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Q. Piacevoli, C. Minto, T. Schnider

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Foreword

Honorary guests, **Chairman of Executive Committee** of the WFSA, President of the Singapore Society of Anaesthesia and Intensive Care, and esteemed Colleagues,

I thank you for warm welcome that I have received, in this beautiful city, Singapore. And I am delighted and honoured to speak to you today as PRESIDENT of the World Scientific Society of Intravenous Anaesthesia. The Society was founded in Venice in the year 2007, it is a non- profit organisation, and since that time there has been an overwhelming response and interest. It has indeed flourished, and I am delighted to say that today World SIVA represents by 64 countries, of which there are 700.

Let me share with you a brief history of the Society. I am excited to tell you that as PRESIDENT OF World SIVA, our membership has now reached over 3,00 members and our Web Site , only in the beginning of this year, has more than 16.000 visits. This is the result of the tireless efforts of a scientific society capable of moving the future of anaesthesia towards the techniques of intravenous anaesthesia.

World SIVA has played an important role in the implementation of patient safety. For example, by offering postgraduate training at the simulation training centre in Rome, where clinical concepts can be put into practice. Also, by offering the opportunity to attend global conferences and workshops, in countries such as Romania, Albania, Greece, Kosovo, etc. SIVA has played an important role in developments in anaesthesiology. For example, TIVA –TCI represents 50% of the all anaesthesiology interventions in Europe.

The World SIVA Scientific Society it is now NOT ONLY a not-for-profit charitable association, with a democratic and transparent governance manifesto, and where all members have equal status and dignity,but also, an Association declared a PUBLIC UTILITY. This is a remarkable achievement and one of the few of its kind in the World. This STATUS, PUBLIC UTILITY, ensures that our funds and governance cannot be challenged nor squandered.

The democratic and transparent governance is guaranteed during these four years by the respect of the bylaw, and by the power of attorney given to the General Assembly.

This particularly status means also that the financial responsibility of the Society is only of the President and not also of the Members of the Board. So all the expenses and the incoming are assessed annually, by an independent Board of International Accounts.

The financial statements of the Society are public.

The World Siva Scientific Society is listed by the Organization of United Nations and we are very close to obtaining official recognition.

This Scientific Society embraces the aims and objectives of the WORLD FEDERATION OF SOCITIES OF ANESTHESIA and recognises it's role within the Federation and with this view in mind, we have avoided to choose venues that could have the possibility to clash with the next Congress of WFSA that will be held in Argentina in 2012.

We are acutely aware of other prestigious scientific organisations dedicated to this field, however, with different characteristics from those that we have championed. The major defining characteristic of our society, WORLD SIVA, is that of it's important role on a global scale. 64 COUNTRIES AND THEIR DELEGATES ARE PROOF OF THAT. We maintain that this is guaranteed linking a scientific movement with its aims and objectives. This is needed in order to spread the culture, the innovation, and the patient safety measures in this field of anaesthesia around the world.

The use of intravenous drugs in the field of anaesthesia is widespread. We use them in the Intensive care unit, we use them for sedation, we use them for pain relief, and, we use them for hypnosis sedation, and so forth. As a result the introduction of new drugs has increased the practice of intravenous anaesthesia. Therefore, it is essential for greater knowledge and understanding of pharmaco-kinetics and pharmaco-dynamic reactions, between intravenous drugs and gas vapours.

The introduction of new infusion pumps which use complex pharmaco-kinetic algorithms for the delivery of opioids, hypnotics or muscular relaxants, have on the one hand, increased the safety for patient administration, but on the other hand, require better knowledge of human factors to operate them safely.

There isa controversy about TCI and the PK, PD models that should be used with these systems. The only way to address these issues is with evidence driven decision making. This can only come about by bringing together investigators from around the world to create a common, transparent and agreed upon consensus of definitions and datasets. The will lead to a greaterunderstanding, and highlight the strengths and weaknesses of existing models.There is a potential for creating unifying models that will become the template for future TCI devices. These results are freely available to ALL companies interested in developing TCI technology as well as the regulatory agencies. Today, I am delighted to kick off the Open TCI Project with the first results that will be discussed by Dr. Minto in his workshop. This project supports and reinforces the bylaws of World Siva. This is a major achievement.

Finally, I would like to thank Dr. Dan Shultz .Dan, Past Director of the FDA has been very supportive for the last 4 years in helping us advance our request to get TCI approved by the FDA.

Professor Thomas Schnider and I, met with Dan, and Michael Husband, FDA Anaesthesiology Commission Chair, for 3 hours in Washington in August 2008, to address all remaining scientific questions about the approval of TCIby the FDA.

The meeting was very fruitful,Dr Schultz clearly defined thenecessary steps to be takenfor the approval of TCI in the United States.

In short, the message conveyed was that ALL clinical issues remaining have been clearly ADDRESSED, and the next step is to convey the message to industry that the FDA awaits the presentation of their devices for registration.

I would like to mention another important project that is:

'The International Sedation Task Force '.Under this umbrella chaired by Dr. Keira Mason and Dr. Green, sedation experts, for both adults and pediatrics. Specialties represented will include: Dental, Hospital, Emergency, Pediatrics, Gastroenterology, and Intensive Care Medicine, as well as Anesthesiology / Anesthesia / Anaesthesia. Specialists from around the world with research and clinical expertise in sedation practice from all the major disciplines, continents and specialties will be represented. Currently, sedation worldwide is being practiced by providers representing a variety of specialties. Each specialty has various drugs, guidelines and recommendations. There is neither agreement nor consensus amongst the specialties worldwide with respect to sedation practice: including patient screening, documentation, monitoring, recovery, training and choice of sedation agents and routes of administration. Most importantly, the definition and identification of adverse events differs between specialties, individuals, institutions and countries. This lack of consensus and agreement makes it challenging to follow sedation practices, for both adults and children, amongst the specialties and around the globe.

This project is also in collaboration with the FDA ,the aim of which is not only togive new guide lines , but also to collect information via the web, here colleagues are able to advise anonymously, on the adverse events that can occur in this field. This technique as WHO states, is the cornerstone to increase safety in any kind procedures.

A vast amount of work has been done from the Pediatric Initiative, chaired by Dr Keira Mason,in order to further the world-wide interest in advancing the research and clinical interest in the application of intravenous anesthesia and sedation to children.

To create a committee represented by a diverse group of international members with a wide breadth of expertise.

To provide a forum for the exchange of ideas and international collaboration of clinical research efforts involving Pediatric TIVA.

To support the goal to increase world interest in Pediatric TIVA, the committee will develop and foster research collaboration, with the aim of producing publications which will represent important contributions to the literature.

To improve the delivery of pediatric sedation by fostering research interests and collaborations involving the pharmacokinetics and pharmacodynamics of specific sedatives in children.

FINALLY, ALL THIS WOULD BE POSSIBLE WITHOUT THE SUPPORT OF ALL OF YOU, COLLEAGUES FROM SO MANY DIFFERENT COUNTRIES, BUT WITH THE SAME PASSION AND LOVE:ANAESTHESIA.

THANK YOU!

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How To Assess Sedation And Analgesia During Regional Anaesthesia

Bosco M.°, Clemente A.*, Monteleone G.°, Polletta A.^, Volturo P.§, Proietti R.°

° *Department of Anesthesiology and Intensive Care, "Columbus" hospital, Catholic University of Sacred Heart, Rome, Italy*
* *Department of Anesthesiology and Intensive Care, IRCCS – I.D.I "Istituto Dermopatico dell'Immacolata", Rome*
^ *Department of Anesthesiology, "San Filippo Neri" hospital, Rome, Italy*
§ *Department of Anesthesiology, "M.G. Vannini" hospital, Rome, Italy*

Summary

Providing sedation and analgesia during regional anesthesia increases patient's satisfaction. A suitable system for assessing sedative level is mandatory. Methods of evaluating the degree of sedation are collected in 3 categories: patient-, observer and machine-based evaluation. Patient's based evaluations are easy and quick to administer but counterbalanced by significant limits. Observer-based scales were designed to standardize assessment. Measurements by electronic devices are perceived as the most objective assessments. The bispectral analysis derivative of EEG (Bispectral Index Scale) was the first approved. The Auditory Evoked response Potentials (AEP) derived from the EEG response to a predefined auditory stimulus. Regardless the new advancement in technology, the use of clinical endpoints remains essential.

Introduction

The increasing use of regional anesthesia for a variety of surgical procedures find its reasons in several benefits it provides either to anesthesiologists and patients. A rapid postoperative recovery, more steady cardiovascular and respiratory stability and a better preservation of protective airways reflexes are the most important advantages for the anesthesiologist's point of view, while patients appreciate the early family contact, early food intake, the possibility to stay awake (1). Providing some form of sedation during regional anesthesia increases patient's acceptance and satisfaction during these procedures (2). 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. In order to grant a safe and

effective sedation, a valid system for measuring the level of patient's consciousness is required.

Methods of evaluating sedation

We can distinguish three major categories of methods for assessing the degree of sedation: patient-based, observer-based and machine-based evaluation. There is an ongoing debate concerning the reliability of how to assess, as most of the tools used are influenced by external factors (noise, light, and so on), moreover, there is an inter-patients variability in response to sedating drugs so that it is essential to use clinical endpoints for defining the stages of sedation.

Patient-based assessment: Patients can express their perception of sedation through one of several visual analog scales ranging usually from 0 to 10 or 0 to 100. The end-points of these scales correspond to the two extremes of a sedation, such as "fully awake" to "extremely sleepy" and the patients is asked to mark a position in between representing their degree of sedation (3). Advantages of such scales are the easiness and quickness in administering them but there are significant limits such as the poor feasibility at higher degrees of sedation or the high variety between patients.

Observer-based scales: Sedation scales were designed to standardize assessment and minimize the interobserver variation in a reliable way. The disadvantages of these instruments are the repeated verbal or even tactile stimulation of the patients in administering them and the observer variance in the assessment. One of the most frequently used for study and clinical purpose is the Ramsey sedation scale (4) developed in the early 1970s, identified six categories, three with the patient awake and three with the patient asleep. The awake levels are: 1. patient anxious and agitated or restless or both; 2. patient co-operative, orientated, and tranquil; 3. patient responds to commands only. The asleep levels are dependent on the patient's response to a light glabellar tap or loud auditory stimulus: 4. a brisk response; 5. a sluggish response; and 6. no response. Although the widespread nature of its use, its validity and reliability have not been reported. Wilson et al. (5) in a study comparing the sedative effects of propofol and midazolam during spinal anesthesia for orthopedic surgery proposed a variation on the Ramsey scale for assessing intraoperative sedation. The Wilson scale is a categorical scale in which an observer rates the degree of consciousness according 5 point: 1. fully awake and orientated; 2. drowsy; 3. eyes closed but reusable to command; 4. eyes closed but reusable to mild physical stimulation (earlobe tug); 5. eyes closed but unrousable to mild physical stimulation. The interrater reliability of Wilson scale was documented to be fairly good for assessing light sedation, with exception of poor discrimination between categories 2 and 3, in fact their descriptions do not identify mutually exclusive states. So a modified Wilson sedation scale was proposed (6), combining these two categories and operationalizing with more specific criteria the descriptions of each of the four categories: 1. oriented, eyes may be closed but can respond to "Can you tell me your name?", "Can you tell me where you are right now?"; 2. drowsy, eyes may be closed, rousable only to command: "(name), please open your eyes."; 3. Rousable to mild physical stimulation (earlobe tug); 4. unrousable to mild physical stimulation. It has an inter-rater agreement of 84%, it is quick and simple to administer; by defining clear endpoints, it can be used either for determining sedation during regional anesthesia or as a reference with which to

OBSERVER'S ASSESSMENT OF ALERTNESS SCALE				
Responsiveness	Assessment Categories		Composite Score	
	Speech	*Facial Expression*	*Eyes*	*Level*
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	1 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	2
Responds only after name is called loudly and repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	-	-	4
Does not respond to mild prodding or shaking	-	-	-	5 (deep sleep)

Figure 1 Observer's Assessment of Alertness/Sedation (OAA/S)

correlate measures obtained from different monitoring devices. One of the few sedation scale whose reliability has been documented is the Observer's Assessment of Alertness/Sedation (OAA/S) (7) (Figure 1), with an inter-rater agreement that could reach 96% depending on the level of sedation. Within each of the four assessment categories, the statement which best described the condition of the patient is checked. Responsiveness is evaluated first. The composite score corresponding to the highest level at which any statement was checked was assigned. It has clearly more items than other scales and it may be the best choice if precise evaluation of sedation is required but it is not ideal for performing rapid, repeated patient's assessment.

Machine-Based Methods: Measurements by electronic devices are generally perceived as the most objective assessments, but they are meaningless numbers unless the mechanical tool has been calibrated according to a known standard to ensure both validity (accuracy) and consistency (reliability). Consciousness is blunted by sedative agents depressing the central nervous system. Electrical activity of the cerebral cortex can be measured using the electroencephalogram (EEG), it is expected that some component of the EEG should relate to adequacy of anesthesia. With the advent of the microcomputer technology, it became possible to reduce the amount of data obtained from an EEG to various processed derivatives described as potential measures of anesthetic effect on the central nervous system. The first technology ap-

proved by the U.S. Food and Drug Administration (October 1996) for marketing as an EEG-based monitor of anesthetic effect is the bispectral analysis derivative known as the Bispectral Index Scale (BIS, Aspect Medical Systems, Natick, MA) (8). BIS is a dimensionless number scaled from 100 - 0, with 100 representing an awake EEG and zero representing complete electrical silence (cortical suppression); it integrates various EEG descriptors into a single variable. The mixture of sub-parameters of EEG activity was derived empirically from a prospectively collected database of anesthetized volunteers with measures of clinically relevant sedative endpoints and hypnotic drug concentrations (8). A good correlation between BIS, OAA/S and hypnotic drug concentration for perioperative sedation, in particular with deeply sedated patients, was demonstrated in several studies (9-11). During propofol sedation the BIS was found to reflect the loss of consciousness and predict the response to simple verbal commands in healthy volunteer (12, 13), it may be effective for preventing inadvertent and unrecognized over-sedation. Studies suggest that BIS values of 65–80 define an acceptable loss in conscious information processing and recall during sedation–hypnosis. BIS indicates both the potential for awareness and of "relative" hypnotic overdose but does not predict movement or hemodynamic response to stimulation, neither can it predict the exact moment consciousness returns. The correlation of BIS with more subtle gradations of sedation (light levels) has not yet been determined, although new technology seems to better filtrate out the EMG artifacts from electrode placement over the frontalis and temporalis muscle which contaminate and falsely elevate the BIS. Moreover, the large inter-individual pharmacodynamic variability of sedative agents and the combination of drugs used for sedation, affecting or not (ketamine, nitrous oxide) BIS values, further complicate the interpretation of data. The imperfect correlation of electroencephalogram modifications to clinical scores is due to the fact that EEG is a passive measure, whereas sedation scores measure the reaction to an active stimulus. To overcome this drawback was proposed an alternative approach: the evaluation of EEG response to standardized external stimuli. Cortical function and responsiveness can be assessed using the long latency evoked potentials (EP), also referred to as event-related potentials (ERP). These potentials reflect both exogenous (appearing after detection of a sensory stimulus) and endogenous (related to cognitive processes) components of the cortical response. Auditory Evoked response Potentials (AEP) are derived from the EEG response to a predefined auditory stimulus and other EEG activity is ignored. Ge et al. (14) demonstrated that mid latency-AEP-index correlates well with sedation level and, in contrast to BIS, it is able to discriminate between all OAA/S-levels in patients sedated with propofol or midazolam. Potentially it is a helpful detector of light anaesthesia with risk of awareness and recall. Moreover, a good correlation of late-latency-AEP with sedation level has been shown in healthy volunteer during infusion of propofol or propofol and remifentanil but not remifentanil alone (15). Limitations associated with AEP include technical problems related to amplification, filtration and sampling in the clinical environment and the delay of the monitor processing time. In fact AEP, as well as BIS, monitors require several seconds in order to produce a value. This, to some extent, could display activity level with up to a minute's delay (16). Until guidelines for its clinical use can be established, AEP as a measure of sedation levels is not ready for routine clinical practice.

Conclusions

The increased use of regional anaesthesia 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. There are three categories of methods for assessing sedation: patients –, observer –; machine –based. Regardless the new advancement in technology, the use of clinical endpoints remains essential.

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Innovation in Sedation in Asia - New aspects of intravenous sedation: Effects on subjective feelings and muscle power

Ichinohe T, DDS, PhD

Professor and Chairman
Department of Dental Anesthesiology, Tokyo Dental College, Chiba, Japan

Summary

This study compared the effects of midazolam (M), propofol (P) and dexmedetomidine (D) on subjective feelings and investigated the effects of P on muscle power. Mental arithmetic task was given as a psychological stressor. Heart rate variability and the faces anxiety scale (FAS) were used for objective and subjective stress evaluations, respectively. Grip strength and bite force were measured to evaluate muscle power. Sympathetic activation was smaller and a reduction in FAS was larger during M sedation than during P sedation. No FAS reduction was observed during D sedation. Grip strength slightly increased and bite force dose-dependently increased during P sedation.

Introduction

Intravenous sedation is widely applied for dental patients such as phobic, medically compromised or disabled patients in Japan. Anxiolysis is the main goal for phobic patients, while hemodynamic stability will be required in patients with circulatory diseases. In mentally challenged patients, control of body movement may be an important factor. This study compared the effects of midazolam (M), propofol (P) and dexmedetomidine (D) on subjective feelings[1,2] and investigated the effects of P on muscle power.[3]

Methods

After institutional approval, we obtained informed consent from each subject.

Study-1: Subjects received M and P in the first group and P and D in the second group, respectively, in a randomized crossover manner. Heart rate (HR), HR variability (HRV), arterial oxygen saturation (SpO_2) and bispectral index (BIS) were continuously

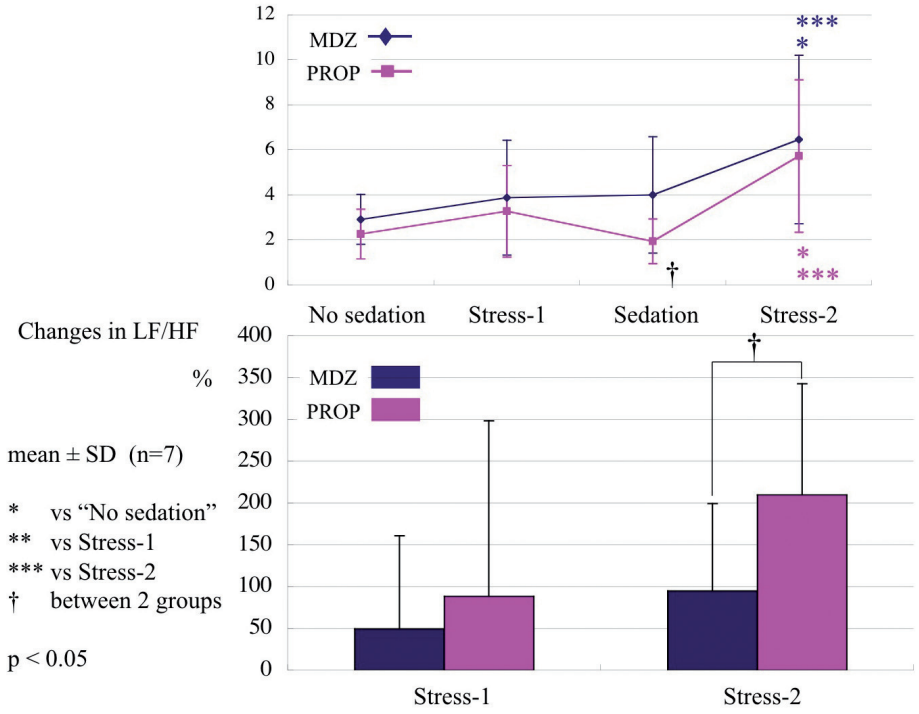


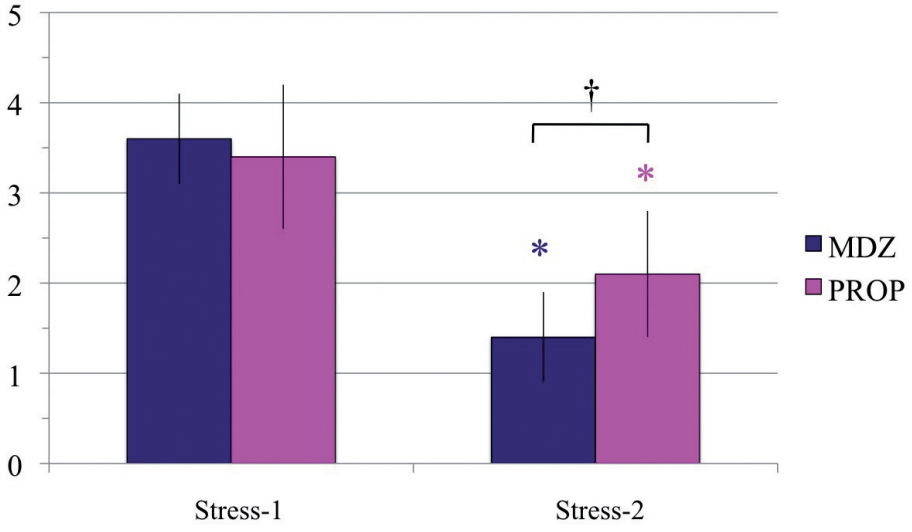
Fig. 1 Comparison between midazolam and propofol – LF/HF

monitored. Mental arithmetic (MA) task was given as a psychological stressor. BIS value of 75–85 was the targeted sedation level. HRV was assessed by power spectral analysis (low-frequency (LF) and high-frequency (HF) components and LF/HF ratio). The faces anxiety scale (FAS) was used to grade stress feelings.

Study-2: Each subject underwent two experiments in a randomized crossover manner (P group and Control group). After control data was obtained, P at predicted effect site concentrations (Ces) of 0.4, 0.8, 1.2, 1.6 and 2.0 mcg/ml was infused in the P group. HR, non-invasive blood pressure, SpO_2, respiratory rate (RR) and BIS value were monitored. Observer's assessment of alertness/sedation (OAA/S) and the correct answer rate of the stroop color word test (SCWT) were assessed. To evaluate muscle power, grip strength and bite force were measured.

Results

Study-1: In the first group, HR, LF/HF and normalized unit LF (nuLF) increased, while normalized unit HF (nuHF) decreased during MA task under M and P sedation. However, percent changes in LF/HF, nuLF and nuHF were smaller and reduction in FAS was larger during M sedation (Figs. 1,2). In the second group, similar changes in these parameters were observed during MA task under P and D sedation. FAS reduction was observed only during P sedation (Figs. 3,4).



mean ± SD (n=7); * p< 0.05 vs Stress-1; † p<0.05 between 2 groups

Fig. 2 Comparison between midazolam and propofol – FAS

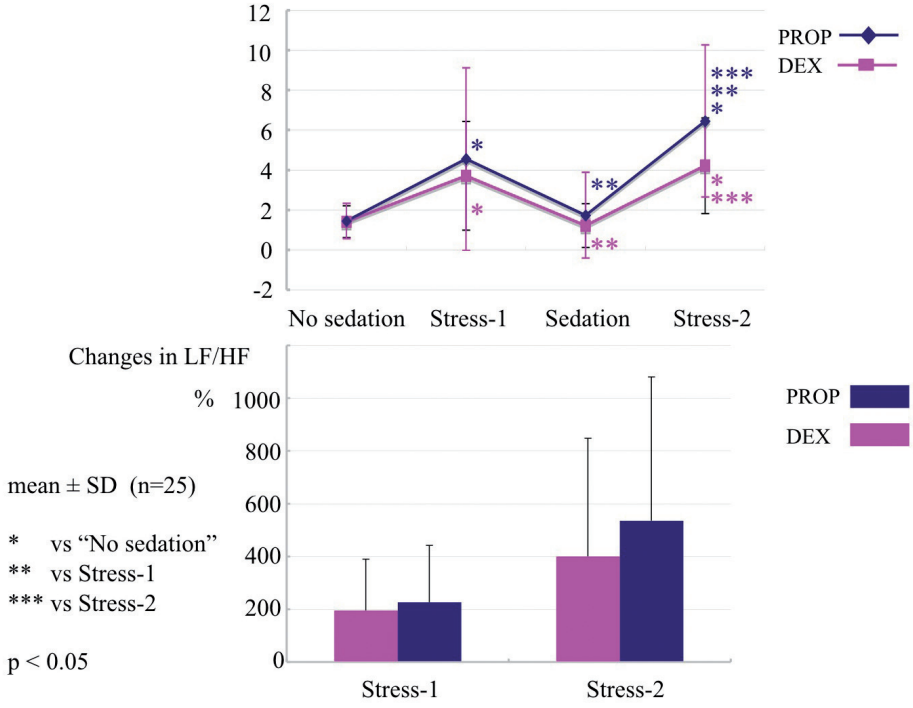
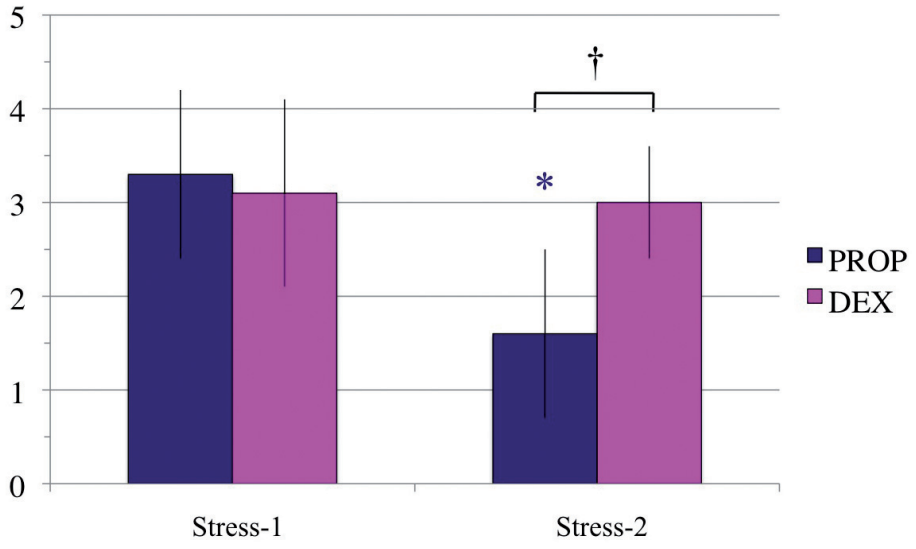


Fig. 3 Comparison between propofol and dexmedetomidine – LF/HF



mean ± SD (n=25); * p< 0.05 vs Stress-1; † p<0.05 between 2 groups

Fig. 4 Comparison between propofol and dexmedetomidine – FAS

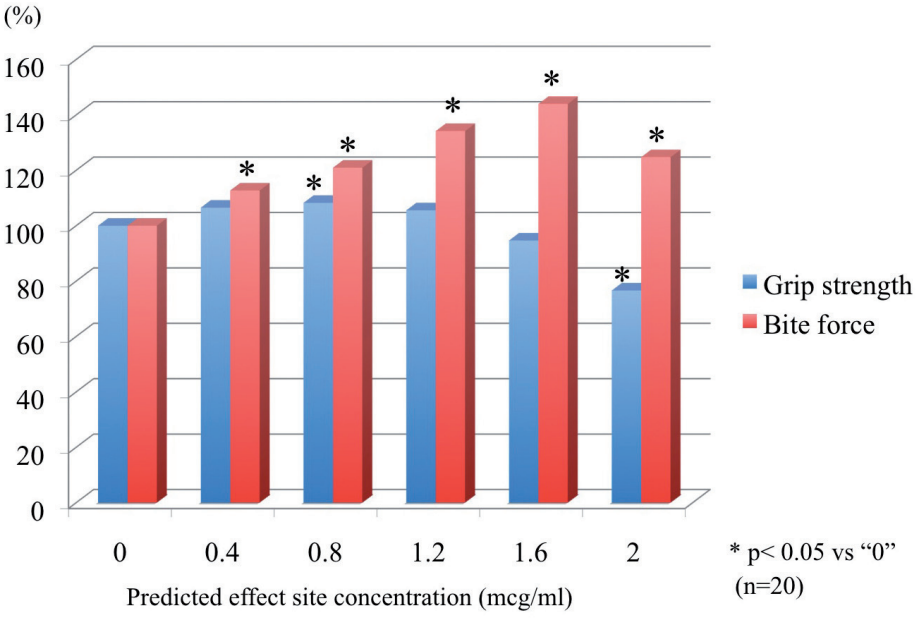


Fig. 5 Grip strength and bite force during propofol sedation

Study-2: BIS value and OAA/S scale dose-dependently reduced during P sedation. At Ces of 2.0 mcg/ml, six subjects became unconscious. Systolic and diastolic blood pressures and SpO_2 dose-dependently decreased while RR increased. The correct answer rate of SCWT reduced at Ces of 1.6 and 2.0 mcg/ml. Grip strength slightly increased at Ces of 1.2 mcg/ml or less and bite force dose-dependently increased. At Ces of 2.0 mcg/ml, both muscle powers began to decrease. When data from 14 subjects who did not become unconscious at Ces of 2.0 mcg/ml were extracted, grip strength and bite force reached the maximum at Ces of 0.8 and 1.6 mcg/ml, respectively (Fig. 5).

Conclusion

M may be most appropriate for phobic patients and P may be indicated for deep sedation or conscious sedation for less anxious patients. Indications of D should be further explored. P dose-dependently increases bite force during light and moderate sedation. When control of body movement is necessary in challenged patients, unconscious level may be required during P sedation.

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The Role of Orexinergic Neuron on Intravenous Anesthesia

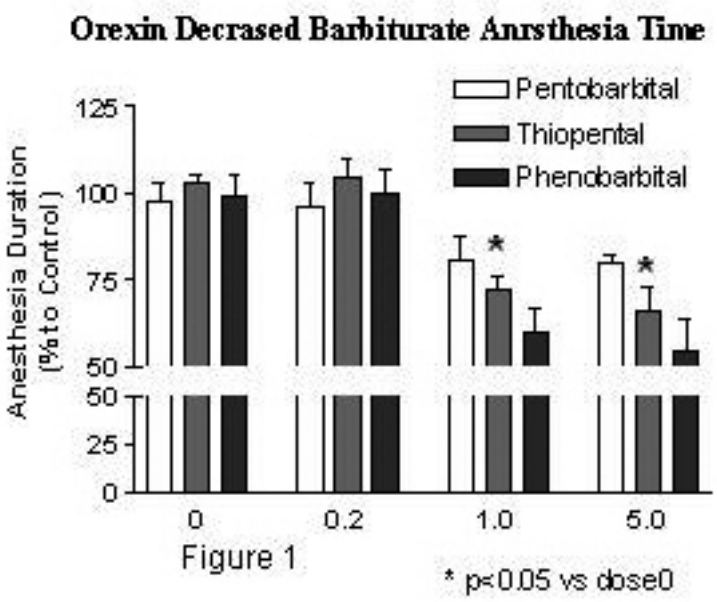
Kushikata Tetsuya 1, MD, Ph.D., Hirota Kazuyoshi 2, MD, Ph.D, FRCA

1 Assistant professor, Department of anesthesia, Hirosaki University Hospital. Hon-cho 53, Hirosaki 0368563, JAPAN
2 Professor, Department of Anesthesiology, Hirosaki Graduate School of Medicine. Zaifu 5, Hirosaki 0368562, JAPAN

Summary

Effect of orexin (OX), an endogenous wake-promoting substance, on anesthesia was studied in vivo and in vitro. In vivo, we found OX decreased barbiturates and ketamine anesthesia time in rats. OXA receptor is responsible for the OX effect. Others reported OX decreased propofol, sevoflurane, and isoflurane anesthesia time. OX did not affect any induction time of these anesthetics. In vitro, we found barbiturates, ketamine, and benzodiazepines attenuated OX-induced noradrenaline release from the rat cerebral cortex. GABAergic neuron would not be involved in this interaction. Plasma OXA and norepinephrine levels were significantly increased after emergence from total intravenous anesthesia (propofol and fentanyl) and inhaled anesthesia (sevoflurane and fentanyl) in human.

Several lines of evidences show that sleep related neuronal activity shares mechanism of general anesthesia especially loss of consciousness.[1] Endogenous sleep related substances plays crucial role in the neuronal activity thus, they could be involved in the mechanism of general anesthesia. Orexin (OX) is one of the sleep-wakefulness substances discovered at 1998.[2] Orexins are classified into two subgroups, Orexin A and B. Orexin A has stronger bioactivity than Orexin B. They are endogenous peptides that promote various bioactivity including feeding behavior, wakefulness, analgesia and sympathetic nerve activity. For example, orexinergic neuron stimulates several brain structures like Raphe nuclei, locus coeruleus, and tubular mammalian nucleus known as wake-promote centers. On the other hand, when orexinergic neuron is inhibited by ventro-lateral preoptic area known as a sleep center, animals go into sleep. It promotes wakefulness, thus lack of its receptor causes sleep disturbance such as narcolepsy in various species. OX also has analgesic and sympathomimetic effects that are components of general anesthesia. Therefore, to study role of OX in general anesthesia would be useful for research of general anesthesia. Because analgesia and sympathetic nervous activity is elements of anesthesia, many anesthesiologists may



interest in Orexin properties in these aspects, but due to space limitation, this proceeding focuses on Orexin in anesthesia time related topics in vivo and in vitro.

Nelson and colleagues reported that changes in c-fos expression during anesthesia in sleep-related brain region is similar to c-fos expression induced by musimol, a GABA agonist. Musimol is a sleep inducer thus, this result suggests anesthesia may share neural components that responsible for sleep-wakefulness.[1] Since this study, several researches were done to clarify role of sleep on the mechanism of anesthesia-induced amnesia.

Based on these findings, we studied if orexin affect anesthesia time using rats. This is our first report that intracerebroventricular (icv) injection of Orexin A (0.2, 1.0, 5.0 nmol) decreased barbiturates-induced anesthesia time. OX A significantly decreased pentobarbital, thiopental and phenobarbital anesthesia times by 15–40% (figure 1). Respiration rates are accompanied with depth of anesthesia thus, increase in respiration rate indicates orexin decreased depth of anesthesia. Indeed, this study is the world first report that showed orexin decreased anesthesia time.[3]

We tested at the same time if orexin A receptor antagonist affected on thiopental anesthesia status. SB-334867-A, an Orexin A receptor antagonist reversed orexin effect on thiopental anesthesia time and respiration rate. These results suggested that Orexin A receptor is involved in action of orexin on anesthesia at least GABA type intravenous anesthesia like thiopental.[3]

Thereafter, we tested effect of orexin on NMDA type intravenous anesthesia, ketamine. One nmol Orexin A icv reduced ketamine anesthesia time by around 75% to control. This dose of Orexin also increased respiration rate during the ketamine anesthesia. SB-334867-A also reversed orexin effect on ketamine anesthesia time and respiration rate. These results suggested that Orexin A receptor is involved in action of orexin on ketamine.[4] Moreover, Orexin decreased propofol anesthesia time. This

action was also Orexin A receptor mediated.[5] Orexin neuronal activity is responsible for isoflurane and sevoflurane anesthesia time.[6]

With these results, it is summarized that Orexin decreased various anesthesia time (duration). Orexin A receptor is involved in this action. There is no evidence that Orexin affect anesthesia induction in all anesthetics tested. These results indicate interesting fact. Mechanism of induction and emergence from anesthesia could be different. Wakeful-promoting substance like Orexin also promotes emergence from anesthesia but not anesthesia induction.

In vitro, we found OX affect sleep-related neurotransmitter kinetics. OX selectively increased noradrenaline release from the rat cerebral cortex.[7] The three kinds of babiturate[3], ketamine[4], and benzodiazepines[8] (midazolam, diazepam, and flunitrazepam) attenuated the OX-induced noradrenaline release from the rat cerebral cortex. Either GABAergic agonist, muscimiol, nor GABAergic antagonist, bicuculline had no effect on this OX-noradrenaline interaction. These results suggest that there could be some pathway responsible for mechanism of anesthesia that is independent GABAergic neuron.[3]

In addition, we have determined whether general anaesthesia would affect plasma orexin A (OXA) and norepinephrine concentrations in human with total intravenous anesthesia (propofol and fentanyl) and inhaled anesthesia (sevoflurane and fentanyl). In both cases, plasma OXA and norepinephrine did not change during anaesthesia but significantly increased after emergence compared with pre-anaesthesia. Orexin level correlated to cortisol and catecholamines.[9] [10]

In conclusion, Orexin is responsible for emergence from various anesthesia. Orexin A receptor is involved in this action. Mechanism of induction is different from recovery from anesthesia. Plasma Orexin increased at the emergence from propofol-fentanyl anesthesia or propofol-fentanyl anesthesia. OX is one of the good tools for research of general anesthesia.

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Development of an informatic application for the administration of intravenous anesthesia.

Vanegas Saavedra Alberto MD

1 The TIVA can be obtained using constants infusion rates administered manually or by means of infusion pumps controlled by computer, using an algorithm that based on pharmacokinetics and pharmacodynamics models calculates the infusion rate needed to keep stable the concentration of the medicaments established by the anesthetist. This methodology is known as target controlled infusion or TCI well is in plasma or in effective site.

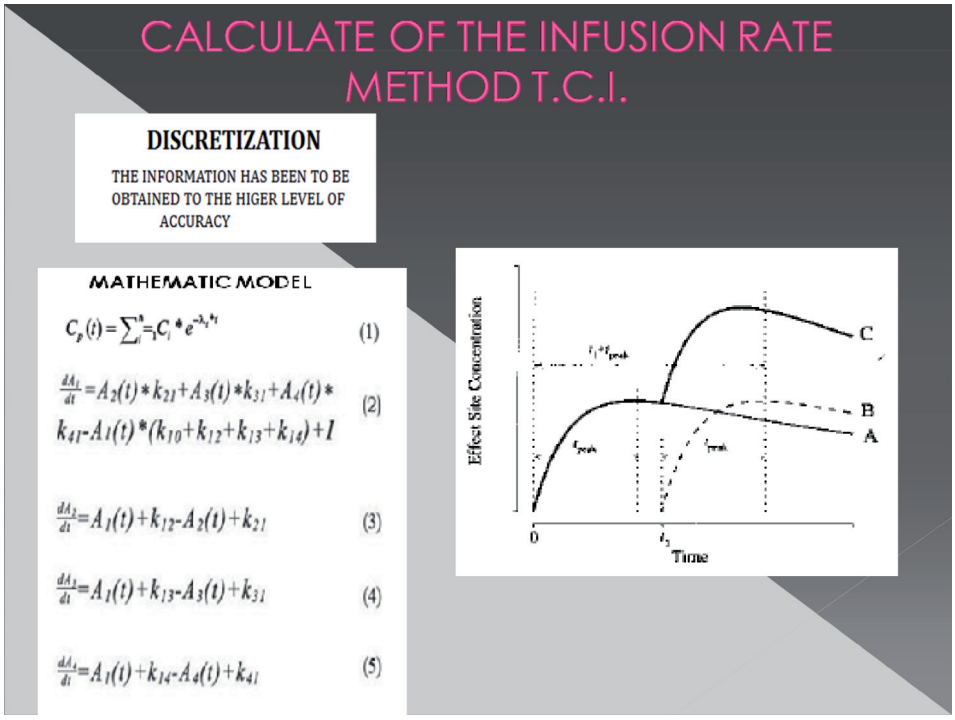
In diverse investigations in universities have come developing systems for the drugs administration assisted by computer. Such systems work in open loop where the anesthetist changes the concentration target in agreement to the vital signs of the patient. But with the appearance of faster processors and the availability of monitors more reliable to measure the effect of the medicaments, the automation applied to the anaesthesiology has gained popularity, and recent works exist with regard to a new system: the closed loop which is capable of taking decisions to manage and to keep the anesthesia depth stable with base in a sign of feedback that might be an indicator of the depth, but as the level of the above mentioned variable cannot be measured directly, monitors have developed that from the digital processing of the sign EEG or the evoked potentials, they calculate the level of depth of the patient. (BIS, PEA of medium Latency and the Entropy)

Materials and Methods

Is an experimental design. We use the model of Marsh developed for the propofol implemented initially for the Diprifusor. Using this model was implemented in the program Matlab, an algorithm developed by Shafer and cols. in Stanford's university for the calculation of the infusion rate in order to keep the concentration of the medicament constant in the effective site.

Then, analyzing the protocol communication between a program for the control of infusion pumps named Stanpump and the Graseby 3400 infusion pump, was implemented also in Labview a program for the respective communication between its.

Finally was developed a loop of feedback that simulates values of the biespectral index and there transformed by means of a quadratic regression, the information of anesthesia depth in information of concentration in the brain. This concentration was



included to the algorithm for the calculation of the infusion rates, and hereby a system was obtained in closed loop.

Mathematical model.

The presented model is linear with regard to the dose and invariant in the time with regard to the constants pharmacokinetics.

Calculate the infusion rate

The methodology used to implement the algorithm of calculating the infusion rate, needs the discretization. **2**

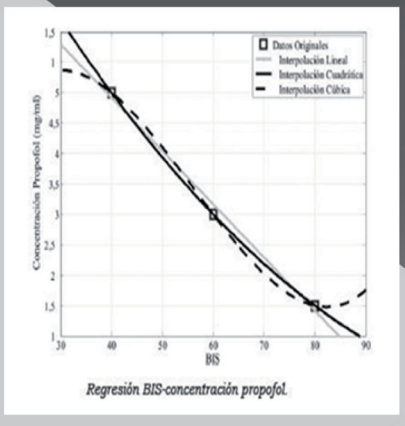
Calculate of the instantaneous infusion rate.

Knowing that the pharmacokinetic model is linear and unvariant with the time, we could apply to him the theorem of overlapping Communication with the infusion pump. For this stage it was used an Graseby 3400 infusion pump and a computer executing the Stanpump program and in other the Protocol analyzer; the communication was established between the program Stanpump and the infusion pump, and at the same time it was monitored the information that allow the control of the pump.

Plasmatic awakening concentration 1.5ug/ml

Concentration (3 - 5ug/ml) BIS 60 – 40

BIS 100 – 40 ----- 1 – 2 minutes



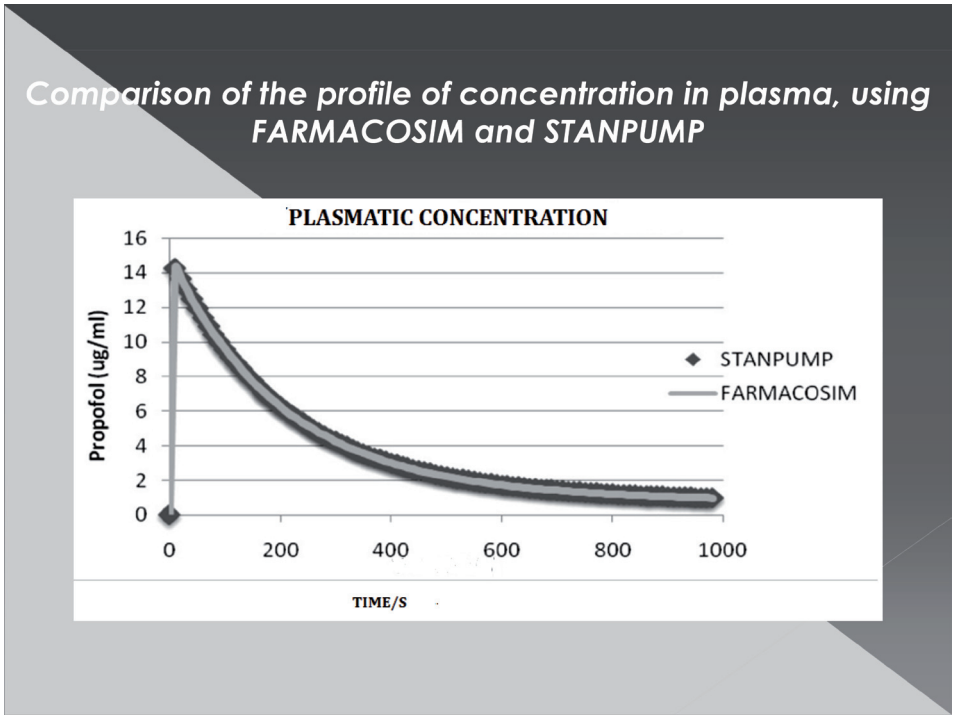
Regresión BIS-concentración propofol.

System in closed loop.

In order that a sign of feedback could be included to the infusion rate calculator, it is necessary to do a transformation of the domain of the pharmacodynamics to the domain of the pharmacokinetics since the information of entry to the calculator is concentrations of medicament in the brain and the sign of re-feeding is in terms of anesthetic depth. The regression that better adjusts to the values is the quadratic that presents the minor residual norm. **3**

The intravenous anesthesia presents a therapeutic range defined for an index of the BIS between 60 and 40 which corresponds to a adapted concentration in effective site from 3 to 5 ug respectively and in this range the patient presents an anesthetic depth but with a minor index of 40 the patient is deeply and with more of 60 it begins to recover the consciousnes. Therefore the loop of feedback must implement a comparer which determines if the sign of feedback is or not inside the therapeutic range and of this remind to take actions of control.

The last phase of the project consists of taking the necessary of the phases previously explained to form a system of closed loop and this way to apply hypnotic depth using propofol.



Validation of the pharmacokinetic simulator.

In order to value the pharmacokinetic model developed, the Farmacosim is compared with the program Stanpump.

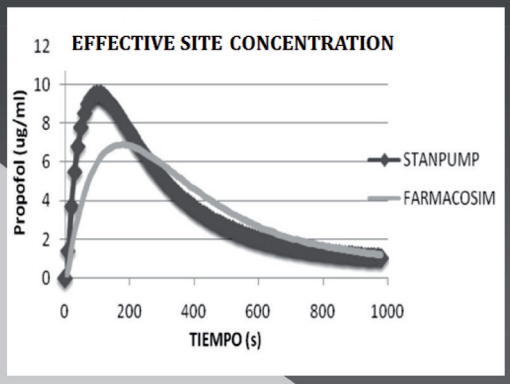
Of the previous results we can see that to the beginning of the induction it might come almost instantaneously the concentration targeted in plasma if it was possible to administer the medicament to a very high speed.**4**

Another interesting result in the comparison is the response obtained for the fourth compartment (effective site) given the same parameters of induction exposed previously.

The previous results, show that there is difference between both models which has demanded a more complete review of the version of Stanpump through which has been found an inconsistency in the selection of the model, but though a simulation is chosen by the model of Marsh, the program always simulates with the model of Schnider who predicts a minor time to reach the concentration we target. To corroborate the detected mistake, there are modified the constants K14 and K41 related to the transfer to and from the effective site according to the model of Schnider. **5**

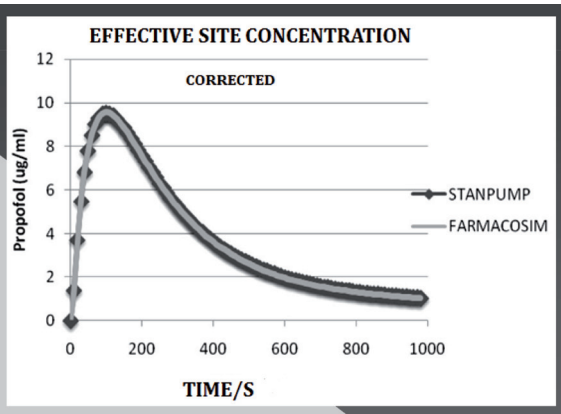
Clinical validation in patients.

Anesthesia have been realized validating the system registering during the procedure the vital signs observing the values of these variables. The intervals can be observed



Comparison of concentrations in E.S. after a 120 mgs bolus.

	STANPUMP	FARMACOSIM
Max. Concentración obtained(µg/ml)	0,5718	0,41371
Peak time (s)	1 min 40 s	3 min 0 s
Correlation index between the curves	0,87	



Comparison of concentrations in E..S. after a 120 mg, bolus with the constants amended.

	FARMA COSIM	STANPUMP
Max concentration obtained (µg/ml)	0,57413	0,5718
Peak time(s)	1 min 40 s	1min 40 s
Correlation index between the curves	0,99	

where the pressure had the lowest values, they were the same in that the concentration in effective site had the highest values. Equal simulation happens with the BIS.

Discussion and conclusions.

An informatic tool has been implemented by a multicompartmental pharmacokinetic model of great academic and clinical interest that as has been demonstrated in quantitative form provides identical results to the offered in the health market of infusion pumps for anesthesia; with important additional advantages like a user's interactive interface and the possibility of simulate anesthesia in closed loop and in a future to re-feed the equipment with a monitor of anesthetic depth to supply the TIVA in closed loop.

Sleep nasendoscopy and propofol: does TCI reproduce a physiologic-like sleep sedation?

Bosco M.°, Clemente A.*, Monteleone G.°, Mennuni G.F.^, Della Marca G.^, Dittoni S.^, Fiorita A. §, Giorgio A. §, Scarano E. §

° *Department of Anesthesiology and Intensive Care, Catholic University of Sacred Heart, "Columbus" hospital, Rome, Italy*
* *Department of Anesthesiology and Intensive Care, IRCCS – I.D.I "Istituto Dermopatico dell'Immacolata", Rome, Italy*
^ *Department of Neurology, Catholic University of Sacred Heart, Rome, Italy*
§ *Department of Otorhinolaryngology, Catholic University of Sacred Heart, Rome, Italy*

Introduction:

To validate the anatomical evaluation of upper airways and obstructions by nasendoscopy under a standardized protocol of sedation using propofol in target controlled infusion (TCI).

Materials and Methods:

The study was conducted jointly by the disciplines of otorhinolaryngology, neurology and anesthesiology. After Ethics Committee approval of the protocol, 34 patients followed at the Sleep Disorder Clinic gave written informed consent and were enrolled. Patients younger than 18 and older than 70, as well as those with co-morbidities at risk for sedation were excluded. All subjects underwent a detailed anamnesis looking for a history of daytime sleepiness, difficulties in daily and work activities, snoring and apneic events during the night. The Epworth Sleepiness Scale and the Berlin Questionnaire focusing on the risk factors and chronic behaviors indicative of a sleep disorder, were also administered. Patients were scheduled to have polysomnography and nasendoscopy in the operating room (Figure 1). After premedication with diazepam 0.2 mg/kg orally and atropine 0.5 mg i.m., they were monitored with ECG, NiBP, SpO2 and BIS. Sedation was started using propofol TCI at 1mcg/ml with increments of 0.5 mcg/ml each minute until patients could not respond to verbal commands, corresponding BIS and TCI values were recorded. No local anesthetic was used in the nasal cavity to avoid anesthesia of the pharynx, larynx and palatal structures minimizing the risk of aspirating secretions. With patients sleeping, while the polysomnograms was recorded, the nasoendoscopy was performed to observe the potential sites of obstruction.

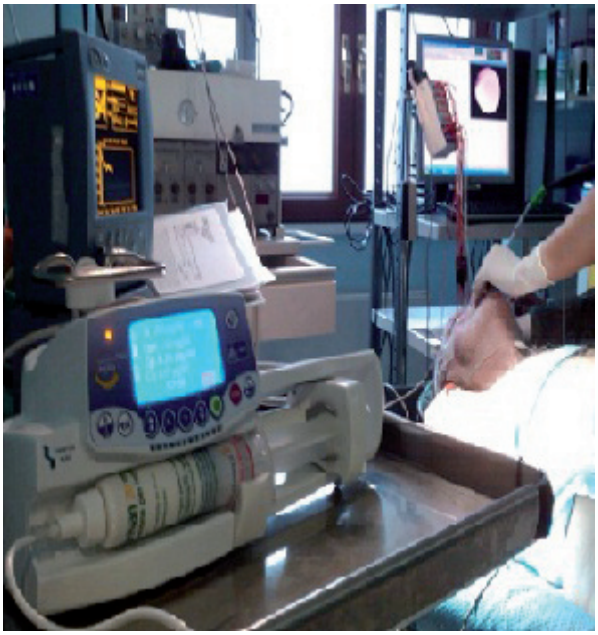


Figure 1 Sleep Nasoendoscopy in the operating room with BIS monitoring and TCI pump.

Results:

34 patients were recruited (22 male/12 female). Mean age was 49 ± 13, with a BMI of 27 ± 2.9. Patients started snoring at an effect site concentration of propofol of 2,42 ± 0,78 mcg/ml with a corresponding BIS value of 71.3 ± 4.2 (all values are expressed as mean ± standard deviation). No prolonged desaturation was observed and all patients completely recovered within less than 30 min. Endoscopic examination revealed only 11.76% of patients with just one site of obstruction, in the majority they presented multiple areas (two or more, 26.47% and 61.77% respectively) (Figure 2). The following sites of obstruction were found: oropharyngeal-retropalatal 89%; oropharyngeal-retrolingual 47%; hypopharyngeal 39.13%; laryngeal 65%. The polysomnographic picture obtained was that of Obstructive Sleep Apnea Syndromes. No complications were noted during the procedures.

Discussions:

Understanding the sites of upper airways collapse and its patterns is mandatory for surgical treatment decision-making and its efficiency (1). Sleep nasendoscopy is a valuable investigation for making an accurate dynamic anatomic assessment in patients with snoring and obstructive features (2). A correct level of sedation is vital to induce symptoms of snoring without causing respiratory depression, our results shows that this is obtainable by appropriate increasing in propofol TCI concentration. Concomitant polysomnographic examination confirmed the onset and duration of sleep. The depth of sedation was also assessed by BIS monitoring (progressively

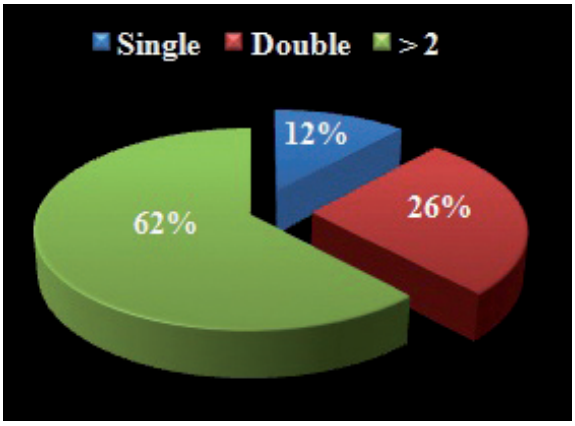


Figure 2 Number of obstructions in a single patient found during nasoendoscopy.

deeper stages of natural sleep in humans have been shown to correlate with lower BIS values) (3).

Conclusions: Sleep nasendoscopy performed by a cautious TCI technique is a useful, specific and sensitive means of assessing patients with sleep related breathing disorders reproducing a sedation similar to physiologic sleep without clinically relevant side effects.

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Patient controlled sedation using Remifentanil in extracorporeal shock wave lithotripsy: comparison between two different dosages.

Cannata F., Spinoglio A., Luzi M., Canneti A., Di Marco P., Del Monte S., Gioia E., Elisa F., Reale C.

Department of anaesthesia, critical care and pain therapy
"Sapienza University of Rome", Rome, Italy

Summary

Patient controlled sedation (PCS) is a technique employed to administer short acting agents like Remifentanil during ambulatory surgery and to titrate dosage of analgesics provided to patients[1]. This study aims to compare efficacy and safety of 10 mcg of remifentanil versus 20 mcg administered in boluses with PCS during ESWL (Extracorporeal Shock Wave Lithotripsy).

Throughout surgical procedure group A (n = 50) received a self administrated dose of 10 mcg of Remifentanil, group B (n = 50) took in a dose of 20 mcg on demand. Patients tolerated 10 mcg dosage better than 20 mcg one, recording the same analgesic effect.

Introduction

PCS is the adaptation of patient controlled drug administration to the provision of intra-operative sedation. Several studies have demonstrated that this technique is safe, effective and associated with high degree of patient satisfaction. PCS allows patients to actively cooperate during surgical procedure and maintain verbal contact with physician.[2].

In the last years ambulatory surgery like ESWL has become a widespread procedure. This evolution has been possible thanks to the use of short acting agents like Remifentanil, that provides a fast recovery

Remifentanil is an ultra-short-acting oppioid, which is quickly metabolized by unspecific blood and tissue esterases[3]. This feature vouches for a predictable pharmacokinetics and makes this drug suitable for administration in continuous intravenous infusion in order to achieve patient conscious sedation during non-invasive surgical procedures. Remifentanil could be particularly useful in day surgery setting, thanks

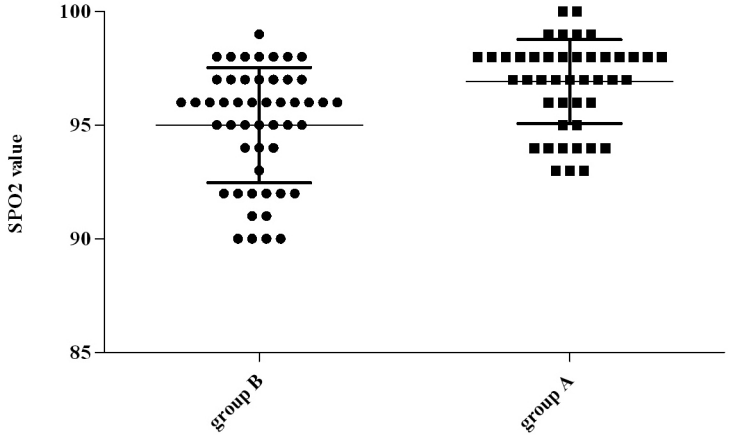

Figure 1. Mean value of oxygen saturation in the two groups.

also to its faster elimination than other oppioids. This property ensure a swift recovery from conscious sedation, reducing the period of time during which patient remains in recovery room and decreasing also the incidence of side effects, like PONV and respiratory depression.

The aim of this study is to compare the efficacy and safety of 10 mcg of remifentanil versus 20 mcg administered in boluses with PCS during ESWL.

Materials and Methods

After a written consent 100 patients have been randomly allocated in two groups:

GROUP A (n=50): patients were destined to receive a self administrated dose of 10 mcg of Remifentanil.

GROUP B(n=50): patients received Remifentanil, using a 20 mcg bolus at demand.

In both groups was planned a lock out interval of 3 minutes and a continuous background infusion of Remifentanil at the infusion rate of 0.05 mcg/kg/min. Patient sedation was judged observing time necessary to reach an observer assessment of allertness sedation (O/ASS) score of 5. Pain intensity was estimated with a 10-points VAS (visual analogue scale). Mean arterial pressure, heart rate and arterial oxygen saturation were registered. Patients's satisfaction was evaluated using a five point Likert scale.

Data were analyzed by Student t test or χ square. Statistical significance was a p value $< 0,05$.

Results

A comparison between vital signs monitored in the two groups showed a significant

lower mean value of oxygen saturation in B than in A, reporting 95 ± 2 % versus 98 ± 1,5 % respectively ($p < 0,05$) (Figure 1).

We also observed a significant decrement in mean arterial pressure, registering throughout the surgery a lower mean value in B than in A, 83 ± 5 mmHg versus 104 ± 4mmHg respectively ($p < 0,05$). Time spent to reach the fifth point of O/ASS score was significantly lower in A than in B, recording a mean time of 3 ± 0,9 minutes versus 4 ± 1 minutes respectively ($p < 0,05$). Only two patients in group B complained nausea and itching. Patients were all satisfied about the anesthesiological procedure ($p = 0.20$).

Remifentanil consumption using PCS was significantly lower in group A than in group B, recording a mean value of 150 ± 20 mcg in A versus 250 ± 25 mcg in B ($p < 0,05$) .

Conclusions

ESWL is a non invasive procedure frequently performed in day surgery regimen. As a consequence drugs administered for ESWL procedure must be highly tolerable, with low incidence of side effects.

PCS is a safe and acceptable method for ESWL, because it allows for rapid individualized titration of anesthetics[1].

Potential advantages of using Remifentanil in this procedure consist of: the quick achievement of wanted analgesic effect and absence of unexpected side effects in presence of renal failure and hepatic dysfunction[4]. We have chosen to administer Remifentanil with PCS associated with a continuous background infusion because we assumed that a continuous basal infusion of this short acting opioid can reduce additional analgesic request and at the same time improve analgesia, decreasing the rate of respiratory depression. This is not consistent with previous studies in which the administration of intermittent doses of Remifentanil provide a more effective analgesia than a continuous background infusion without increasing incidence of side effects. [5].

We have preferred to administer Remifentanil rather than another opioid or the association with an intravenous sedative because according with the opinions of other authors remifentanil is associated with lower incidence of nausea, vomiting and respiratory depression[6].

PCS with Remifentanil administration was well tolerated in both groups, but in A better values of oxygen saturation and arterial blood pressure were registered and patients spent less time to accomplish the O/ASS score of 5 too. We attribute these results to the lower dosage of Remifentanil administered in group A. Further investigations are necessary to confirm these results.

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Ketamine and Dexmedetomidine Infusion in Conjunction with Multiple Peripheral Nerve Blocks For the Relief of C.R.P.S.-I

Hagen Christopher, DO,* Maani Christopher, MD, Hansen Jacob, DO****

**Department of Anesthesia and Operative Services, Brooke Army Medical Center, Fort Sam Houston, Texas; **Department of Anesthesia, U.S. Army Institute of Surgical Research, Burn Center, Brooke Army Medical Center, Fort Sam Houston, Texas*
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The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Abstract

Background. Complex regional pain syndrome (CRPS) is a multi-faceted compilation of painful conditions characterized by disproportionate regional pain (spontaneous and/or evoked) that is disproportionate in time or degree to the anticipated course of any known trauma. Presenting features of CRPS fall into four broad categories: Sensory, motor, autonomic dysfunction, and trophic changes located in a region rather than a dermatome.

Design. Case report.

Setting. Military medical and research center.

Patient. In this report we present the case of a CRPS patient in whom a continuous ketamine and dexmedetomidine infusion was administered for analgosedation. Multiple continuous peripheral nerve blocks were simultaneously implemented, with the goal of maximal nociceptive blockade.

Results. We reported an improvement in pain control, with a 97% reduction in morphine equivalents administered at day 22 post-intervention.

Conclusions. The combination of ketamine and dexmedetomidine for analgosedation, and peripheral nerve blockade with local anesthetic was an effective treatment for CRPS in our patient. Further study of this intervention is warranted to further establish its reproducibility and clinical utility.

Key Words. Complex Regional Pain Syndrome; CRPS; Ketamine; Dexmedetomidine; Regional Anesthesia; Nerve Blocks

Introduction

Complex regional pain syndrome (CRPS) has classically been treated from a multidisciplinary approach. Mainstay of therapy commonly involves oral NSAID's, opioids, oral gabapentin agonists, oral N-methyl-D-aspartate (NMDA) antagonists (memantine), anti-depressants (tricyclic or serotonin-norepinephrine reuptake inhibitors), sympathetic blocks, behavioral health for treatment of coexisting anxiety and depression, coupled with physical therapy. Early therapy is critical to positive outcomes, with a reported 90% of patients recovering spontaneously when therapy was initiated within one month from symptom onset. Those who begin therapy later in the disease progression typically experience poorer results. Those who choose to not seek treatment frequently become functionally disabled. Physical therapy plays a pivotal role in the treatment of this syndrome with oral medications and sympathetic blocks serving to facilitate the patient's ability to participate in therapy. (1, 10)

Case Presentation

A previously healthy 25 year old active-duty male presented to our institution for further treatment of injuries sustained from blast-related trauma.

The patient's past medical history was significant for recently diagnosed anxiety, depression, suicidal ideation, traumatic brain injury, post-traumatic stress disorder (PTSD), and poly-trauma, all secondary to his traumatic event. The patient's severe poly-trauma consisted of extensive soft tissue, bone and nerve injuries to his left upper and lower extremities and soft tissue wounds to his axilla. The patient underwent a left below-the-knee amputation, a latissimus dorsi flap to his left axilla and several skin excision and grafting procedures to his left upper and lower extremities.

A multi-disciplinary team approach was deployed in the effort to maximize the patient's plan of care. The patient's medication list included methadone 15mg by mouth every 8 hours, hydromorphone PCA 0.8mg IV every 10 minutes, pregabalin 200mg by mouth every 8 hours, clonidine 0.1mg by mouth twice daily, and hydromorphone 1-2mg IV bolus doses every 1-2 hours as needed. After several days it was observed that while on a substantial narcotic load, the patient continued to request more and would become very upset, anxious and uncooperative when asked to participate in physical therapy or have his dressings changed. An anesthesia pain consult was placed to evaluate the patient's allodynia and hyperalgesia, with the goal of improving the patient's pain control and his ability to be involved in therapy. At this time the patient was noted to be four months out from his traumatic event. During the initial interview, the patient reported pain in both lower extremities, his left upper extremity and his back, which had recently been harvested as a donor site. He quantified his pain as a constant 8-10/10, describing it as sharp, throbbing and diffuse in his injured extremities. Further, the worst pain occurred in his entire right lower extremity, and his left anterior and medial lower extremity. He also noted that the pain was exacerbated with any movement or touch. The patient repeatedly asked to be "knocked out" during his dressing changes, stating he could not endure them with simple IV narcotics and oral medications.

The physical exam of the patient was notable for diffuse pallor and diaphoresis. Mentally the patient appeared constantly anxious and upset. Communication was

difficult due to his apparent depressed mentation and anxiety. It was assumed this was multi-factorial, with important contributing factors being traumatic brain injury and his increased medication demands.

After an extensive review of the patient's medical chart and multiple discussions with the patient's mother, nursing, and behavioral health, it was the general consensus that the patient's uncontrolled pain, complicated by his anxiety, depression and PTSD, was severely compromising his recovery process. Based on the patient's syptomatology and comorbid psychological issues, a diagnosis of complex regional pain syndrome was made and the decision to perform a continuous ketamine and dexmedetomidine infusion in conjunction with regional anesthesia to break the sympathetically-mediated pain cycle. We planned left femoral, right femoral, and right sciatic continuous nerve blocks, as an epidural was impractical due to fresh wound beds from graft donor sites on his back.

The patient was transferred from the floor to an ICU bed for an anticipated 48 hour period of time. A bispectral index (BIS, Aspect Medical Systems, Inc, Norwood, MA) monitor was utilized and placed just prior to the procedure, allowing the team to better monitor the patient's level of sedation. This was important to the team given the patient's tolerance to both ketamine and narcotics. Ketamine was bolused through the patient's IV in increments of 50mg to a total of 200mg, resulting in a BIS value of 40- 60 with subsequent maintenance bolus as needed to maintain this range. Once the patient was sufficiently sedated, the peripheral nerve catheters were placed. Utilizing sterile technique and a peripheral nerve stimulator a left femoral continuous nerve catheter (CNC), a right femoral CNC, and a right sciatic CNC were placed and secured with a transparent bio-occlusive dressing. Each catheter was connected to a continuous disposable pump set to deliver ropivicaine 0.2% at 8ml per hour. Ketamine (10-30 mcg/kg/min) and dexmedetomidine (0.7-1.0 mcg/kg/hr) infusions were initiated and titrated to a BIS value of 40-50. These infusions were maintained for the next 24 hours. During this time, all regularly scheduled opiate narcotics were held. At the end of 24 hours the ketamine infusion was slowly decreased over a 12 hour period until it was discontinued, while the dexmedetomidine infusion was maintained for continued light sedation for an additional 24 hours. As the patient's mentation improved, lorazepam was incorporated for acute anxiety, while hydromorphone 2mg IV was added as needed for breakthrough pain. At the end of 72 hours the patient was deemed stable for transfer back to the floor. The patient's continuous peripheral nerve catheters were maintained in place for as-needed bolus administration; however, the pumps were discontinued. The patient indicated that the peripheral nerve blocks were functioning adequately and that his pain in all affected extremities was greatly improved. His main complaint of pain at this time was the donor site, which was noted to be stable at rest and only painful during his dressing changes. The patient's narcotic regimen was noted to be significantly diminished at 22 days post intervention (day 0, 566.5 morphine equivalents vs day 22, 15 morphine equivalents; see table 1 below), with improved nursing assessments and patient participation as noted by physical therapy. The patient was noted to be performing daily living activities with greater ease, and began to make excursions to the cafeteria utilizing his wheelchair with minimal assistance at approximately 14 days after his intervention.

Table 1: Pain-related medication administration record, including pain scores, for day 0 and day 22, representing pre-intervention and post-recovery timeframes.

Day 0

Time	0600	1000	1400	1800	2000	2200
	Methadone 15mg IV	Methadone 15 mg IV	Lyrica 200mg	Morphine 2mg IV	Morphine 2 mg IV	Morphine 2mg IV
	Dilaudid PCA 0.4mg Q10min – 17mg in 24 hours	Clonidine 0.1mg PO	Lithium 200mg	Methadone 20mg PO	Percocet 2 tabs	Seroquel 100mg
	Morphine 2mg IV	Cymbalta 30mg				Lyrica 200mg
	Ativan 2mg IV					Cymbalta 30mg
	Lithium 300mg					Mirtazapine 15mg
	Lyrica 200mg					Lithium 300mg
						Klonopin 1mg
Pain	5-8/10	8/10	5-8/10	7/10	8/10	8/10

Day 22

Time	0800	1000	1400	1800	2000	2200
	Lyrica 200mg PO	Clonidine 0.1mg PO	Lyrica 200mg PO	Clonazepam 1mg	Lyrica 100mg PO	Clonidine 0.1 mg PO
	Percocet 2 tabs	Cymbalta 30mg PO		Methocarbamol 500mg PO		
Pain	2/10	0/10	0/10	0-2/10	0/10	0/10

Discussion

Complex regional pain syndrome (CRPS) is a multi-faceted compilation of painful conditions characterized by regional pain (spontaneous and/or evoked) that is disproportionate in time or degree to the anticipated course of any known trauma. This syndrome has been sub-divided into two sub-types: CRPS-I and CRPS-II. CRPS-I is associated with an initiating traumatic event or noxious stimuli to tissue (previously known as reflex sympathetic dystrophy); while CRPS-II is attributed to direct nerve damage or injury (previously known as causalgia). (10) Of the two types, CRPS-I is the most common syndrome seen clinically. A wrist fracture is the most common traumatic event noted in patients presenting with symptoms of CRPS-I. There is almost always an inciting or triggering event in conjunction with symptom onset; however, idiopathic CRPS has been reported. (10, 11, 12)

Incidence and Risk Factors

In North America, the reported incidence of CRPS is 5.5 per 100,000 person-years, whereas the reported incidence in Europe is 26.2 per 100,000 person-years. This discrepancy may be related to differences in statistical and case validation methodologies. (10) The incidence of CRPS in the military population has not been well-investigated, though one study from the Veteran's Affairs hospital in Tampa, FL showed that 47% of veterans reported at least a mild level of pain, with 28% characterizing the pain as moderate to severe. In those with chronic pain (duration ≥1 month), the pain was attributed to musculoskeletal or connective-tissue diagnoses in 82% of cases. (19)

Risk factors for CRPS include previous trauma (may range from minor to severe),

nerve injury, previous surgery, work-related injury, and female sex. (20) Females have a significantly higher risk ratio, approximating 3.5. (10) A recent study evaluating genetic factors in CRPS showed that HLA-B62 and HLA-DQ8 alleles were significantly associated with development of CRPS. (21)

Disease Progression

Generally, CRPS onset is acute, with cardinal symtoms appearing within hours to days of inciting insult. Onset symptoms are usually spontaneous pain (disproportionate), generalized swelling, and temperature asymmetry (usually warmer initially). (23) Three phases of syndrome progression have been described. Phase one represents the Acute phase consisting of the first through the third months. During this time the pain is localized, severe and described as burning. The skin is usually warm and dry. Phase two is the Dystrophic phase consisting of the third through sixth months. At this time the pain is characterized as diffuse and throbbing while the skin typically is cold, edematous and diaphoretic. Phase three is the Atrophic phase. At this stage the pain is characterized as less severe but often involves other extremities. The skin is noted to be glossy while the muscles are noted to be atrophied and occasionally accompanied by contractures. This phase of the syndrome represents the chronic stage at its worst and without treatment the patient could maintain in this phase indefinitely. (1) However, the appropriateness of this method of staging has been questioned, some preferring an approach that focuses on symptom intensity to characterize the disease progression, as in mild, moderate or severe. (23)

Common Symptoms

Commonly presenting features of CRPS fall into four broad categories: Sensory, motor, autonomic dysfunction, and trophic changes located in a region rather than a dermatome. (10, 13) Sensory dysfunction typically manifests as a burning or throbbing pain out of proportion to the inciting event, which may be provoked by thermal or mechanical changes. Sensory dysfunction is commonly summed up by the terms allodynia (noxious perception of a non-noxious stimulation), and hyperalgesia (excessive hypersensitivity to pain). Motor dysfunction is typically seen in chronic phases of the disease progression. At this stage muscles begin to atrophy, and joints begin to lose mobility either from lack of use or from inflammatory changes as part of the chronic disease progression. Autonomic dysfunction presents as hyperhidrosis, vasodilation (acute phase), or vasoconstriction (dystrophic or atrophic phase), in conjunction with edema of joints. Trophic changes typically observed again in the chronic stage of the disease involve hair (hypertrichosis – typically over the affected region) and nail and skin changes. (10, 14, 15)

While there are no official criteria for diagnosis of the syndrome, several diagnostic criteria models have been suggested to help guide clinicians in their practice. A summary of criteria for diagnosis is in table 2. (14)

Proposed Pathogenic Mechanisms

Recently, progress has been made in our understanding of the causality of CRPS as a combination of neurological, inflammatory, and psychological factors. It is important to note that these interactions are still primarily speculative; however, placing CRPS

Table 2 Proposed Clinical Diagnostic Criteria for CRPS (Harden [14])

To make the *clinical* diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event.

2. Must report at least one symptom in *three of the four* following categories:
____ Sensory: Reports of hyperesthesia and/or allodynia.
____ Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry.
____ Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry.
____ Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

3. Must display at least one sign at time of evaluation in *two or more* of the following categories:
____ Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement).
____ Vasomotor: Evidence of temperature asymmetry (>1 degree Celsius) and/or skin color changes and/or asymmetry.
____ Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
____ Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

4. There is no other diagnosis that better explains the signs and symptoms.

in the context of a multifactorial model aids in understanding the wide variability in clinical presentation and disease severity. (22) Several proposed interactions and mechanisms are listed and depicted below. (See Figure 1. Modified from de Mos et al. [10])

1. Hypoxia as a trigger for an inflammatory response.
2. Continuous nociceptive input (hypoxia, inflammation, or sympathetic stimulation) may lead to central sensitization and alteration of sensory and motor units.
3. Neuropeptides (substance P) may facilitate sensitization via NK-1 and NMDA receptors.
4. Impaired blood flow due to sympathetic dysfunction may contribute to tissue hypoxia.
5. Immune system-related mechanisms: Catecholamines can modulate cellular immunity via adrenergic receptors on immune cells., Additionally, inflammation may play a role in altering sensitivity or expression of α-adrenergic receptors on nociceptive fibers.

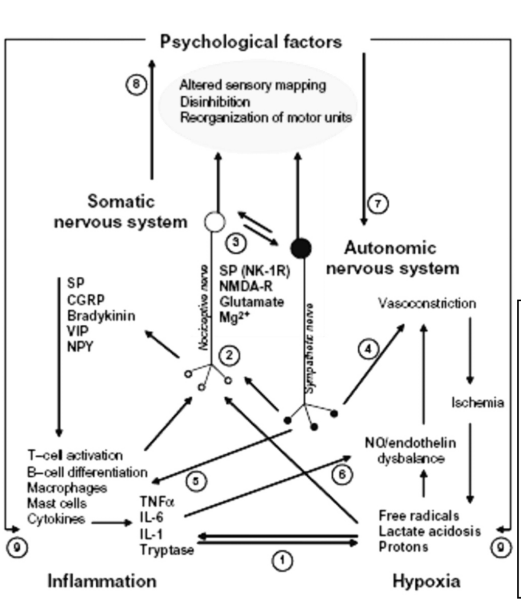

Figure 1. Interaction between the pathogenic mechanisms underlying CRPS. *CGRP*, calcitonin gene-related protein; *IL*, interleukin; *Mg2+*, magnesium ions; *NK-1R*, neurokinin-1 receptor; *NMDA-R*, N-methyl-D-aspartate receptor; *NO*, nitric oxide; *NPY*, neuropeptide Y; *SP*, substance P; *TNFa*, tumor necrosis factor a; *VIP*, vasoactive intestinal peptide.
From de Mos, et al. (10) Used with permission.

6. Cytokines alter the nitric oxide/endothelin balance contributing to hypoxia.
7. Psychological distress may increase sympathetic tone.
8. Severe chronic pain potentiating/worsening psychological distress.
9. Fear of movement-induced pain results in the accumulation of free radicals and inflammatory cytokines, preventing desensitization.

Treatment

The approach to treatment must be individualized, and will depend largely on the time course and severity of symptoms. Patients presenting in the acute phase of the disease typically respond very well to physical therapy, oral anti-inflammatories, anticonvulsants, antidepressants, andopioid narcotics. This conservative approach is intended to optimize pain relief, allowing maximal involvement in the recovery or rehabilitation process. Other modalities that can be added to facilitate this goal are transcutaneous electrical stimulation (TENS), regional anesthetic nerve blocks, and psychological therapy. Patients in the acute phase should be approached cautiously with the concept of behavioral health involvement. Many are not clinically depressed at this stage, and while upset regarding their symptoms do not view themselves as requiring psychological therapy. (16, 17) Negative stereotypes of mental illness are difficult to overcome and the concept of a team approach with behavioral health as part of the team should be presented to the patient. Patients seeking treatment in the chronic phase are often battling severe depression/anxiety and as such are usually open to the idea of behavioral health involvement. (19)

Partial response or overt failure of conservative therapy warrants consideration of alternative approaches. Epidural blocks, neuromodulation via spinal cord stimulation or

peripheral nerve stimulation, intravenous drug therapy and/or intrathecal drug therapy may be considered. Continued failure to achieve adequate response to therapy may lead to discussion of therapeutic sympathectomy as an option. This is a controversial intervention due to its potential for complications and insufficient evidence of long term benefit to the patient. (16, 17)

The role of NMDA antagonism in the treatment of CRPS has been touted and vital, though clinical studies are scant. Ketamine, dexamethorphan, and memantine are examples. Ketamine, while not a first-line drug and often perceived as only an anesthetic adjunct due to its negative side effect profile, has long been known to be an effective agent for the treatment of neuropathic and chronic pain. Its action as an NMDA antagonist has been proven to reduce the sensitivity and number of α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid (AMPA) receptors whose activation, with NMDA, are primary triggers for enhancing synaptic conductance of nociceptive neurons. The number of active AMPA and NMDA receptors as well as their degree of activity help to determine the level of pain perceived. Ketamine, by antagonism of the NMDA receptor, causes either a diminution of the excitatory signal potentiating the AMPA receptor, or down-regulation of the number of AMPA receptors expressed as a result of the loss of excitatory signal. (2, 3, 4) Several studies and clinical trials have shown that prolonged ketamine infusions in conjunction with standard therapy have resulted in prolonged periods of analgesia with diminished need for supplemental opioid. (5, 6) The duration of the successful results seems to correlate to the length of time the ketamine infusion lasted. Those infusions which were given over longer periods of time were noted to have greater degrees of success in both pain diminishment and duration of relief. Several patients reported complete resolution of symptoms and are noted to be pain free today. (7, 8, 9)

Discussion:

Complex regional pain syndrome is a variable, complicated constellation of symptoms often requiring a lengthy time to diagnose resulting in frustration on both the part of the patient and the provider. In this case report the patient was diagnosed and therapy initiated within the first four months. Since early treatment is key to positive patient outcomes and given that the syndrome had not entered the chronic phase, he was an excellent candidate for early aggressive treatment. Normally the treatment goals and therapy would have graduated through several phases as discussed in the background portion of this report; however, the patient's inability to participate prevented and confounded the efforts made by physical therapy and behavioral medicine. This prompted our plan to incorporate multiple interventions to maximize the patient's opportunity of success.

It is difficult to say what role the patient's other surgical procedures might have played in obscuring our assessment of the patient's CRPS. It was noted post procedure that his donor site continued to cause pain, requiring the reinstitution of narcotics to his daily regimen. As his donor site healed, however, the narcotics were tapered off culminating in the three-week findings listed in the table above. Classification into CRPS-I or CRPS-II is also difficult, given the complexity and extent of the patient's injuries which possibly could have been CRPS-I or –II. Due to the predominance of tissue trauma over direct neural injury the patient's syndrome was classed predomi-

nantly into CRPS-I category. Of note, classification into either category would not have altered therapy for the patient. Another factor to take into consideration is the possibility of opioid-induced hyperalgesia (OIH) as a possible alternative diagnosis to CRPS. OIH, like CRPS, is believed to be multifactorial and is also poorly understood. OIH is treated in a similar fashion to CRPS, with a reduction in opioids and the usage of ketamine and other non-opioid analgesic adjuncts having shown benefit. With this in mind, it is possible to speculate that the improvement seen in our patient's condition might have been the result of withdrawing his narcotics in conjunction with ketamine and dexmedetomidine infusion, thus breaking the cycle.

It is important to note that before initiating the procedure the patient's surgeons were contacted and queried regarding plans for further procedures in his immediate future, and that close contact was maintained between both departments throughout. It was important to establish that there would be no major inciting events to reverse or disturb any progress made by the therapy, and to assure that post-procedure narcotic goals could be achieved and maintained.

There are many options available for the treatment of chronic regional pain syndrome. This case report highlights the utility of continuous peripheral nerve blocks to blunt peripheral nociception, in conjunction with ketamine and dexmedetomidine infusions to facilitate central nociceptive attenuation. Further study regarding this particular technique in the poly-trauma population may result in further improved patient outcomes and a better understanding of treatment modalities for this syndrome.

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Treatment of Refractory Fever in the Burn ICU with an Intravascular Temperature Management Catheter

Hansen Jacob J., DO,* Hardin Mark, MD, Simmons Deondra P, MD,*** DeSocio Peter A., DO,**** King Booker T., MD,* White Christopher E., MD,* Ritchie John D., MD,** Chung Kevin K., MD,* Blackbourne Lorne H., MD,* Maani Christopher V., MD***

**U.S. Army Burn Center, U.S. Army Institute of Surgical Research, Fort Sam Houston, TX; **Dept of Surgery, Brooke Army Medical Center, Fort Sam Houston, TX; ***Dept of Anesthesia, Wilford Hall Medical Center, Lackland AFB, TX; ****Dept of Anesthesia, Ohio State University, Columbus, OH.*

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Introduction

Loss of thermoregulation is one of many problems experienced by patients with severe burn injury. [Insert Reference Here]. Loss of skin integrity compromises intrinsic thermoregulatory mechanisms. Maintenance of normothermia in the perioperative period has been extensively studied. [Insert Reference] Known benefits for the patient include surgical hemostasis, improved wound healing, reduced surgical site infection, reliable drug metabolism, reduced shivering, and improved patient comfort. Hypothermia is also the most frequent temperature-related malady in the operating room, occurring initially from the redistribution of core heat to the periphery, followed by a negative balance of heat production to environmental heat loss. Forced-air warming is the most frequently used and effective modality to prevent intraoperative hypothermia, being widely available, inexpensive and safe (X). Hypothermia in burn patients is independently associated with poor outcomes. (X)

Conversely, perioperative hyperthermia is also a serious condition with deleterious effects on homeostasis. This may be a consequence of multiple factors, including inflammation, infection, adverse drug reaction, blood product administration and malignant hyperthermia. There are many non-invasive and invasive methods to carry out the cooling of a patient. Frequently, these are applied in an escalating fashion, attempting the least invasive before resorting to the more invasive modalities. There is currently no consensus of expert opinion regarding the best or most effective modality for treatment of severe hyperthermia (or hyperpyrexia, T >41.5ºC).

Intravascular temperature management (IVTM) involves the use of a device placed into the central venous circulation, which can be externally adjusted to a target temperature. There are various models available, including solid-core devices and catheter-based devices. The added benefit of the central venous catheter thermal regulator is the ability to use it for infusion of resuscitation fluids, blood products or medications. One such device is the ThermoGard XP™ (Zoll/Alsius Corp., www.alsius.com), which circulates cool or warm saline in a closed-loop circuit through balloons that surround the catheter.

Case Review

Patient 1: A 19-year-old healthy young man sustained multiple traumatic injuries following an explosion. His initial injuries included burns to 52% total body surface area, bilateral lower extremity above-knee-amputations, right upper extremity mid-humerus amputation, left upper extremity mid-forearm amputation, inhalational injury, and intra-abdominal trauma. Initial care involved resuscitation, completion of multiple extremity amputations, exploratory laparotomy, and wound debridement. During his admission to the Burn Center, his hospital course included multiple procedures to excise and graft burn wounds, revise amputations, and explore the abdomen. Critical care in the Burn Intensivie Care Unit (BICU) included ventilatory support for respiratory failure, pneumonia, persistent renal failure requiring continuous renal replacement therapy (CRRT), and sepsis related to multidrug resistant *Pseudomonas aeruginosa.*

As part of severe sepsis, the patient developed a fever refractory to standard treatment methods. Over a period of ten hours, his core body temperature increased from 38.5°C to 39.6°C. Initially treated with ambient air cooling and acetaminophen, the fever improved to a nadir of 38.1°C over four hours. Thereafter, the core body temperature increased more aggressively, climbing from 38.1°C to 42.3°C over a course of thirteen hours. Fever was associated with additional signs of systemic inflammatory response, including tachycardia and hypotension, with peak documented heart rate (HR) of 148 bpm, and a nadir mean arterial pressure (MAP) of 49 mmHg. (See fig 1)

Efforts to cool the patient, including administration of acetaminophen, use of a cooling blanket, ambient temperature cooling, groin and axillary ice packs proved ineffective. At this point an Icy® catheter was placed into the patient's right femoral vein. The device was connected to the ThermoGard™ 3000 system (Zoll/Alsius Corporation, Irvine, CA), which was set for intravascular cooling with maximum flow rate and target temperature of 38.0°C. Within 30 minutes following initiation of intravascular cooling, the patient's core body temperature had decreased to 40.0°C; then to 38.0°C after 90 minutes using the IVTM device. Over this same period of time, the HR decreased to 116-128 bpm, and the MAP increased to 64-68 mmHg. Upon reaching the target temperature in fever mode, the device was set to a maintenance mode, and the core body temperature remained within 1°C of the target (38.0°C).

Patient 2: A 55 year-old civilian emergency patient with multiple pre-existing medical co-morbidities (morbid obesity, hypertension, insulin dependent diabetes mellitus, chronic kidney disease, stroke) was admitted to the Burn Center after sustaining a 4% TBSA burn to the right lower extremity. On admission the patient was noted to have onset atrial fibrillation. The patient underwent excision and grafting of his

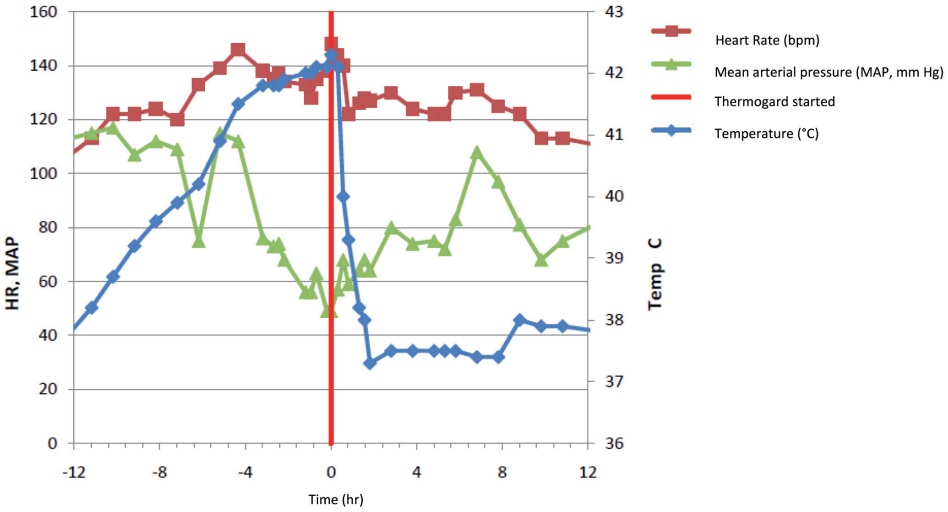

Fig. 1. Vitals trend for Patient 1.

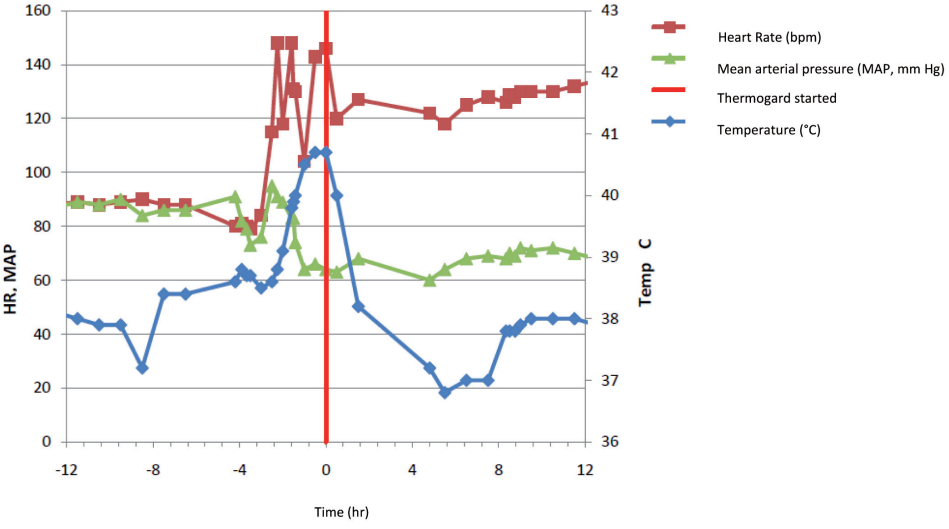

Figure 2: Vitals Trend for Pt 2

burn wound on hospital day 7. The perioperative course was complicated by suspected aspiration during awake-fiberoptic intubation. Postoperatively, he was transfused 2 units of packed red blood cells. Within minutes of receiving the blood products, the patient demonstrated generalized shivering and tremor accompanied by the rapid development of a fever to 40.7°C; he remained hemodynamically stable and alert.

The transfusion was immediately stopped and conservative cooling measures were initiated with acetominophen, meperidine for shivering, ambient air cooling, and application of ice packs. After failure of conservative management, IVTM by placing an Icy® catheter into the patient's left femoral vein, which was connected to the ThermoGard™ 3000 system (Zoll/Alsius Corporation, Irvine, CA), which was set for intravascular cooling with maximum flow rate and target temperature of 38°C. After 90 minutes, the patient's core body temperature had decreased to 38°C with resolution of the tremor.

Discussion

While fever is a normal physiologic response to optimize the body's ability to defend against pathogens, the treatment of fever remains a challenge for those involved with providing perioperative, as well as intensive care. Treatment remains targeted at the suspected cause. On the other hand, excessive production of heat may lead to dysregulation of normal physiologic processes, hyperdynamic cardiovascular physiology, or damage to vital organs. In this regard, there is no global consensus as to what constitutes a maximum acceptable temperature.

Hyperthermia is a generic term defined as a core body temperature exceeding 37.9C. Hyperthermia can be further characterized as uncontrolled or controlled (2). Controlled hyperthermia or fever is characterized by an increase in the hypothalamic temperature set-point. This is most commonly triggered by an immunologic process, in which prostaglandins and cytokines play an important role in the increased set-point. Uncontrolled hyperthermia is characterized by full activation of the body's homeostatic mechanisms to maintain normothermia, but these are overwhelmed by intrinsic or extrinsic factors producing heat. Heat stroke is a classic example of an extrinsic cause of uncontrolled hyperthermia, whereas malignant hyperthermia or thyroid storm are examples of intrinsic causes.

Intravascular temperature management (IVTM) is one modality available for the treatment of fever, and may be accomplished by the use of a catheter with balloons in a closed circuit, which circulate warm or cool saline. Similar to the device used in the patient presented above, the ThermoGard XP™ system has specific indications in the US market, which vary based on the type of catheter used. The broadest indications apply to the larger catheters intended for femoral vein use, and include perioperative maintenance of normothermia in cardiac patients, as well as global temperature management in neurosurgical patients. Both the American Heart Association (AHA) and the American Association of Neurological Surgeons recommend maintenance of normothermia in brain-injured patients (x.y.).

Literature specific to the safety profiles of such devices is scant, with the best information coming from literature applying the device to cardiac arrest patients. In a retrospective cohort study, Holzer, et al. (8) found no significant differences in the rate of adverse events, with the singular exception of bradycardia, being more prevalent in the IVTM group. Diringer, et al. (9) conducted a multi-center prospective, randomized, non-blinded trial comparing conventional treatment of fever (acetaminophen and cooling blankets) to conventional treatment plus IVTM in neurological ICU patients. They showed that there was no significant difference in the morbidity or mortality profiles between the two groups. Furthermore, the study

group had a 64% reduction ($p < 0.01$) in fever burden compared with the conventional treatment group.

In a study comparing conventional treatment of fever to several other interventions, the IVTM group had both the most rapid reduction in fever (1.46 °C/hr), and the most consistent in-range profile (88.8%) (3). Therapeutic hypothermia has been shown to improve survival (OR 2.5) in cardiac arrest patients (4), and is now recommended by the AHA. While it is known that fever in neurologically injured patients is associated with poor outcomes (5), it has not been shown that induction of hypothermia improves outcomes over maintenance of normothermia in humans (2,10). Clifton, et al have demonstrated that for neurotrauma patients presenting with hypothermia (age ≤ 45 yrs), maintenance of hypothermia was associated with significantly fewer poor outcomes compared with those who were warmed to a normothermic state, although induction of hypothermia after acute brain injury did not improve outcomes. (11,10)

There is very little data related to the use of IVTM catheters in burn patients. A recent study conducted in France demonstrated the safe and effective use of IVTM for maintenance of normothermia in burn patients in the operating room. (12) Additionally, application of IVTM may be extended to the burn ICU for the same purpose. Based upon previously examined effects of hypothermia among combat casualties, there is also potential application of IVTM for combat casualty care. A comprehensive review of the literature pertaining to safety, efficacy, and cost would be useful to elucidate the clinical utility of increased use of IVTM in perioperative and critical care applications.

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Comparison of the effectiveness of metoclopramide and ondansetron, on the prevention of nausea and vomiting after rhinoplasty.

Hemyari;H 1, Razavi A 2

1.Assistant professor ,Anesthesiologist ,Department of anesthesiology.Tehran Medical Unit . Islamic Azad university .Tehran Iran
2.General Physician

Summery

Introduction:

The aim of this study is to evaluate the prophylactics effect of metoclopramide and ondansetron on PONV after rhinoplasty.

Material and methods:

This is clinical trial, double-blind study performed in 100 patients whom were admitted for rhinoplasty The operation was done with local anesthesia and intravenous sedation, .They randomly divided in 2 groups , one group received metoclopramide 10 mg and the other ondansetron 4 mg intravenous .The incidence of PONV was recorded by someone who was not known about the type of drug.

Results:

There is no significant difference between two groups on age,sex,weight and duration of operation.

Introduction

Postoperative nausea and vomiting (PONV) is a common problem in the ambulatory surgery , occurring in an estimated 35% of all patients(1) As many as 70% to 80% of patients at high risk may be affected. PONV results in increased patient discomfort and dissatisfaction and in increased costs related to length of hospital stay.

One study revealed that the time to discharge was increased by 25% in patients with PONV. Serious medical complications such as pulmonary aspiration, and suture dehiscence although uncommon, are also associated with vomiting. (2)

Risk factors for PONV are: female sex; non-smoker; history of PONV or motion sickness. use of volatile anaesthetics; use of nitrous oxide; use of opioids; high doses of neostigmine: duration of surgery.Prevention of PONV in high-risk patients

significantly improves postoperative ratings of well-being and satisfaction. , Metoclopramide has been used for decades to prevent PONV. Its antiemetic properties are primarily mediated through its anti-dopaminergic action and it also probably has prokinetic properties (3). Small doses of metoclopramide (10 mg) became established in clinical practice. However, this amount has been not proven to be clinically effective. Consequently, Wallenborn comparing either 10, 25, or 50 mg metoclopramide. The efficacy of 25- or 50-mg doses seems to be comparable to that of other well-established antiemetics (4).

Droperidol is a highly potent D_2-antagonist with well-proven antiemetic properties at intravenous doses as small as 0.625 to 1.25 mg for nausea, vomiting, and PONV. Furthermore, it is similarly effective compared with ondansetron, for PONV . Compared with placebo, droperidol is associated with increased sedation but with a decreased incidence of headache (5).

Diphenhydramine, cyclizine, and promethazine are effective for the prevention of PONV. Promethazine has also been reported to cause vascular necrosis requiring plastic surgery of skin lesions and/or limb amputations, leading to the FDA safety alert in 2006 (6)

Ondansetron was the first serotonin antagonist, and its introduction was a in the prevention of early chemotherapy-induced nausea and vomiting. It was considerably more effective and had fewer side effects (no extrapyramidal symptoms or sedation) compared with all previous antiemetics. This perception was further duplicate studies that, according to analyses by Tramer and coworkers,(7) would lead to a 23% overestimation of ondansetron's effectiveness if included in a meta-analysis. . ondansetron has a plasma half-life of 4 hours lead to decreased efficacy due to ultrarapid metabolism. (4)

Rhinoplasty is one of the most common operation that has done in Iran. PONV is a complication of rhinoplasty because the patients swallow much blood and because of closed of noise and use of opiod although use of prophylaxis of anti vomiting drugs but PONV is still sever.

The aim of this study is to evaluate the prophylactics effect of metoclopramide and ondansetron on PONV after rhinoplasty

Material and methods:

This is clinical trial, double-blind study performed in 100 patients whom were admitted for rhinoplasty .All patients are in ASA class 1. The operation was done with local anesthesia and intravenous sedation, With fentantyl, midazolam and infusion of remifentanyl. All patients who got general anesthesia or whom that have especial diseases are excluded from study .The population of study with power of study 80% and coefficient rate of 95% was calculated and with evaluation of past study was 50 case in eah group we interview with patients to be agreed with study. In the operation room the patients got intravenous sedation and local anesthesia. At the end of operation and before putting splint in the nose the patients were given ondansetron 4mg or metolopromide 10 mg IV. The drugs were injected by some one who didn't know the type of drugs. Blood pressure and pulse rate was controlled by nitroglycerin and propranolol. After operation in the recovery and in the ward the patienets were evaluated for nausea and vomiting ,also asked for their satisfaction. The data were added and examined by SPSS. the descriptive tests were analyzed by k2 test.

Results:

Mean of age of all cases was 25 year and the minimum of age were 16 year and the maximum of ages were 38 years in this group. Also in the ondansetron group the mean of age was 25.6 and in the metolopromide group the mean of age was 24.8 year .16 (16%)of all cases were male and 84 case (84%) were female. In the ondansetron group 12% 6 case were male and 44 case 88% were female.in the metoclopromide group 20% male and 80% female .The mean of weight in all group were 62.5 kg with standard deviation 9.74 that minimum of weight 50 kg and the maximum of weight was 85 kg .in the ondansetron group the mean of weight is 62.7 and in the metolopromide group was 62.3. the mean of the duration of operation is 99.2 minute and with standard deviation 24.5 with minimum time 60 minute and the maximum time 165 min .the mean of the time of operation in the ondansetron group was 97.8 min and in the metolopromide group 100.6 minute .in the all cases 42%case don't have PONV and 32% case have slightly PONV and 12% have moderatly PONV and 8% have sever PONV. In the ondansetron group 48% don't have PONV and 32% have slightly and 8%have moderately and 12% have sever PONV. In the metoclopromide group 36% don't have nausea and vomiting 44% have mild ,16%moderate and 4% have sever nausea and vomiting.there is not meaningful differene. The incidene of PONV in the 21 year group was sever in the 25 year was moderate and in the 27 year group was mild ,in the 24 year there wasn't PONV. 62% of male don't have PONV, 47% have mild PONV and no body has moderate or sever PONV.in the female group 38% don't have nausea and vomiting 38% mild ,14% moderate and 9% have sever PONV.

Relation of the duration of rhinoplasty with PONV in the mean of 101 minute there isn't PONV and in 99 min there is mild and moderately and in the 86 minute there was sever nausea and vomiting. Satisfaction of the patients 44% patients moderately satisfy, 56% have sever satisfaction.

Discussion

In the study of kumar effectiveness of ondansetron and metocolopramide was compared in 159 patients undergoing day-case obsterical and gynnecological surgery. Incidence of vomiting in ondansetron group was much less (20 percent) than control and metoclopramide (8).

In the study of sandhu in the eighty patients who underwent elective laparoscopic cholecystectomy. Ondansetron 4 mg given intravenously at the end of surgery is effective for preventing vomiting after laparoscopic cholecystectomy (9) also in another study comparison of ondansetron and dropridol, ondansetron was superior to droperidol when used with patient-controlled analgesia and causes less sedation. (10)

In the study of Wilson prophylactic administration of metoclopramide or ondansetron significantly reduces the incidence of postoperative vomiting for laparoscopic cholecystectomy, but neither drug was found to be significantly more effective than the other. (11) In the meta analyse of Karen B. Domino ondansetron tended to be more effective than metoclopramide in reducing postoperative nausea; (P = 0.125). (12)

In this study we saw that ondansetron 4 mg has the same efficacy as metoclopromide 10 mg in preventing nausea and vomiting after rhinoplasty.also there was no

correlation between weight and age ,duration of operation and the degree of PONV.. In our study also there was no meaningful difference of PONV in using metoclopromide and ondansetrone.

Conclusion:

With finding new drugs but there is not absolute management for prophylaxis of PONV and it needs more and more investigation.

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Sedation to prevent hypotensive-bradycardic events during surgery in the beach chair position

Jensen K, MD, BBA, associate professor; Børglum J, MD, PhD, MBA, associate professor

Department of Anaesthesia and Intensive Care, Copenhagen University Hospital: Bispebjerg, Denmark

Summary

The incidence of hypotensive-bradycardic events during arthroscopic shoulder surgery in the beach chair position with interscalene nerve block were investigated. Patients were divided into three groups according to preoperative anxiety and intraoperative demands for sedatives. For comparable levels of preoperative anxiety, we found that even small amounts of sedation increased the risk of hypotensive-bradycardic events. Furthermore, most of these events occurred at late stages of surgery, suggesting that diminished venous return rather than vaso-vagal reflexes were responsible for their occurrence, and that sedatives may blunt inherent haemodynamic corrections.

Introduction

Hypotensive-bradycardic events (HBE) occur in 7-29% of patients having shoulder surgery performed in interscalene nerve block (1-3). Its pathophysiology is complex and probably involves a combination of an activation of the Bezold-Jarisch reflex and/or a reduced cardiac preload due to venous stasis resulting from the beach chair position itself. The Bezold-Jarisch reflex is an autonomic reflex which paradoxically activates the parasympathetic nervous system causing HBE with bradycardia, hypotension, loss of consciousness and apnoea (4). While increased sympathetic activity precedes the reflex, it is triggered by sudden stressful sensory perceptions, anxiety, hypovolaemia, dehydration and upright posture (beach chair) with pooling of blood in the lower extremities.

Previous studies have found that many patients are fearful of anaesthesia and surgery (5); this anxiety is increased in women, the young, in patients about to undergo extensive surgery, and low familiarity with the procedures (6, 7). Furthermore, observational studies have shown that high levels of preoperative anxiety dispose to increased pain and disability following surgery (8, 9). Surgical anaesthesia can be

Table 1. The Amsterdam Preoperative Anxiety and Information Scale (APAIS).

- I am worried about the anaesthetic.
- The anaesthetic is on my mind continually.
- I would like to know as much as possible about the anaesthetic.
- I am worried about the procedure.
- The procedure is on my mind continually.
- I would like to know as much as possible about the procedure.

Table 2. HBE according to demographics.

	Event-free surgery	Surgery with HBE
N	159	31
Mean BMI	26.0	26.8
Males	52%	52%
Mean age	50 years	42 years

achieved for shoulder surgery with an interscalene nerve block. Surgical anaesthesia can be supplemented by infiltration analgesia in the port holes during surgery, but otherwise the patients are awake and alert. Intravenous sedatives during surgery are also often administered on demand. In principle, sedatives are thought to be beneficial by reducing patient anxiety and stress. However, studies suggest that the use of local vasoconstrictors and systemic opioids may in fact be related to the occurrence of HBE (10, 11). We wanted to investigate if sedatives were beneficial or counterproductive for the prevention of HBE during shoulder surgery in the beach chair position.

Methods

A cohort of 190 consecutive patients undergoing shoulder surgery were included. Surgical anaesthesia was provided by an interscalene nerve block using 20-40 ml of ropivacaine or bupivacaine. The interscalene nerve block was administered preoperatively guided by either ultrasound or electrical nerve stimulation. Patient characteristics were identified at the preoperative meeting, including the Amsterdam Preoperative Anxiety and Information Scale (APAIS, Table 1). On the day of surgery, all patients were placed in the beach chair position, with compression stockings to reduce venous

Table 3. HBE according to preoperative anxiety and sedatives given.

Patient groups	No sedative given	One sedative given	Several sedatives given
Anxious (APAIS >12)	38%	35%	76%
Risk of HBE	9%	21%	21%

Notes: An arbitrary cutoff point has been chosen for grouping patients according to low (6-12 points) or high (13-30) preoperative anxiety by the APAIS.

pooling in the lower extremities. No local vasoconstrictors were used. Sedation was graded according the number of sedatives used (no drugs; one drug; several drugs). Drugs used for sedation were midazolam, remifentanil and/or propofol. All patients had a Ramsay sedation scale of 2 (cooperative, oriented, calm) during surgery (12).

The APAIS was originally intended to replace the Spielberger State and Trait Anxiety Index (STAI) (13, 14) since it was considerably easier to apply and therefore more clinically useful. Its validity has since been documented and its use is increasing (15, 16).

Results

The overall risk of HBE was 16% (Table 2). HBE occurred more frequently among the young. Three patient groups were useful for comparison:

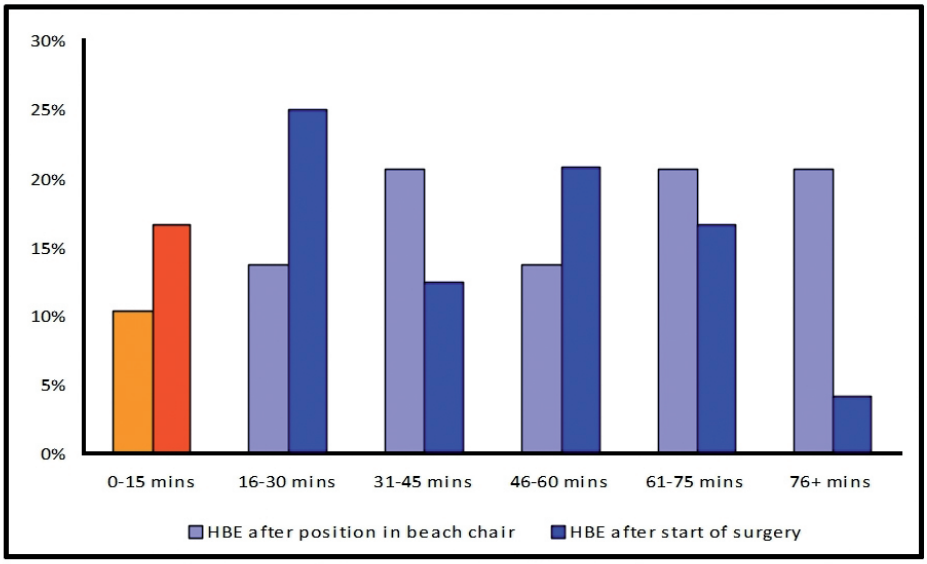
1. moderately anxious, no sedative given
2. moderately anxious, one sedative given
3. highly anxious, several sedatives given

We found that among patients where sedatives were administered, the highly anxious patients demanded stronger sedation, but the amount of sedatives did not influence the risk of HBE (Table 3). Among patients with comparable levels of preoperative anxiety, the use of sedatives was related to a significantly increased risk of HBE (Table 3). We investigated the time of occurrence of HBE in relation to positioning in the beach chair or start of surgery and found that most events occurred late and did not relate to stressful surgical events (Table 4).

Discussion

Whether sedatives are administered will depend on patient demands, department logistics and tradition. Strong sedation is frequently administered to anxious patients. Highly anxious patients (requiring strong sedation during awake surgery) are plausibly at increased risk of HBE by way of mental stress and vaso-vagal reactions. However, among comparable patients (in terms of anxiety) moderate sedation does not prevent HBE, and HBE most often occurs late. These results suggest that the pathogenesis of HBE may be caused by circulatory disruptions due to venous pooling during prolonged upright positioning rather than neurocardiogenic reflexes. Although the design of the study limits further conclusions, the results suggest that sedatives may blunt impor-

Table 4. The number of HBE occurrences at different time intervals after positioning in the beach chair or after start of surgery.



Notes: Shades of red denote the time interval in which anxiety-based reactions should most likely occur. Shades of blue denote the time intervals in which vasomotor reactions due to pooling of blood in the lower extremities are most likely to occur. It is evident that anxiety-induced HBE occurs infrequently, whereas late HBE seems to be the most prevalent.

tant autonomic functions. We conclude that all patients undergoing awake shoulder surgery where anaesthesia is provided by an interscalene block and where patients are subjected to the beach chair position must be closely monitored, that sedation should be kept at a minimum, and that a focus on fluid therapy is mandatory.

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S-Ketamine: Implications for the Military and Austere Medicine Community

Maani Christopher V., MD, Bahr Micah, MD*, Hansen Jacob J., DO**, Castro Leandro, MD*****

Anesthesiology Resident, San Antonio Uniformed Services Health Education Consortiuum, San Antonio, TX; **US Army Burn Center, US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, TX. * Anesthesiologist, Coordinator of Tactical Rescue, Special Operations Unit, Rio de Janeiro, Brazil.*
The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Introduction

The challenges faced by the men and women in today's military, as well as in the pre-hospital and austere medicine communities are distinctly different from the everyday challenges faced in a modern medical facility. The number and type of injuries can be overwhelming and catastrophic. The recent conflicts of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) have resulted in greater than 41,583 Soldiers, Sailors, Airmen, and Marines combined, who have been wounded in action. (1) A significant amount of these injuries are traumatic, involving multiple surgeries and leading to prolonged pain management. From 01 Sept 07 – 21 May 09 US service members presenting to Level 2 and 3 Theater Emergency Departments reported the following pain scores: Mild (Score of 1 – 3): 360 (24%); Moderate (Score of 4 – 6): 410 (27.4%); and Severe (Score of 7 – 10): 728 (48.6%). (2) Treatment of pain is vital to the care of patients and it is a serious and costly health problem. The American Pain foundation estimates that over 76 million Americans are affected by pain, which is more than heart disease, diabetes, and cancer combined.

Pain

Pain presents a serious problem both in civilian and military worlds. In a study of 970 OIF and OEF veterans from Southeastern VA, 82% (n=793 / 970) had pain scores documented. Of those with pain, 47% (n=369 / 793) of these had pain > 1/10 while 28% (n=219 / 793) had moderate to severe pain. Based on the VA national

policy that pain rated > 4/10 is considered to be clinically significant pain, 60% of patients with pain reported significant pain (219/369). (3)

Pain control has become increasingly important to many people and has emerged as one of the primary goals of medical treatment. Recent advances show this important trend. In 1982 the World Health Organization (WHO) expert group on cancer pain relief convened and developed the "three-step ladder" for analgesia. (4) In 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), developed new mandatory standards for pain assessment and management. In addition, in 2001 the U.S. Congress declared 2001 to 2010, the Decade of Pain Control and Research. Pain is a highly visible area of medical concern that makes a profound impact on millions of lives every day.

Pain is defined as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." *International Association for the Study of Pain (IASP definition)* Pain is subjective and a complex problem with multiple signaling pathways. Optimal pain control often requires a "pain soup" model, referring to the technique of utilizing several medications with different receptor targets to affect pain transmission, perception, and psycho-physiologic responses.

Pain is listed as the top-ranked postanesthetic problem, with up to 60% of post-surgical patients still significantly undertreated. In fact, 57% of surgical patients cited pain as their primary concern after surgery, yet only 42% of hospitals had acute pain management programs. (5) Some of the consequences of unrelieved postoperative pain include: increased heart rate, blood pressure, cardiac work, respiratory muscle spasm, diaphragm dysfunction, hypoxemia, impaired immune function, anxiety, increased hospital stay, and increased health care costs. (6)

Goals for pain management are aimed at decreasing the frequency and /or severity of the pain, and treating it as early as possible before pain amplification mechanisms aggravate symptoms further. Complete treatment of surgical pain via different mechanisms (ie: periphery vs spinal vs supra-spinal) is key. An opioid-sparing strategy is necessary to avoid opioid-induced hyperalgesia, and to minimize tolerance and dependence. Pre-emptive analgesia (PEA) reduces pain in the postoperative period. The best results occur when blockade of noxious stimuli is complete and extended into the initial postoperative period.

A current multimodal approach to pain management consists of NSAIDs, opioid narcotics, anti-depressants, anti-convulsants, ketamine or other NMDA antagonists, local anesthetics, corticosteroids, bisphosphonates, calcitonin, clonidine and Ritalin (methylphenidate). Nonpharmacological approaches may include acupuncture/pressure, hypnosis, or immersive virtual reality. Pain affects multiple systems and can cause serious long-term sequelae affecting immune function, healing, coagulation, the neuroendocrine system, and psychological effects. Complete pain-treatment strategies are dynamic and must account for all of these factors. A search for improved pain management adjuncts is vital to treat our Wounded Warriors as effectively and as completely as possible.

Military Needs

Even with all these approaches available to minimize pain and improve outco-

mes, today's treatment of pain in the military, at the point of injury and throughout the spectrum of care, is lacking. Today's military needs more options to treat pain early and effectively. Pain treatment on the battlefield is still predominately via the morphine auto-injector. While effective, it comes with the associated risks of slow onset, respiratory depression if given in high doses, and the duration of action makes it harder to titrate without exacerbating some of the side effects. Early pain therapy can help to minimize the occurrence of PTSD, which is a major factor in today's military. Early adequate treatment of pain in trauma allows for better postoperative pain control and decreased stress for the patient.

The military has specific objectives for medications to treat wounded warriors. Ideally these are medications that are safe and effective, with a long shelf-life, minimal cardio-respiratory effects, easily transported and portable, and stable in harsh environments and at the extremes of temperature & pressure. This leads to the ideal anesthetic and analgesic traits of a medication for battlefield use: proven effective in both anesthesia and analgesia; multiple routes of administration; easily administered and titratable; low volume for reduced logistical burden on medics; effective across a wide range of clinical needs and indications; stable with a good half life; and a minimal side effect profile. The availability of a medication fitting this profile will improve our service members' ability to stay in the fight and preserve the fighting force. Current practices for operative pain control are regional techniques, total IV anesthesia (TIVA), morphine or other opioids, or tolerating under-treatment in favor of patient stability. While some of these options work well, leaders still call for improved pain control; one that is safer, simpler, more effective, easy to push forward, with a minimal logistical footprint, low cost and high portability.

S-Ketamine

Ketamine is a medication (used as a racemic mixture of R and S-ketamine in the United States) that induces a state referred to as "Dissociative Anesthesia." It has a wide range of effects in humans, including: anesthesia; analgesia; sympathomimesis, with associated bronchodilation/relaxation, and elevation of blood pressure and heart rate. It is sometimes associated with hallucinations, which are more prevalent if treated with a single drug and close to the traumatic incident. Its use in trauma is favored because it helps maintain cardiac output, preserves respiratory drive, and prevents bronchospasm.

The (S) enantiomer of ketamine, used widely in Europe and South America for almost 2 decades, has favorable properties when comparing it with existing FDA-approved drugs on the battlefield (morphine and fentanyl). In comparison, S-ketamine has superior properties over fentanyl and morphine in regards to the rapidity of onset, cardiovascular stability, lack of respiratory depression, and the lack of tolerance and physical dependence with increasing concentrations, a known limitation in treating pain with opioids. (7,8) An additional benefit of S-ketamine is its noted ability to minimize or abolish the effects of opioid-induced post-infusion hyperalgesia in the postoperative setting. (9)

The pharmacologic properties of (S)-ketamine, while comparable to the racemic compound, represent a clinical advancement. When compared with R,S-ketamine, the analgesic and anesthetic potency of S-ketamine is two-fold greater, enabling a

50% reduction of dosage for comparable clinical results. The elimination half-life is decreased, allowing for more precise anesthetic titration to effect. In summary, the pharmacologic improvements of S-ketamine produce a reduced drug load and a more rapid recovery.

S-ketamine shows significant traits of the ideal battlefield pain management drug with its combination of analgesic and anesthetic properties, and the maintenance of cardio-respiratory function. At different doses, S-ketamine can be applied for use in analgesia, anesthesia, and conscious sedation. In addition, it has proven its outstanding importance in emergency and disaster medicine in civilian and military settings in Europe and Latin America, demonstrating minimal logistic requirements with the availability of intramuscular administration.

Vignettes

The ability of S-ketamine to maintain hemodynamic stability in trauma victims is demonstrated in the following vignettes, shared by our Brazilian colleague. (12) An adult male trauma patient suffered complex gunshot wounds to the right shoulder and hand. With developing shock and in severe pain, he was administered an initial dose of 40mg of S-ketamine as well as 2mg of midazolam. Subsequent doses of 10 and 15mg provided the patient with great pain control and stable hemodynamics during transport, enabling him to reach the OR for definitive treatment.

A second vignette that illustrates the hemodynamic stability of S-ketamine involved a complex thigh gunshot wound and hemorrhagic shock. A tourniquet was applied and the patient was administered 2mg of midazolam and 40mg of S-ketamine, enabling adequate stability so the patient could make it to surgery. Both individuals sustained major traumatic wounds, similar to what is seen daily on the front lines today. In both instances, use of the standard medication, morphine, could have been catastrophic, worsening hypotension and causing respiratory depression. S-ketamine, with its low cost, rapid onset, high potency, and rapid metabolism affords the medics and physicians on the front lines and in trauma, with a safe, effective, titratable medication, administered alone or in combination with a benzodiazepene, which can treat acute pain and provide hemodynamic stability so the patient has the chance to reach definitive treatment. While normally used in conjunction with a benzodiazepene to block potential hallucinations, as a single medication S-ketamine has been shown to have a decreased incidence of these negative psychotropic effects, in contrast to racemic ketamine. (10)

The Way Ahead

The ideal route for S-ketamine to obtain FDA approval is with an indication for ‘anesthesia’ with regulation as a schedule III drug, as R,S-ketamine is currently regulated. An indication for ‘analgesia’ could be explored at a future time. The 505 (b)(2) approval strategy for achieving FDA approval for use in the United States represents a timely, cost-effective way to make this drug available by utilizing prior studies on racemic ketamine data from Europe, and fast-tracking the approval process. (11) This would provide a meaningful and versatile supplement for rapid evacuation and medical treatment for the single casualty and for MASCAL incidents, especially for medics in the US military.

S-ketamine has a proven track record; it has already been used in tens of thousands of patients in Germany, Netherlands, India, Brazil, etc. Racemic ketamine, which is 50% S-ketamine, has been used in millions of patients. The initial proposed use of S-ketamine would be for military use at/near point of injury by medics as well as along the trauma continuum of care. As a support for '*point of injury'* use for acute trauma-related pain, S-ketamine is very stable at 40°C but the stability for use and storage at temperature extremes (below zero and zero to 50°C and 60°C) and with stress temperature cycling (high and low), is unknown. Additional funding and research into S-ketamine is warranted to evaluate and validate it for administration and treatment of trauma and battlefield casualties.

Trauma-related pain is a complex, but natural consequence of injury and medical management of combat-related injuries. Wounded Warriors need more effective analgesia on the battlefield and during transport to higher levels of medical care. Opioid narcotics are the current cornerstone of acute pain management, but significant negative effects include hypotension, apnea or hypoxia, sedation, confusion, nausea, ileus, hyperalgesia, immunosuppression and chemical dependence. The major objection to current non-opioid formulations such as racemic (R,S-) ketamine is the high incidence of neurocognitive disturbances. A novel non-opioid drug is needed for tactical environments, where an effective fighting force is maintained (with minimal mind-altering effects), improved hemodynamic profiles are realized and effective analgesia is provided to Wounded Warriors. Although not FDA approved, S-ketamine has been used in Europe for two decades and is a preferred analgesic for military and pre-hospital use considering potency is 2-3 times greater than R,S-ketamine. It maintains cardiopulmonary stability, has rapid onset and clearance, and offers multiple routes of administration for easier delivery in tactical environments. S-ketamine has a very favorable profile for consideration as a battlefield analgesic; faster and markedly improved pain control with improved toxicity profile; reduced incidence of altered metal status, hallucinations, and nausea/vomiting; and decreased abuse potential.

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Military Relevance of Total Intravenous Anesthesia with Target Controlled Infusion

Hansen Jacob J., DO*, Maani Christopher V., MD*

**US Army Burn Center, US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, TX.*
The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Introduction

Ongoing military operations have taken a significant toll on the lives of US and allied service members. To date, coalition forces have sustained more than 6986 casualties. (1) Of those, 5814 are direct US service member casualties, and over 41583 US service members have been wounded in action. (2) Provision of emergency surgical care to those wounded in the combat environment presents many unique challenges. Anesthesiologists and nurse anesthetists are challenged with providing safe and effective perioperative care for patients, despite limited resources in areas affecting medication and equipment availability, as well as logistical and systems limitations.

TIVA in the combat environment

The ability to provide total intravenous anesthesia (TIVA) significantly reduces the logistical and equipment burden on anesthesia providers. This becomes especially important in combat and other austere medicine settings, where every effort is made to reduce the impact of supplies and equipment required.

The utilization of TIVA in the combat setting for US forces has gained popularity in years. Forward surgical teams are equipped with mechanized pumps and anesthesia providers to operate them. Innovative providers have described successful efforts in delivering TIVA under more austere conditions, including medications delivered to the patient via a microdripper, with the anesthesiologist counting the drip rate under red-light conditions, to deliver the desired amount of anesthetic agent.

Vigilance is paramount in the provision of anesthesia care, and the need for continuous reassessment of the patient is a cornerstone of our profession. However, quality of care incrementally decreases, as the number of variables to observe increases. TIVA, with the need to manually adjust and re-adjust rates of infusion on

an ongoing basis, has become a second-line practice for many anesthesiologists. To a large degree, this is due to the lack of feedback relating to anesthetic level in the patient's system. Processed EEG monitoring, including bispectral index (BIS), has been generally validated (3), but presents its own significant logistical burden. Providers are left to make adjustments based solely on standard physiologic monitors.

The Combat Medic as first-line provider

The combat medic has evolved to play a vital role in the care of wounded service members. While all soldiers are trained to provide first-aid or "buddy care," the combat medic brings an exponentially expanded skill-set to the battlefront. Medics embedded in Ranger and special operations units bring an even greater capability. Extreme conditions on the battlefield, such as complicated polytrauma, enemy fire, and extended evacuation times, may require the combat medic to provide damage control surgical intervention to save the life of a soldier.

Under such circumstances, the combat medic would need the capacity to administer analgesics and anesthetics sufficient to care for the soldier safely. Currently, morphine and fentanyl lozenges are the only analgesics available to medics, other than NSAIDs. Select units with advanced capabilities may have additional resources, but this is not universal. Yet it is an enticing notion, that we might enable the combat medic to deliver TIVA to a wounded soldier under such austere circumstances. While marginally expanding the equipment required to be carried by the medic, it would incrementally enable life-saving care for soldiers that may otherwise perish.

Limitations to this are manifold, including inexperience and human error, increased cost of anesthetic agents, limited monitoring capabilities, and increased training burden on the medic.

Target-controlled infusion as a far-forward tool

Advances in target controlled infusion (TCI) systems to deliver TIVA provide a significant expansion of capability in combat medical care. Drugs such as opioids, propofol, and ketamine need to be administered when, where, and at the doses they are needed. Unfortunately, the therapeutic window for many analgesics and anesthetics is narrow, and even expert use is routinely associated with uncontrolled pain from underdosing, or hemodynamic and respiratory compromise from overdosing. Automated analgesic and anesthetic infusion could dramatically improve pain control and sedation of injured warfighters. Current TCI instruments are limited to those using a pharmacologic model to predict drug distribution in the patient, though none are FDA-approved, nor available for use by military medical providers.

A deployable closed-loop system would be a medical force multiplier that significantly improves care, safety and outcomes. Research has indicated that closed-loop systems for TIVA based on BIS values are superior to manually administered delivery. (7,8,9) Improved treatment of acute pain and stress also could decrease the incidence and severity of post traumatic stress disorder (PTSD).

A major obstacle that has blocked clinical use of target controlled infusion anesthesia (TCIA) has been the lack of a sensor that can detect the administered drug in blood or exhaled breath in a clinically relevant manner. Drug detection in combination

with relevant physiologic monitors and control algorithms could overcome regulatory hurdles and permit widespread implementation.

TIVA has been opposed by some due to a perception that it increases the cost of delivering an anesthetic. Some studies point to the intraoperative cost of TIVA-TCI technique being greater than alternatives. (4) Others have found no significant difference in the overall encounter cost, including the entire duration of care within the hospital for a specific surgical encounter. (5) This is largely due to an improved recovery profile. Data from psychometric testing of geriatric patients after general anesthesia showed that reaction times at 30 minutes were significantly shorter for the TIVA group compared to the volatile gas anesthesia group. (6) The geriatric population is considered especially vulnerable to adverse cognitive effects of general anesthesia.

Conclusion

The advantages of target controlled infusion technologies in TIVA systems are great, providing more stable hemodynamic control, more rapid recovery, and decreasing human error. The introduction of the technology to combat medicine environments would obviate a significant capability gap in the delivery of anesthesia.

A recent memorandum from the Surgeon General's Consultants in both Anesthesiology and Anesthesia Nursing also strongly supported the introduction of TCI technology at the forward surgical team (FST) and combat support hospital (CSH) levels. In discussions with these Consultants, the question of training of both Anesthesiologists (physicians) and Certified Registered Nurse Anesthetists in the use of TCI technology was explored; both stated that TIVA is among the skills taught to both groups of providers, and the introduction of TCI technology would be easily incorporated into the training programs without a need to extend the training period. While this support does not yet extend to combat medic capability, it does move us in the right direction, which is better care for the combat-wounded, with improved resource utilization.

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Efficacy and safety of analgesia based sedation of mechanical ventilated patients

Malenkovic V.M. [1],Vojinovic-Golubovic V[2], Nedic O[3], Marinkovic O[1]

[1]Department of Anaesthesia and Intensive Care Unit, CHC Bezanijska Kosa, [2]Institute of Radiology and Oncology, [3]Institute for Nuclear Energy, Belgrade, Serbia

Summary

The consequences of inadequate sedation and analgesia with patients undergoing mechanical ventilation can be substantial. Therapeutic sedation has inherent risks, particularly when excessive or prolonged. The pharmacodynamic effects of traditionally used sedative and opioid drugs are unpredictable and often prolonged in the critically ill patients for various reasons. The pharmacokinetics is altered with different volumes of distribution and elimination half-times. The opioid part of a sedation regime is kept to a minimum to protect against opioid accumulation and an unpredictable recovery/weaning from mechanical ventilation. The study compared the safety and efficacy of an analgesia based sedation regime using remifentanil with a conventional hypnotic-based sedation regime in critically ill patients requiring mechanical ventilation for up to 72 hours in comparison with a standard sedative regime of propofol and morphine. The efficiency of remifentanil was assessed by the primary endpoint of time from starting the study drug until extubation time. The safety profile of remifentanil was assessed by monitoring hemodynamic parameters and recording adverse events throughout the study period. Analgesia-based sedation with remifentanil was well tolerated. No significant difference in mechanical ventilation duration of critically ill patients and total mortality rate is noticed, but it is decided that it definitely improves the healing process in comparison to standard hypnotic-based sedation regimes in Intensive care unit (ICU) patients requiring ventilation for up to 72 hours.

Background

Mechanically ventilated patients sedation is necessary in terms of both medical and ethical reasons. Sedation choice usually influences recovery outcome, need for artificial ventilation and stay in the ICU. The objective of sedation is to have optimally sedated patients which means they are calm co-operative, comfortable and communicative. The inadequate treatment of pain can result in increased morbidity and mortality through

long-lasting psychological effects together with adverse hemodynamic changes. Studies have demonstrated that analgesia-based sedation with remifentanil allows effective provision of optimal sedation in mechanically ventilated patients.

Remifentanil, a potent selective-opioid agonist, is indicated for the provision of analgesia and sedation in the mechanically ventilated intensive care patients. Remifentanil has a number of benefits making it suitable for use as the opioid component in combined analgesia and sedation in the ICU. Remifentanil is a highly-potent opioid. Precise doses and infusion rate defining is a precondition of both adequate analgosedation and prevention of adverse effects. There is no opioid activity in period longer than 5-10 minutes after the infusion stops which helps faster levels of conscience and breathing problems estimation while it also creates a possibility for separation from the respirator.

Patients and methods

In this prospective, randomized, single-cantered study, a total of 60 patients, who had undergone abdominal surgery following six weeks, were postoperatively assigned to one of two treatment regiments for sedation in the ICU for up 72 hours. Patients in the first group (n=30) received remifentanil (6 mμ - 9 mμ /kg/ h). Patients in the second group (n=30) received propofol (20mg/h) and morphine (3mg/8h). Patients were sedated to an optimal Riker Sedation Agitation Scale (RcSAS) score of -1 or 1, Ramsy score (RS) of 1 to 3 and a pain intensity (PIS) score of 0 or2. Heart rate (HR) and mean arterial pressure (MAP), APACHE ll and SOFA score were continuously monitored throughout the treatment period and were recorded at the time of each bolus dose and/or change in infusion rate of any of the study drugs. Adverse effects were recorded from the start of the drug study until the end of the post-treatment period. Clinical estimation of patients is necessary*: sedated or aware patient.*

Sedation: analgesic protocol

- Remifentanil infusion: 0.1-0.15 μg/kg/min = 6-9 μg/kg/h = 0.4-0.6 mg/h with patients weighing up to 70 kg.
- Titrated remifentanil infusion: 0.025 μg/kg/min = 1.5 μg/kg/h = 0.1 mg/h for patients as of 70 kg to adequate sedation level, Ramsy 2-3.
- If analgesia is inadequate, morphine 3mg iv should be added.

Research results

There was no significant statistical difference in terms of age structure, body weight, physiological and pathological characteristics of patients by groups. (See. Table 1) From 30 patients receiving analgesia based sedation (ABS), 29 of the patients received remifentanil without the use of supplementary hypnotic agents. In the hypnotic based sedation (HBS) with 20/30 of patients morphine was used as the analgesic agent, titrated to obtain adequate pain control. The variation in the mean RSAS over 24 hours was -1 to +1 for remifentanil group and -2.7 to +3.0 in the comparator group (See. Table 1). The variation in the mean PIS over 24 hours was 1.5 to 1.6 for the remifentanil group and 1 to 3.7 for the comparator group (See. Table 1). Variation of MAP, HR,

Table 1

Patients data

Groups	Group 1 (Remifentanil)	Group ll (Propofol- Morphine)	p value
Number of patients	30	30	
Mean age (years)	65 ± 8,1	66,5± 7,0	NS
Male/female	21/ 9	23/ 7	NS
Mean weight (kg)	80± 12,7	83,9 ±12,1	NS
Type of surgery (E/H)	25 / 5	23 / 7	NS
RcSAS (-3 to +3)	-1 to +1	-2,7 to +3	□ 0,05
PIS (0-5)	-1,5 to +1,6	-1 to +3,7	□ 0,05

*There is a significant difference between sedation and pain intensity in group I and II. Values are mean ± standard deviation. *T* test. NS, not significant.

Table 2

Hemodynamic and respiratory parameters of patients according to groups

Hemodynamic and respiratory parameters follow-up in 72 hours	Group 1 (Remifentanil)	Group ll (Propofol-Morphine)	p value
MAP (mmHg)	60± 20	100± 40	□ 0,05
HR (beats per minute)	75±25	120± 40	□ 0,05
RR (breaths per minute)	12 ±6	18± 8	□ 0,05
pCO2 (kPa)	5,6 ±2,6	6,7± 3,2	□ 0,05

*There is a significant statistical difference ($p < 0,05$) in the mean arterial pressure rate (MAP), heart rate (HR), respiratory rate (RR) and partial carbon dioxide pressure in arterial blood between two groups. Values are number of patients with event; multiple entries per patient possible. Fisher's exact test, two tails, significance level 0, 05. NS, not significant.

and pCO2 was less in remifentanil than in control group (See. Table 2). There were significantly more adverse effects (See. Table 3) in the group ll (Propofol-Morphine) in comparison with the group l (Remifentanil).

Discussion

The care of patients in the ICU is highly challenging, not least because of differences between patients that can significantly affect the outcome of management. Age, personal characteristics, underlying disease, and the nature of the insult leading to admission to the ICU all profoundly affect the decision-making process for patient management. Sedation is a key part of treatment in the ICU. Patients adapt more easily

Table 3

Adverse effects profile

Adverse effects	Group 1 (Remifentanil)	Group 11 (Propofol- Morphine)	p value
Shivering	8/30	2/30	NS
Pain	1/30	10/30	< 0,05
Delirium	0/30	0/30	NS
Tachycardia	2/30	10/30	< 0,05
Hypertension	3/30	13/30	< 0,05

*Pain, tachycardia and hypertension are more frequent in group ll in comparison with group 1 (p< 0, 05). NS, not significant.

to intubation and mechanical ventilation when they receive the appropriate sedative and pain medication. Sedation must be individualized to the patient. Benzodiazepines may be appropriate for one patient, whereas propofol may be preferred for another. Many critically ill patients fall into special clinical situations that must be taken into consideration when instituting sedation. An analgesic-based approach ensures that the patient is pain-free and reduces the time spent in ICU.

Advantages of analgesic sedation regime in comparison with the hypnotic one are displayed in greater comfortability of both mechanically ventilated and the ICU staff. Patients are more cooperable with longer awareness periods, so recovery is much easier. Implementation of both diagnostic and intervention procedures is also much easier with patients cooperation. In hypnotic ventilation regime cooperation with patients is more difficult, awareness and sleep pace is disturbed and presence of pain can result in patients' agitation which disturbs recovery. Separation from the respirator is also more difficult with this ventilation regime. Remifentanil enables a shorter weaning time and a reduction in the time spent on mechanical ventilation compared with traditional opioid analgesics.

Conclusions

1. Analgesia-based sedation with remifentanil was well-tolerated.
2. No significant statistical difference in duration of mechanical ventilation of critically ill patients and total mortality rate is noticed.
3. Remifentanil improves the healing process in comparison to standard hypnotic-based sedation regimes in ICU patients requiring ventilation for up to 72 hours.

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Effect of high dose remifentanil on bispectral index during propofol anesthesia

Morimoto Yasuhiro

Department of Anesthesiology, Ube Industries Central Hospital

Summary

We evaluated the effect of high dose remifentanil on bispectral index during propofol anesthesia. The high dose (0.5 μg/kg/min) of remifentanil affects the EEG and results in low BIS values when comparing with low (0.1μg/kg/min) to moderate (0.25μg/kg/min) dose of remifentanil.

Introduction

Remifentanil is commonly used during propofol anesthesia. However, the effects of remifentanil on the electroencephalogram including bispectral index is complex. Remifentanil, when administered with propofol, is generally reported to have no effect on BIS (1) but occasionally found to results in an increase (2) or a decrease (3). In this study we sought to evaluate the effect of high dose remifentanil on bispectral index during propofol anesthesia.

Materials and Methods

Twelve patients scheduled for elective orthopedic surgery were enrolled in the study. The study protocol was approved by the IRB, and written informed consent was obtained from each patient.

Before the induction of anesthesia, the electrodes for BIS were applied to the forehead region. The EEG was monitored continuously by the using an Aspect A-2000 monitor. The EEG raw wave form, BIS, and spectral edge frequency 95% were recorded continuously during the anesthesia.

Anesthesia was induced by target controlled infusion of propofol with initial target blood concentration of 3 μg/ml, continuous infusion of remifentanil and rocuronium. The laryngeal mask airway (LMA) was inserted and the lungs were ventilated with 60% oxygen. Mechanical ventilation was adjusted to maintain an end-tidal carbon dioxide partial pressure of 35-40 mmHg. Noninvasive mean blood

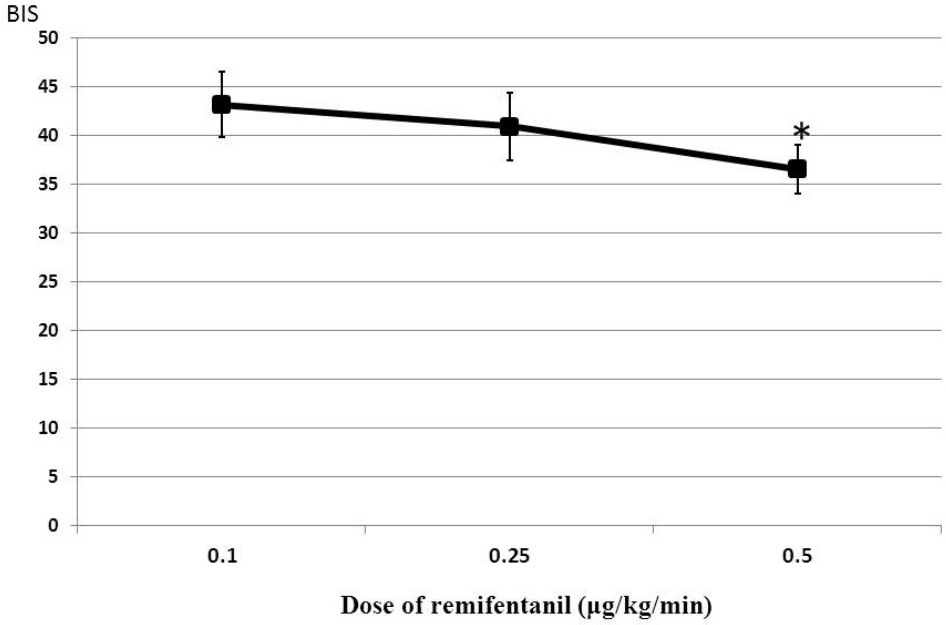

Figure 1

pressure (MBP), heart rate (HR) were monitored continuously and maintained within a normal range.

After LMA insertion, the target propofol concentration was adjusted to maintain the BIS values between 40 – 50 at remifentanil infusion rate of 0.1 µg/kg/min, then the target propofol concentration was maintained during the surgery. After start of surgery, the remifentanil infusion rate was adjusted to 0.25 µg/kg/min, then increased to 0.5 µg/kg/min. At each remifentanil infusion rate, the BIS values, SEF, MBP, and HR were recorded.

Results

The patient age were 35 ± 16 (15 - 54) yr. The male patients were ten and female were two.

The effect site propofol concentration after LMA insertion were 2.8 ± 0.6 µg with BIS values of 43 ± 3. The BIS values at remifentanil infusion rate of 0.5 µg/kg/min were significantly lower than those at 0.1 and 0.25 µg/kg/min (Figure 1). SEF at remifentanil infusion rate of 0.25 µg/kg/min and 0.5 µg/kg/min were significantly lower than those at 0.1 µg/kg/min (Figure 2).

The raw EEG wave form at 0.5 µg/kg/min showed low amplitude slow wave comparing to those at 0.1µg/kg/min and 0.25 µg/kg/min (Figure 3).

MBP and HR did not change significantly during the study.

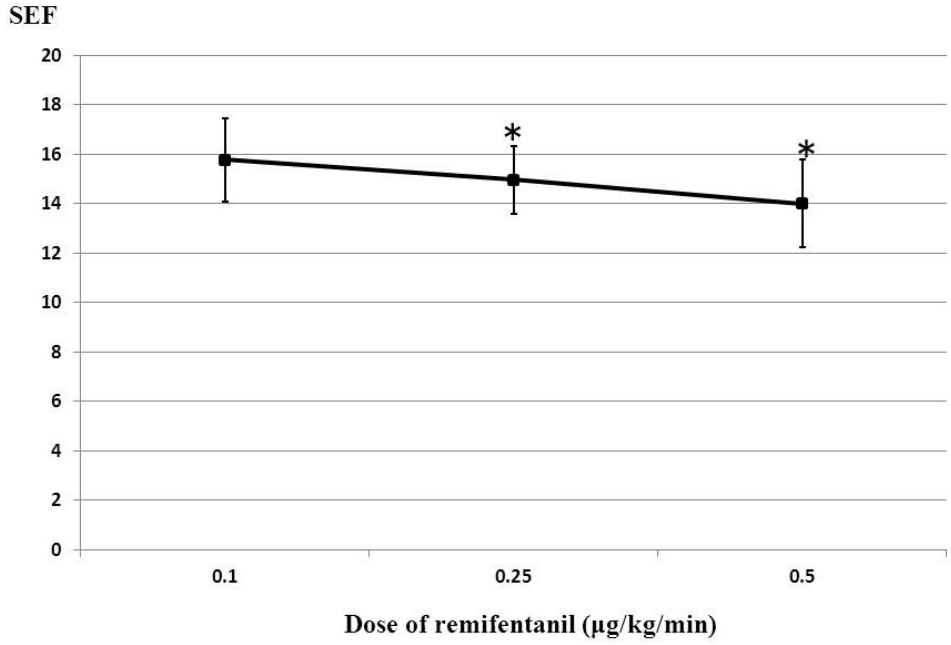

Figure 2

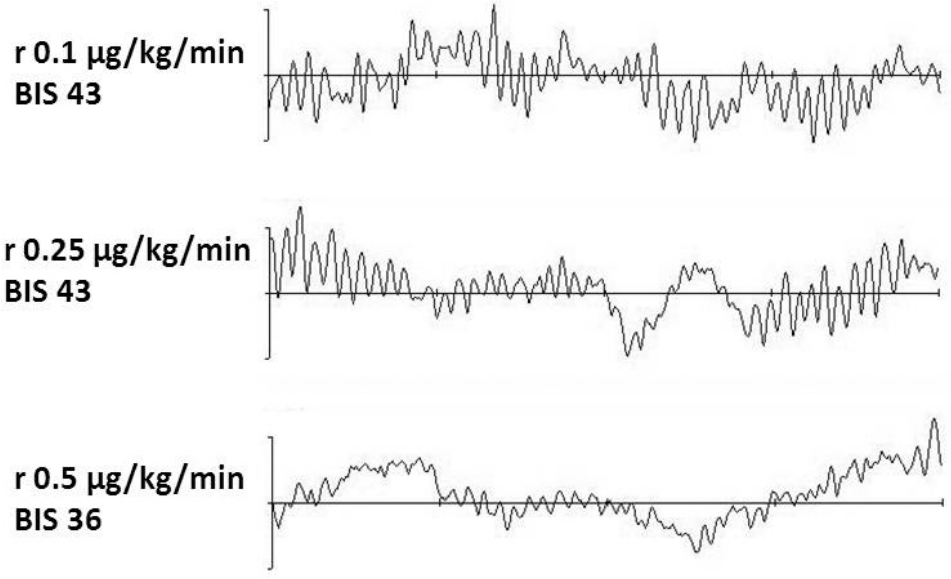

Figure 3

Conclusions

This study indicates that the high dose (0.5 μg/kg/min) of remifentanil affects the EEG and results in low BIS values. One case report indicate the EEG derived index during high dose of remifentanil might lose reliability and cause intraoperative awareness. Because high dose of remifentanil itself slows the EEG, the interpretation of BIS values should be paid attention.

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