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THE EARLY AND DELAYED ANALGESIC EFFECTS OF KETAMINE AFTER TOTAL HIP ARTHROPLASTY: A PROSPECTIVE, RANDOMIZED, CONTROLLED, DOUBLE-BLIND STUDY

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Abstract

The purpose of this study was to analyze the clinical presentation, treatment, and complications of malignant hyperthermia (MH) cases reported to the North American MH Registry from 1987 to 2006.

Background  MH is an inherited, autosomal dominant muscle disorder that results in a hypermetabolic state and is usually triggered by exposure to triggering agents, such as succinylcholine or volatile anesthetics. There have been no systematic evaluations of clinical characteristics associated with suspected cases of MH since 1970. Therefore, this study presents the epidemiologic characteristics of MH cases reported to the registry during 1987 to 2006.

Methodology  All MH registry adverse metabolic and/or musculoskeletal reactions to anesthesia (AMRA) reports between 1987 and 2006 were analyzed. Each AMRA report was ranked by an MH clinical grading scale (CGS) as “very likely” or “almost certain” to be an MH event. Cases were excluded if a pathological condition other than MH (e.g., Duchenne muscular dystrophy) or the surgical procedure were deemed to be a likely cause.

Result  A total of 47.9% (n = 286) of all AMRA cases met inclusion criteria. The table below provides a summary of case demographics:

<table>
<thead>
<tr>
<th>CGS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“very likely”</td>
<td>39.2% (n = 112)</td>
</tr>
<tr>
<td>“almost certain”</td>
<td>60.8% (n = 174)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>22 years (range, 116 days to 78 years)</td>
</tr>
<tr>
<td>&lt;19 years old</td>
<td>45%</td>
</tr>
<tr>
<td>Males</td>
<td>74.8%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>69.4%</td>
</tr>
<tr>
<td>Muscular build</td>
<td>29%</td>
</tr>
</tbody>
</table>
In a majority of cases, pulse oximetry (99.3%), capnography (96.2%) and temperature monitoring (90.9%) were used. In 10 cases skin liquid crystal temperature indicators did not accurately trend core body temperature (maximal temperature 40.0°C, range, 36.5°C - 41.2°C). Patients <19 years old were 11.6 times more likely to have received an inhalation induction alone, and had a shorter time to discontinuation of the volatile agent (45 minutes, range, 19-90 minutes) vs. patients >19 years old (112 minutes, range, 60-180 minutes) (P<0.0001).

For 255 cases there was a median of 4 signs noted (range 1-9) (i.e., masseter muscle spasm, hypercarbia, sinus tachycardia, muscle rigidity); the first and only sign in these cases was: hypercarbia (38%), tachycardia (31%) and masseter spasm (20.8%). The five most frequent clinical signs were hypercarbia (92.2%, n = 235), sinus tachycardia (72.2%, n = 186), rapidly increasing temperature (64.7%, n = 165), elevated temperature (52.2%, n = 133), and generalized muscular rigidity (40.8%, n = 104). Temperature abnormalities tended to occur late; they were the first to third sign to appear in 63.5% of cases (median = 3), with a maximum median temperature of 39.1°C. In 196 cases of MH (58.2%), both respiratory (ETCO2 >55) and muscular signs (masseter spasm or muscular rigidity, CK >10,000 U/L, or K+ >6.0 mEq/L) occurred.

The time between first sign and discontinuation of volatile was 10 minutes (range 2 to 30 minutes). Time to first dantrolene dose was 30 minutes (15 to 60 minutes). Patients administered dantrolene were 2.97 times more likely to have an “almost certain” case of MH. The most common adjunctive therapies included hyperventilation (87%), IV fluid loading (76.8%), active cooling (70.4%), bicarbonate (53.9%), anesthesia circuit change (48.2%), and mannitol (34.2%). At least one or more complication occurred in 34.8% of cases, with complications being 1.61 times more likely for every 30 minute increase in time between the first sign and first dantrolene dose, and 2.85 times more likely for every 2° C increase in maximum temperature. The median initial dose of dantrolene was 2.4 mg/kg, with total median dosage of 5.9 mg/kg.

**Conclusion** In addition to hypercarbia, sinus tachycardia or masseter muscle spasm, and temperature abnormalities may also be an early sign of MH. Accurate temperature monitoring may aid in the early diagnosis and treatment of MH.
It is essential that anesthesia providers be able to recognize and quickly treat MH, and this study I believe will help anesthesia providers achieve this goal. Some important points are that MH cases since 1987 occurred most often in young males who did not report a family history of MH, and had received ≥ 2 previous uncomplicated general anesthetics. The lack of a reported family history may be due, in part, to the lack of time to obtain an accurate family history, given the fact that 25% of MH cases occurred during emergency surgery. It is important for anesthesia providers to keep MH in their differential diagnosis, even if a patient has had no suspected MH events with past general anesthetics.

I think one of the most important points that I took from this study is that skin temperature probes are not very accurate in helping identify MH early. This latter point is critical given delayed diagnosis is associated with slower time to administration of dantrolene, and that the higher the temperature, the more likely complications will occur. Anything we can do to increase our odds of recognizing MH earlier will ultimately reduce the associated morbidity and mortality.

Dennis Spence, PhD, CRNA

The appendix in the article provides case histories for selected MH events that I encourage our subscribers to read. Below is a list of recommendations made by the authors:

1. Unless a thorough history and review of medical records reveals otherwise, any patient with a suspected history of an MH type event be administered a non-triggering anesthetic.
2. Do not recommend the use of liquid skin temperature probes for the detection of MH.
3. Do not withhold dantrolene or continue administering triggering agents when MH is suspected.
4. Given the rising obesity epidemic, in some locations of the country >36 vials of dantrolene may be needed (original recommendation was for 36 vials which was based on a 70 kg person).
5. Suggest that mannitol be added to MH carts and included on the MHAUS treatment protocol.
6. Recommend core temperature monitoring for general anesthetics that are >30 minutes.

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, Department of Defense or the United States Government.
abstract

Purpose The purpose of this article was to determine through preexisting literature if there is a link between degenerative neurological disease, aging, and anesthesia.

Background General Anesthesia is widely accepted as safe and effective. As our population ages, there is an increased societal burden to care for the aged. It is estimated that 100 million people will suffer from Alzheimer’s Disease (AD) by 2050. Determining whether or not inhaled anesthetic agents play a role in enhancing or increasing the level of neurocognitive decline in elderly patients as opposed to younger patients may influence our choice of anesthetic technique.

Methodology This article was a summation/analysis of the recent literature in both animal and human models. This was a review of current literature that relates to cellular changes of aging and the effect of general anesthesia.

Result As the result of a review of 58 articles related to aging and general anesthesia, the authors deduced that elderly patients are more susceptible to Post Operative Cognitive Dysfunction (POCD) than any other group. Since the long term effect of POCD in the elderly is poorly studied, there is a need for more research in this area. In animal models both Isoflurane and Sevo flurane induce the formation and/or activation of markers that initiate cellular changes or death. Because of the nature of inhalational anesthetics, they are highly lipid soluble and rapidly enter the brain in high concentrations. We do not know exactly how inhalation agents work. There is currently some concern that inhalation agents may increase the risk of cellular damage in certain at risk pathologies. An interesting fact is that POCD has the exact same set of risk factors as AD (age, educational level, and genotype). One study found that anesthesiologists had a significantly higher rate of Parkinson’s disease than internists.

Conclusion We do not know the full extent of what inhaled anesthetics do. More research is needed to find the answers. Since most people receive general anesthesia at some point in their lifetime, it would be helpful to know if individuals at higher risk for POCD and/or AD to choose the most appropriate anesthetic technique

Comment

I found this article to be interesting. I am not sure I am willing to leap to the same conclusions with an obvious lack of scientific research, but it is interesting nonetheless. There is no doubt that reports of Postoperative Cognitive Dysfunction will continue if not increase as the population ages. Future research will determine whether or not anesthesia contributes to neurodegeneration in susceptible individuals.

Gerard T. Hogan, Jr., DNSc., CRNA
DEXAMETHASONE FOR POSTOPERATIVE NAUSEA AND VOMITING PROPHYLAXIS: EFFECT ON GLYCAEMIA IN OBESE PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE

Eur J Anaesthesiol 2009;4:318-21

Nazar C, Lacassie H, Lopez R, Munoz H

Abstract

Purpose The aim of this study was to evaluate the blood glucose levels of bariatric surgery patients who have a history of impaired glucose tolerance, after they received IV dexamethasone following the induction of general anesthesia, for the purpose of preventing postoperative nausea and vomiting.

Background Dexamethasone is a synthetic adrenocorticosteroid demonstrated to be effective in preventing postoperative nausea and vomiting (PONV). Due to its glucocorticoid properties, it can induce hyperglycemia. For a variety of well understood reasons, the obese patient undergoing laparoscopic bariatric surgery is considered high risk for the development of postoperative nausea and vomiting. Dexamethasone is frequently used to prevent PONV in this patient population; however, since it induces hyperglycemia the patient with pre-existing impaired glucose tolerance may develop significant postoperative surgical complications related to elevated glucose levels. The researchers hypothesized that using dexamethasone for PONV prophylaxis in obese patients with impaired glucose tolerance worsens hyperglycemia postoperatively.

Methodology This study was conducted as a prospective, double blinded, randomized controlled clinical trial. Patients who gave written informed consent, ASA II or III with a history of impaired glucose tolerance and scheduled to undergo laparoscopic Roux-en-Y gastric bypass surgery, were enrolled. Using a computer generated randomization technique, patients were placed in to one of two groups: Group 1 received dexamethasone immediately after induction, 8 mg IV, and the control group, Group 2, received 2 mL of isotonic saline IV also immediately following the induction of anesthesia. Anesthesia was induced and maintained using a standardized protocol. Glucose measurements were made at the following times:

- Baseline—at the time of the IV catheter insertion (which was surgery room- in time)
- Every 2 hours after the beginning of the surgical procedure
- Continuing until the 12th hour following the start of the procedure

Blood glucose levels were not corrected during the study period.

Results Clinical and demographic data of those in the study did not differ significantly. Baseline blood glucose values were similar in both groups; 90 ± 10.8 mg/dL (5.0 ± 0.6) in the dexamethasone group versus 88.2 ± 9 mg/dL (4.9 ± 0.5 mmol 1⁻¹) in the control group. Blood glucose measurements taken from both groups after the beginning of surgery (at the 2 h time frame) were higher than baseline values. The between group comparison demonstrated that the dexamethasone group had higher blood glucose...
values compared to the control group beginning at the 6th hour after the administration of study drugs until the end of the study (12th hour) (P < 0.05). The numbers of measurements above 180 mg/dL (10 mmol 1⁻¹) from the 2nd to the 12th hour were significantly greater in the dexamethasone group (P < 0.0001). The highest blood glucose value obtained was in the control group, at the 8th hour, and measured 237.6 mg/dL (13.2 mmol 1⁻¹). The highest blood glucose value observed in the dexamethasone group was 235.8 mg/dL (13.1 mmol 1⁻¹).

**Conclusion**

This study demonstrated that obese patients who have impaired glucose tolerance undergoing laparoscopic Roux-en-Y bypass surgery developed post-operative hyperglycemia made worse by a single dose of 8 mg dexamethasone.

**Comment**

The evidence is conclusive: severe hyperglycemia causes decreased phagocytosis, impaired neutrophil chemotaxis, decreased superoxide radical production, and decreased granulocyte adherence. All of these ‘negative’ physiologic responses instigate a decreased immune function response and increase one’s susceptibility to postoperative surgical site infections. The bariatric patient already has several existing co-morbidities due to their large BMI that lead to impaired wound healing and predispose them to infections. Impaired glucose tolerance is very common in this population and only adds to this challenge. While we must acknowledge the significance of preventing postoperative nausea and vomiting in this patient population, we should be cognizant of the side effects of the medications we use and be very particular in treating all patients based on their unique individual physiologic state.

Mary Golinski, PhD, CRNA

Prediabetes, as defined by the American Diabetes Association (ADA), is the state that occurs when blood glucose levels are higher than normal but not high enough for a diagnosis of diabetes. According to the ADA, approximately 11% of people with pre-diabetes who participated in the ADA Prevention Program, developed type 2 diabetes during a 3 year follow up from the program. Other research has demonstrated that a moderate to large number of people with pre-diabetes developed type 2 diabetes within 10 years.

The ADA confirms that the term prediabetes is synonymous with impaired glucose tolerance.

The reader is referred also to the WHO Health Organization/International Diabetes Federation, Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia; 2006.

To convert mmol/l of glucose to mg/dl, multiply by 18.
THE RISK AND SAFETY OF ANESTHESIA AT REMOTE LOCATIONS: THE US CLOSED CLAIMS ANALYSIS


Metzner J, Posner KL, Domino KB

Abstract

Purpose This study evaluated the American Society of Anesthesiologists (ASA) Closed Claims database for anesthetic-related injuries and liabilities in remote locations to determine patterns of injury and liability.

Background Anesthesia services outside the OR have flourished in recent years due to the advent and improvement of numerous diagnostic and interventional practices, as well as cost containment and the overall "push" towards outpatient services, and patient desire for pain relief and loss of consciousness. Unfortunately, locations where remote anesthesia is performed are often unfamiliar environments that lack anesthesia support, resources, and are variable in monitoring capabilities (i.e., capnography).

Methodology This study reviewed the ASA closed claim database for claims resulting in adverse anesthetic outcomes. Of the 8,496 closed malpractice claims occurring from 1990 to the time of the review, only anesthesia associated claims in remote locations and operating room were reviewed. The reviewer of each claim analyzed it for theoretical preventability (additional or improved monitoring) and appropriateness of the anesthetic technique (categorized as standard, substandard, or impossible). Remote location and operating room claims were compared, and an in-depth analysis was done to assess any contributory role of sedation.

Result In this study 87 remote location claims were compared to 3,287 OR claims. The mean age in both locations was 48 y/o; however, 20% of the patients in the remote setting were ≥70 y/o, 69% were ASA 3-5, and 50% of remote cases were MAC. Mortality was significantly higher in the remote location when compared to the operating room (54% vs. 29%, P < 0.001). There were about twice as many respiratory events in the remote location (44% to 20%, P < 0.001). Inadequate oxygenation and ventilation occurred seven times more often in the remote location.

Within the remote locations, the GI suite had the most anesthesia associated claims (32%). Over sedation was identified in over half of the GI suite claims and more than half of these where associated with ERCPs and upper GI endoscopies. In the radiology suite, 70% of claims involved over sedation in the MRI scanner. Other disciplines associated with poor outcomes in remote areas included cardiology catheterization suites and emergency departments (25% and 20%, respectively). In 54% of remote location claims, anesthesia care was deemed substandard compared to 37% of OR claims (P <0.01). Complications were preventable in 32% of remote claims vs. 8% of OR claims, most frequently with better monitoring (P <0.001).

In 92% of cases resulting in death or brain death, over sedation was found to be the primary factor. Contributing factors associated with over sedation leading to respiratory depression were ASA 3-5 (54%), obesity (56%), age >70 years (27%), and the use of propofol. Additionally, most cases of over sedation involved a polypharmacy regimen. In these claims, anesthetic care was substandard in 86% of cases and the complication could have been prevented by better monitoring in 62% of claims. Capnography was used in a minority of these cases (15%).
Conclusion  

Administration of anesthesia in remote locations is associated with significant risk, particularly with MAC. With continued demand upon anesthesia to provide care outside the OR it is imperative the anesthetist maintain adequate knowledge of the pharmacokinetics of the drugs administered, be vigilant when assessing a patient's ventilatory status and ensure adherence to monitoring standards. Continuous monitoring of respiration with capnography is recommended, and general anesthesia may be safer than deep sedation in some patients and procedures (e.g., ERCP).

Comment  

Every person who participates in remote location anesthesia (i.e., Surgeons, Gastroenterologists, Cardiologists, Nurses, Anesthesiologists, CRNAs, and technicians) should read this article. It is very enlightening. The findings are sobering to me because it demonstrates the risk associated with remote site anesthesia.

The most common claim was secondary to over sedation with subsequent unrecognized respiratory depression during a gastroenterology procedure (EGD or ERCP) that resulted in death or brain damage. The biggest take home messages I got from this article were that we must be hyper-vigilant when providing anesthesia in remote locations and ensure we are using appropriate monitoring, especially when providing monitored anesthesia care.

Why do we need to be hyper-vigilant and what can we do to lessen the risk associated with remote site anesthesia? First, we are out of our comfort operating room zone, which has an anesthesia machine, monitors (e.g., capnography), extra equipment (i.e., difficult airway cart) and experienced support personnel who can quickly respond to emergencies. In some facilities it can take a considerable amount of time for another anesthesia provider to arrive, which might mean the difference between life and death. Second, remote locations are many times dark, cramped and suboptimal. Sometimes the patients are inaccessible (i.e., in the MRI scanner) or in less than optimal positions (i.e., prone for ERCP). These factors can make it difficult to recognize and manage an airway obstruction, especially if capnography is unavailable or not used. Third, remote site physicians, nurses, and technicians, while very good at what they do, may not have a firm understanding or appreciation for the comorbidities patients present with, the drugs we give, the risks involved, and how all three can contribute to a potential bad outcome. And, unlike an experienced OR nurse, personnel in these locations may not know what to do or how to help in the event of an emergency.

So what can we do to decrease the risks associated with remote site anesthesia? I think the key to minimizing risk is proper preoperative screening and preparation, having situational awareness, and open and clear communication with all personnel involved in the case.

1. Request an orientation to all remote locations prior to administering anesthesia in these sites. Know what equipment and drugs are available. Whenever possible during MAC cases, use a capnography monitor. Know where the crash cart is.

2. Have a firm understanding of the procedure, positioning, level of sedation, airway management required, and potential complications.

3. Think through a worst case scenario. What do I do if the patient becomes apneic in the prone position? What do I do if the patient has an anaphylactic reaction after receiving IV contrast? How do I call for help (code blue, pager, cell phone)? Who is available to help? How long will it take for help to arrive? What resources do I have?

4. Minimize polypharmacy whenever possible. In over half the cases in this study the provider co-administered propofol with benzodiazepines, opioids, or both. Think about the onset, duration, and synergistic effects the anesthetic agents may have on a patient who is at higher risk for complications (ASA 3 patient with obesity and OSA). Remember the peak effect may occur after the noxious stimuli.
5. Communication is critical. If you are concerned or feel a case is unsafe to be performed in a remote location, let people know who are making these decisions. Ask for an extra pair of anesthesia hands ahead of time. Clearly communicate your concerns to the provider performing the procedure and tell them what you think can be done to increase patient safety. If there is a problem during the procedure ask the provider to stop, if possible. You may have to be very direct in how you communicate, since the provider may be focused on the procedure and not realize that you are having problems.

Dennis Spence, PhD, CRNA

I would like to thank Eric Bopp CRNA, MS for his assistance in preparing this abstract.

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, Department of Defense or the United States Government.
THE EARLY AND DELAYED ANALGESIC EFFECTS OF KETAMINE AFTER TOTAL HIP ARTHROPLASTY: A PROSPECTIVE, RANDOMIZED, CONTROLLED, DOUBLE-BLIND STUDY


Abstract

Purpose The purposes of this study were to assess the effects of ketamine in combination with NSAIDs and acetaminophen on: 1) the total dose of morphine needed for postoperative pain (morphine sparing effect) and 2) ketamine’s ability to reduce the incidence of chronic pain.

Background Low-dose ketamine has been shown to reduce the need for morphine for postoperative pain. The mechanism of this morphine sparing effect is at least partially due to a central antihyperalgesic effect. Improving postoperative analgesia has been shown to result in improved rehabilitation after total joint replacement. Effective immediate postoperative analgesia has also been shown to reduce the incidence of chronic postoperative pain. Most previous studies have compared ketamine to placebo alone when assessing morphine sparing effects. Clinically, however, nonsteroidal antiinflammatory (NSAID) drugs and acetaminophen are commonly used as well. These drugs also demonstrate an antihyperalgesic effect. Ketamine may not provide additional analgesic effects in the presence of NSAIDS.

Methodology This prospective, randomized, double-blind study included adult patients undergoing total hip replacement. Exclusion criteria included chronic treatment with drugs for neuropathic pain, chronic oral morphine intake > 10 mg a day (or equivalent), and chronic cutaneous fentanyl administration.

All patients received premedication with either hydroxyzine or alprazolam (Xanax). General anesthesia was induced with 2-3 mg/kg propofol and 0.4 µg sufentanil. Anesthesia was maintained with up to 60% nitrous oxide and sevoflurane. Before skin closure, each patient received 1 gm acetaminophen IV and 50 mg ketoprofen (an NSAID, not to be confused with ketAMINE) and these doses were repeated every 6 hours for 24 hours. Primary postoperative analgesia was provided with morphine patient controlled analgesia (PCA). The PCA solution included 5 mg droperidol added to each 100 mg morphine. PCA was set to deliver 1 mg morphine with a 7 minute lockout, maximum 15 mg in 4 hours, and no background infusion. This morphine, droperidol, acetaminophen, NSAID pain management constituted the control group.

In addition to the control group analgesic regime, patients in the ketamine group received a bolus dose and infusion of ketamine. A ketamine bolus of 0.5 mg/kg (50 mg maximum) was administered IV between induction and skin incision. A ketamine infusion was run separate from the PCA morphine at 2 µg/kg/min for 24 hours (8.4 mg/h in a 70 Kg patient).

In addition to pain assessments while in the hospital, patients were called on postoperative days 30, 90, and 180 to assess pain location and intensity at rest and while walking.

Result The completed study included 75 control patients and 79 ketamine patients. Six patients were excluded from analysis because their surgery was cancelled or because of the discovery of exclusion criteria. Post-discharge follow up at days 30, 90, and 180 was completed for 74, 72, and 70 of the 75 control patients and 76, 75, and 72 of the 79 ketamine patients. Demographic characteristics were similar between the groups. PCA was used for two days by 66 patients in the control group and 63 patients in...
the ketamine group, for three days by 11 patients in each group, and for four days by 1 patient in each group.

Morphine consumption during the first day was 28% lower in the ketamine group (P = 0.004). The ketamine group also used less morphine during the first seven days postoperatively (P = 0.038). Pain scores at rest, getting out of bed for the first time, during the first steps, and the highest pain scores through day 7 were similar between groups.

After hospital discharge, ketamine patients stopped using crutches faster. Pain at rest was less frequent in the ketamine group at 30 days, 90 days, and 180 days (P = 0.008). At 180 days ketamine patients reported 67% less pain at rest than control patients. Also at 180 days, 21% of control patients reported pain at rest compared to 8% of ketamine patients. Also at 180 days ketamine patients tended toward reporting less pain while walking but the difference compared to control patients did not reach statistical significance.

**Conclusion**

A bolus dose of 0.5 mg/kg ketamine followed by a low dose infusion for 24 hours reduced the need for morphine analgesia even in the presence of multimodal analgesia with NSAIDs and acetaminophen. In total hip replacement patients, ketamine improved postoperative rehabilitation at 30 days and reduced pain at rest for at least 180 days.

**Comment**

I have long added 50 mg ketamine to my propofol induction sequence and my anecdotal observations confirm this finding. While “preemptive analgesia” may not be achievable in all patients following all types of surgery, I’m convinced it is a real phenomenon that can benefit our patients.

This fairly well done study showed that a modest dose of ketamine at induction followed by a very modest infusion for 24 hours reduced immediate postoperative pain a little bit. In the past, running an infusion during a general anesthetic was not uncommon, but in recent years production pressure has motivated us to skip infusions unless we really needed them. I doubt many of us would be too motivated to institute 24 hour ketamine infusions simply to reduce pain in the first postoperative day a modest amount. But the real news in this study, and what I hope is the motivation to become willing to run a ketamine infusion for 24 hours, is the easy to overlook information about the effects of low dose ketamine up to 6 months postop! Patients in the ketamine group reported significantly less pain than control patients 6 months after their surgery; and 62% fewer of them reported pain at rest.

Multimodal analgesia is key to both immediate postop and long term pain relief following orthopedic surgery. Ketamine is, I believe, the strongest NMDA receptor blocking drug feasible to use during general anesthesia. NMDA receptor blockade is one mechanism by which the central sensitization responsible for hyperalgesia can be prevented. A preincision ketamine bolus often significantly reduces postoperative pain. Adding an infusion of ketamine increases both the magnitude and duration of the pain control. It is gratifying to know that the little bit of extra work an infusion entails can improve a patient’s comfort for months after their joint replacement.

Michael Fiedler, PhD, CRNA
A COMPARISON OF PROPOFOL AND DEXMEDETOMIDINE FOR INTRAVENOUS SEDATION: A RANDOMIZED, CROSSOVER STUDY OF THE EFFECTS ON THE CENTRAL AND AUTONOMIC NERVOUS SYSTEMS

Anesth Analg 2010;110:415-418

Okawa K, Ichinohe T, Kaneko Y

Abstract

Purpose The purpose of this study was to compare the autonomic and anxiolytic effects of propofol and dexmedetomidine during light sedation.

Background Propofol is commonly used for sedation but causes respiratory and some cardiovascular depression. Dexmedetomidine produces sedation without respiratory depression and usually minimal cardiovascular depression. No studies have been performed comparing the autonomic effects and anxiolysis of propofol and dexmedetomidine during sedation.

Methodology This prospective, crossover, single-blind study included 25 healthy, adult, male volunteers who had not previously experienced sedation with either propofol or dexmedetomidine. Each volunteer experienced sedation with both drugs separated by a seven day period. The order in which they received the drugs was randomized. Prior to sedation, an IV was started and monitors were applied. Subjects were instructed to close their eyes except when performing a mental arithmetic task designed to be anxiety producing.

Baseline vital signs and mental arithmetic scores were recorded before sedation was begun. Then, anxiety was assessed with the Faces Anxiety Scale (FAS) scored from “0” (no stress) to “5” (worst stress) The FAS has previously been shown to correlate well with the Hospital Anxiety and Depression Scale. Saliva was collected to measure α-amylase, shown to correlate with psychological stress. Within two minutes after amylase collection an IV infusion of either propofol or dexmedetomidine was started.

Propofol was administered according to a “target-controlled” algorithm starting at an effect site concentration of 0.7 µg/mL. Dexmedetomidine was administered as a loading dose of 0.1 µg/kg and an infusion of 0.4 µg/kg/hour. These doses produced an Observer’s Assessment of Alertness / Sedation score of 4 (“Lethargic response to name spoken in normal tone” on a scale of 0 – “Does not respond to deep stimulus” to 6 – “Agitated”). The sedation level was planned to be “light” compared to often used clinical sedation levels. After the sedation infusions had been running for 10 to 15 minutes the second mental arithmetic test was administered. Once the mental arithmetic test was completed, vital signs, the Faces Anxiety Scale score, and amylase samples were collected.

Result Oxygen saturation values decreased only during propofol sedation, from 97.6% ± 1.0 to 96.9% ±1.1. The decrease was statistically but not clinically significant. Heart rate slowed slightly in both groups. Faces Anxiety Scale scores and the percentage of correct answers on the mental arithmetic tests decreased only in the propofol group (less anxiety). Saliva α-amylase
levels were lower in both the propofol and the dexmedetomidine groups (less psychologic stress). The reduction in α-amylase levels was 32% in the dexmedetomidine group but only 22% in the propofol group (P < 0.05). Propofol was preferred by 17 of 25 subjects. Dexmedetomidine was preferred by no subjects.

**Conclusion** Both propofol and dexmedetomidine inhibited sympathetic activation during psychological stress. Anxiety, measured by the Faces Anxiety Scale, was lower in the propofol group. Psychological stress, measured by α-amylase levels, was lower in the dexmedetomidine group. Propofol may be better than dexmedetomidine for sedation because it produced subjectively more pleasant feelings in those receiving sedation.

**Comment**

This study was headed in the right direction but it couldn’t figure out whether it was trying to determine which drug was most effective for sedation or which drug made subjects feel the most mellow. From what I know I have no doubt that propofol makes people feel “better.” Inexplicably, the investigators actually concluded that propofol was a better sedative based partially upon the Faces Anxiety Scale. Of course, the problem with that conclusion is that they measured anxiety with two tools and the other tool (α-amylase levels) showed dexmedetomidine to be the better antianxiety agent at these doses. Of course, we can change the doses. The doses in this study were pretty low, as evidenced by the infinitesimal reduction in oxygen saturation seen in the propofol group, who were not on supplemental oxygen. Problem is, if one turns the propofol up to produce deeper sedation, as is often the case clinically, some patients are going to have airway and breathing problems pretty quickly and everyone is going to have airway and breathing problems eventually. Not so with dexmedetomidine.

While propofol works well in our hands, we’ve done an airway assessment so we have an idea how big an airway problem is likely to be if an airway problem occurs and we can manage the airway if anyone can.

I continue to preach that the problem with anything but the lightest propofol sedation is the very narrow margin of safety, especially when opioids are coadministered. I encourage all of us to produce sedation with the greatest airway margin of safety possible. This not only makes our lives easier, it reduces patient risk, and it is a better example to non-anesthesia providers who often take their sedation cues from us. Dexmedetomidine has a much wider margin of safety in the area of respiratory depression. (Ketamine can also be useful especially in combination with propofol). I see dexmedetomidine’s lack of respiratory depression as more important than the fact that propofol feels better to patients and reduces one kind of anxiety better than dexmedetomidine. Adding a little midazolam to the dexmedetomidine will likely solve this problem and result in a much wider margin of safety.

Michael Fiedler, PhD, CRNA
MONITORED ANESTHESIA CARE WITH DEXMEDETOMIDINE: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL

Anesth Analg 2010;110:47-56

Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY

Abstract

Purpose The purpose of this study was to determine the safety and efficacy of dexmedetomidine as the primary sedative agent in non-intubated patients having monitored anesthesia care.

Background Current Monitored Anesthesia Care (MAC) techniques often include the use a combination of midazolam, fentanyl and propofol. Unfortunately, all of these agents can cause some degree of respiratory depression. A 2006 review of the American Society of Anesthesiologists (ASA) Closed Claim Database revealed that over sedation was a critical factor in MAC related anesthetic injury claims. Dexmedetomidine is a centrally acting α-2 receptor agonist that can be titrated to produce predictable sedation without respiratory depression. Dexmedetomidine also has analgesic-sparing effects, decreasing the need for supplemental opioid administration. There are anecdotal reports of successful dexmedetomidine sedation in a wide variety of practices including dental, orthopedic, and diagnostic imaging. Since there has been no rigorous multicenter evaluation of the use of dexmedetomidine for MAC, the authors developed and executed this study.

Methodology This study was a prospective, randomized, double-blind, placebo-controlled, Phase III study conducted at 26 investigational sites throughout the United States. The protocols were standardized and approved by all institutional IRBs. All patients scheduled for elective procedures performed in either an operating room or procedure room that required an anesthetic provider to be present and were expected to last a minimum of 30 minutes were eligible for enrollment. All patients were 18 years of age or older. Exclusion criteria included anyone who had received: (1) a general anesthetic within the past seven days, (2) an α-2 agonist or antagonist within the previous 14 days, and/or (3) an IV opioid agent within 1 hour of their elective procedure. Patients with unstable angina, acute MI, or diagnosed hypotension were also excluded.

Patients were randomized using a computer generated schedule. The treatment group received either 0.5 µg/kg or 1 µg/kg loading doses followed by a 0.6 µg/kg/hr infusion of dexmedetomidine or placebo prior to the procedure start. All patients received a local block before the procedure started. Patients were observed and assessed at predetermined intervals for level of sedation using the Observer’s Assessment of Alertness/Sedation Scale (OAA/S). Infusions were titrated to maintain a score of 4 or less. If sedation was inadequate, rescue midazolam was available to the anesthesia providers. Patients remained in PACU for one hour after the termination of the infusion. Chi square analysis of the data was accomplished, as well as two-sided t tests for data such as vital signs. Any P value greater than or equal to 0.05 was considered significant.

Result A total of 326 patients were included in the study, 134 received dexmedetomidine and 129 received a placebo. There were many interesting findings. A significantly lower number of dexmedetomidine patients required rescue midazolam...
compared to placebo. Significantly fewer patients in the treatment group required supplemental fentanyl. Assessment data showed that anesthesia provider satisfaction with sedation was significantly better in the dexmedetomidine group. Using the Iowa Satisfaction with Anesthesia Scale, patient satisfaction was significantly higher in the dexmedetomidine group. The only drawback noted was a significantly longer median time to recovery and readiness for discharge from PACU in the dexmedetomidine groups than in the placebo group. The most common adverse effect in the treatment group was hypotension. Co-administration of fentanyl and/or midazolam with study drug showed no statistically significant change in mean arterial pressure. The incidence of absolute respiratory depression (defined as a respiratory rate of 8 or less) was significantly lower in the dexmedetomidine groups than the placebo group.

**Conclusion**

Dexmedetomidine was an effective and well tolerated sedative agent that caused no significant respiratory depression, satisfactory sedation, and a decreased requirement for rescue drugs such as fentanyl or midazolam. Better anesthesia provider and patient satisfaction was noted in the dexmedetomidine group.

**Comment**

This was a very interesting article. As dexmedetomidine use moves away from the ICU (it’s original indication) and into anesthesia departments, a revolutionary change in the way we provide MAC will occur. I was disappointed to see that discharge from PACU times were prolonged. In many institutions PACU can be the “bottleneck” of patient movement through the perioperative continuum. I will actively seek opportunities to use dexmedetomidine in my current practice to produce my own conclusions. I believe that additional research is needed to delineate the types of cases that dexmedetomidine is ideal for. There is conflicting literature regarding its safety and efficacy in GI and cataract procedures. Time will tell if dexmedetomidine usage rivals that of propofol for MAC sedation.

Gerard T. Hogan, Jr., DNSc., CRNA
A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY TO ASSESS THE EFFICACY AND SAFETY OF FOSPROPOFOL DISODIUM INJECTION FOR MODERATE SEDATION IN PATIENTS UNDERGOING FLEXIBLE BRONCHOSCOPY

Chest 2009;135;41-47

Silvestri GA, Vincent BD, Wahidi MM, Robinette E, Hansbrough JR, Downie GH

Abstract

Purpose

The primary purpose of this study was to evaluate the safety and efficacy of fospropofol in patients undergoing flexible bronchoscopy.

Background

Benzodiazepines are often combined with opioids to provide sedation for flexible bronchoscopy; however there use may be associated with prolonged recovery times. Fospropofol, a water soluble pro-drug of propofol, has been reported to have similar pharmacokinetic / pharmacodynamic properties as propofol, that has been reported to have an acceptable safety profile.

Methodology

Subjects were randomized to receive fentanyl 50 mcg followed by either 2 mg/kg (non-therapeutic dose) or 6.5 mg/kg of fospropofol. Subjects could receive up to three supplemental doses to achieve a Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) score of ≤ 4 (measured every 2 minutes until fully alert by blinded observer). Subjects with a MOAA/S score ≥ 4 and purposeful movement could be administered supplemental boluses at ≥ 4 minute intervals. They received 25% of the initial dose in the 2 mg/kg group or 1.63 mg/kg in the 6.5 mg/kg group. ASA III & IV subjects, those > 65 years old, or subjects < 60 kg or > 90 kg had doses decreased by 25%. Sedation failure was defined as requiring > 3 supplemental boluses of fospropofol to achieve a MOAA/S scores ≤ 4.

The primary study end point was sedation success, defined as three consecutive MOAA/S scores of ≥ 4 after fospropofol administration and completion of the procedure without other sedatives or manual or mechanical ventilation. Secondary indicators included treatment success, provider and patient satisfaction, frequency of recall, supplemental fentanyl amount, level of and duration of sedation, and time to readiness for discharge (defined as Aldrete Score ≥ 9). Adverse Event (AE) frequency was analyzed.

Result

Data from 252 subjects from 24 centers was analyzed (2 mg/kg: n= 102; 6.5 mg/kg: n=150). Greater than 40% of all subjects were > 65 y/o with 37.3% in the 2 mg/kg group and 46% in the 6.5 mg/kg group, being ASA 3 or 4. Sedation success was significantly higher in the 6.5 mg/kg group (88.7% vs. 27.5%, P<0.001), as was treatment success (91.3% vs. 41.2%, P<0.001). Sedation failure was defined as requiring > 3 supplemental boluses of fospropofol to achieve a MOAA/S scores ≤ 4.

A total of 13 of 24 (54.2%) subjects who went to deep sedation (MOAA/S score of 0 or 1) experienced sedation-related Adverse Events, compared to 17 of 125 (13.6%) patients with minimal or moderate sedation (P<0.0001). Median time to sedation and median time to full alertness was shorter in the 6.5 mg/kg group (4.0 min and 5.5 min, respectively) compared to the 2 mg/kg group (18 min and 3 min, respectively). Median time to readiness for discharge was approximately 8 min in both groups. Provider and patient satisfaction scores were higher in the 6.5 mg/kg group. Significantly more patients in the 6.5 mg/kg group said they would...
receive fospropofol again (94.6% vs. 78.2%, P<0.01). A total of 83.3% of subjects in the 6.5 mg/kg group compared to 55.4% in the 2 mg/kg group had recall of the procedure (P<0.001).

Adverse events were self-limiting, transient, and of mild to moderate severity. Paresthesias (47.6%) and pruritis (14.7%) were the most common AEs. The most common cardiopulmonary AEs were hypoxemia (14.3%) and hypotension (3.2%). In the 6.5 mg/kg group, 21.5% of subjects required some form of airway assistance (i.e., increased O2 flow, jaw thrust) compared to 13.6% in the 2 mg/kg group. One subject in the 6.5 mg/kg group had a 3.1 min apnea/hypopnea event which occurred 14 min after the first fospropofol dose.

**Conclusion**

Fospropofol provides effective, predictable moderate sedation with an acceptable safety profile for patients undergoing flexible bronchoscopy.

**Comment**

This study was one of the last phase 3 studies sponsored by the drug manufacturer of fospropofol (MGI PHARMA, Inc, Bloomington, MN), prior to the drugs approval by the FDA in December 2008. Fospropofol (Lusedra®) is currently being marketed by Eisai Inc. (New Jersey) as an agent for providing monitored anesthesia care (MAC). It has also been labeled as a Class IV Controlled Substance. The FDA has required labeling that fospropofol should only be administered by persons trained in the administration of general anesthesia and not involved in conducting the procedure.(1) This is despite, what I assume, was active lobbying by some professional organizations (e.g., American Society for Gastrointestinal Endoscopy) who feel that propofol and fospropofol can be safely administered by RNs under the supervision of gastroenterologists.(2) In fact the authors of this study stated they administered fospropofol without anesthesia supervision because it is not a general anesthetic and was being used to provide moderate sedation only. Many gastroenterologists and pulmonologists(3) feel because fospropofol is not an induction agent that they can safely supervise RNs administering the drug. I think this latter statement reflects an under appreciation for the potential cardiopulmonary effects of this drug as well as propofol. As can be seen in this study, 14.3% of patients administered larger dose experienced hypoxemia with an SaO2 < 90% for >30 sec; and 21.2% required some form of airway assistance with the recommended dose of 6.5 mg/kg. Fortunately, it appears that the statements provided by the ASA and AANA to the FDA contributed to the stricter labeling requirement.

Overall, this was a well designed study. The authors did not compare it to traditional sedation regimens used by pulmonologists (i.e, midazolam and fentanyl), but rather chose to combine a non-therapeutic fospropofol dose (2 mg/kg) with fentanyl. Therefore, based on these results, it is difficult to determine how fospropofol compares to these drugs. Additionally, future anesthesia studies should compare fospropofol with propofol in a similar population.

Looking at the results it would appear that time to readiness for discharge was similar (approx. 8 min) with both doses, which is not surprising with the lower dosage given more midazolam and fentanyl was required to provide adequate sedation.

The results for the 6.5 mg/kg dose demonstrate that it has a longer onset time (~4 min) than propofol. This latter finding is important because providers administering this drug may be tempted to administer an additional dose sooner or supplement with other sedatives or opioids before the peak effect occurs. In my opinion this is one of the most important points that anesthesia providers should consider when administering this drug, and supports the argument that only anesthesia providers should administer fospropofol, because of our in-depth understanding of the pharmacokinetic / pharmacodynamics of these medications and how they interact with patient comorbidities.

The safety data from this study were similar to other studies, which found paresthesias and pruritis (i.e., perianal itching) were the most common side effects. These side effects are common with agents that contain phosphate ester formulations. Given that fospropofol is converted to propofol, it is no surprise that most common cardiopulmonary adverse events were hypoxemia (14.3%)
What is concerning from this study is that one subject had a 3 min apneic event 14 min after receiving an initial bolus. I would like to have seen more information on the patient such as ASA status and comorbidities. Additionally, the authors should have presented the median with the range, or minimum / maximum, for certain outcome variables (i.e., median time to sedation, median to full alertness, readiness for discharge). This information would allow the reader to better evaluate the safety and efficacy of the drug, as well as help in anticipating how long it will take for drug onset and duration of action. Thus, future prospective studies are needed to evaluate these effects and determine the safety of the drug in large, diverse populations undergoing monitored anesthesia care.

One important point that should be made is that the researchers with MGI PHARMA, Inc, who published the original pharmacokinetic studies on fospropofol, have since reported problems with the assay, which may invalidate results of six previous studies.(4) The editors of Anesthesiology, Anesthesia & Analgesia and the European Journal of Anesthesiology response to this issue is to recommend more studies to verify the pharmacokinetic results, and that if these studies are not completed that all previous pharmacokinetic studies published in these journals will be retracted. Anesthesia providers should thus read these previous studies cautiously and be careful in basing clinical decisions on those published pharmacokinetic results.

Dennis Spence, PhD, CRNA


Fospropofol labeling recommends a starting bolus dose of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg as needed, and should not exceed an initial bolus of 16.5 mL and the supplemental doses should not exceed 4 mL apiece. Patients age 65 years or older or who have severe systemic disease should receive 75% of the recommended doses. Patients with extremes of weight >90 kg or <60 kg should receive doses intended for a 90 kg person or 60 kg person, respectively.1

This topic was requested by Katherine Wang, CRNA.

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, Department of Defense or the United States Government.