so as to prevent the problem of awareness during CPB should they be discontinued[liv].
There are various publications advocating the cardio protective effects of volatile agents over
propofol by means of preconditioning the myocardium or minimizing ischemia-reperfusion injury[lv,lvi].A recent meta-analysis suggested a possible benefit in mortality with volatile agents; however, all studies included except one were under-powered[lvii]. As risk prediction for cardiac surgery shifts towards biomarker screening alongside scoring individual patients' risk factors, the likelihood that the presence or absence of one particular intervention within the highly complex perioperative process of cardiac surgery will consistently affect mortality remains highly speculative.
TIVA with propofol has been shown to be associated with less postoperative analgesic requirement and even shown to decrease incidence of hyperalgesia following remifentanyl infusion probably due to propofol's NMDA receptor blocking action.
Neurocognitive protection: Various degrees of cognitive dysfunction are common after cardiac surgeries. There is a possible association between exposure to volatile anesthetic agents and the formation of neurofibrillary tangles and amyloid plaques in patients with Alzheimer disease[lviii,lix]. In contrast, propofol has been shown to elicit direct neuroprotection by attenuating inflammatory responses during CPB[lx], by scavenging hydroxyl radicals formed by brain injury[lxi],and by reducing the infarct size after experimental ischemia-reperfusion (neuroapoptosis challenge) in the brain[lxii].
The benefits of TIVA include organ protection; patient well-being; and enhanced recovery after cardiac surgery, especially when propofol is combined with remifentanil,
which also contributes to cardioprotection[lxiii].

Conclusion: TIVA is safe practical anaesthesia solution. Although a number of trials showing mortality and morbidity benefit of inhalational anesthesia over TIVA in cardiac surgical patients, definitive and undisputable evidence of the same is still lacking. Till better designed and larger RCTs answer the question of superiority of a specific anesthetic technique over other in cardiac surgery, TIVA with its multi-pronged ability to address all the components of balanced anesthesia together, especially with the help of various sophisticated delivery systems with multiple safety features incorporated in them, will continue to share an important place in the armamentarium of the cardiac anaesthesiologists..

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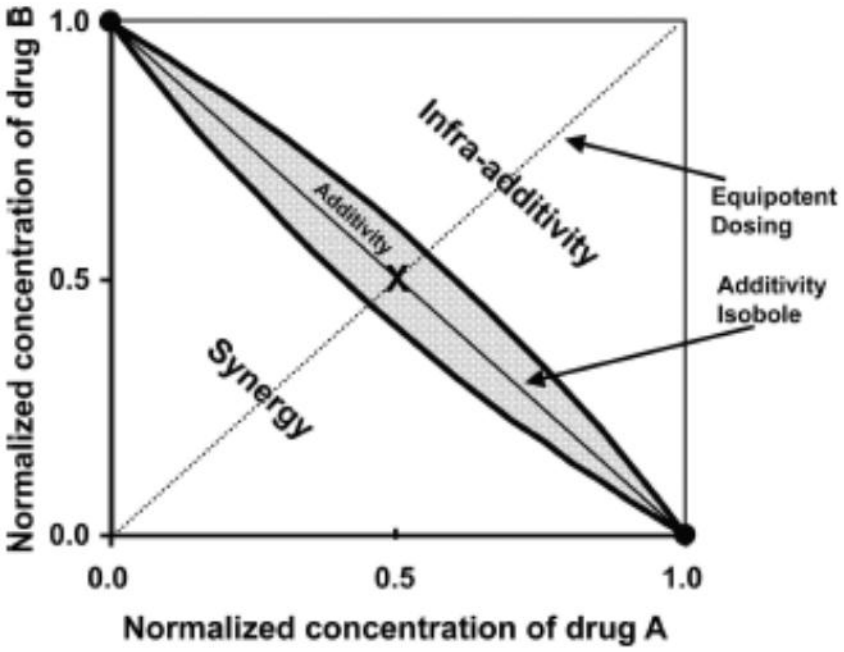
THE SYNERGISM: THE KEY OF TOTAL INTRAVENOUS ANAESTHESIA.

Del Gaudio Alfredo

Synergism is a variety of Pharmacodynamic interaction: this one is an interaction which involves two drugs which are exerting their activity by joining to the same receptor. Both the drugs are causing pharmacological action on the same physiological system. Synergism instead is a pharmacodynamic interaction that results in more intensive effect than the sum of the effects of the two interacting drugs. It is explained as 1+1 > 2 .Intravenous anaesthesia is obtained when two or more drugs are associated to guarantee the control of

hypnosis and analgesia. This association guarantees the patient and gives him the possibility to bear the surgical procedures. This association is positive when drugs are synergic. This interaction guarantees the reduction of the dosages of both the drugs with increase of analgosedation and reduction of collateral effects such as bradicardia or hypotension. In the last years the association between propofol (P) and remifentanil (R) has been evaluated by a lot of studies. The synergism can envolve three or more drugs: P and R have been associated to Midazolam (M) and Clonidine (C) or Magnesium (M). These drugs can be considered adjuvant and guarantee a further reduction of the drugs dosage and an increase of the pharmacologic effect. In this point of view the synergism has to be considered the central key of total intravenous anaesthesia (TIVA).



WHICH TYPE OF ANESTHESIA AND MONITORING IN MAJOR HEPATIC SURGERY.

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Major Liver surgery is routinely performed in high volume centers by trained surgeons, nurses and anesthesiologists to manage a wide range of malignant and benign pathology.
Today primary or secondary malignant tumors of the liver represent thes most common indications for hepatic resection. Segmentectomy or more extensive and large volume hepatic resections are performed in relation to expected liver regeneration estimated in each single patient under control of a multidisciplinary team involving surgeons and medical oncologists with the support of a committed anesthesiologists team. Some patients have insufficient liver regeneration and can develop postoperative liver failure, so hepatic resection is not Indicated to patients where the residual future liver is < 20% of the total volume of the liver.
In some cases, prior to large volume resection (Right Lobe lesions), Preoperative Portal Vein Embolization (PVE) is performed in order to stimulate liver hyperplasia and surgery can be performed in 2 steps: limited exeresis + PVE and then second time surgery to complete exeresis.
Different types of hepatic resections can be performed by open or laparoscopic technique and the choice depends upon the location of the lesion(s) and the possibility to control vascular structure access, particularly to gain access to the suprahepatic and infrahepatic vena cava.
Preoperative evaluation involves metabolic and cardiopulmonary risk assessment as well as the evaluation of postoperative liver reserve, especially in cirrhotic patients.

One of the most significant problems in this type of surgery is the control of bleeding, tackled by new surgical and instrumental techniques and an accurate anesthetic management.
Hepatic resection is performed under general anesthesia with or without epidural anesthesia/analgesia. Epidural analgesia reduces stress response, blood loss and e.v. opioid consumption, thus securing an optimal postoperative analgesia.
The choice of positioning an epidural catheter must take in account intra and postoperative coagulation changes, possible dislocation of catheter and choice of the optimal timing of its removal.
Another option is the intrathecal administration of morphine which produce long standing analgesia but this can expose to the risk of respiratory depression just as it can via the epidural route.
General anesthesia can use, particularly for prehepatic resection phase, volatile agents or intravenous agents usually Propofol/remifentanil (TIVA/TCI System Infusion). The role of halogenated volatile anesthetics is associated with the induction of important anti-inflammatory, anti-necrotic and antiapoptotic effects, particularly during and after ischemic and inflammatory conditions during the perioperative period.
In liver surgery ischemic preconditioning manoeuvres and particularly the Pringle manoeuvre (Hepatic Pedicle Clamping) performed by many surgeons to achieve an optimal bleeding control, have been demonstrated to have beneficial effects against ischemia-reperfusion injury syndrome (IRI).
IRI syndrome is a common problem in relation to the clamping manoeuvres and the total time of vascular exclusion which can increase the risk of major complications in about 10% - 20% of patients including bile leak, pulmonary complications, acute kidney injury (AKI) and liver failure. In patients with normal liver function, after hepatic resection, complications of any sort occur in up to 40% of the total. Surgical mortality following hepatic resection is 1% - 3% at high-volume centers. Different studies demonstrated anesthetic preconditioning properties as well as other studies showing anesthetic post-conditioning phenomenon when volatile agents are administered after the end of ischemic injury.
International guidelines report that there is no evidence to suggest a difference in myocardial ischemia/MI rates between the use of volatile anesthesia and total intravenous anesthesia in patients undergoing noncardiac surgery. In liver surgery sevoflurane preconditioning showed a significant decrease in postoperative elevation of transaminase levels.
Total Intra Venous Anesthesia offers some advantages like quick titration of anesthesia to the desired clinical effects in relation to the synergism between Propofol and opioid, rapid recovery from anesthesia, reduction of PONV, aids controlled hypotension, facilitates neuromonitoring and EEG monitoring, improves postoperative pain control.
Recent studies have demonstrated that there is little or no difference between the two techniques (TIVA or Volatile Agents) if postoperative enzymes of liver damage are considered. Our personal data experience suggests the same conclusion.
Basic monitoring in general anesthesia usually includes standard ASA monitors but in major surgery it is always mandatory to use other additional monitors: Anesthetic depth monitoring, neuromuscular blockade monitoring and mini-invasive cardiovascular monitoring.
In liver surgery monitoring arterial blood pressure, central venous pressure, peripheral oxygen saturation and urine output are frequently used to evaluate intravascular volume status and guide fluid therapy but these static parameters guide is not able to prevent hypovolemia or hypervolemia.
Blood loss represents one of the principal risk factors related to intraoperative and postoperative complication. In order to achieve an optimal control of bleeding and reduce the risk of allogenic blood transfusion, it is widely applied practice to maintain a low central venous pressure (CVP) $\leq$ 5 mmHg using volume restriction, pharmacologic approach (vasodilators, diuretics, and anesthetics) and body position (reverse Trendelemburg position).
Major concerns are present about the effectiveness of low central venous pressure, it really reduces blood loss but it's not well known if maintaining an intraoperative low CVP really reduce morbidity and mortality. The validity of CVP measurement is discussed and criticized in some studies also in relation to possible complications like renal failure, pulmonary complications and liver failure.
Hemodynamic changes are well reported in the studies of Delva, with a low reduction of cardiac output and systolic pressure. Relevant hemodynamic modifications are present if a total vascular exclusion is necessary. Volume restriction is not always well tolerated, especially in patients with co-existing disease (cardiac, pulmonary, kidney) and the use of vasoactive drugs like norepinephrine is often necessary.
Today the use of dynamic indices suggested and applied to guide intraoperative fluid management (Goal-Directed Fluid Therapy GDT) is considered better for detecting the hemodynamic response to a fluid challenge. Dynamic variables monitoring includes Transesophageal Doppler or monitors that use arterial wave form analysis (Systolic Pressure Variation, Pulse Pressure Variation, Stroke Volume Variation).

Left ventricular cavity size is usually the dynamic parameter to assess fluid responsiveness in TEE monitoring.
Low TV, cardiac arrhythmias, and the calculation method can all substantially reduce the predictive value of the automatically computed systems.
In our institution 2120 hepatic resections were performed between January 1992 and December 2015 with a significant increase in the period 2000 – 2015. We divided in our retrospective analysis the case studies in three periods of eight years, with an increase between each one: 322 in the first period (1992 – 1999), 509 in the second one (2000 – 2007) and 458 in the last one (2008 – 2015).
Mean age increased from 55.1 years in the first period to 61.3 years in the third one.
Indication to resection for malignant disease are increased from 74.0% to 88.6% with a significant increase for colorectal metastasis (MECR) and hepatocarcinoma (HCC).
Our anesthesia setting is based today on volatile agents (sevoflurane or desflurane) maintenance and opioid administration generally fentanyl or sufentanyl for induction and remifentanil for maintenance.
Two peripheral veins are cannulated and in addition to basic monitoring we always apply: anesthetic depth monitoring (BIS), neuromuscular blockade monitoring (NMT) and an arterial line for Invasive Blood Pressure (IBP). In major resections Flow – Track sensor connected to an EV 1000 Platform allowed SVV monitoring with a target value between 10 – 15%, for a better control of intraoperative fluid management. Maintaining a low central venous pressure (CVP) is not mandatory but a restrictive fluid administration in prehepatic resection phase is always necessary.
In major liver resections, we often perform Central Venous Cannulation (Internal Jugular Vein) not only for Central Venous Pressure (CVP) monitoring but also for vasoactive drug administration (Norepinephrine) to maintain mean arterial pressure ≥ 65 - 70 mmHg and preserve organ perfusion. Body and fluid warming systems are employed in all patients.
For open hepatic resections, Thoracic Epidural Analgesia (TEA) is considered a good choice but we prefer, according also to ERAS Guidelines, to approach the problem with a Multimodal analgesia with opioids or Tramadol PCA and local anesthetics administered performing subcostal Transversus Abdominal Plane Block (Ultrasound technique). In our experience a reduction of postoperative opioid consumption is obtained with subcostal TAP block.
At the end of surgery most of patients can be faster extubated in the operating room and then admitted to a Post Anesthesia Care Unit for some hours and then transferred to the ward.
Patients submitted to Major complex resections or long-time surgery need Intensive Care Unit (ICU) monitoring for one night or more.
In our case studies, there was a decrease of transfusions from 11.3% (2000-2007) to 7.9% (2008-2015).
Postoperative complication rate and mortality rate decreased significantly in recent years due to application of new surgical techniques and anesthesia/monitoring optimization.

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SESSION D2 11:15 – 13:20 CANCER AND ANESTHESIA

REGIONAL ANESTHESIA AND IMMUNE SYSTEM

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Introduction: Surgical stress is followed by profound endocrine metabolic changes, which have been demonstrated to influence the host defense response, presumably by directly affecting the immune system or activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. 1
This immunosuppression in cancer patient may accelerate the growth and metastasis of residual cancer cells; this suggests that restriction of surgical or anesthesiological stress should be recommended. The advent of minimally invasive surgical approaches allows similar surgical outcomes with less overall tissue trauma and results in a reduced need for postoperative analgesia while recent epidemiological evidence has suggested that the selected anesthetic and analgesic management modalities for perioperative period appear to be associated with a better immunocompetent system.
We'll analyze briefly how the immune system works, the factors that could compromised it perioperatively and the role of the anesthesiologist in limiting the damage.

The immune system: Immune system is an equilibrium between innate immunity and adaptive immunity, during our life many agents could influence this reaction: trauma, surgery, drugs, infections, native predisposition, behaviors 2.
Innate immunity (called natural or native immunity), is our first line of defense. Principal components are epithelial membranes, phagocytic cells (neutrophils and macrophages), dendritic cells, natural killer (NK) cells, and several plasma proteins, including the complement system. Most important cellular reactions of innate immunity are inflammation (process in which phagocytic cells are recruited and activated to eliminate microbes) and virus elimination, mediated by dendritic and NK cells.
The adaptive immunity, also called acquired or specific immunity, consists of mechanisms that are induced by microbes and are capable of specifically recognizing microbial and non-microbial molecules called antigens. The adaptive immune system consists of lymphocytes and their products, including antibodies and cytokines.
Endocrinal modulators play a fundamental regulation in immunological process; the cortisol, for example is released in response of an injury and has an anti-inflammatory function: inhibiting the activation of innate and adaptive immune cells, inducing apoptosis in lymphocytes, inducing the release of neutrophils from the bone marrow and from the marginated pool within tissues.
There is a huge literature showing that both surgery (as tissutal trauma) and general anesthesia can modify this equilibrium changing the response of adaptive immunity and influencing cancer recurrence 3.

Immunosuppressive perioperative period: Many perioperative factors affect immunocompetence and therefore may alter the incidence of perioperative infection or the body's response to cancer.
Transfusion-Related Immuno-Modulatory (TRIM) effects produce a measurable impact on immune function and include increased susceptibility to infection and promotion of tumor growth. Specific TRIM effects include: decreased NK cell and phagocytic function, impaired antigen presentation, suppression of lymphocyte production. 4
By far the most important influence on immune function is the Neuroendocrine Stress Response initiated by activation of the autonomic nervous system and the hypothalamic-pituitary axis. Surgical stress induces release of catecholamines, corticotropin, and cortisol. Monocytes, macrophages, and T cells possess β 2 - adrenergic and glucocorticoid receptors. Monocyte and macrophage activation lead to the release of cytokines such as IL-1, IL-6, and tumor necrosis factor-α, which further stimulate the hypothalamic-pituitary axis. The aim of this immunosuppression is to minimize the inflammatory response caused by surgical trauma but the downside is an increased vulnerability to infection and tumor proliferation. 5
Other factors in the perioperative period could weaken the immune system 6: Acute pain, Hypothermia, Tissue hypoxia and Hyperglycemia.

Anesthetic drugs and immunity: Considerable in vitro and in vivo evidence from animal studies suggest that anesthetics and analgesics also have an impact on the immune response. The magnitude of this effect is probably considerably less than that of the surgical stress itself, but an additive effect may be important. Several immune functions are modified after the administration of anesthetic drugs by direct or indirect effects on stress responses. Significant activities such as phagocytosis, respiratory burst, proliferation and cell count are modified after anesthetic procedures. Anesthesia also affects the immune response by suppressing or promoting the release of different cytokines affecting the inflammatory response. Anesthetic drugs exert different effects on each of immune cell subpopulation acting on GABA's receptors that are present on immune cells, and are a potential site of drug action. 7
Ketamine, thiopental, and all the volatile anesthetics appear to reduce NK cell activity and/or number. Volatile anesthetics also impair neutrophil function by inhibiting the respiratory oxidative burst mechanism and

reducing lymphocyte proliferation. The impact of propofol on immune function is less clear, but propofol bears a chemical resemblance to the antioxidant α-tocopherol and may possess anti-inflammatory and antioxidative properties that tend to inhibit neutrophil, monocyte, and macrophage activity. 8
Regarding the clinical practice, it has been reported that some alterations in the immune system persist several days after the end of the anesthetic exposure. However, the post-anesthetic immunological complications are rare in patients with proper immune system function; while in patients with certain immunodeficiency, the choice of appropriate pain therapy should be carefully selected, considering that the interactions between anesthesia and immune system can lead to complication.
Regional techniques, such as epidural or spinal anesthesia, with an afferent neural block by local anesthetics are expected to profoundly inhibit hormonal and metabolic stress responses. Combining epidural analgesia with general anesthesia showed increased levels of anti-inflammatory cytokines such as IL-4 and IL-10 compared with general anesthesia alone 9. This anti-inflammatory influence of regional anesthesia may support a beneficial effect on host immune resistance to malignancy. Recent randomized trials confirmed the anti-inflammatory role of epidural even more than spinal anesthesia 10 in surgical not cancer patients.

Conclusion: Transient depression of adaptive immune cell function is commonly observed in the perioperative period. Regional anesthesia can attenuate several perioperative risk factors for immunosuppression because it decreases the neuroendocrine stress response to surgical tissue injury as well as the surgical stress-induced increase in proinflammatory cytokines, relieves perioperative acute pain, eliminates or reduces the need for general anesthesia, and minimizes opioid requirement. The spread of alternative techniques as opioid-free anesthesia, fascial block (Transversus Abdominis Plane Block, PECtoral nerveS block ….) and safe ultrasound guided regional technique represent power instruments to re-evaluate the anesthesiologic choices.

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LOCAL ANESTHETICS AND CANCER: DO LOCAL ANESTHETICS HAVE ANTIPROLIFERATIVE EFFECTS ?

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In the last years, increasingly emerging evidence suggest that perioperative interventions may influence cancer patients' outcome after surgery1,2.
Thus it has been shown that regional anesthesia, perioperative NSAID and propofol may decrease the incidence of recurrences after surgery in cancer patients.

Regional anesthesia decreases stress response to surgery, the opioid consumption and the needs for volatile anesthetics, all potential mechanisms that may influence the recurrences after surgery1-4.

NSAIDs influence cancer cells proliferation due to COX-2 receptors expressed by different cancer cells1-2. It has been shown that both acute (even a single preoperative dose) and chronic use of NSAID in cancer patients have been associated with tumor regression, probably through the inhibition of COX-2 and prostaglandin synthesis; alternative COX-independent pathways cannot be excluded2,5,6.

Propofol was reported to have some antineoplastic effects either by decreasing production of prostaglandins7 or due to its chemical structure8, or by different cellular mechanisms related either to cell-surface death receptor (extrinsec) or to and the mitochondrial (intrinsic) pathway: DNA fragmentation, activations of caspase etc9. A recent retrospective study reported a hazard ratio of 1,46 of death for volatile anesthesia as compared to TIVA10. Further prospective studies to compare the effects of inhalation anesthesia and TIVA on postoperative outcome in cancer patients are needed to confirm the in vitro results. Some such studies are ready and hopefully the results will come up soon.

Local anesthetics are widely used perioperatively both as a component for regional anesthesia or as i.v. infusion. It has been shown that perioperative infusion of lidocaine decreases intraoperative opioids, the severity of postoperative pain and postoperative opioids, fastens recovery of bowel function and reduces length of hospital stay and the incidence of chronic pain11-12.

In the same time, for local anesthetics (LA) a number of in vitro studies have confirmed antiproliferative and cytotoxic effects in cancer cells in the last years13-15. Responsible mechanisms for antiproliferative effects include inhibition of epidermal growth factor, DNA demethylation and reduced mesenchymal stem cell proliferation13-15. Inhibition of Na+ channels (especially neonatal Nav1.5 which is highly expressed in certain tumor cells) and of the protooncogene Src have been also identified as main mechanisms of antitumor effects of LA16. Moreover these effects seems to be dependent on the concentration and on the tumor type; such effects have been reported in tongue, colon, and breast cancer cells, etc13-14. Recently these antiproliferative effects have been confirmed in human hepatocarcinoma cells in a time- and dose-dependent manner17-18. Xing and Jurj also described new potential intracellular mechanisms of antitumor effects of lidocaine, p38MAPK and p53 pathways, respectively, both implicated in cell cycle and cell proliferation17-18.

Xing's study also provided the first animal model experiment showing that lidocaine suppressed hepatocellular carcinoma development and sensitized hepatocarcinoma cells to cisplatin in vivo17.

In conclusion, a number of studies have confirmed that LA have antiproliferative and apoptotic effects in different cancer cells in vitro in a dose- and time dependent manner. Responsible cellular mechanims are both intrisec and extrinsec and includ a puzzle of actions in which the most important seems to be Na+ channels blocking effect; most recent studies have focused on MAPK family pathways.

At the moment there are only a very few studies confirming these effects on animal models. Lidocaine's effect of sensitizing cancer cells to chemotherapeutic agents also has been confirmed in animal models.

In future large RCTs in humans (e.g. our study NCT02786329 - Anesthesia and Postoperative Outcome in Colorectal Cancer Patients) will have to confirm the antiproliferative and apoptotic effects of LA, and the most efficient dose and time of administration for these drugs. If so, future guidelines will have to includ perioperative infusion of LA as an anesthetic intervention that may decrease the incidence of recurrences and ameliorate postoperative outcome in cancer patients.

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DOES ANAESTHETIC TECHNIQUE DURING SURGICAL TUMOUR EXCISION DIRECTLY INFLUENCE METASTATIC CELLS AND CANCER RECURRENCE?

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Several retrospective analyses support a positive association between regional anaesthesia and a reduced likelihood of cancer recurrence following surgical tumour excision (1-3). However, data from prospective clinical trials provide insufficient evidence of a relationship between anaesthetic approach and prognosis (4). A recent consensus statement recognised the existence of conflicting evidence and emphasised the need for additional data (5). The first recommendation urged caution: "While the concept that anaesthetic or analgesic technique might affect cancer outcomes is intriguing, there is currently insufficient evidence to support any change in clinical practice". The final recommendation states: "Based on recent experimental research, the expert group calls for randomized clinical trials to evaluate the effect of adjunct medications used during anaesthesia for primary cancer surgery on cancer recurrence or metastasis".

It is important to carefully consider the design of future clinical trials as it would be very unfortunate to miss a link between anaesthesia and cancer; it is unlikely that there will be many opportunities for sufficiently powered clinical trials. For the greatest chance of success, the trial design should be informed by rigorous preclinical research investigating the actions of anaesthetics on cancer biology. Such studies have revealed numerous mechanisms that may contribute to beneficial effects of regional anaesthesia. For example, regional anaesthesia reduces the requirement for general anaesthesia and opioids, factors that may adversely affect the stress response, the immune system and natural killer cells (1). Through these mechanisms general anaesthetics and opioids may reduce the clearance of circulating cancer cells during the critical perioperative period. Therefore, by reducing the requirement for general anaesthesia and opioids, regional anaesthesia may provide an indirect beneficial effect. Most of the ongoing clinical trials investigating associations between anaesthetic technique and cancer recurrence are designed with this hypothesis in mind. However, local anaesthetics used for regional anaesthesia may also have direct beneficial effects. Some are anti-inflammatory

and/or interact with second messenger systems to reduce cell proliferation and migration (6). Furthermore, the presence of voltage-activated sodium ion channels (VASCs) on metastatic cancer cells (including those from prostate, lung, breast and colon tissue) may provide a direct target for beneficial effects of local anaesthetics (7-9).

The objective of our research was to explore a possible relationship between VASC activity and the metastatic potential of colon cancer cells. In order to achieve this we used the patch-clamp technique to record the activity of either recombinant NaV1.5 expressed in human embryonic kidney cells or native channels in SW620 colon cancer cells. We also quantified invasion of SW620 cells through Matrigel, an artificial basement membrane. Having established a relationship between NaV1.5 activity and invasion, we examined the ability of several local anaesthetics to inhibit these channels and reduce the metastatic potential of colon cancer cells.

We demonstrated that lidocaine and ropivacaine potently inhibit the activity of NaV1.5 channels expressed by metastatic colon cancer cells decreasing the activity of specific kinases, leading to reduced invasion (9-11). Importantly, these inhibitory effects occur with concentrations of local anaesthetics achieved in the circulation during regional anaesthesia (10). Surgery can release metastatic cancer cells, which may either self-seed at the original tumour site and lead to recurrence, or invade into distant secondary tissues creating additional tumours. Therefore, accumulation of systemic local anaesthetic during surgery might contribute to the apparent beneficial effect of regional anaesthesia by directly inhibiting VASC activity on circulating cancer cells. None of the current clinical trials, investigating associations between anaesthetic technique and cancer recurrence optimally, exploits this potential mechanism for the beneficial effects of local anaesthetics. While regional anaesthesia may help reduce cancer recurrence and metastases following tumour excision, direct local anaesthetic administration, either intravenously or onto tumours, would likely maximise any direct beneficial effects. A drawback of such an approach is the possibility of systemic toxicity which occurs largely through the blockade of ion channels in cardiac tissue and other excitable cells.

The NaV1.5 channel, which may contribute to beneficial effects of local anaesthetics on metastatic cancer cells, is also found in the heart where its blockade would be detrimental to cardiac function. This raises the critical question of how to inhibit VASCs on cancer cells without adversely affecting the heart. NaV1.5 channels on metastatic breast and colon cancer cells include a neonatal variant, which is not found in adult heart (10). This may provide an opportunity to target VASCs on cancer cells while sparing cardiac function. In addition, metastatic colon cancer cells have a membrane potential that is considerably more depolarised than the resting potential of cardiac cells and neurones, resulting in a predominance of NaV1.5 inactivation. The inactivated state of VASCs is only briefly visited under normal physiological conditions in excitable cells. Therefore drugs that bind preferentially to the inactivated-state of NaV1.5 channels may preferentially target cancer cells.

We are exploring the dependence for inhibition by low concentrations of lidocaine, levo-bupivacaine and ropivacaine of alternative splicing and the inactivated-state of NaV1.5. Our findings reveal that NaV1.5 plays a key role in metastatic behaviour of colon cancer cells. Results of our ongoing work will help in the design of a clinical trial that will maximise the likelihood of beneficial effects of perioperative local anaesthetics during surgical colon cancer excision.

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INTRAVENOUS AND INHALED ANAESTHESIA. SIMILARITIES AND DIFFERENCES

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For many years, there has been an opposition between inhalation and intravenous anaesthesia. In the history of the application of both methods of anaesthesia, there were remarkable discoveries and failures, periods of excessive enthusiasm and disappointments, improvements and borrow of technology.1

In this paper on the basis of a complex analysis, clinical and methodological parallels, features of impairment, advantages and disadvantages of the two methods of anaesthesia are discussed. It is demonstrated that there are more similarities between the two main methods than differences. Concerning pharmacodynamics, these are similar profiles of systemic and organ hemodynamics (excluding ketamine). The application of both methods conforms the same principles of pharmacokinetics, including multicompartmental models, context-sensitive half-time eliminations, drug interactions.2 Dosing is based on titration of the drug, the principle of controlling the target concentration of intravenous anaesthetic (plasma, effect-site) and inhalation anaesthetic (end-expiratory concentration) is implemented.3 The same systems are used to monitor hemodynamics, respiration, electrical activity of the brain, neuromuscular conduction, the same parameters are evaluated. With the proper use of intravenous anaesthesia, the risk of intraoperative awakening is not higher, just as inhalation anaesthesia does not guarantee protection from intraoperative awakening. Not only volatile anaesthetics, but also opioids and propofol have organoprotective properties and are able to provide pre- and post-conditioning. Total intravenous anaesthesia is certainly more ecological and is accompanied by a lower frequency of postoperative nausea and vomiting. Economic aspects are not so unambiguous. There is evidence of a greater risk of cancer recurrence after inhalation anaesthesia, although this requires further study.

The general conclusion drawn in the paper is the need to use both methods judiciously, based on specific clinical goals, and not oppositions.

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THE COMPARISON OF PROPOFOL OR SEVOFLURANE ANAESTHESIA ON BRAIN DAMAGE AND INFLAMMATORY RESPONSE DURING BRAIN TUMOUR SURGERY

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Background: Anaesthetic technique for craniotomy has to reduce stress response to pain during intubation and surgical manipulation. Emergence from anaesthesia has to be rapid and smooth allowing early postoperative neurological evaluation. Short-acting opioid remifentanil is commonly used for neurosurgical procedures since it allows perfect titration of the analgesic effect to various noxious stimulation intensities, along with rapid recovery and early neurological evaluation (1-5). The combination of remifentanil and either propofol or sevoflurane has proved a useful anaesthesia technique in elective neurosurgery (6-10).
It is very important to prevent brain oedema and provide optimal cerebral perfusion and oxygenation during neurosurgical procedures (1-3). Optimal neuroprotective strategies include appropriate patient positioning, management of systemic and cerebral haemodynamics, maintenance of fluid, electrolyte and coagulation balance, and postoperative prevention and treatment of pain and postoperative nausea and vomiting (2).
Tissue damage is inevitable following major surgery and induces a complex host-immune response. Anaesthetic technique plays a key role in modulating the perioperative immune response. There is a delicate balance between the release of proinflammatory (IL-6, IL-8) and anti-inflammatory (IL-10) cytokines. The cell-mediated immune response can increase the rate of postoperative complications, such as infection, compromised wound healing, cognitive impairment, and cancer progression (11-17). An exaggerated proinflammatory response, such as a systemic inflammatory response (SIRS) may lead to haemodynamic decompensation and multi-organ failure (MOF) (11-17).
Anaesthesia and surgery exert an effect on the central nervous system (CNS) via a burst of inflammatory mediators which communicate with CNS by vagal afferents and by crossing the blood brain barrier. This results in neuroinflammatory response which may damage synapses and neurones, and lead to postoperative cognitive disfunction (POCD) (18-22). Neurological biomarkers are produced as a result of brain damage and the inflammatory response (23). It would be of great help to have an indicator of perioperative neurological dysfunction. The most studied neurological biomarkers are protein S100 B, neuron specific enolase (NSE), Tau protein and metalloproteinase and until today we still have not find the ideal one (23-40). Anaesthesia or anaesthestics appear to play a smaller role than surgery in enhancement of perioperative brain damage, although their potential to modulate the inflammatory response remains understudied (18,19)
Thus, we hypothesized that intravenous anaesthesia compared to inhalational anaesthesia attenuates inflammatory response.
The purpose of this randomised, single-centre study was to prospectively investigate the impact of anaesthetic techniques for craniotomy on the release of markers of brain damage (NSE-nevronal, S100B-glial) and cytokines IL-6, IL-8, IL-10, and to determine whether intravenous anaesthesia compared to inhalational anaesthesia attenuates the inflammatory response.

Methods: The study enroled 40 patients undergoing craniotomy, allocated into two equal groups to receive either sevoflurane (n=20) or propofol (n=20) in conjunction with remifentanil and rocuronium. The lungs were ventilated mechanically to maintain normocapnia. Remifentanil infusion was adjusted according to the degree of surgical manipulation and increased when mean arterial pressure and the heart rate increased by more than 30% from baseline. The depth of anaesthesia was adjusted to maintain a bispectral index of 40-60. Invasive haemodynamic monitoring was used. Serum levels NSE, S100B, IL-6, IL-8 and IL-10 were measured before surgery and anaesthesia, during tumour removal, at the end of surgery, and at 24 and 48 hours after surgery. Postoperative complications (pain, vomiting, changes in blood pressure, and infection, pulmonary, cardiovascular and neurological events) were monitored during the first 15 days after surgery.

Results: Compared with patients anaesthetised with sevoflurane, patients who received propofol had higher levels of IL-10 (p = 0,0001) and lower IL-6/IL-10 concentration ratio during and at the end of surgery (p = 0,0001). Both groups showed only a minor response of IL- 8 during and at the end of the surgery (p = 0,57). Serum levels of NSE and S100B were not significantly different between the groups. Postoperative complications were not significantly different between the groups.

Conclusions Patients who received propofol had higher levels of IL-10 during surgery. Neither sevoflurane nor propofol had any significant impact on the serum levels S100B, NSE and occurrence of postoperative complications. The major advantage of our study is that the observation period was extended to 48 hours postoperatively. Postoperative results failed to show clinical advantage of one anaesthetic technique over the other. However, we did not assess postoperative cognitive functions, long-term neurological morbidity and mortality, and quality of life. Our findings should incite future studies to prove a potential medically important anti-inflammatory role of propofol in neuroanaesthesia and the usefulness of markers of brain damage for evaluation of optimal neuroprotective technique.

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SATURDAY, SEPTEMBER 30th

SESSION E1 08:30 – 10:45 OPIOIDS

OPIOID HYPERALGESIA

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Opioid analgesics continue to be the mainstay of pharmacologic treatment of moderate to severe acute and chronic pain. Common concerns regarding the use of opioids are the potential for detrimental side effects, physical dependence, and addiction. However, opioids may yet cause another problem, often referred to as opioid-induced hyperalgesia (OIH).
Clinical evidence suggests that besides their well-known analgesic activity, opioids can increase rather than decrease sensitivity to noxious stimuli. OIH is frequently conflated with opioid tolerance in the literature as the clinical features are similar, in fact they are different phenomena but related on the same continuum of pain sensitization processes. Increasing opioid dose aggravates pain in OIH, whereas tolerance does not (1).
OIH can clinically manifest as hyperalgesia, allodynia or both especially during or after opioid treatment (2).
Opioid induced hyperalgesia contributes to the development of perioperative hyperalgesia together with nociceptive pain induced by surgical trauma and inadequate control of pain in the perioperative setting (3-5).
Persistent uncontrolled postoperative pain may transform into chronic or neuropathic pain, OIH seem to be one of the main cause. (3,5)

Multiple underlying pathways may contribute to the development of OIH, and the mechanism may vary with the duration of opioid exposure, dose, type and route of administration (1).
Several mechanisms associated with opioid induced hyperalgesia have been identified.
Glutamate activation of N-methyl-D -aspartate (NMDA) receptors causes spinal neuron sensitization; increased levels of dynorphins lead to the release of excitatory neuropeptides such as calcitonin gene-related peptide (CGRP) from primary afferent neurones and enhance nociceptive inputs at the spinal level. Descending facilitation the RVM may promote spinal nociceptive processing and thus contribute to OIH. In the periphery, TRP-V1 and cytokines appear to be involved in OIH (1,2,6).
Mu opioid receptor (MOR) variants and interactions of MOR with different proteins have important role in OIH. At the molecular level, Toll-like receptor 4 and the anti-opioid systems as well as some other excitatory molecules, receptors, channels, chemokines, pro-inflammatory cytokines or lipids are involved (6). Several factors have been shown to influence OIH including the genetic background, sex differences as well as the opioid regimen (6).
Prevention is the best strategies in OIH management and is based on a multimodal approach, including choice of opioid, dose limitations and addition of nonopioid analgesics (3).
Non-opioids (COX 2 inhibitors), adjuvants, propofol, combined regional/local anesthesia, and gradual withdrawal of opioids at the end of surgery to reduce intraoperative administered opioid doses seem to be beneficial in preventing OIH (1-3). Adjuvant therapies such as NMDA receptor antagonist, $\alpha 2$ agonist, gabapentinoids could be beneficial in OIH by tempering nociceptive sensitisation and by reducing the required dose of opioid. Long term strategies include opioid rotation, slowly reduce doses of or even completely discontinue opioids (1-3).
In conclusion OIH is a complex syndrome with a variety of proposed underlying mechanisms, which also appears to be influenced by individual factors and is correlates with the risk of developing persistent pain after surgery.

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OPIOIDS AND CANCER

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Introduction: Although significant success has been made toward effective medical and surgical treatment, cancer pain management presents a unique and continuing challenge and opioids are the leading drugs. However, opioids have many non-analgesic effects, including direct and indirect effects on immunity with consequences on cancer cells and anti-tumour immunity.
Direct effects on immune cells are manifested via opioid receptors, whereas indirect effects are manifested via the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. Many immune cells are involved in anti-tumour immunity including natural killer (NK) cells, T cells and macrophages, as well as soluble immune mediators such as cytokines and chemokines. Opioids can also decrease/alter immune cell infiltration into the tumour microenvironment.

Moreover, surgery and anesthesia are the major traumatic elements implicated in causing postoperative immunosuppression. Different investigative groups have found a similar association between opioid-sparing anesthetic techniques and disease-free survival for a number of malignancies including breast cancer, non–small cell lung cancer, ovarian carcinoma, and colorectal adenocarcinoma. 1,2
In this review, we analyze the role of immune system on cancer and how opioids can influence it.

Immune system and cancer: Immune system plays a pivotal role in cancer control. More recent iterations have incorporated the role of the adaptive and innate immunities in policing cancer.
The immune system plays at least three distinct roles in preventing cancer 3:
protects against viral infection so suppressing virus-induced tumors;
prevents the establishment of an inflammatory environment that facilitates tumorigenesis;
eliminates tumor cells in certain tissues because nascent transformed cells often co-express ligands for activating receptors on innate immune cells and tumor antigens that are recognized by immune receptors on lymphocytes of the adaptive immune system.
There is a balance of mechanisms that are both tumour suppressive and promoting which has being coined 'cancer immunoediting' and it is described as a three phases process: elimination, equilibrium and escape. 4
Elimination: The immune systems work to detect the presence of a developing tumor and destroy it before it becomes clinically apparent. NK cells are an integral part of the tumour ligand-activated innate response. Both innate and adaptive (including the propagation and expansion of CD4+ and CD8+ T cells) are required.
Equilibrium: Rare tumor cell variants may survive the elimination phase and enter the equilibrium
phase, in which the adaptive immune system prevents tumor cell outgrowth and sculpts the immunogenicity of the tumor cells. The adaptive system plays a pivotal role, highlighted by the development of latent tumours after immune system compromise.
Escape: tumor cells acquire the ability to circumvent immune recognition and/or destruction. Progression from equilibrium to the escape phase can occur because the tumor cell population changes in response to the immune system's editing functions and/or because the host immune system changes in response to increased cancer-induced immunosuppression or immune system deterioration.
Together, these theories and clinical observations are consistent with the hypothesis that malignancies arise in certain permissive microenvironments created by immunosuppressive regimens that suspend or severely compromise the elimination and/or equilibrium phases of cancer immunoediting. 5

Opioids and immune system: The traditional notion of opioids is immunosuppressive. Recent studies indicate that the role of opioid receptors on immune function is complicated, working through various mechanisms. Different opioids or opioids administrations show various effects on the immune system: immunosuppressive, immunostimulatory, or dual effect.
T lymphocytes: the primary cells of human cellular immunity, they also regulate the activity of other lymphocytes, monocytes, and natural killer cells via neuroendocrine mechanism or cytokines. Evidences indicate that T lymphocyte express all three kinds of opioid receptors. Present findings indicate that signaling through different opioid receptor in T cells leads to different immune effects, and the mechanisms of these actions has not been clarified. 6
B lymphocytes: the primary cells of humoral immunity mainly by producing antibodies and memory cells. They also express μ, δ, and κ opioid receptors. Appropriate concentration of opioid substances like morphine may lead to the increase of IL-2, IL-6 secretion in T lymphocytes. IL-2 can stimulate B lymphocyte differentiation and enhance the function of producing antibodies, thus increasing the humoral immunity. However, formation of an antibody response always requires interaction of macrophages, T cells, and B cells.
NK cells: specific cytotoxic lymphocytes and major components of the innate immune system. The effects of opioids on NK cells are ambiguous and it seems to be dose-related. A low dose of morphine can enhance NK cell cytotoxicity while higher doses have shown inhibition capability. 7,8 A human study indicates that NK cells from opioid treated patients do not show any signs of immunosuppression. 9
Macrophages: first line of defense in the innate immune system. Their phagocytosis and chemotaxis play a significant role in the process of invading pathogens removal. Morphine has been shown to alter many macrophage functions in humans such as phagocytosis and tumoricidal activity. An increasing number of studies indicate that there is a dose-dependent relationship. 10,11

Opioids and cancer recurrence: A leading hypothesis for the apparent association between opioids and cancer recurrence rates is that chronic μ-opioid receptor (MOR) agonism results in direct stimulation of neoplastic cells and associated cellular pathways essential to tumor cell growth and metastatic spread. Although MORs are also present in normal tissue, the density of MORs has been found to be increased on

malignant (vs normal) tissue and on malignant tissue with clinical lymph node progression compared with tissue without clinical lymph node invasion 12. Stimulation of opioids receptors has also been found to regulate growth factor–induced EGF receptor signaling that is crucial for consequent malignant cell proliferation and migration 13. Another popular hypothesis is that immediate stimulation of the central nervous system with MOR agonists causes sympathetically mediated suppression of NK cell activity 14.

Pain and cancer: The mechanism of pain is associated with impaired immune function by affecting the hypothalamo–pituitary– adrenal (HPA) system, and by suppressing NK cells 15.
In treating moderate to severe cancer pain, strong opioids are still the foundation of therapy and this is supported by different scientific societies 16.
Studies that have demonstrated the immunosuppressive effects of morphine include those in which morphine is being investigated in isolation and not in the context of pain. Pain itself is known to result in the release of endogenous opioids such as b-endorphin. Investigating the effects of morphine in a rodent pain model, Page et al. 17 demonstrated the immunosuppressive effects of pain and the recovery in cellular mediated immunity with the addition of adequate analgesia such as morphine. Appropriate management of pain is crucial in preventing the pro-metastatic immunosuppressive changes.

Conclusion: Although studies have demonstrated that opioids can have differential effects on the immune system and differential interaction within the immunocytes, the conclusions are variable. Not all opioid drugs share the same immune profile, probably due to a combination effect of opioid drugs' direct effects on immunocytes, and the systemic production and release of immunomodulatory mediators.
We can say that there is currently insufficient evidence to support any change in clinical practice.
Therefore, the use of strong opioids lasts mandatory for the treatment of moderate-to-severe pain as supported by international guidelines. Without a doubt, the possibility to reach adequate and equivalent pain control choosing either proper opioid drugs and suitable opioid-sparing techniques could represent a key point to be considered in the future of pain therapy.

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NO OR FEW OPIOIDS AVAILABLE, HOW CAN I GIVE A BALANCED ANESTHESIA?

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Introduction: In 1926 Lundy introduced the concept of "balanced anesthesia" as a balance of anesthetic agents and techniques to be used in such a way that none will produce undesirable side effects as if given alone. Basically, a balanced anesthesia includes amnesia, analgesia, abolition of autonomic reflexes and muscle relaxation.
Because of their unique properties and their supra-additive synergy with hypnotics, the opioids remain widely used for the analgesia during a balanced anesthesia, although we are also aware about their role in the development of hyperalgesia, or development of metastasis.
The International Narcotics Control Board (INCB) reported in 2015, opioids are not available in any equitable way: three fourths of the world population live in countries whith no or limited access to these drugs, mostly the poorest countries of the planet. In such conditions, delivering quality anesthesia and postoperative care in those countries becomes a challenge.
So, "no or few opioids" is a topical question: de facto, in some countries the anesthesiologists will face a shortage of opioids, while in other countries, using less opioids may also be a deliberate, scientific choice.
In certain situations, regional anaesthesia can totaly obviate the need for opioids but this lecture will focus on adjuvant agents which have opioid-sparing effects and/or can fulfill some of the anesthesia's objectives usually provided by opioids.

1. Ketamine: Ketamine is an arylcyclohexylamine derivative which binds noncompetitively to NMDA receptors and also modifies them by allosteric mechanisms. It is the unique intravenous anesthetic agent with analgesic properties correlated with the inhibition of NMDA receptor-mediated pain facilitation and a decrease in activity of brain structures involved in noxious stimuli response. Intravenous subanesthetic ketamine added to general anesthesia, reduced postoperative pain and opioid requirements in a variety of surgeries (1, 2, 3). The required dose of morphine is lowed by 30-50% (4). Ketamine concentrations for analgesia are 200 ng/ml, and a suitable analgesic effect occurs from 40 ng/ml levels, intravenous doses of 0.2-0.75 mg/kg or intramuscular doses of 2-4 mg/kg. (5). Ketamine regimens vary amongst the studies but one proposal is :
- In painful surgery, a 0.5 mg/kg bolus of ketamine before incision, followed by 30 min time intervals injections of 0.25 mg/kg or an infusion of 500 microg/kg/hour.
- In less painful procedures, a 0.25 mg/kg ketamine bolus before incision; followed by 30 min time intervals injections of 0.125 mg/kg or an infusion of 250 microg/kg/hour. For surgeries lasting longer than 2 hours, drug administration should end at least 60 min before the end of procedure to prevent prolonged recovery (6).
Side effects of ketamine are delirium, hallucinations, sensation of floating and vivid dreams. However they are mild or absent when subanesthetic ketamine doses are administrated (7). The adverse effects of ketamine can be prevented or minimized by premedication with benzodiazepines.

2. Lidocaine: Lidocaine is an amide local anesthetic agent which blocks sodium channels in the neural cascade. Intravenous lidocaine has analgesic, anti-hyperalgesic and anti-inflammatory properties. Perioperative lidocaine infusion reduces postoperative pain and opioid consumption and improves functional outcome in many settings : abdominal procedures, open prostatectomy, thoracic procedures and major spine surgery (8, 9). A 35% reduction in morphine consumption between 0 to 72 hours has been reported after major abdominal surgery (10). However, no benefit has been shown in patients undergoing total abdominal hysterectomy, total hip arthroplasty, or renal surgery (8, 9). Furthermore, perioperative lidocaine infusion

shortens the duration of postoperative ileus, decreases the incidence of postoperative nausea and vomiting (PONV), reduces the length of hospital stay and reduces anesthetic requirements. Different regimes are described in the literature but in most of the studies lidocaine was used in bolus of 1,5-2mg/kg at induction followed by infusion of 1,5-3 mg/kg/hour intraoperatively until the end of the surgery (11). Toxicity from perioperative lidocaine administration is rare.

3. Alpha-2 adrenergic receptor agonists: clonidine and dexmedetomidine: Clonidine and dexmedetomidine are alpha-2 adrenergic receptor agonists. Alpha-2 agonists produce sedation, hypnosis, anxiolysis, sympatholysis, and analgesia. Their analgesic effect results in the stimulation of alpha-2-adrenoreceptors located in the central nervous system and spinal cord. Alpha-2 agonists administration reduce morphine consumption postoperatively: at 24 hours, the decrease in cumulative morphine equivalents was approximately 25% and 30% with respectively clonidine and dexmedetomidine. They also decrease the pain intensity at 24 hours by about 0.7 cm on the 10 cm visual analog scale (12). Moreover, alpha-2 agonists potentiate the anesthetic effects of all intraoperative anesthetics, regardless of method of administration and also decrease the incidence of PONV. Side-effects of alpha-2 agonists are bradycardia, hypotension and sedation. Various regimes are described : the optimal regime for post-operative analgesia with clonidine is a bolus of 3 mcg/kg followed by a continuous infusion of 0.3 mcg/ kg/h (13). A bolus of 1mcg/kg followed by continuous infusion of 0,5 – 1mcg/kg/h is proposed for dexmedetomidine.

4. Dexaméthasone: Dexamethasone is a corticosteroid without mineralocorticoid effects. A 100mcg/kg dose reduces analgesic requirements postoperatively (14). Reduced pain scores and decreased PONV last more than 24 hours after surgical procedure. This may result in the anti-inflammatory effects of dexamethasone on the wound. The optimal dose suggested is 0.1-0.2mg/kg (15), given prior to incision as proper timing may be important in limiting inflammation.

5. Magnesium. Magnesium is a non-competitive antagonist of NMDA glutamate receptors. It analgesic effect results in prevention of depolarization and transmission of pain influx.
According a systematic review there is no convincing evidence of favorable effects of perioperative administration of magnesium on postoperative analgesic requirements, but most of the trials were small (16). However, magnesium may lower the remifentanil induced-hyperalgesia. Differents regimes are used : a bolus of 50 mg/kg administrated over 30 min or a continuous infusion of 10 mg/kg/hour.

6. Gabapentinoids: gabapentine an pregabaline: Gabapentinoids inhibit the calcium influx in cortical and dorsal horn neurons, therefore they attenuate the release of excitatory neurotransmitters. 300mg of Gabapentine or 50mg of pregabaline given 2 hours before surgery will produce a powerful, longlasting opioids-sapring effect from 20 to 62%. A reduction of some of the opioids side effects -like nausea, pruritus is also observed. However, patients may experience some discomfort with somnolence, dizziness, headache and balance problem (17).

Conclusion: Given available evidences, the perioperative use of ketamine, lidocaine, alpha-2 agonists, dexamethasone, magnesium and gabapentinoids have benefits including opiods-sparing, reducing anesthetic requirements and enhancing recovery after surgery.
Some of these drugs have moreover the advantage to be cheap and already available in most developping countries and regarding the side effects the intraoperative use of high doses of opioids a new approach of balanced anesthesia is necessary. However, for clinical decision-making, benefits must be weighed against side-effects of these drugs. For routine usage it will be necessary to train anesthesia providers on the new usages of these drugs and to adapt operating rooms and post anesthesia care units according to their side-effects.
Their being easily available does not preclude the need to improve the avalability of opioids everywhere in the world because for many patients and many procedures surgery cannot be performed without opiods. Finally, it is good to remind that opioids are submitted to specific prescription and dispensation rules and that their presence in an operating suite entails rigorous controls of storage, distribution, usage and return. Similar regulation is now proposed for ketamine in several countries and this may restrict its availability and be a matter of concern in countries where ketamine is essential for anesthesia care.

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IV KETAMINE AS ANAESTHETIC AGENT IN RURAL INDIA

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IV ketamine is used in rural areas in small setups inahalationalanaesthetic agents are unavailable.
It can be used in remote areas where lifesaving surgeries are being conducted.Due to the low cost,it is easily affordable in rural and poor economic set ups.
it is useful to treat patients of trauma and emergency in rural set up as it causes the elevates blood pressure in shock patients.In emergency situations, particularly obstetrics cases and full stomach cases,it is very useful as it does not abolish airway reflexesviz-cough and gag reflexes.
Ketamine can safely be administered by paramedical people rather than trained anaesthetists,which are scarce to find in rural areas making it useful in delivering health care to the patients without delay.
Ketamine is safe anaesthetic agent and is quite effective when used as sole anaesthetic agent.
It is also a good drug for management of paediatric emergency department procedures(3).
It provides safe as well as quick analgesia.As ketamine can also be delivered intramuscularly,this mode can be used in children for better analgesia.
Ketamine has both analgesic andanaesthetic properties.Ketamine maintains airway responsiveness and adequate oxygen saturations. Ketamine is an ideal drug for use in many prehospital situations.Prehospital analgesia for trauma victims improves physiologic severity indicators in a low-resource trauma system(1).
Prehospital analgesia for trauma victims improves physiologic severity indicators in a low-resource trauma system(2). It causes bronchodilatation and no apnea episodes,it can be given to asthamatic patients.It can also be given to post-partum hemorrhage patients. It can be used in burn dressing and opioid resistant cancer pain.

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PERIPHERAL AND NEURAXIAL BLOCKS IN OPIOID SPARING REGIMEN

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Perioperative multimodal analgesia uses combinations of analgesic medications that act on different sites and pathways in an additive or synergistic manner to achieve pain relief with minimal or no opiate consumption. Although all medications have side effects, opiates have particularly concerning, multisystemic, long-term, and short-term side effects, which increase morbidity and prolong admissions. Enhanced recovery is a systematic process addressing each aspect affecting recovery 1.

Inflammation can be defined as the host response when confronted with an aggression. The purpose of the inflammatory reaction is the defense of the host for re-establishing the baseline homeostasis of the organism. Compared to the neuroendocrine changes associated to the stress response to injury, the inflammatory reaction is the major determinant of patient's recovery in the perioperative period. Perioperative inflammation is involved in the occurrence of various postoperative adverse outcomes other than only acute pain. By consequence, perioperative strategies which limit or control the inflammatory response might have beneficial effects on patient's recovery.

Opioids are the most commonly used analgesics in the perioperative period. In healthy humans and in those with cancer, the administration of fentanyl or morphine is associated with increased plasma concentrations of IL-10, suggesting a predominant antiinflammatory and immune suppressive profile 2.

For instance, surgical stress induces the release of catecholamines that act on adrenergic receptors located in the membrane of cancer cells, thus stimulating their proliferation and invasiveness 3.

Hence surgical anaesthesia with haemodynamic stability and opioid-free analgesia both in fragile and pediatric patients can theoretically be provided with regional anesthesia.

Regional anesthesia through its components i.e. local anesthetics and analgesic adjuvants like alpha-2 adrenergic agonists (clonidine, dexmedetomidine) modulates the inflammatory response consecutive to tissue injury by various mechanisms, at different levels.

While experimental studies have shown that RA techniques modulate both local and systemic inflammatory reactions, in contrast, clinical findings are inconsistent as actual RA techniques fail to impact major patients' outcomes beyond immediate postoperative analgesia.

Hence Enhancement of perioperative pain management protocols has resulted in accelerated rehabilitation and individualized management of the patients is the way to follow.

It was not long ago that patients who received total joint replacement were kept in
the hospital for weeks and were not mobilized immediately but rehabilitated progressively as the physiologic responses from surgery abated. Since that time, there has been a progressive shift toward anesthetic and surgical optimization to allow for immediate rehabilitation starting even the day of surgery. We have to keep in mind that muscle function is clearly weakened by surgery and arthrogenic muscle inhibition (AMI), in addition to any preoperative weakness 4,5.

This persists for weeks and months after surgery and is a variable independent of anesthetic
or surgical type (patient factors are a major contributor).

Future developments of tools to quantify inflammatory and immune profile of patients might certainly lead to exciting findings and to major improvements in perioperative medicine.

As we better understand the neural mechanisms of AMI, may CNB (continuous nerve blocks) even improve muscle function in the long run and enhance rehabilitation.

Nerve blocks have been also investigated for the treatment and prevention of PLS. Epidural and peripheral blocks limited to the first three postamputation days can only reduce acute pain but cannot prevent the later development of PLS. Recent studies have shown that ambulatory prolonged peripheral nerve block (up to 30 days postamputation) may represent a possible option to treat phantom pain and prevent the development of PLS and chronic pain.

Concerning to trauma patients pain is frequently severe, but is often undertreated.
Opioids are widely used to treat pain in injured patients but have a broad range of undesirable effects in a multitrauma patient such as neurologic and respiratory impairment and delirium. In contrast, regional analgesia confers excellent site-specific pain relief that is free from major side effects, reduces opioid requirement in trauma patients, and is safe and easy to perform 6.
Changing field of surgery, in 2011 a new way of providing pain relief to breast surgery was published. Blanco labelled this simple fast and effective alternative the Pecs block as its main effect was on the pectoral nerves and intercostal nerves directly involved into the innervation of the hemithorax. Its simplicity caught the attention of anesthesiologists around the world based on the complexity of the techniques used to that date, paravertebral blocks and thoracic epidurals but also based on the fact than more than 90% of the breast surgery is done in day case units and there is very little interest in techniques with devastating consequences if complications arise at home (pneumothorax is one of the most feared ones)7.
Evidence indicates that multimodal pain management is the best way to reduce opioid consumption. Multimodal analgesia includes local anaesthetic as well as systemic drugs and aim to reduce the dose of any single agent thereby reducing the potential for adverse effects.

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SESSION E2 11:15 – 13:20 TIVA-TCI: NOT ONLY

KETAMINE: OLD DRUG, NEW OPTION

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In 1957, Woodbridge spelled out the criteria for an ideal anesthetic: producing blockade of sensory, motor, autonomic, and cognitive functions. The search for agents that produce such a state led to the development of a promising class of drugs called cyclohexylamines in the 1950s by the Parke-Davis pharmaceutical company. The first compound to undergo clinical testing was Sernyl, better known as phencyclidine or PCP. Clinical studies with this compound showed severe and prolonged psychotomimetic effects in a large proportion of the patients.
In 1962, a PCP derivative was synthesized called 2(O-Chlorophenyl)-2-methylaminocyclohexanone or CI-581, subsequently known as ketamine. This compound appeared more promising in animal studies, producing anesthesia and analgesia similar to phencyclidine but with a shorter duration of action and less propensity to produce convulsions.
Commercial ketamine is a racemic mixture consisting of two optical enantiomers, R(-) and S(+), and the preservative benzethonium chloride. Pharmacokinetically, ketamine has relatively short distribution and elimination half-lives: the a-elimination phase lasts only a few minutes, and the p-elimination half life is 2-3 hours.

Classic ketamine anesthetic effects are best described as a dose-dependent central nervous system (CNS) depression that leads to a so-called dissociative state, characterized by profound analgesia and amnesia but not necessarily loss of consciousness. Although not asleep, the subject seems completely unaware of the environment. Suggested mechanisms for this form of catalepsy include electrophysiologic inhibition of thalamocortical pathways and stimulation of the limbic system.
Ketamine has other effects besides analgesia and amnesia. Effects on the respiratory system are generally beneficial: it is a well documented bronchodilator, it causes minima respiratory depression with only mild hypercapnia in clinically relevant doses, and protective airway reflexes are more likely to be preserved than with other IV anesthetics. However, increased oral secretions can occur. Ketamine often produces significant increases in blood pressure and heart rate, and increases in pulmonary artery pressure have been reported, especially in patients with preexisting heart disease. These effects are due to sympathetic stimulation; ketamine's direct effect on the heart is depressant, S(+) less than R(-) . Recovery time is dose-dependent, and emergence is, at times, complicated by psychotomimetic reactions (hallucinations, vivid dreams), which can be highly unpleasant.
The manufacturer lists the presence of uncontrolled arterial hypertension or hypersensitivity to the drug as contraindications to the use of ketamine. However,caution has also been suggested when the drug is used in patients with coronary artery disease or right heart failure.

Mechanisms of Action: Ketamine's neuropharmacology is complex. The compound interacts with multiple binding sites, including N-methyl-D aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic, and monoaminergic and opioid receptors. In addition, interactions with voltage-dependent ion channels such as Na and L-type Ca channels have been described.
Inhibition of neuronal Na channels provides a modest local anesthetic effect of the compound, whereas Ca channel blockade may be responsible for cerebral vasodilation.
All of these interactions may play a role in ketamine's pharmacological and clinical properties. However, NMDA receptor antagonism accounts for most of the analgesic, amnestic, psychotomimetic, and neuroprotective effects of the compound.
NMDA Glutamate Receptors: The NMDA receptor is an ionotropic receptor (ligandgated ion channel) that is activated by glutamate, the most abundant excitatory neurotransmitter in the CNS. The channel is permeable to Ca and, to a lesser degree, to Na and K. It requires glycine as an obligatory co-agonist and is inhibited by Mg in a voltagedependent manner. NMDA receptors are, among many other functions, involved in the so called wind-up phenomenon, which plays a major role in the development of chronic pain.
The NMDA receptor is the postsynaptic site of action in ketamine's reduction of polysynaptic stimulation in the CNS. Ketamine binds to the phencyclidine receptor in the NMDA channel and thus inhibits glutamate activation of the channel in a noncompetitive manner.
The phencyclidine binding site partly overlaps with a binding site for Mg. The blockade is time-,concentration- and stimulation frequency-dependent (use-dependent). The S(+) enantiomer has a three to fourfold greater affinity for the receptor than the R(-) form, as reflected in the observed differences in their analgesic and anesthetic potencies. Although the precise interactions between ketamine and NMDA receptors are still being elucidated, enough evidence suggests a relation between ketamine's analgesic and anesthetic properties and NMDA channel blockade to consider the NMDA receptor ketamine's primary site of anesthetic action. However, there are interactions
with other systems that may also be relevant.
Non-NMDA Glutamate Receptors: Non-NMDA glutamate receptors exist in several classes, which are activated selectively by the agonists quisqualate, AMPA, or kainate. These receptors were previously thought not to interact with ketamine, but this was disproved in recent animal studies, which demonstrated inhibition by ketamine. The effects are probably mediated through the glutamate/NO/cGMP system. Not only NMDA receptor activation stimulates NO synthesis (which then increases intracellular cGMP production), but non-NMDA receptor activation does so as well. Besides playing a possible role in ketamine's neuroprotective and sympathetic activating actions, ketamine-induced NO synthase inhibition may be involved in its analgesic effects. NO is known to play a role as a neurotransmitter, centrally as well as peripherally, and pain perception and NO are connected at least at the spinal level. In an animal model, the intrathecal administration of the NO-synthase inhibitor L-N monomethylarginine induced a dose-dependent antinociceptive response. Other analgesic substances (acetaminophen and other nonsteroidal anti-inflammatory drugs) similarly interact with NO metabolism. These findings may partly explain some properties of ketamine not caused by NMDA interaction alone.
New options: Ketamine and Preemptive Analgesia: At small doses (0.1-0.5 mg/kg), ketamine has a noticeable analgesic action, which can be used to supplement regional or local anesthesia. A number of studies have

suggested that administration of ketamine before the noxious stimulus occurs is even more effective. This effect is referred to as preemptive analgesia.

The goal of preemptive analgesia is to prevent or reduce the development of a "memory" of the pain stimulus in the nervous system (54,55), thereby lessening postoperative analgesic requirements. When a massive barrage of afferent nociceptive impulses reaches the spinal cord, a hyperexcitable state of CNS sensitization known as wind-up results (55). NMDA receptors seem to be responsible for pain memory (as they are responsible for other forms of memory), and their blockade can contribute significantly to the prevention of pain (56). NMDA antagonists prevent the induction of central sensitization and even abolish hypersensitivity once it is established (56). Ketamine is the only NMDA antagonist approved by the Food and Drug Administration (although magnesium also has significant NMDA receptor-blocking properties), and several studies have demonstrated the effect of preemptive administration of small doses of ketamine on postoperative pain, measured as a reduction in opioid requirements. These effects require remarkably small doses of the drug and last for a relatively prolonged period of time (~6 h). For example, patients undergoing gallbladder surgery who received ketamine were found to have diminished analgesic requirements after a single dose of 0.25 mg/kg IV ketamine versus patients who did not receive ketamine. When presurgery versus postsurgery administration was compared, ketamine administered before skin incision (0.5 mg/kg bolus followed by continuous rate of 10 PLg * kg-' * mini') provided better pain control than ketamine given after wound closure.

Although the administration schedule and dose varies among studies, preoperatively (preemptively) administered ketamine seems to reduce the amount of narcotics required postoperatively for pain control.

Opioid requirements were reduced 40%60% on average. Whether this translates to a lower incidence of opioid-related adverse effects is as yet unknown, although it seems likely. Psychotomimetic responses to these small ketamine doses have not been found troublesome. The role of S(+) ketamine in preemptive analgesia has not yet been studied.

Ketamine and Neurosurgery

Historically, ketamine has been felt to be contraindicated in patients at risk of increases in intracranial pressure (ICI'). However, reports about its neuroprotective actions have led to a reevaluation of this issue.

Effects on ICP

ICI' can increase after the administration of racemic ketamine (no data are available yet for S(+) ketamine). This is especially true when the ICI' is already increased before ketamine administration and when the drug is given at doses >l mg/kg IV. Two reasons are provided for the effect on ICI': cerebral blood volume may increase passively, caused by increased arterial pressure during a period of impaired cerebrovascular autoregulation; and (probably more important) increases in arterial Pco,, due to ketamine-induced ventilator depression, may contribute. It could be shown that, independent of the preexisting ICI', ketamine administration (0.5-5 mg/kg) did not increase ICI' when normocapnia was maintained with controlled ventilation.

Although some studies show an ICI' increase during normocapnia after the administration of 2 mg/kg ketamine, this increase could be avoided by mild hyperventilation or the administration of benzodiazepines. This is not different from the situation with most volatile drugs, which are used routinely in patients with increased ICI'. It has been shown that neither 1.5, 3, nor 5 mg/kg IV ketamine increased ICI' in patients with head trauma during controlled ventilation and sedation with propofol; instead, the ICI' decreased after ketamine administration.

Effects on Cerebral Blood Flow: Studies in dogs have shown that racemic ketamine increases cerebral blood flow (CBF) in the presence of the cerebral vasodilator N,O. In contrast, other animal studies using barbiturates as a background anesthetic showed a decrease in CBF after ketamine administration. This suggests that the cerebrovascular effects of ketamine are related to the preexisting cerebrovascular tone. When ventilation is not controlled, part of the vasodilatory effect may result from increased Pco,. However, ICI' can increase even when the Pco, is constant, and stimulation of cerebral metabolic rate by ketamine has been suggested to explain the increase in CBF. Ketamine inhibits certain cerebral regions and stimulates others at the same time, changes which are reflected as decreased CBF in areas with reduced metabolism
and increased CBF in areas with higher metabolism. The net balance of these determines the total effect on CBF. In addition, ketamine acts in zlitvo as a Ca channel antagonist and increases blood flow by direct vasodilation.

In summary, racemic ketamine can increase CBF dependent on preexisting vascular resistance. The mechanisms most likely involve hypercapnia, regionally specific stimulation and inhibition of cerebral metabolism, and direct vasodilation by Ca channel block.

The response of the cerebral autoregulation to racemic ketamine has not been systemically studied yet, but S(+) ketamine does not affect this autoregulation. It also has been proven that ketamine does not trigger

seizure activity but, much more likely, prevents seizures by NMDA receptor antagonism. Neuroprotection and Neuroregeneration Cerebral hypoxia/ischemia initiates a pathophysiologic cascade that leads to membrane and cell destruction and neuronal death. In this cascade, the activation of NMDA and non-NMDA receptors plays an important role. If these receptors are stimulated by very high levels of glutamate or aspartate, the resultant transmembrane flux and intracellular accumulation of Na and Ca leads to cell swelling and activation of cellular pathways, eventually inducing cell death. In particular, NMDA receptor antagonists have received attention as neuroprotective drugs, although neuronal degeneration correlates more closely with the distribution of AMPA than of NMDA receptors, and AMPA antagonists prevent the degeneration at least as effectively as NMDA antagonists. In animal studies, ketamine, given in large doses before the insult and continuously infused thereafter, reduced the hypoxic/ischemic neurodeficit. In contrast, smalldose bolus application or administration after the ischemit event did not show an effect. However, in a study using a standardized head trauma model in rats, it was shown that the administration of ketamine 180 mg/kg intraperitoneally can reduce infarct size and neurologic deficit when given 2 h postinjury.

The protective properties of S(+) ketamine have been studied in a rat model of incomplete cerebral hemispheric ischemia. S(+) ketamine in large doses (1 mg * kg-' . min-') minimized neurologic deficits to a greater extent than did smaller doses (0.25 mg * kg-i * min-') and was also more protective than fentanyl/ N,O. The neurologic deficit correlated closely and positively with the plasma levels of dopamine and norepinephrine. The literature on the subject is confusing because of differences in experimental models.

Ketamine in major depressive disorder. Although the molecular action of pharmacotherapeutic treatment for major depressive disorder (MDD) is immediate, it may take weeks for the therapy to be effective. Evidence suggests that ketamine, an arylcycloalkylamine-derived NMDA receptor antagonist, produces rapid-onset antidepressant action in patients with MDD. Twenty-nine studies have evaluated the antidepressant effects of ketamine with response rates from 25–100% and time to attainment of response typically within hours; however, there were no comparators to control for the subjective effects of ketamine in these studies which may indicate an enhanced placebo effect. In animal studies, the acute administration of ketamine consistently produced an anti-depressant like effect of rapid onset in rodent models with depression, although this is not definitive for clinical antidepressant activity.

The mechanism of action is unknown but it is proposed that it is due to the targeting of sites including the AMPA receptor, neurotrophins, MTOR, GSK-3, GABA, and others. Because ketamine can cause psychotomimetic disturbances similar to PCP (phencyclidine) such as visual and auditory hallucinations, sedation and possible sleep disturbances, diarrhea, and impairment of certain types of memory, it is not likely to be a first-line medication for most MDD patients but continues to be recognized as a potential treatment with rapid-onset antidepressant effects.

Ketamine to prevent opioid-induced acute tolerance. Although opioids are often used as sole analgesics during anaesthesia and for postoperative pain control, opioids have been reported to produce hyperalgesia and tolerance These effects are particularly important in patients suffering from intractable severe pain caused by malignancy, trauma, or neuropathy. Tolerance and dependence result from long-term exposure, high-dose exposure, or both to opioids. Basic research suggests that receptor desensitization comprising loss of receptor function and internalization is involved. Changes in opioid receptor conformation caused by agonist-induced receptor phosphorylation increase opioid receptor affinity for cytosolic β-arrestins. Interaction of β-arrestins with opioid receptors results in redistribution of opioid receptors from the plasma membrane to intracellular vesicles. This process has been defined as opioid receptor internalization. β-Arrestin also desensitizes cells to opioid by functional uncoupling μ-opioid receptors It is important, however, to remember that these general processes are opioid-dependent. Noxious stimuli such as surgery may also produce opioid receptor internalization via NMDA receptor-mediated opioid release. Pretreatment with NMDA receptor antagonists (MK801, AP5, MRZ2/576, and MRZ2/596) significantly inhibited μ-opioid receptor internalization in neurones caused by laparotomy in guinea pigs. In this context, ketamine is a non-competitive antagonist of the NMDA receptorIn addition, at clinically relevant concentrations, ketamine interacts with the phencyclidine (PCP)-binding site leading to a significant inhibition of NMDA receptor activity. This interaction with the PCP-binding site appears to be stereoselective with affinity (Ki) values of 3.2 and 1.1 μM for S(+)- and R(−)-ketamine, respectively, implying that subanaesthetic concentrations of ketamine inhibit the NMDA receptor via the PCP-binding site. It could therefore be predicted that ketamine could inhibit opioid receptor internalization. Indeed, ketamine prevents opioid-induced hyperalgesia and acute tolerance. In rats, fentanyl produced analgesia but also induced early (hours) and long-lasting hyperalgesia (days) and acute tolerance to the analgesic effects of morphine, but ketamine pretreatment completely prevented both hyperalgesia and tolerance. After systemic administration, ketamine is rapidly metabolized in the liver and lung to norketamine. Norketamine has been reported to have antinociceptive actions and to enhance morphine's antinociceptive action to thermal nociception, peripheral neuropathy, and tonic inflammatory pain

and blocked tolerance. Therefore, we believe that norketamine could maintain (parent) potentiation of opioid analgesia and prevention of both hyperalgesia and tolerance.

Ketamine and postoperative pain. Knowing that ketamine has some analgesic effect in surgical patients begs the question as to whether it should be used more frequently as an adjuvant to multimodal perioperative analgesia. When administered intravenously during anaesthesia in adults, ketamine decreases postoperative pain intensity up to 48 h, decreases cumulative 24 h morphine consumption, and delays the time to first request of rescue analgesic. When assessing the clinical relevance of these potentially beneficial effects, several issues need to be considered. Firstly, pain intensity was decreased by about 1 cm on a 10 cm pain scale at 6 h; at subsequent time points, this benefit further decreased but the effect was still statistically significant at 48 h. In control groups, pain intensity was about 4 cm on the 10 cm scale; thus, patients who received ketamine had a decline in pain intensity of about 25% at 6 h and of about 20% at 24 h compared with those who received a placebo. Since patients in control groups did not experience very severe pain, the clinical relevance of this improvement remains unclear (Kalso et al., 2002). Secondly, in clinical practice, both decreased pain intensity and decreased opioid consumption may be regarded as two linked proxies of analgesic efficacy, and it may not be feasible to clearly separate between these two endpoints. During the first 24 postoperative hours, controls consumed about 40 mg of morphine on average; this corresponds to the usual average amount of morphine consumed during the first day after major surgery (Walder et al., 2001). In four of five trials, this dose of morphine was reduced by 27–47%, and at the same time, patients had a reduction in pain intensity. Thus, the beneficial albeit moderate effect of ketamine on pain intensity should be interpreted in conjunction with the opioid-sparing effect.

Thirdly and interestingly, there was no decrease in the incidence of morphine-related adverse effects although morphine consumption was clearly reduced with ketamine. One reason may be that these trials mainly concentrated on efficacy and did not systematically evaluate and report on adverse effects. This limitation on the reporting of adverse effects has been described in other pain settings (Edwards et al., 1999). Another reason may be that the decrease in morphine consumption was not strong enough to impact the incidence of morphine-related adverse effects; this would weaken the clinical relevance of the opioid-sparing. Finally, with ketamine, the delay until patients requested the first rescue analgesic was prolonged by about 16 min. This result was statistically significant but of no clinical importance; however, it was consistent with the overall analgesic

efficacy of ketamine. One trial only looked at long term outcomes (De Kock et al., 2001). Although that study included a limited number of patients, the authors were able to show a beneficial effect of ketamine on the persistence of painful sensations around the scar for up to 6 months after surgery. These data support the biological basis of ketamine as an antagonist at the NMDA receptor.

In children, there was some evidence for an analgesic effect with intravenous or caudal ketamine. All paediatric trials concluded that ketamine may be of use. The role of ketamine as an adjunct to morphine-PCA, however, remains unclear. A further issue that needs to be considered when discussing the usefulness of ketamine as a component of perioperative analgesia is harm. The risk of psychomimetic adverse effects such as hallucinations is perhaps the main reason why many clinicians are apprehensive in using ketamine. Sensitivity analyses provided some evidence that

patients' vigilance, and less so concomitant use of benzodiazepines, had an impact on the risk of hallucinations.

Three conclusions may be drawn. Firstly, in anaesthetized patients, the risk of ketamine-induced hallucinations is minimal. Secondly, benzodiazepines should not be regarded as an universally effective protection against hallucinations; even with benzodiazepine premedication, one in 35 nonanaesthetised patients will have hallucinations who would not have done so had they not received ketamine. Finally, ketamine should be given very carefully to patients who are not anaesthetised; patients should be informed about this potential risk and they should be carefully observed during the procedure. There were also other ketamine-related adverse effects described such as pleasant dreams or visual disturbances; the clinical relevance of those is not obvious

Conclusions: The indications for ketamine may have to be revised based on current knowledge. The separation of the enantiomers S(+) and R(-) has revealed the S(+) enantiomer to be a potentially valuable drug for modern IV anesthesia. S(+) ketamine has been found to be a very potent and effective anesthetic with less prominent side effects (more rapid emergence from anesthesia and fewer unpleasant psychotomimetic emergence reactions) than racemic ketamine. Its recent commercial introduction on the European market may lead to widespread use and will undoubtedly provide

much insight into its pharmacological properties and indications K&amine may have neuroprotective and even neuroregenerative

effects. Some authors are reserved or even skeptical, others see the results obtained thus far more positively and even propose
new indications. Although many issues (such as time of administration and dose) remain to be resolved, the preponderance of evidence favors a neuroprotective action. Inconsistencies among studies probably arise from the complexity of the injury cascade initiated after brain injury. It seems likely that neither racemic nor S(+) ketamine will be clinically successful if used as sole therapy; only when used in combination with other drugs and treatments can secondary injury be effectively limited. It seems confirmed that ketamine does not increase ICP when the blood pressure is controlled and mild hypocapnia is achieved. Thus, the contraindication for ketamine use in neurosurgical patients is only a relative one, and when further preclinical and clinical studies confirm a neuroprotective effect of the compound, ketamine and, more likely, S(+) ketamine may well find a place in the neuroanesthesiology drug cart.
Finally, the analgesic properties of small-dose ketamine have been rediscovered. Current data strongly suggest that the preemptive administration of ketamine can have profound effects on postoperative analgesic requirements with minimal risk and side effects. This provides the anesthesia practitioner with another useful tool in the management of perioperative pain. Another new indication are the use of Ketamine on preventing opioid-induced acute tolerance and in major depressive disorder.

COMBINED SPINAL – EPIDURAL ANESTHESIA FOR ABDOMINAL HYSTERECTOMY

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Abdominal hysterectomy is one of the most frequently performed surgical procedures throughout the world as well as in our hospital. The choice of anaesthetic technique depends on many factors mainly on patient condition and preference of the anesthesiologist and the gynecologist.
Patients of all ages are susceptible to all types of anesthesia, however, some of the regional anesthesia ones, foremost spinal and epidural, are more suitable in certain cases because they maintain the stability of the cardiovascular system and they decrease the intraoperative bleeding. These types of anesthesia have provided less complications, but general anesthesia is the primary choice regarding abdominal hysterectomy for it allow better conditions in the course of the procedure and a swift and complete rehabilitation.

Advantages and restrictions: Spinal anesthesia is performed with a special needle which is inserted through the dura mater in the spinal space that is filled with fluid. The impulses for pain are interrupted in both directions (towards the brain and from the central nerve system towards the periphery) with the admission of the anesthetic. Hence, the muscles don't receive the needed commands to contract and they remain relaxed.
The disadvantage of this anesthesia is this effect of blocking the nerve fibers, especially the tonus nerve of the muscle fibres. The decrease of tonus in the blood vessels results in expansion of the peripheral vascular system and consequently a drop in blood pressure. Extreme hypotension can occur in some instances. Additionally, leakage of the fluid can result in a very unpleasant headache which can be solved in the postoperative period with compensation of liquids and analgesics.
The anesthetic in epidural anesthesia is applied in the peridural space which means that there is no direct contact with the sensitive spinal space as in spinal anesthesia and consequently no possibility of infections and complications e.g. meningitis. The possibility of nerve damage is also minimal. Epidural anesthesia boasts fewer instances of recorded hypotension, as well as extremely rare headaches. The technique is slightly more complex and subtler.
Central blocks are used in abdominal surgery, like abdominal hysterectomy for following reasons:
1. Decreases stress response to surgery
2. Decreases cardiac complications
3. Decreases respiratory complications (such as atelectasis, pneumonia) since respiration is protected
4. Increases motility due to sympathetic inhibition of intestines affected by many negative factors with abdominal surgery.
5. Increase splanic blood flow due to sympathetic inhibition and therefore preventing anatomic leakages,
6. Reduce blood loss
7. Minimizes insulin resistance and limits protein catabolism.

8. Decrease thromboembolic risk.
9. Increases the oxygenation of surgical wound and therefore decreases wound infection and enhances healing.
10. Increase surgical exposure by deep muscle relaxation and intestinal contraction.
11. Prevent postoperative pain effectively with minimal side effects.

By all these effects, use of central blocks decreases the length of hospitalisation in patients who underwent abdominal surgery, like abdominal hysterectomy. However, complications including higher blockage, systemic and local toxicity, infection, headache and back pain and contraindication limits the use of spinal and epidural anesthesia.

Abdominal hysterectomy is usually performed in general anesthesia but general anesthesia in high risk surgical patients with significant pulmonary disease can trigger many adverse effects. Among the various regional anesthesia techniques that can be used for total abdominal hysterectomy combined spinal epidural anesthesia has gained popularity over the years and has become a popular technique for various gynecological operations. Various advantages of CSE technique include fast and reliable segmental anesthesia with minimal risk for toxicity followed by excellent analgesia in the postoperative period. (4) A review of 141 prospective randomized trials (1) showed that regional anesthesia compared with general has an advantage of decreased incidence of deep vein thrombosis, renal failure and reduced postoperative risk of pulmonary, cardiovascular complications as well as decreased mortality. Retaining the conscious state and spontaneous breathing is also very important part of regional anesthesia.

All patients with chronic obstructive pulmonary disease (COPD) are with increased risk for intra and postoperative complications during abdominal surgery. Arozullah et al. (3) published the largest study investigating the risk index for postoperative respiratory failure and pneumonia in non thoracic surgery. COPD was found to be a major predictor for postoperative complications. The definition of severe COPD (from the National Surgical Quality Improvement Program-NSQIP) is chronic obstructive pulmonary disease resulting in any one or more of the following: functional disability from COPD (e.g., dyspnea, inability to perform activities of daily living), hospitalization in the past for treatment of COPD, chronic bronchodilator therapy requirement with oral or inhaled agents or a forced expiratory volume in 1 second (FEV1) of <75% of predicted on pulmonary function testing. (2) Compared with general anesthesia, the use of regional anesthesia in patients with severe COPD is associated with a lower incidence of postoperative pulmonary complications. One recent study from 2015 (5) that included more than 5000 surgical patients with COPD, half of them receiving general, other half regional anesthesia showed us that in a COPD patient regional anesthesia alone is associated with lower incidences of composite morbidity, pneumonia, prolonged ventilator dependence and unplanned postoperative intubation. This association is most notable in patients receiving spinal anesthesia. In this study all these advantages did not extend to mortality, which was similar between groups. A meta-analysis of older studies (1) that compared 9559 patients found a one-third reduction in mortality with regional anesthesia, but the study was not limited to COPD patients.

Conclusion: Constant advances in anesthesiology techniques especially the combined spinal-epidural technique led to much safer anesthesia and extension of operative indications. Combined spinal epidural anesthesia provides good hemodynamic stability, big patient satisfaction, less composite morbidity shown by fewer pulmonary complications in patients with COPD. Encouraging this anesthesia technique might increase the safety margin of surgery in patients with severe pulmonary diseases.

Using regional anesthesia with spontaneous breathing should be offered to high risk patients whenever it is possible. Use of regional anesthesia during abdominal surgery is associated with shorter hospitalization, decreased risk of complication, decreased used of analgesics, lower cost and increased patient comfort and satisfaction.

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TOTAL INTRAVENOUS ANAESTHESIA (TIVA) AND TARGET CONTROLLED INFUSIONS (TCI) IN RESOURCE POOR LOCATIONS: QUO VADIS?

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Background: TIVA-TCI in clinical practice in resource poor locations has been erratic despite the known advantages. Total intravenous anaesthesia (TIVA) is a technique of anaesthesia which has become widely popular in the developed world with the availability of computerized infusion devices and appropriate drugs making its use easy and safe for the practitioner, and acceptable, tolerable and cost-effective for the patient. Such infusion devices and new drugs are not readily available in the developing world, although infusion devices may be obtained through medical equipment companies now established all over Africa. Numerous studies have shown that TIVA is followed by a significant reduction in the incidence of PONV in day-case surgery, including laparoscopic cholecystectomy, where the incidence of PONV can reach 70% according to some studies. TCI is the TIVA technique that maintains a constant plasma concentration due to pharmacokinetic models incorporated in TCI device that inject the anesthetic agent. TIVA could lead to a faster recovery of cerebral function, which may lead to a better behavior and advantages in the postoperative management.

Aim and objectives: To bring to the fore the neglected aspects of TIVA and TCI in Resource Poor Locations in basic anaesthesia management. To analyze the need for anaesthesia care system with adequate provision of options for TIVA and TCI in Resource Poor Locations and to attempt to chart a course and make predictions for the future projections for the practice of TIVA and TCI in Resource Poor Locations. This paper aims to discuss TIVA giving insights into its practice in a developing economy without the use of sophisticated equipment and drugs, in order to encourage practitioners to use the technique.

Materials and methods: Review of several literature from various online sources and databases to critically evaluate the practice of TIVA and TCI at various levels of health care in Nigeria, Africa and similar low resource settings.

Results: In developing countries only a limited range of drugs and equipment are available for the safe conduct of anaesthesia. The advent of new infusion pumps with pharmacokinetic models of remifentanil, sufentanil and propofol opens a new chapter in TIVA and aligns the low resource settings with the world tendency in TCI. However, the most important conclusion refers to the economy, since most developing countries are not able to afford such expensive equipment because of low budgetary allocation to healthcare. An alternative method of TIVA administration is the age-old gravimetric method of continuous intravenous infusion whereby the IV anaesthetic is pre-mixed in the infusion container with a suitable crystalloid IV fluid and allowed to flow under gravity. A study by Amadasun and colleagues was designed to assess the effectiveness of TIVA using the gravimetric method of propofol infusion, with intermittent subhypnotic IV ketamine injections as analgesic adjunct. This technique and other modifications of manual TIVA is more commonly practiced in low resource settings. Use of TCI is limited to large urban tertiary hospitals in most cases. The current role of TIVA in both children and adults is limited because of hardware limitations, and pharmacokinetic and monitoring issues. Nonetheless, the role of TIVA has been increasing in the past decade, in part because of surgical and medical indications. If TIVA is to become more widely used, it must be easy and simple to set up, without serious drawbacks and without added risks.
If TIVA/TCI are to become household anesthetic delivery systems, we require pumps that are simple to use, small, stackable, and durable. They should be portable with both alternating current and battery power sources

to transport children within and between hospitals. Battery life must be several hours in duration. The pumps should be compatible with all sizes of syringes, easy to load, and include a self check system.
Weninger B and colleagues conducted a study titled 'Comparison between TCI-TIVA, manual TIVA and balanced anaesthesia for stereotactic biopsy of the brain.' The aim of this prospective, single-blind study was to compare the hemodynamics, the postoperative recovery period, the side-effects and the need for additional cardiovascular medication during and after the operation between the three study groups.
Each of the three techniques compared in the study was found to be suitable for anaesthesia in diagnostic neurosurgery. Since fast recovery of vigilance is important to justify the neurological outcome, none of the methods seemed to be superior to the others. The hemodynamics were largely stable with a strong trend towards minor necessity for hemodynamic intervention in the TCI-TIVA group. This is also the best method from the subjective point of view of the anaesthesiologist due to the easy handling and the low number of interventions. They concluded that use of newer TCI-systems (e. g. fm-controller, Braun, Melsungen) not operating with special application syringes will cheapen TCI-TIVA.
We have developed manual way of administering TIVA in low resource settings where the syringe pumps and infusion pumps are not available using Propofol and or ketamine. The options include:
a) Intermittent bolus injections: For short procedures e.g. evacuations and other minor gynaecological procedures.
b) Bolus + Continuous infusion: For induction- Bolus dose of propofol 2mg kg-1 after premedication with atropine 0.6 mg in a fit adult. Maintenance- Continuous infusion of 1 part 1% propofol to 4 parts 5% dextrose to a total dose of 2mg ml-1.

Conclusions: Total intravenous anesthesia (TIVA) offers some important advantages over inhalation anesthetics, including rapid recovery with minimal hangover and a low incidence of nausea and vomiting. TIVA may be the technique of choice for some operations. Safe and effective anaesthesia can be administered with propofol-based TIVA using the manual gravimetric methods of drug delivery. The absence of a computerized syringe infusion pump should not be an impediment to providing TIVA services. Manual TIVA is a cost effective and safe method of administering anaesthesia and is very use in countries where resources limited. Genuine efforts should be made by all concerned to get more TIVA and TCI equipment and build capacity in poor countries where resources are limited so that we can all achieve the ideals of safe surgery and anaesthesia with universal health coverage. We recommend the use of newer TCI Systems not operating with special application syringes to make TCI-TIVA cheaper and more affordable in low resource settings. In the absence of these equipment, improvised manual TIVA or gravimetric methods remain the mainstay for the conduct of TIVA in resource-limited settings.

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TOTAL INTRAVENOUS ANESTHESIA AT HIGH ALTITUDE

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Aims:
1. To acknowledge anesthetic problems peculiar to high altitude.

2. Discussing selective anaesthetic agents for total intravenous anaesthesia and anesthesia delivery systems for total intravenous anesthesia at high altitude.
3. Total intravenous anesthesia at high altitude with respect to end points like anesthetic agents' requirements, the haemodynamic responses to surgical stress and recovery after anaesthesia.

Peter Safar in 1956 shared his initial observations on 'Anesthesia at high altitude' when he had the opportunity of giving anesthesia to patients at an altitude of 12,200 feet in the Peruvian Andes.1 However, the high altitude anaesthesia literature is relatively scarce.

Summary of anesthesia related problems at high altitude in general:

1. Physiological adaptive changes (altered cardio-respiratory reserve) in the individual at high altitude need to be dealt with while conducting anesthesia at high altitude.
2. Instrument malfunction: Standard flow-meters read lower than actual flow and most capnographs have been designed for use at low altitudes, not for high altitude.
3. Physical behaviour of anesthetic gases at high altitude e.g., inhalational anesthetics show relatively less potency because of decreased partial pressure in the atmosphere and low boiling point of volatile agents. Vaporisers output may alter due to low barometric pressure though the partial pressure of anaesthetic agents delivered may not change much but the out put measured as concentration may increase.
4. Sedation agents (e.g., long-acting and short acting benzodiazepines, ketamine) impair respiration at high altitude at doses which have no effect on respiration at low altitude. Reason- The catalytic activity and expression of certain isoenzymes of cytochrome P450 at high altitude are modified, leading to changes in relative drug metabolism and pharmacokinetics.

Use of total intravenous anesthesia at high altitude: Of various agents used in TIVA, use of selective drugs like ketamine, propofol, fentanyl etc have been reported in literature. Contrary to the common belief the recovery from different anaesthetic agents including narcotics is fairly rapid after short to medium duration of anaesthesia of 1-3 hours.

Propofol: In a study published in 2008 (Dr. Puri and colleagues)2 regarding anaesthetic requirements of propofol at high altitude anesthesia when compared with anaesthesia at low altitude, it was observed that the high-altitude group required a considerably larger propofol dose to achieve the target BIS of 50 (2.31 ± 0.64 vs. 1.41 ± 0.24 mg/kg, $P < 0.0001$) and significantly larger amounts of propofol infusion (6.22 ± 1.14 vs. 4.61 ± 1.29 mg/kg/h, $P<0.01$) during the maintenance phase of anaesthesia to keep BIS 50 ± 10. Possible explanations by authors- Firstly, higher propofol requirements may be a result of the higher cardiac output in the Leh (high altitude place in India, 3505 metres above sea level) group as increased cardiac output has been shown to be one of the compensatory mechanisms at high altitude to compensate for the decreased oxygen content of the blood due to low oxygen tension. Increased cardiac output has been shown to increase propofol requirement. However, there are conflicting reports about this compensatory response. Secondly, Regional blood-flow alterations with respect to cerebral blood flow have also been reported, which might affect the delivery of intravenous anaesthetics to the brain. Third, possible pharmacogenetic differences in propofol metabolism or susceptibility to drug effect can be contributory to the higher requirement in the ethnic population at high altitude.

Fentanyl: The safe use of fentanyl, a short acting meperidine congener has been documented for short duration surgeries.2 Its safety characteristics for longer surgeries needs to be studied; as fentanyl pharmacokinetics over extended durations tend to become non-linear.

Ketamine: More accounts of ketamine as the sole agent have its focus on the prevalence of hypoxaemia during this anaesthesia; the authors primarily document its safety in the absence of qualified personnel or appropriate equipment. Grocott and Johannson used ketamine to achieve anaesthesia in a patient with hypovolaemic shock secondary to primary postpartum haemorrhage requiring an emergency procedure at 4243 m above sea-level.3 The authors report that ketamine at a dose of one quarter to one half of the recommended intravenous dose resulted in sustained apnoea. Reasons- firstly, impaired function of peripheral chemoreceptors in the carotid bodies under the influence of sedating substances at altitude. Secondly, an impairment of the central chemoreceptors in the medulla seems plausible.

Total intravenous anaesthesia delivery system: Techniques: manual titration or automated drug delivery

The safety of Closed Loop Anaesthesia Delivery System (CLADS) was tested in challenging anaesthesia environments of high altitude.4 The system performance was adequate and no adverse events (intraoperative awareness) were recorded. The quick awakening time with the use of CLADS might be especially important

at high altitude, where the attendant hypoxaemia can be further aggravated by anaesthetic-induced respiratory depression. CLADS was used safely for intraoperative anesthetic management during an emergency exploratory laprotomy at Leh (unpublished data).
Hemodynamic responses to surgical stress. Most of the studies are in agreement about the relatively low heart rates at rest in highlanders. In addition, persistence of this phenomenon during anaesthesia and surgery related stress has been documented. Reason- enhanced parasympathetic neural activity and reduced sympathetic tone. Clinical implication: 1. This phenomenon reinforces the general understanding that depth of anaesthesia cannot be adequately titrated on the basis of haemodynamics alone. 2. Vigilance is warranted while using propofol + fentanyl in the background of relative hypoxia.
Recovery from total intravenous anesthesia at high altitude:
Short recovery time and achieving baseline room air saturation levels within a reasonable time after surgery in highlanders has been noted especially with short duration anesthesia. This is probably due to the short context sensitive half time of propofol for the durations of anaesthesia and the use of fentanyl, a short acting opioid.
Advantages of total intravenous anesthesia at high altitude
1. Decreased incidence of postoperative nausea and vomiting with TIVA is of importance at high altitude.5
2. TIVA is not a respiratory tract irritant and does not contaminate the air in the operating room.

Conclusion: Knowledge of the effects of total intravenous anesthesia at very high altitude is till now guided by clinical experience gained from isolated cases and few studies. Patient population like newcomers to high altitude, patients with history of cardiovascular and / or pulmonary diseases etc. needs to be studied for high altitude anesthesia. TIVA offers advantage like shorter recovery times and less postoperative nausea and vomiting.

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SEDATION IN EMERGENCY

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Diagnostic and therapeutics procedures are often required a sedation in the Emergency Medicine.
The procedurale sedation in emergency medicine has many dangers due to high-risk patients and different patient groups (children, adults), time pressure and limited personnel and structural circumstances. In preclinical emergency medicine, sedation techniques are restricted to a few medications, especially in rescue services that do not have an emergency physician, and the guidelines are based on regional circumstances.
Clinical procedural sedation, on the other hand, can be based on several techniques, and International Guidelines by several specialist societies describe the structural, personnel and material prerequisites for conducting sedation in a hospital setting for emergency physicians.

In order for the techniques to be uniform and structured, to be known to all, to take account of patient safety and enable an evalution a medical and nursing staff training is necessary. The training must be standardized and ensure constant training.
At the emergency department of the University Hospital of Berne, a training concept for sedation was developed, which was interprofessional and interdisciplinary. Doctors and nurses had to develop the theoretical content in self-study, carried out an airway skill training and simulation based team training in the simulation center. To evaluate the learning curves, all participants had to complete self-evaluation questionnaires before and after each training.
We could see that by the structured education, learning was independent of the previous knowledge. No differences could also be found in the outcome of the patients before the introduction of the training concept

ADJUVANT THERAPIES IN SEPSIS MANAGEMENT

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Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Sepsis is a syndrome shaped by pathogen factors and host factors with characteristics that evolve over time. In India, 28 day mortality in sepsis has been reported at 65%, which is higher than reported in western literature (35% to 40%). Pathophysiology of sepsis is characterized by microvascular dysfunction leading to hypoperfusion/hypoxia which in turn causes organ dysfunction. Cytokine storm induced by inflammation due to bacterial infection plays important role in pathophysiology of sepsis induced ischemic organ injury. Despite advanced treatment strategies in sepsis management, mortality remains high. Adjuvant therapies which targets immunological response induced by inflammatory process in sepsis address the gaps existing in current sepsis management strategies. Ulinastatin is serine protease inhibitor exists naturally in human body. During stress antecedent (IαTI) is influenced by activated neutrophil elastase, changing in to Ulinastatin. Ulinastatin was first innovated by Japanese company Mochida and currently available in 5 countries including India. Ulinastatin is Endogenous Cytokine Inhibitor which has effect on various proteases. Ulinastatin reduces proinflammatory cytokines like TNF-α and Interleukin-6 and increases anti-inflammatory cytokines like Interleukin-10. It Suppresses the activity of neutrophil Elastase and prevents progression to MOD's in Sepsis and also reduces New onset organ-dysfunction. Ulinastatin reduces overall mortality in sepsis. Multicentre Randomized Controlled Trial in severe sepsis conducted in India showed 13% absolute reduction (significant) in 28 days all-cause mortality and 26% absolute reduction(significant) in new onset organ dysfunction. Similar results obtained in clinical studies conducted by Javeri et al, Mehta etal and Bashir et al. Choudhary et al showed that early Ulinastatin therapy has even better results in sepsis patients.

POST-DURAL PUNCTURE HEADACHE IN AN OBSTETRIC PATIENT: AN OLD PROBLEM – NEW SOLUTIONS IN OUR CONFERENCE

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Objective: Review the newest literature on the prevention and treatment of post-partum headache in pregnant women.

Introduction: Epidural analgesia is widely considered as the most effective method of providing pain relief during labor, and the number of women receiving epidural analgesia for labor and delivery is increasing worldwide. Post-dural puncture headache (PDPH) also known as spinal (or post-spinal) headache still remains a disabling complication of needle insertion into the subarachnoid space. Pregnant women are at particular

risk of dural puncture, and the subsequent headache, because of sex, young age, and the widespread application of regional anesthesia.

History: One of the mile stones in the development of spinal anesthesia (and first descriptions of its complications) was the work of the German surgeon Augustus Bier. Using himself as subject, more than 100 year ago, Bier demonstrated spinal anesthesia (with subarachnoid injection of local anesthetic - cocaine) one day, and spinal headache widely known today as post-dural puncture headache (PDPH) the following morning.

Pathophysiology: Bier is credited with the first description of the pathophysiology (leakage of CSF) of PDPH, and today there is no doubt that loss of CSF initiates the syndrome.
Although the loss of CSF and subsequent decrease of the CSF pressure is not disputed, the actual mechanism producing the PDPH remains unclear. The widely accepted theory explaining the pathophysiology of PDPH is based on the assumption of persistent leakage of CSF through the hole made by the spinal or epidural needle and decrease in CSF volume or pressure, or both, which leads to shifts of intracranial contents and traction on pain sensitive structures. Loss of CSF leads to intracranial hypotension and a demonstrable reduction in CSF volume and pressure.

Incidence: Post-dural puncture headache is an iatrogenic complication of neuraxial blocks for labor analgesia. There is considerable variability in the incidence of PDPH, which is affected by several factors including age, gender, pregnancy, and needle type (design) and size (Table 1).
Unintentional dural puncture complicating epidural anesthesias vary in incidence from 0.19-4.4%. The incidence of epidural needle-induced PDPH in parturients has been reported to range 76-85%. It has been suggested that the incidence of unintentional dural puncture during epidural anesthesia is inversely related to operator experience.

Symptoms: Postpartum headache in a parturient almost always raises concerns about accidental dural puncture during administration of labor analgesia. Post-dural puncture headache is a well-known complication of procedures in which the dura mater of the spinal cord is punctured. The classic symptoms of PDPH consist of photophobia, nausea, vomiting, neck stiffness, tinnitus, diplopia and dizziness in addition to the often, severe cephalgia (Table 2). The differential diagnosis of PDPH is often clear from the history of dural puncture and the presence of a severe postural headache. However, it is important to consider alternative causes of headache (Table 3).

Prevention: In 2003 Kuczkowski and Benumof reported that following accidental dural puncture with an 18-gauge epidural needle in pregnant women, sequential (Table 4) (1) injection of the CSF in the glass syringe back into the subarachnoid space through the epidural needle, (2) insertion of a epidural catheter into the subarachnoid space, (3) injection of small amount of preservative free saline (3-5 ml) into the subarachnoid space through the subarachnoid catheter, (4) administration of bolus and then continuous intrathecal labor analgesia, and (5) leaving the catheter in-situ in the subarachnoid space for a total of 12-20 hours decreased the incidence of PDPH from 76-85% to 14 % .
Since their original report the authors encountered (2004-2005) eight more pregnant women in whom the performance of epidural analgesia was complicated by an accidental dural puncture with an 18-gauge epidural needle. In all eight additional cases, the accidental dural puncture was followed by the same five maneuvers and no PDPH was reported in any of these patients. These additional eight cases combined with the original seven patients (N=15) suggest that following an accidental dural puncture with an 18-gauge epidural needle in parturients, sequential performance of these five maneuvers decreased the incidence of PDPH from 76-85% to 6.6 % (PDPH occurred only in one out of our total number of fifteen pregnant patients). All of these five components were aimed at maintaining CSF volume.

Treatment: Theophylline, caffeine, sumatriptan, epidural saline, epidural dextran, and epidural blood patch (EBP) include some of the current treatment modalities for PDPH (Table 5). However, only the EBP seems to have apparent benefits.

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