There are two topics in this issue of Anesthesia Abstracts that I believe many of you will be especially interested in and which are exceptionally timely. The first examines the role of beta blockers in preventing perioperative cardiovascular complications in high risk patients. As you may know, for some time now there have been conflicting reports on the benefit of perioperative beta blockade in patients at high risk for postoperative cardiac events. Some studies have shown great benefit while others have not. From time to time biomedical journals publish early reports online before they appear in the “official” paper copies of the journal. Fortunately for us, Dr. Mary Golinski, PhD, CRNA noticed a pre-release of the Peri-Operative Ischemic Evaluation (POISE) trial on the website of the journal, LANCET and has reported on it in this issue. The findings are quite remarkable, and, at the same time, somewhat bewildering. We will update the web site with the citation for the POISE trial report when the article is published in LANCET.

The second topic of special interest is a series of three case reports about the use of 20% lipid emulsion for the treatment of local anesthetic toxicity. We have been following reports of the successful treatment of local anesthetic toxicity with Intralipid closely. Some cases report recovery from local anesthetic toxicity that is quite amazing. Evidence is rapidly mounting that an infusion of 20% lipid emulsion should be considered as an early treatment for local anesthetic toxicity. The three reports included in this issue add to that evidence.

I hope you find this issue of Anesthesia Abstracts enlightening and take advantage of the Continuing Education credits. It is our mission to provide the discerning anesthetist with up-to-date resources for evidence based practice. Your comments and suggestions are always welcome.

Michael A. Fiedler, PhD, CRNA

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DOES THE TIMING OF TRACHEAL INTUBATION BASED ON NEUROMUSCULAR MONITORING DECREASE LARYNGEAL INJURY? A RANDOMIZED, PROSPECTIVE, CONTROLLED TRIAL


Abstract

Purpose The purpose of this study was to evaluate the connection between degree of muscle relaxation at the time of intubation and the incidence of laryngeal injury.

Background Postoperative hoarseness (PH) and sore throat (ST) are associated with vocal cord injury (VCI). Factors that have been found to contribute to laryngeal intubation trauma in previous studies include sex, weight, smoking, GI reflux, endotracheal tube size, cuff design and pressure, stomach tube, use of a stylet, and duration of surgery.

A previous study conducted by these authors demonstrated that using a neuromuscular blocking agent prior to intubation, as opposed to normal saline, resulted in fewer incidences of VCI, PH, and ST. Those who were given blocking agents had a laryngeal trauma incidence of 12% while those given normal saline had an incidence of 42%. During the previous study, the role of block intensity was not examined. This study examined the association between poor neuromuscular blockade at the time of intubation and an increased incidence of PH, ST, and VCI.

Methodology Sixty (60) adult patients between the ages of 18 and 70 years were studied. All the patients were either physical status I or II and undergoing elective ear surgery. The study excluded patients with pre-existing vocal cord pathology, ST, hoarseness, obesity, and those with a suspected or known difficult airway. Patients were randomly divided into two groups of equal size. Group one was intubated two minutes after the administration of a non-depolarizing muscle relaxant. Group two was monitored for optimal neuromuscular block prior to intubation. The anesthetic induction technique and depth of anesthesia was standardized and the patients were all initially ventilated with 100% oxygen by facemask. Ten minutes into the induction, each patient was given 0.5mg/kg of atracurium. In group one, the patient was intubated exactly two minutes after injection of the atracurium. In group two, the patient was intubated when monitoring indicated maximum twitch depression. All tracheal intubations were performed by the same anesthesia provider. Also standardized was tube size, use of stylet, use of lidocaine gel and intracuff pressure. All patients were examined prior to surgery to exclude anyone with preoperative VCI, and again at 24 hours and 72 hours to indentify post operative VCI. Patient questioning was conducted on post op day one, two, and three to determine the presence or absence of persistent ST or PH.

Result After excluding five patients because of post induction identification of a difficult airway, the study included 27 patients in group one (two minute group), and 25 patients in group two (monitored group). There were no significant differences in demographic data, duration of anesthesia, intubation time or intubation attempts between the two groups. Excellent intubation conditions existed more frequently with the monitored group. Intubation time for the monitored group was significantly longer than the two minute group (120-320 seconds).

VCI was present postoperatively in 14 patients, PH in 15 patients, and ST in 19 patients. The difference between the groups in any of the three categories was not significant.
**Conclusion**

The study demonstrated that better intubation conditions were obtained with monitoring the twitch response to atracurium rather than waiting a fixed period of time (two minutes) prior to intubation. However, excellent intubation conditions did not result in less VCI, PH, or ST.

**Comment**

This study was well done, well controlled, and provided what I think was a surprising result. In spite of more excellent intubating conditions when the patient’s block was monitored, it did not result in a decreased incidence of vocal cord injury, sore throat, or postoperative hoarseness. I do not think you could find a better controlled study where you can pretty much control all of the variables such as anesthesia technique, provider, depth of anesthesia, surgical procedure, and many other factors. Few studies in anesthesia can be this well controlled.

I did find this research team’s prior study a bit interesting. Comparing patients intubated with a neuromuscular blocking agent verses those intubated with normal saline? There are just some studies that you have to give the “duh” factor to. Few of us could imagine intentionally shoving an endotracheal tube through a set of unparalyzed vocal cords without expecting significant trauma.

I do think this study revealed something very important. The importance is that arbitrary time to intubation techniques that many providers use (two minutes) may not be adequate in many patients. This results in suboptimal intubation conditions which may not result in more tracheal trauma according to this study, but it sure can contribute to provider stress. It would only make sense that suboptimal conditions in the hands of less experienced providers may indeed result in a higher incidence of tracheal trauma.

Steven R Wooden, MS, CRNA

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THE EFFECTIVENESS OF 4% INTRACUFF LIDOCAINE IN REDUCING COUGHING DURING EMERGENCE FROM GENERAL ANESTHESIA IN SMOKERS UNDERGOING PROCEDURES LASTING LESS THAN 1.5 HOURS

AANA J 2008;76:105-108

Wetzel LE, Ancona AL, Cooper AS, Kortman AJ, Loniewski GB, Lebeck LL

Abstract

Purpose The purpose of this study was to determine if the installation of 4% lidocaine in the endotracheal tube cuff of smokers undergoing short anesthesia procedures would reduce the incidence of postoperative coughing.

Background Stretch receptors in the trachea are prone to stimulation by the endotracheal tube. This is pronounced in smokers, occurs most frequently on emergence from anesthesia, and can create postoperative complications such as increased intraocular pressure, increased intracranial pressure, dysrhythmias, hypertension, wound dehiscence, and bronchospasm. Because the stimulation is superficial, it is possible that the use of a local anesthesia at the stimulation site might reduce this response. Intravenous narcotics, intravenous and topical lidocaine, and deep extubation have been used to reduce the cough response. Each has limitations, however. Finding an effective method to reduce the cough response with minimal complications may lead to reduced postoperative morbidity.

The study was limited to smokers because of the increased airway reactivity demonstrated in these patients. Previous studies using intracuff lidocaine were completed on procedures lasting longer than 1.5 hours, and successfully demonstrated a benefit to its use. This study focused on shorter procedures to determine if lidocaine would diffuse across the cuff membrane in shorter periods of time.

Methodology Patients were selected who were older than 18 years, smoked at least one half pack of cigarettes per day, and were classified as physical status I – III. Patients who could be harmed by post operative coughing, had respiratory infections, airway pathology, or trauma were not included. Procedures lasting less than 1.5 hours were selected. This was a randomized, double blind study evaluating the effectiveness of 4% intracuff lidocaine on reducing post operative coughing. Prior to each qualifying procedure, the anesthesia provider was given a 5cc syringe to fill the endotracheal tube cuff. Each syringe was either filled with normal saline (control) or 4% lidocaine. The provider was blinded to the content of the syringe.

Post operative cough assessment began at the time all anesthetic gases were turned off and 100% oxygen was administered. Coughing was defined as “forceful expiration after inspiration.”

Result Thirty eight (38) patients were included in the study. Demographic data and confounding variables such as narcotic use and intravenous lidocaine use was not found to be significant between the two groups. Zero coughs were counted in 3 patients from the lidocaine group and 5 from the saline group. Each group had the same number of patients reporting coughs of between 1 and 30, and the same number between 31 and 60.

Conclusion Lidocaine has been demonstrated in a number of studies to be effective in reducing the cough reflex especially when applied to the airway topically. Some success has been reported as well with intravenous lidocaine. Studies reviewing the use of intracuff lidocaine indicated that the polyvinyl membrane allows diffusion of lidocaine across it. It appears that this lidocaine...
diffusion is both concentration and time dependent. This study concluded that there was no significant decrease in emergence coughing between the control and study groups. This study did not preload the cuffs, did not evaluate cuff pressures, and defined cough very broadly. Each of these items, if handled differently, might have changed the outcome of the study.

Comment

I was intrigued by the concept behind this study, but disappointed in the study’s limitations. The post study power analysis indicated that almost twice as many patients were needed in order to obtain significant findings. The lack of sufficient study subjects is one of many reasons I find the results of this study lacking. From a clinical point of view I think it is important for practitioners to be able to dissect a clinical study and determine if it is valid for their practice or even valid at all. I am not trying to say that this particular study is useless. I appreciate the attempt by these researchers to evaluate an interesting approach to a common clinical problem.

I agree that post operative coughing, especially in the smoking population, can create problems. It certainly is appropriate to look for new and creative ways to decrease the cough response while minimizing side effects. The Fagan and Sconzo studies mentioned in this article showed promise for the use of intracuff lidocaine in longer cases, but it is possible under more controlled circumstances that intracuff lidocaine could provide benefit in shorter cases.

Steven R Wooden, MS CRNA


**Cardiovascular**

**EFFECTS OF EXTENDED-RELEASE METOPROLOL SUCCINATE IN PATIENTS UNDERGOING NON-CARDIAC SURGERY (POISE TRIAL): A RANDOMISED CONTROLLED TRIAL**

Published as an early release article by the Lancet. When the article is published in the regular issue of the Lancet this citation will be updated on the Anesthesia Abstracts web site. The article is currently available at www.thelancet.com

The POISE study group

**Abstract**

**Purpose**

Research conducted thus far regarding the efficacy (defined as improving outcomes by minimizing cardiac events) of peri-operative beta-blockers for non-cardiac surgery remains contentious. The purpose of this study (POISE = Peri-Operative Ischemic Evaluation Trial) was to investigate the effects of perioperative beta-blockers in those undergoing non-cardiac surgery.

**Background**

Approximately 1% of patients worldwide who undergo non-cardiac surgery will experience major cardiovascular complications. These non-cardiac procedures are known to precipitate a rise in intrinsic catecholamines resulting in tachycardia, hypertension, and increased free fatty acid concentrations. The result is an increase in myocardial oxygen demand which can be, and often is, detrimental. Beta-blockers attenuate the effects of this rise in catecholamines and may prevent perioperative cardiovascular complications.

Many of the clinical trials conducted to date are flawed for a variety of reasons; however, a metaanalysis of non-cardiac surgery randomized controlled trials does suggest that beta-blockers may prevent major cardiovascular events. But this decrease in cardiovascular events sometimes comes at a price, increased risk of clinically significant hypotension and bradycardia. The POISE study was conducted to compare the effects of extended release metoprolol succinate with placebo on the 30-day risk of major cardiovascular events in those undergoing non-cardiac surgery who had, or were at risk for, atherosclerotic heart disease.

**Methodology**

This study was conducted as a randomized, controlled, clinical trial. It included patients from 190 hospitals in 23 countries. Recruitment of subjects took place between 2002 and 2007. Inclusion criteria included inpatients having non-cardiac surgical procedures who were greater than 45 years of age, who were going to remain hospitalized for at least 24 hours post-operatively, and fulfilled one of the following five criteria:

1. History of coronary artery disease (CAD)
2. History of peripheral vascular disease (PVD)
3. History of stroke
4. History of congestive heart failure (CHF) within 3 years
5. Undergoing major vascular surgery (excluding carotid endarterectomy),

Or three of the following seven criteria:

1. Intrathoracic or intraperitoneal surgery
2. History of congestive heart failure
3. History of transient ischemic attacks
4. Diabetes mellitus
5. Serum creatinine > 170 mmol/L
6. Age >70 years
7. Urgent or emergent surgery

See notes section for exclusion criteria.

Subjects were randomly assigned to receive metoprolol or placebo according to the following protocol: The first dose of the study drug, 100 mg of metoprolol (or placebo), was administered 2 to 4 hours before surgery if the subjects’ heart rate was >50 bpm and systolic BP was >100 mmHg. At any time during the first 6 hours after the surgery was completed, or if the heart rate was >80 bpm or systolic BP was >100 mmHg, a second 100 mg dose of metoprolol (or placebo) was administered. If this dose was not given during the first six hours post-operatively due to the patient’s vital signs, it was administered at the sixth hour post-operatively. Twelve hours after the first post-operative dose, 200 mg of metoprolol (or placebo) was administered; this was continued every day for 30 days. Equipotent doses of metoprolol were administered intravenously if the patient was not tolerating oral medications in the immediate post-operative period. EKGs were completed and troponin or CK-MB levels were drawn 6 to 12 hours post-operatively and on the 1st, 2nd, and 30th days post-operatively.

The primary outcome assessed was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest within 30 days after randomization. Comprehensive demographic data was obtained for all subjects. Monitoring of the study consisted of a central data “consistency check,” statistical monitoring, and on-site monitoring. The needed sample size was calculated at 8000 patients; the investigators aimed for 10,000 patients. Subgroup analyses were completed based upon a variety of clinical and demographic factors.

**Results** A total of 8,351 patients were enrolled from 190 hospitals in 23 countries. The 30-day follow-up was complete for 99.8% of participants. Atherosclerotic heart disease (AHD) was the most common co-morbidity; 83% of the patients in the metoprolol group had AHD. In the placebo group, 82% of the patients had a history of CAD, PVD, or stroke. Temporary discontinuation of the study was carried out as necessary on an individualized basis. For example, when significant hypotension and/or bradycardia ensued, study drugs were temporarily discontinued and/or their dose adjusted.

Significantly fewer patients in the metoprolol group experienced a primary end point of cardiovascular related death, MI, or cardiac arrest (p=0.0399). In contrast, more individuals in the metoprolol group experienced a stroke (p=0.0053). Of the 60 strokes that occurred in the metoprolol group, 49 were ischemic and 3 were hemorrhagic. The type of stroke was uncertain for the remaining cases. More patients died (in total) in the metoprolol group than in the placebo group (p=0.0317). The only reported cause of death that was significantly different between the two groups was death due to sepsis or infection. This cause of death was more common in patients who received beta-blockers (see notes). Additional subgroup analysis did not demonstrate significance differences related to mortality, myocardial infarction, or stroke. This was done to assess whether or not individuals with these outcomes (mortality, MI, or stroke) correlated with geographic location (e.g. Asia, Europe, etc), whether or not on-site research monitoring occurred, or whether cardiovascular disease was present. Post-hoc analyses was completed to assess how the metoprolol might have increased the risk of death and stroke. Clinically significant hypotension had the largest population attributable risk for death and the largest intra-operative or post-operative risk for stroke.

**Conclusion** This research demonstrated that peri-operative metoprolol reduced the incidence of MI, cardiac revascularization, and clinically significant atrial fibrillation in high-risk patients undergoing high-risk surgical procedures for 30 days.
post-operatively compared to placebo. Unfortunately, it also demonstrated a significant increase in the overall risk of death, stroke, and clinically significant hypotension and bradycardia. Even though these findings are consistent with other trials, it is duly noted that another beta blocker or a different dosing regime could possibly achieve differing results. This trial suggested that for every 1000 patients with a similar risk profile undergoing non-cardiac surgery, metoprolol would prevent 15 patients from having an MI, 3 from having to undergo cardiac revascularization, and seven from developing significant atrial fibrillation. It also showed that for every 1000 patients who received peri-operative metoprolol therapy there were an additional eight deaths, five patients who experienced stroke, 53 who experienced clinically significant hypotension, and 42 who experienced significant bradycardia. Hypotension may have been the reason for the increase in the risk of stroke, however, identified risk factors explain only half the strokes. More trials are urgently recommended.

**Comment**

This study appeared to have been conducted with sound scientific methodology and rigor. The researchers, the operations team that designed the trial, the sophisticated statistical analysis and monitoring, and the methodology, were all impressive. The two key components that are of great concern, and possibly explain the results, are the dosing regime of metoprolol, and the heart rate and blood pressure parameters used for treatment. With this high risk population, the treatment protocol may simply have been too aggressive. The administration of the study drug was held or the dose reduced only when heart rates were less than 50 bpm or when systolic blood pressure was less than 100 mmHg. That seems extremely aggressive, especially understanding the pathophysiology of atherosclerotic heart and vascular disease. Additionally, the dosing of metoprolol may have been too assertive even though sound explanation was provided by the study group.

This large multicenter, multicountry study was, I’m sure, intended to clarify the disparate findings of previous beta blocker studies. Previous studies in patients at high risk for perioperative cardiovascular complications have shown benefit, no benefit, or increased risk to perioperative beta blocker treatment. Previous studies have been structured quite differently in regards to drug dosing, when doses were withheld, when treatment was started, and how long treatment was continued. While we strive to practice based upon the best evidence, the evidence has been confusing at best.

Unfortunately, the POISE study has not cleared everything up. Why not? The researcher would say that cardiovascular disease responds to a large number of variables that “confound” (statistical speak) or distort the results of any study. Perhaps a less agreeable explanation is that sometimes protocols just don’t achieve the results we want. Treatment protocols have the advantage of standardizing a proven treatment strategy so that large numbers of clinicians can provide the advantages of that treatment to their patients. But when a clinical problem has too many patient variables or includes areas of limited scientific and clinical knowledge protocols may fail us. In those circumstances using available knowledge to customize treatment for specific patients may make more sense than a protocol. In the case of perioperative beta blockade the evidence appears to indicate significant benefit in some cases. Rather than seeing beta blockade as a mixed bag and simply not bothering with it, perhaps we should tailor beta blockade to individual patients without a protocol.

With further study we may yet find the perioperative beta blockade protocol for patients at high risk for cardiovascular complications. Until then, let’s use what we do know rather than pretending we don’t know anything.

Mary A. Golinski, PhD, CRNA
Exclusion criteria included the following:

- Heart rate <50 bpm
- Existing 2nd or 3rd degree heart block
- History of asthma
- Patients already receiving beta-blocker therapy
- Those with adverse reactions to beta-blockers
- CABG procedure in the preceding 5 years with no current CAD
- Those undergoing low-risk surgical procedures
- Patients on verapamil

Sepsis or infection was the only cause of death that was significantly more common among patients in the beta-blocker group. It is postulated that hypotension following the administration of beta-blockers may have precipitated nosocomial infections. Additionally, by blocking tachycardia, there may have been a delay in the recognition of sepsis and/or infection, therefore delaying treatment, and subsequent resistance to treatment with resultant mortality.
SHORT TERM STABILITY OF pH-ADJUSTED LIDOCAINE-ADRENALIN EPIDURAL SOLUTION USED FOR EMERGENCY CAESAREAN SECTION

Int J Obstet Anesth 2008;17:118-122

Tuleu C, Allam J, Gill H, Yentis SM

Abstract

Purpose The purpose of this study was to determine how quickly epinephrine degraded in a mixture of lidocaine, sodium bicarbonate, and epinephrine which is often used for an epidural block for cesarean section.

Background Lidocaine is a weak base. Lidocaine with epinephrine is manufactured as an acidic solution to make the lidocaine more soluble and to prevent the break down of epinephrine. Epinephrine is often added to the lidocaine to slow systemic absorption and prolong the epidural block. Epinephrine breaks down in solutions with a pH greater than 5.5 (a pH of less than 4 is optimal to prevent the degradation of epinephrine).

Weak bases are highly ionized in an acidic solution. Ionized lidocaine is water soluble and does not cross lipid membranes well so regional blocks with an acidic lidocaine solution set up slowly. Adding bicarbonate to the lidocaine solution increases the pH and thus the percent of non-ionized, lipid soluble drug that penetrates nerves well. The net result is a faster onset of block. Previously, the epinephrine in a mixture of lidocaine, epinephrine, and sodium bicarbonate has been shown to degrade within 24 hours.

Methodology A solution was prepared with 2 mL of 8.4% preservative-free sodium bicarbonate, 20 mL of 2% lidocaine hydrochloride, and 5 µg/mL epinephrine (0.1 mL of a 1 mg/mL epinephrine solution). Syringes containing this solution were divided into two experimental groups. One group of syringes was stored under an artificial daylight lamp and the other group was stored in a dark cupboard. Two groups of control syringes were also prepared without bicarbonate and stored either at 4°C protected from light or at room temperature exposed to light. Samples from all experimental and control groups were analyzed by High Performance Liquid Chromatography (HPLC) when the local anesthetic solution was prepared (time zero) and 2, 4, 6, and 20 hours later.

Result The pH of bicarbonate containing syringes was 8 ±0.5. The pH of syringes without bicarbonate was 6 ±0.5.

The concentration of epinephrine in syringes stored in light decreased rapidly. Six hours after solutions were prepared, the concentration of epinephrine in syringes exposed to light had decreased by 30%. The concentration of epinephrine in syringes protected from light was reduced by less than 10% twenty hours after the solutions were prepared.

The concentration of epinephrine in both control groups without bicarbonate was essentially unchanged from baseline 20 hours after preparation. There was no significant degradation of lidocaine concentration in any of the experimental or control syringes.

Conclusion The concentration of epinephrine in solutions of lidocaine with epinephrine to which bicarbonate has been added decreases rapidly when exposed to light. Six hours of light exposure resulted in a 30% decrease in epinephrine concentration.
Comment

My favorite local anesthetic solution for epidural cesarean sections is 2% lidocaine with epinephrine, fentanyl, and bicarb so this study was especially interesting to me. While I am sometimes critical of the relative lack of depth and long range research planning in the anesthesia world there is a place for simple, “puzzle solving,” totally clinical studies such as this one. It is very narrow but the information it provides is clinically useful. That makes it worthwhile.

While the information in this study is worth knowing if you add bicarb to lidocaine with epi, it may not be as valuable as it first appears. The study showed that at 10 hours the concentration of epinephrine in syringes exposed to light was reduced by about half. At 20 hours the epinephrine was basically gone. We have long used higher concentrations of epinephrine than we really needed to prolong local anesthetic blocks. Previous research has shown that in epidural blocks about 1.8 µg/mL epinephrine prolongs the block just as well as 5 µg/mL. I’m guessing few of us would use a local anesthetic solution that we had prepared 10 or 20 hours earlier. If we made up a solution with 5 µg/mL of epinephrine there would still be about 2.5 µg/mL remaining 10 hours later; which is probably still more than enough.

I’m curious about one aspect of this study. The investigators chose to use “daylight lamps” as the light source for the syringes exposed to light. I don’t see much daylight in the places where I use local anesthetics. More often the lighting is fluorescent. Fluorescent lamps produce different wavelengths of light than the sun. I don’t know what wavelength(s) is / are responsible for the degradation of epinephrine but I wonder if the results of this study would have been different if the investigators had used a different light source.

For a host of reasons, including infection control, we are probably better off preparing local anesthetics for injection shortly before use. When more time passes between local anesthetic preparation and injection it is good to know that protecting the syringe from light will help insure that the dose of epinephrine we drew up is the one we’ll be injecting.

Michael Fiedler, PhD, CRNA

REFLEX PUPILLARY DILATATION IN RESPONSE TO SKIN INCISION AND ALFENTANIL IN CHILDREN ANAESTHETIZED WITH SEVOFLURANE: A MORE SENSITIVE MEASURE OF NOXIOUS STIMULATION THAN THE COMMONLY USED VARIABLES

Br J Anaesth 2006;96:614-619

Constant I, Nghe M, Boudet L, Berniere J, Schrayer S, Seeman R, Murat I

Abstract

Purpose The purpose of this study was to test the hypothesis that in the pediatric population, pupillary reflex dilation may allow assessment of noxious stimulation and the analgesic affect of alfentanil, during sevoflurane anesthesia. The researchers sought to compare the changes in pupil size with the changes in standard hemodynamic values (blood pressure and heart rate) and BIS values, to assess the sensitivity of these parameters to noxious stimulation.

Background The bi-spectral index has been correlated with the expired concentration of volatile anesthetics or with the plasma concentration of hypnotic drugs. Pain and the effects of opioids are thought to be poorly assessed by EEG based monitors, such as the bi-spectral index monitor. When anesthetizing children, estimation of analgesia has the potential to be imprecise relative to the estimation in the adult population. Previous studies have demonstrated that noxious stimulation induces pupillary dilation in anesthetized and non-anesthetized adults. In the anesthetized pediatric population, no studies have been conducted assessing pupil changes during noxious stimulation and the possible effect of narcotics. Age-dependent differences in cardiovascular autonomic control of the pediatric patient do exist; additionally, mechanisms involved in pupillary autonomic functions, both sympathetic and parasympathetic, may differ.

Methodology This study was conducted as a pilot. Twenty-four pediatric patients (ages 2-15 years) undergoing short orthopedic procedures on the lower limb were enrolled. A standardized anesthetic induction took place and immediately preceding intubation, visualization of the pupils in a central position was noted. No anti-cholinergic drugs were administered. Anesthetic maintenance was standardized for all children. Once the inspired concentration of sevoflurane achieved 1.5 MAC (with a 50/50 oxygen N₂O mixture) for 15 minutes, skin incision was performed. Sixteen patients received an IV bolus of alfentanil 10 mcg/kg one minute after skin incision. An additional group of 8 children were enrolled after completion of the study. This second group received an IV bolus of alfentanil 10 mcg/kg 2 minutes after skin incision. The second group of study patients were enrolled to decrease the effect of timing of narcotic, as well as to eliminate the occurrence of spontaneous decrease of pupil size. Pupil size was monitored and recorded using an infrared pupillometry system. The infrared system tracks the pupil and quantifies pupillary dilation. Systolic and diastolic blood pressure, heart rate, and BIS were recorded before the induction of anesthesia, just prior to skin incision, and every 30 seconds up to the end of the fourth minute after skin incision.

Result All 24 children were enrolled in the study. Just before skin incision (the control period), pupils were constricted in all patients (no difference in sizes). In both groups, pupil size increased (dilation) immediately after surgical incision. In the second group, changes from the first to the second minute after stimulation were limited to an additional +10% pupil dilation compared to the one minute dilation. After alfentanil administration, pupil size decreased by 35% within 30 seconds in both groups. Pre-stimulation pupil size returned within two minutes after alfentanil injection. Heart rate increases were minimal in both groups (11 and 12 bpm respectively), and systolic blood pressure responses were also minimal (9 and 12 mm Hg respectively), however both were
statistically significant (p< 0.001). In both groups, the pre-incision values of heart rate and systolic blood pressure were restored 2 minutes after alfentanil administration. There were no significant changes associated with the BIS values after noxious stimuli or alfentanil administration.

**Conclusion**  It appears that the pupillary response to surgical incision (noxious stimuli) is greater than the changes seen in heart rate or blood pressure in children anesthetized with sevoflurane and 50% N₂O. When alfentanil was administered, the result was a rapid decrease in pupil size. Only two children demonstrated an increase in either heart rate or systolic blood pressure ≥20% one minute after skin incision, whereas all subjects demonstrated at least a 125% increase in pupil size. This result suggests that pupil response, specifically dilation following noxious stimuli, is a very sensitive indicator of nociception. Previous works have demonstrated that under inhalation or propofol anesthesia, opioids do not significantly decrease pupil size, as the pupil is already maximally constricted. This data provide evidence that in children, noting pupillary activity after noxious stimuli may alert us sooner than changes in vital signs. Pupillary dilation as a sensitive index of nociception seems to be independent of age for those greater than 2 years.

**Comment**

I found this article very intriguing. There exists a sophisticated piece of technology called a ‘pupillometry system’ which monitors and records pupil size using an infrared light source, a camera, video monitor and video processing software. The system captures the pupil diameter as a real time analogue signal. This technology detects pupil response to noxious stimuli faster than hemodynamic changes are captured on a standard monitor used in the operating room. The benefit of detecting a response to noxious stimuli quickly may be extremely valuable when any increases in heart rate and/or blood pressure could be detrimental to the patient. It appears that in a select population, outcomes have the potential to be improved simply by detecting a sympathetic response via pupil size, versus waiting to see changes in heart rate or blood pressure. Opioids can be administered sooner because detection of noxious stimuli is noted immediately; instability of the patient may be prevented.

Mary A. Golinski, PhD, CRNA
EFFECTS OF AGE AND EMOTIONALITY ON THE EFFECTIVENESS OF MIDAZOLAM ADMINISTERED PREOPERATIVELY TO CHILDREN

Anesthesiology 2007;107:545-552


Abstract

Purpose This study evaluated the effects of preoperative oral midazolam sedation in pediatric surgical patients on reduction of anxiety during induction.

Background It is estimated that up to 50% of children exhibit anxiety prior to surgery. Oral midazolam at an average dose of 0.5mg/kg is the most frequently used medication in children prior to surgery to relieve anxiety. However, there have been reports of midazolam sedation in children being ineffective. Other studies have not provided reliable measurements of “satisfactory anxiolytic response.” In order to overcome the limitations of previous studies, this study used a valid and reliable anxiety measurement tool, a clinically valid dose of oral midazolam, and measurement of blood midazolam levels. It also controlled preinduction and induction variables that may have influenced patient anxiety and response.

Methodology The study subjects were children 2 to 12 years old, undergoing general anesthesia for elective outpatient surgery, and had a physical status of I to III. Excluded were children who were developmentally delayed, had chronic illnesses, any GI disorder, or had ingested anything that might inhibit or induce cytochrome P-450 activity. Parental participation in the induction of anesthesia was prohibited.

Baseline behavioral measurements were obtained by trained research personnel. Standardized tools were used to set baselines and measure outcome. The tools included the Instrument of Child Temperament (EASI), Yale Preoperative Anxiety Scale (mYPAS), State-Trait Anxiety Inventory (STAI), Induction Compliance Checklist, and Miller Behavioral Style Scale.

During the recruitment phase, baseline measurements of the child and parent were obtained using the EASI (child temperament), STAI (anxiety level), and Miller Behavioral tools. Prior to surgery both the child and parent were assessed for level of anxiety using the STAI (anxiety level), and the child then was given 0.5 mg/kg of oral midazolam. The child was separated from the parent at between 20 and 40 minutes after the administration of midazolam. Once in the operating room, the YPAS (preoperative anxiety score) was obtained to evaluate the child’s anxiety level while a standard inhalation induction was administered using oxygen, nitrous oxide, and an increasing concentration of sevoflurane. If the child became uncooperative the mask induction was continued while the child was restrained. After induction was complete, an intravenous line was started and blood was drawn to determine midazolam levels.

The child’s anxiety level as well as interaction between the parent and child were analyzed. An a priori YPAS (preoperative anxiety score) score was selected (>72.9) to indentify a level of anxiety for which it was determined the oral midazolam was ineffective. This score was determined by agreement of a group of providers (anesthesiologist, psychologist, statistician, pediatrician, and developmentalist) who reviewed video tape of children undergoing induction of anesthesia.

Result A total of 262 children from age 2 to 10 years old participated in the study. Oral midazolam was an ineffective anxiolytic in 14.1% of the children. Analysis of midazolam blood levels showed no significant difference between children in whom midazolam was effective and those in whom it was ineffective. In addition, there was no significant difference found between these two groups when evaluating the times between midazolam administration and induction of anesthesia, or any other variable of interest.
determined by the various behavioral/anxiety evaluation tools. There was, however, a small but significant positive correlation between those children showing greater anxiety preoperatively and those showing greater anxiety on induction (Spearman rho = 0.174, P<0.01). In evaluating the impact of age, it was found that midazolam was significantly less likely to be effective in children less than 4 years old (P=0.001).

**Conclusion**  This study determined that 14.1% of children who received 0.5 mg/kg of oral midazolam 20 to 40 minutes prior to the induction of anesthesia exhibited extreme anxiety and distress during induction. Children who did not respond adequately to midazolam were more likely to be younger than 4 years old or exhibit a high anxiety level prior to sedation. Higher doses of midazolam and / or nonpharmacologic antianxiety techniques might be more effective in these children.

Other large studies have indicated an age dependent effective intravenous dose in adults, but no other studies have found age to be a factor with children. Perhaps this finding was the result of different measurement tools, and this study’s use of psychometric tools might have helped to reveal this finding. Also of interest was the finding that greater emotionality, which was age independent, contributed to midazolam ineffectiveness.

**Comment**

I found this to be an excellent, well controlled study that validated what I have witnessed in my practice. I find a large group of children that respond poorly to oral midazolam sedation. This is not to say that I think oral midazolam is a poor choice for preoperative sedation in children. It just confirms my thoughts that pharmacologic antianxiety intervention with some children is not effective.

It is not surprising to me that high preoperative anxiety was correlated with ineffective sedation. What was surprising was the inclusion of information from other studies that stated preoperative preparation of children does not reduce anxiety levels. I do not believe this. Nor do I believe that preoperative preparation of children in community hospitals is “not the standard of care.” I am a firm believer in the use of both pharmaceutical and psychological preparation of children and their parents prior to surgery. I believe that the parent’s anxiety contributes greatly to the child’s level of anxiety. In rare circumstances, I have consulted with the parents primary care physician and suggested that they, and their children, might benefit if the parents were prescribed a single dose of a benzodiazepine preoperatively. In these unusual cases, a parental anxiolytic was effective in diffusing an extremely stressful situation.

I do find it very useful to know that a well controlled study has found consistent blood levels of midazolam in children 20 to 40 minutes after receiving oral midazolam. It is also nice to know that children under 4 years old and those with high preoperative anxiety might benefit from higher doses of oral midazolam.

I have been using oral midazolam since long before the current oral preparation became available. Like many of my older colleagues, I found that mixing the intravenous midazolam preparation with some type of syrup to reduce the extreme bitterness, provided safer and more effective pediatric sedation than the other choices available at the time. I have yet to find a better preoperative sedative than oral midazolam in my 26 years of practice. It is safe and effective. However, as this study shows, it is not always predictable in children. But I can live with that considering the benefit it has provided to many anxious children and their parents.

Steven R Wooden, MS, CRNA
INTERRUPTION OF TREATING LARYNGOSPASM IN PEDIATRIC PATIENTS

Pediatric Anesthesia 2008;18:297-302

Burgoyne LL, Angheleschu DL

Abstract

Purpose The purpose of this study was to describe the incidence and treatment of laryngospasm in a large pediatric population.

Background Laryngospasm is an important airway complication associated with general anesthesia. It is reported to be more common in children (17.4 per 1000 general anesthetics) than in the general population. The largest study of laryngospasm in the general population included almost 137,000 patients and reported an incidence of 8.7 per 1000 general anesthetics but this study is over 20 years old and anesthesia agents and techniques have changed during that time. Some studies have reported that laryngospasm occurred most commonly during induction while others report emergence as the period of greatest risk. Laryngeal Mask Airways (LMAs) and traditional face masks have been associated with laryngospasm primarily during induction and maintenance. Studies of laryngospasm in children associated with the removal of LMAs have reported conflicting results; some showing increased risk with awake removal while others showing increased risk with removal before awakening.

Immediate aggressive intervention is recommended in response to a laryngospasm. No algorithm for management of laryngospasm is agreed upon. The most common general order of laryngospasm treatment involves airway manipulation followed, if necessary, by pharmacologic intervention.

Methodology This retrospective review of a quality improvement database included all recorded laryngospasms during general anesthesia over a 42 month period at a children’s cancer hospital. Complications could be entered into this database by anesthesiologists, CRNAs, and recovery nurses. No mechanism was identified that insured that all laryngospasms were recorded in the database. Laryngospasm was defined as the inability to ventilate accompanied by arterial oxygen desaturation which was not resolved by usual methods to open the airway.

All inhalation inductions were performed with sevoflurane followed by maintenance with either sevoflurane or isoflurane. All IV inductions were performed with propofol. Almost all the anesthetics provided outside the operating room (81% of all anesthetics in the study) were Total Intravenous Anesthetics (TIVA) with propofol.

Result A total of 21,452 general anesthetics were administered during the period examined. Patients ranged in age from 9 months to 20 years old. General anesthesia was delivered in the operating room in 19% of cases or at the location of a diagnostic or therapeutic procedure outside the operating room in 81% of cases.

The quality improvement database included 21 cases of laryngospasm among these anesthetics for an overall rate of approximately 1 per 1000 general anesthetics. Laryngospasm was most frequent during emergence from anesthesia; 10 of 21 patients or 47.6%. Laryngospasm occurred during induction in 6 patients or 28.6% and during maintenance in 5 patients or 23.8%. Most laryngospasms (81%) occurred during inhalation anesthesia and 47.6% of all laryngospasms occurred during inhalation anesthesia with an LMA. This, in spite of the fact that almost all anesthetics administered were TIVA with propofol.
Laryngospasm was successfully treated with airway manipulation and positive pressure with 100% oxygen in 38.1% of cases. Anesthesia was deepened with propofol or lidocaine in 9.5% of cases. Muscle relaxants were used in 47.6% of cases. In one case intubation was performed without any other interventions.

**Conclusion**

This retrospective review of laryngospasm in pediatric patients identified an incidence of 1 per 1000 general anesthetics. Most laryngospasms occurred during the minority of cases performed with potent inhalation agents. Most laryngospasms occurred during emergence.

**Comment**

The results of this study are difficult to incorporate into my practice due to a number of limitations. First, the method of data collection was by retrospective review of a database that tracked laryngospasms. The authors noted a significantly lower incidence of pediatric laryngospasm than previously stated in the literature. The fact is that there is no guarantee that the database, compiled based on self-reported cases, is an accurate reflection of the true number of occurrences. Could it be that more laryngospasms occurred during the time frame but were not identified in the database because the clinical definition was too narrow? The clinical definition of "inability to ventilate associated with arterial oxygen desaturation unrelieved by optimization of upper airway position" may not have applied to some patients who did indeed experience laryngospasm, but never desaturated or responded to initial airway manipulation. Another limiting factor in this study is the two very distinct types of cases examined: those in the operating room and those for diagnostic and therapeutic procedures. The former used mostly inhalation anesthesia and airway management with either an LMA or an endotracheal tube. The later cases, which made up the majority of cases, were performed with mostly TIVA and a face mask. If a comparison is to be drawn between previous results and those of this study, it seems obvious that the results are not generalizable due to the dissimilarities of the cases. The final limitation relates to the timing of the laryngospasm and the intervention required. I would like to see more information related to correlations between laryngospasm and the type of anesthesia, airway management, timing, and intervention. The application of the results of this study to my practice is difficult due to the many limitations, the greatest of which is the retrospective view.

Terri M. Cahoon, MSN, CRNA
THE USE OF DROPERIDOL BEFORE AND AFTER THE FOOD AND DRUG ADMINISTRATION BLACK BOX WARNING: A SURVEY OF THE MEMBERS OF THE SOCIETY OF AMBULATORY ANESTHESIA


Habib AS, Gan TJ

Abstract

Purpose This report described the use of droperidol by some members of the Society of Ambulatory Anesthesia (SAMBA) before and after the Food and Drug Administration (FDA) instituted a “black box warning” for droperidol.

Background Droperidol is an effective and inexpensive antiemetic. Droperidol 0.625 mg to 1.25 mg was long recommended as a first-line antiemetic. In December of 2001 the FDA issued a “black box” warning against droperidol based upon concerns of ECG QT prolongation and potentially fatal cardiac arrhythmias. The warning was based upon 273 cases over a four year period. Of the 89 reported deaths associated droperidol administration, most involved doses of between 25 mg and 250 mg. Only two deaths were associated with doses of 2.5 mg or less. The FDA’s warning has been challenged in regards to the doses of droperidol commonly used by anesthesia. “Adverse cardiac events” occurred in 10 cases associated with droperidol doses between 0.625 mg and 1.25 mg but analysis of these cases revealed confounding factors that prevented any determination of the cause of the cardiac events. Evidence of a causal relationship was notably lacking. Subsequent studies have not shown any significant increase in the QT interval following low-dose droperidol. One study comparing QT prolongation following droperidol and 5-HT₃ receptor blockers showed no difference between the drugs.

Methodology Visitors to the SAMBA web site were invited to complete a set of questions regarding their use of droperidol over time. No attempt was made to design or secure the participation of a representative sample of SAMBA members. All information was based upon self report.

Result A total of 295 physicians completed the survey; 62% practiced in a private hospital and 38% practiced in an academic institution. Droperidol was still available to 74% of respondents. Eleven percent reported that droperidol had been available before the black box warning but was not available afterward. After the FDA warning, 42% of respondents reported that the never use droperidol. Almost all, 92%, believed the black box warning to be unjustified.

Droperidol was used as a first line prophylactic antiemetic by 47% of respondents before the FDA warning but only 5% after the warning. First line antiemetic prophylaxis was managed by a combination of antiemetics not including droperidol by 5% of respondents before the FDA warning but 20% of respondents after the FDA warning. The rate at which droperidol was used for treatment of established PONV was 38% before the FDA warning but only 8% after the warning.

Conclusion The use of droperidol for prophylaxis and treatment of PONV has decreased since the institution of the FDA’s black box warning despite the fact that the vast majority of respondents believed the warning to be unjustified.
Comment

The best part of this report (it cannot properly be called a study) was the literature review. It has value in reminding us of the lack of evidence against use of droperidol in low doses as an antiemetic. It also gives us a rather blurry view of how some ambulatory surgery anesthesiologists used, and view the use of, droperidol before and after the FDA’s black box warning.

The chief problem with the report, and the reason I do not view it as a study, is that the sample was not random, purposeful, nor representative of even the population of SAMBA members. (Even if it had been, one could rightly ask what the significance of SAMBA members as a subset of all anesthesia providers was with regards to droperidol use.) The survey questions were simply placed on the SAMBA web site and those who learned about it and wanted to complete it could do so. A minority of association members completed the survey questions. The authors almost identified this important limitation when they said in their discussion, “BECAUSE IT IS UNKNOWN WHETHER THE PHYSICIANS RESPONDING TO THE SURVEY WERE SYSTEMATICALLY DIFFERENT FROM NONRESPONDERS, THERE IS NO ABSOLUTELY ACCEPTABLE LEVEL OF RESPONSE.” But this misses the point. For without a plan to secure a representative sample of SAMBA members, there was no way to accurately describe their droperidol use patterns short of the participation of all members of the association. To compound the error, the next sentence states, in part, “... THIS SURVEY REFLECTS A SIGNIFICANT DECREASE IN DROPERIDOL USE ...” Again, without a representative sample, neither significance nor the level of droperidol use can be established. Appropriate statistical tests for the data collected and the reporting of P values can’t overcome the lack of a representative sample.

This report does give us some information about the droperidol use patterns before and after the FDA black box warning in a group of almost 300 anesthesiologists. It also gives us some information about how this same group views the evidence (or more precisely, the lack thereof) against the continued use of droperidol as an antiemetic. In that regard there is something we can learn from it, but only within the context of its true limitations.

Michael Fiedler, PhD, CRNA
SUCCESSFUL RESUSITATION AFTER ROPIVACAINE AND LIDOCAINE-INDUCED VENTRICULAR ARRRHYTHMIA FOLLOWING POSTERIOR LUMBAR PLEXUS BLOCK IN A CHILD

Anesth Analg 2008;106:1572-1574


Abstract

Purpose The purpose of this report was to describe the treatment of ventricular arrhythmias with an IV infusion of 20% lipid in a 13 year old following a psoas compartment block with ropivacaine and lidocaine.

Background Intravenous infusion of 20% lipid has been shown to increase the lethal dose of local anesthetics in animals. In humans, case reports describe effective treatment of cardiovascular toxicity due to excessive systemic concentrations of ropivacaine and bupivacaine even after conventional resuscitative therapy has failed. Lumbar plexus block has been associated with a higher risk of systemic absorption toxicity than other regional anesthetics.

Methodology A 13 year old, ASA physical status I, 55 kg female was scheduled to undergo knee surgery with a combined regional and general anesthetic technique. She was taking no medications. After premedication with hydroxyzine general anesthesia was induced and maintained with sevoflurane in 50% nitrous oxide and oxygen. Her baseline blood pressure (BP) was 88/45 and baseline oxygen saturation was 99%. A posterior lumbar plexus block was performed with an 18 gauge needle. After negative aspiration a 2 mL test dose of equal parts 1% lidocaine and 0.75% ropivacaine with 5 µg/mL epinephrine was injected with no change in vital signs. A total of 20 mL of the same solution was injected in divided doses over two minutes without consequence. (This amounts to a total of 1.82 mg/kg lidocaine, 1.36 mg/kg ropivacaine, and 100 µg epinephrine.)

Result Fifteen minutes after the end of the local anesthetic injection the patient exhibited ventricular tachycardia with wide QRS complexes and a rate of 150 bpm. Her BP had increased to 120/92 and her oxygen saturation decreased to 92%. Sevoflurane concentration was reduced, nitrous oxide was discontinued, and 150 mL of 20% intralipid (3 mL/kg) was administered over 3 minutes. Immediately thereafter, BP decreased to 100/48, HR decreased to 100 bpm, oxygen saturation increased to 97%, and the QRS complex narrowed to within a normal range. A significant ST depression had developed and persisted for 30 minutes after normalization of vital signs. The lumbar plexus block was later found to be completely effective. ECG and echocardiograph were normal the next day and the patient was discharged without sequelae.

The delay between local anesthetic injection and symptoms of local anesthetic toxicity are consistent with absorption toxicity. General anesthesia with sevoflurane likely masked evidence of neurotoxicity.

Conclusion Local anesthetic induced ventricular arrhythmias were successfully treated with 20% lipid emulsion. Lipid emulsion should be available with other emergency drugs where regional anesthesia is performed.

Comment

This abstract is part of a three abstract series about treating local anesthetic toxicity with an intravenous lipid infusion. Please see the comment following the third abstract.

Michael Fiedler, PhD, CRNA

REVERSAL OF CENTRAL NERVOUS SYSTEM AND CARDIAC TOXICITY AFTER LOCAL ANESTHETIC INTOXICATION BY LIPID EMULSION INJECTION

Anesth Analg 2008;106:1575-1577

Litz RJ, Roessel T, Heller AR, Stehr SN

Abstract

Purpose The purpose of this report was to describe the treatment of systemic mepivacaine and prilocaine local anesthetic toxicity with 20% lipid solution.

Background Laboratory studies have shown that lipid emulsion infusion can treat local anesthetic induced systemic toxicity after traditional resuscitation measures have failed. The mechanism by which lipid emulsion antagonizes local anesthetic toxicity is unknown, but cardiac bupivacaine concentrations decrease after lipid infusion in a laboratory setting. Case reports have described successful resuscitation of patients following cardiac arrest due to ropivacaine and bupivacaine toxicity.

Toxic local anesthetic concentrations exhibit wide interindividual variability. On average the toxic plasma concentrations of both mepivacaine and prilocaine are reported to be near 6 µg/mL.

Methodology A 91 year old, ASA physical status III, 57 kg man was scheduled to undergo shoulder surgery with an infraclavicular brachial plexus block. His history included COPD, hypertension, ischemic heart disease, myocardial insufficiency, and esophageal reflux. His block was performed with a 22 gauge “B” bevel insulated needle and nerve stimulation. Blood was aspirated during the procedure and the needle redirected. After negative aspiration, 30 mL of plain 1% mepivacaine was injected slowly (5.26 mg/kg). Fifteen minutes later the ulnar nerve was supplemented with an axillary injection of 10 mL 1% prilocaine.

Result Within five minutes after the supplemental injection (20 minutes after mepivacaine injection) the patient complained of dizziness and nausea and became unresponsive. Oxygen was administered. His heart rate increased from 76 to 92 bpm and blood pressure increased from 160/70 to 190/90. The ECG showed supraventricular extrasystoles with occasional bigeminy. An IV bolus of 20% Intralipid 1 mL/kg was injected and repeated three minutes later. Next a continuous infusion of Intralipid was begun at 0.25 mL/kg/min. Within five minutes after the first injection the patient regained consciousness but ectopic beats continued on the ECG. When the total volume of 20% Intralipid infused reached 200 mL the ectopic beats disappeared. The brachial plexus block was satisfactory and surgery was performed as planned.

Plasma mepivacaine and prilocaine levels were drawn immediately before lipid administration and 20 and 40 minutes after lipid administration was begun (20, 40, and 60 minutes after the block was dosed with mepivacaine). Serum concentrations of mepivacaine were 4.08, 2.30, and 1.73 µg/mL respectively. Prilocaine concentrations were 0.92, 0.35, and 0.24 µg/mL.

Conclusion Central nervous system local anesthetic toxicity due to mepivacaine and/or prilocaine was antagonized with the IV injection of 2 mg/kg of 20% Intralipid. Antagonism of the cardiac toxic effects required an additional 2 mg/kg of Intralipid.
Comment

This abstract is part of a three abstract series about treating local anesthetic toxicity with an intravenous lipid infusion. Please see the comment following the third abstract.

Michael Fiedler, PhD, CRNA
INTRAVENOUS LIPID INFUSION IN THE SUCCESSFUL RESUSCITATION OF LOCAL ANESTHETIC-INDUCED CARDIOVASCULAR COLLAPSE AFTER SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

Anesth Analg 2008;106:1578-1580

Warren JA, Thoma RB, Georgescu A, Shah SJ

Abstract

Purpose  The purpose of this report was to describe the treatment of systemic mepivacaine and bupivacaine local anesthetic toxicity with a lipid infusion.

Background  Bupivacaine has a narrow margin of safety. Animal studies have shown that bupivacaine-induced cardiovascular collapse can be delayed and successfully treated with an infusion of lipid emulsion. Case reports have described successful resuscitation of patients following cardiac arrest due to ropivacaine and bupivacaine toxicity.

Methodology  A 60 year old, 83 kg man was scheduled to undergo a revision of a basilic vein fistula with a supraclavicular brachial plexus block. His history included, hypertension, a previous myocardial infarction, diabetes mellitus, and end stage renal disease. He was last dialyzed within the previous 24 hours (K+ = 3.8 mEq/L). Oxygen 3 L/min by nasal cannula was administered and 6 mg midazolam was titrated IV. The patient remained easily arousable. His block was performed with a 22 gauge “B” bevel needle. The needle was advanced to the first rib where the full dose of local anesthetic was injected. No attempt was made to elicit paresthesia or to identify needle location by nerve stimulation. First, 30 mL of 1.5% mepivacaine (5.42 mg/kg) and 3 mL of sodium bicarbonate was injected. Next, 10 mL of 0.5% bupivacaine (0.6 mg/kg) was injected from a separate syringe. Both local anesthetic solutions contained 5 µg/mL epinephrine. During local anesthetic injection, aspirations for blood were repeatedly negative.

Result  Five minutes after the local anesthetic injections were complete the patient’s breathing became difficult, though bilateral breath sounds were still present. He quickly became apneic, unresponsive, and pulseless. CPR was started immediately. He received 1 mg atropine, three doses of 1 mg epinephrine, 40 U vasopressin, 2 amps of sodium bicarbonate, 6 gm magnesium sulfate (infused over 10 minutes), and 11 counter shocks with a defibrillator. This therapy resulted in several brief periods of a perfusing rhythm that was not sustained.

Ten minutes after the initiation of CPR, an intravenous infusion of 20% fat emulsion was begun. Over the following 30 minutes 250 mL was infused during resuscitation. Defibrillation attempts produced longer and longer periods of a perfusing rhythm as more lipid emulsion was infused. Lipid infusion was continued and an additional 15 shocks were delivered before resuscitation was successful. Two hours after the incident, an examination of the extremity revealed a complete motor and sensory block. A 12-lead ECG and serial cardiac enzymes were unremarkable and the patient was discharged three days later.

The unbound bupivacaine levels were drawn 2 minutes after the lipid infusion was started and were 0.49 µg/ml. Central nervous system effects of local anesthetic toxicity has been reported with levels of 0.11 µg/ml. The mechanism of enhanced resuscitation with lipid infusions is not completely understood.

Conclusion  The results of the improvement of resuscitation were less dramatic than previous reports, but the authors surmise that this is due to the fact that the lipid was given via IV infusion instead of IV bolus. Lipid emulsion 20% should be available where local anesthetics are administered.
Comment

Comments follow by two contributing editors.

This report speaks to a promising treatment option for local anesthesia toxicity that is refractory to resuscitation. There have been multiple cases of improved resuscitation with the use of IV lipids. Many people forget that local anesthetics block not only Na⁺ channels, but also interact with other receptors such as β-adrenergic receptors, voltage-gated K⁺ and Ca²⁺ channels, and NMDA receptors. The interaction at these receptors may be responsible for the lack of response to standard ACLS protocol.

The mechanism of action of the lipid infusion is still not clear. However, it seems that since the lipids are safe, it is definitely worth trying, especially since the there are few drug choices available for the treatment of local anesthetic toxicity. I agree with the authors of this article: Lipid infusion should be available in care areas where local anesthetic toxicity may occur.

Lisa Osborne, PhD, CRNA


Regional anesthesia is an important technique for both surgical anesthesia and pain management. It may well be an underused technique. We have always known that local anesthetics, like any other drug, could result in toxicity and patient harm or even death. And we have long understood that bupivacaine has greater myocardial toxicity than other local anesthetics, especially in pregnant women. While we can largely manage CNS local anesthetic toxicity with depressants such as benzodiazepines or general anesthetics, managing cardiovascular toxicity has always been more difficult. This is especially true when cardiac arrest is caused by bupivacaine, which too often results in patient death.

I’m not aware of any source that provides clear evidence about how frequently local anesthetic toxicity occurs during regional anesthesia but I’m beginning to think it occurs much more frequently than we may believe. It is fairly clear that the incidence of local
anesthetic toxicity decreased in the early 1980’s when a number of practices designed to reduce the rate of intravascular injection began to be emphasized (e.g. aspiration for blood before and intermittently during injection of local anesthetics). In studies published since 1995, the incidence of systemic local anesthetic toxicity following peripheral nerve blocks has ranged between 0.08% and 0.2%.¹

One of the reasons local anesthetic toxicity continues to occur is that there is a high degree of variability in the dose of local anesthetic that can be safely injected into an individual patient. While textbooks teach “maximum allowable doses” of local anesthetics with, and without, epinephrine added to slow systemic absorption, absorption is also dependent upon the vascularity of the site of injection which varies greatly. In reality, each block and each injection site has a unique “maximum allowable dose” of local anesthetic based upon the patient’s weight. Additionally, maximum allowable doses are based upon normal healthy patients. Patients with a variety of pathologies or departures from average are at greater risk for local anesthetic toxicity, even when recommended or clinically usual doses are not exceeded.

This issue of Anesthesia Abstracts includes three new case reports in which lipid emulsion was used successfully to treat local anesthetic toxicity. In one report, 20% lipid emulsion terminated CNS signs of local anesthetic toxicity. In another it halted the progress of a developing cardiovascular collapse. In the last case it contributed to the resuscitation of a patient whose local anesthetic toxicity resulted in cardiac arrest refractory to usual resuscitative techniques. These case reports add to a growing body of evidence that 20% lipid emulsion may be the “magic bullet” against local anesthetic toxicity.

While case reports can be instructive, they constitute a fairly low level of evidence upon which to base our practice; just above “expert opinion.” Normally, we’d like to base practice upon very large randomized controlled trials, metaanalyses, systematic reviews, smaller controlled trials, or even non-randomized descriptive studies before case reports alone. In this case, however, it is difficult to imagine a way to ethically conduct a randomized study of the effectiveness of lipid emulsion to treat local anesthetic toxicity in humans. And even if it were possible, the study would take years to collect enough patients who experienced local anesthetic cardiovascular toxicity. The other unique aspect of lipid emulsion is that it is not a “new drug” that must go through a complex and expensive safety investigation. Lipid emulsions have long been used in parenteral nutrition and their lipid droplet size mimics that of the chylomicrons the body normally uses to transport fats in the blood stream. So, from a risk : benefit perspective, there would seem to be little risk in administering lipid emulsion and an enormous potential benefit in preventing or terminating the cardiovascular complications of local anesthetic toxicity.

We still need to know more about how 20% lipid emulsion terminates local anesthetic toxicity. We need to know more about how much to give, how fast to give it, and when to start giving it. But while we learn these things, it is time to have 20% lipid emulsion available as an emergency drug in all locations where local anesthetics are administered for regional anesthesia.

Michael Fiedler, PhD, CRNA

**BACTERIAL COLONIZATION OF EPIDURAL CATHETERS USED FOR SHORT-TERM POSTOPERATIVE ANALGESIA**

Anesthesiology 2008;108:130-137


**Abstract**

**Purpose** The reported rates of epidural catheter-related infection are low, however when they do occur they are often critical and life threatening. The purpose of this study was to determine the incidence of microbial colonization of epidural catheters that were inserted for postoperative pain management after all types of surgical procedures. Additionally, potential routes and risk factors for microbial colonization were assessed.

**Background** Epidural catheter placement for postoperative analgesia is extremely common. As with any other invasive modality requiring sterile technique for initiation, there is a risk of bacterial contamination and subsequent infection, especially with a break in sterile technique. Infections such as epidural abscesses can be life threatening if not diagnosed and treated immediately. Minimal research has been conducted for the purpose of identifying the ‘route’ of infection specific to this technique, or to examine patient / provider / environmental risk factors for post-epidural catheter placement infectious processes. It remains unknown whether or not microbial colonization of an epidural catheter normally causes a clinical infection.

**Methodology** This research was conducted as a prospective, non-randomized study. Patients were enrolled via convenience sampling. Those who received an epidural catheter for post-operative analgesia were consented. If the principal investigator (PI) was present to obtain a culture of the epidural catheter at the time of removal the patient was included in the study. A total of 205 patients consented to participate; any noted exclusion criteria were upheld. The participants underwent a variety of surgical procedures including cesarean sections.

The epidural catheters were all placed either in a the preoperative holding area immediately before surgery, or one day preoperatively. Standardized techniques were used for placement and postoperative management. Bacterial filters were only used for those patients scheduled for lower abdominal or lower extremity procedures. Surgical antibiotic prophylaxis was noted, but not controlled by the study protocol. All patients were maintained on postoperative epidural infusions, either patient controlled or via a set infusion rate.

Culturing took place upon catheter removal and was conducted only by the PI. Cultures were taken from the following locations:

- Contents of any remaining infusate
- Catheter hubs / injection ports
- Skin at the insertion site (swabbed)
- The tip of the epidural catheter
- The “subcutaneous section” of the catheter

Any cultures that grew in their appropriate medium were identified for type, amount of growth (which defined severity), and...
colonization. Patients were also followed up for identification of clinical infections at one week, one month, and three months after epidural catheter removal.

Additional critical data was also collected. (See the notes section following the abstract and comment.)

**Result**

Thirty eight percent (38%) of the sample had positive cultures on the skin around the epidural catheter insertion site. Of those, 20 cultures had “heavy growth.” Positive cultures were present in 10.5% of the subcutaneous culture sites. The tip of the epidural catheter cultured positive in 12.2% of patients. No patients were noted to have a clinical infection related to the epidural catheter during any of the three follow up periods.

There was a strong linear relationship between bacterial colonization of the skin around the insertion site and the subcutaneous and tip segments of the epidural catheter. Interestingly, the same types of microorganisms were isolated from each of these three sites. The most commonly identified organism in each culture group was coagulase-negative staphylococcus. This was also the most common organism isolated from skin cultures that demonstrated heavy growth and from catheter samples that had ≥15 colony forming units (CFUs) (15 CFUs defined “colonization” of the catheter tip).

A significant correlation existed between catheter tip colonization and Tegaderm changes and/or accidental hub disconnection (p=0.003), between catheter tip colonization and blood transfusion while the catheter was in situ (p=0.029), and between tip colonization and the positive culture from the skin swabbed around the insertion site (p<0.001). Additional analysis revealed that blood transfusions while the catheter was in place (p=0.014), catheter related “break in integrity” events (p=0.004), and positive skin cultures (p<0.001) were risk factors for positive catheter-tip cultures.

**Conclusion**

As epidural analgesia remains extremely effective in the management of post-operative pain, the thought is that we may see a proportionate rise in the infection rates. This study demonstrated that 12.2% and 5.4% of the catheter tips had ≥1 CFU and ≥15 CFU bacteria, respectively upon removal. The investigators believe these percentages reflect true bacterial colonization rates of the epidural catheter tip because they disinfected the skin around the epidural catheter before catheter removal (not routinely done or standard of practice). Despite this frequency of colonization, a causative relationship between catheter colonization and catheter related infections was not established, in this study or others.

This study demonstrated that bacterial migration along the catheter track was the most likely cause of epidural catheter colonization, and that catheter related ‘events’ while in situ, as well as blood transfusions while in situ, were risk factors for epidural catheter colonization. Strict aseptic technique is warranted during catheter placement as well as during catheter maintenance. Sterility maintained around the insertion site will reduce colonization of the catheter tip and may decrease catheter related infections.

**Comment**

There are processes that we commonly take part in that will prevent infections in patients we care for; processes over which we have total control. Unfortunately, there also exist situations that may predispose individuals to infections over which we have no control. Maintaining sterile technique during the insertion of epidural catheters and teaching staff who care for patients with epidural catheters postoperatively, are two such processes that we can control. Whether or not the patient receives blood transfusions we truly do not have any control over; however, if the care of the catheter is scrupulous, even those who receive transfusions may experience fewer catheter related infections. The facts are that hospitals and physicians who have admitted patients that acquire an infection while in the hospital will clearly be risking reimbursement payments in the near future; they actually will be withheld. While this is not a reality for epidural catheter related infections (yet), our patients, and the care we administer, are our top priorities. If we provide the highest quality care and adhere to standards of practice, reimbursement will follow accordingly and more likely be upheld.

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NOTES: The additional data that was collected included: the catheter insertion site, the number of attempts to insert, the total insertion process time, training levels of the providers who inserted the catheters, technical difficulty during insertion requiring a the intervention of another anesthesia provider, use of the bacterial catheter filter, catheter line integrity breaks, types of infusion solutions, length of time of catheters were in place, perioperative temperatures, infections at other sites, antibiotic treatment, ventilator use, blood transfusions, and other co-morbidities.