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Abstract

Purpose  The purpose of this study was to compare the effects of P6 electrical stimulation + dexamethasone vs. tropisetron + dexamethasone vs dexamethasone alone on PONV in women undergoing laparoscopic gynecologic surgery. Secondary purposes were to observe the need for rescue antiemetics and assess patient satisfaction.

[Editor’s Note: Tropisetron is a 5-HT3 antagonist unavailable in the USA. It is used in a number of developed nations in other parts of the world.]

Background  Postoperative Nausea and Vomiting (PONV) is one of the most common and disliked events following general anesthesia. Some rate PONV as being more bothersome than pain. The incidence of PONV in high-risk patients, such as women having laparoscopic gynecologic procedures, has been reported to be up to 80%. Vomiting can sometimes result in significant postoperative complications, some of which, such as wound dehiscence and bleeding, pose major risks to the patient. Even moderate PONV can delay hospital discharge. Despite extensive research and development of management guidelines, inadequate prevention of PONV remains common. While 5-HT3 antagonists and dexamethasone often prevent PONV in patients at low or moderate risk of PONV, they are insufficient in high-risk patients. Numerous studies have shown that stimulating the Pericard 6, P6, or “Nei Guan” position can reduce PONV. The P6 position lies 4 cm proximal to the distal wrist crease on the inner forearm and between the flexor carpi radialis and palmaris longus tendons. Several studies have shown the effectiveness of P6 stimulation alone or combined with droperidol or ondansetron for prevention of PONV. Unknown is how P6 stimulation compares to 5-HT3 antagonists in combination with dexamethasone.

Methodology  This was a prospective, double blind, randomized, controlled study of 153 adult female patients with ASA physical status I or II. Each underwent elective laparoscopic gynecologic surgery. Exclusion criteria, in part, were:

- recent antiemetic use
- recent emetogenic drug administration
- recent opioid use
- recent glucocorticoid use
- nausea or vomiting within 24 hours pre-op
- surgery-related postoperative complications

Women were randomly allocated into one of three groups:

- P6 acustimulation + dexamethasone
- tropisetron + dexamethasone
- dexamethasone only

P6 acupoint electrical stimulation and the corresponding placebo were set up by the same investigator who was not involved in delivery of the anesthetic. In the P6 acustimulation group, the
stimulating electrode was applied at the P6 acupoint location. The other electrode was placed on the dorsal forearm. The stimulating current was delivered at 2 Hz with square wave pulses of 0.2 ms in duration. Current began at 1 mA and was increased until the patient felt discomfort. Ultimately, delivered current ranged from 6 mA to 20 mA. This stimulation began 30 minutes before induction of general anesthesia and continued until PACU discharge. In the tropisetron and dexamethasone only groups, P6 acustimulation was set up the same way but no current was delivered to the patient. Patients were told they might or might not feel the acustimulation.

Patients in the tropisetron group received 5 mg tropisetron when skin closure began. All others received the same volume of a saline placebo. Patients in all three groups received 10 mg dexamethasone IV after induction of general anesthesia.

Patients in all three groups received a standardized general anesthetic which included:

• midazolam 0.05 mg/Kg
• propofol 2-3 mg/Kg
• fentanyl 2-3 µg/Kg
• succinylcholine 1 mg/Kg
• lidocaine 1 mg/Kg
• rocuronium
• sevoflurane 1.0-1.5 MAC
• oxygen 100%

At the end of surgery, all patients received parecoxib 40 mg IV, and their wounds were infiltrated with ropivacaine 0.5%. [Editor’s Note: parecoxib is a COX2 selective NSAID in the same category as Celebrex and Vioxx and is approved for use in Europe but not in the USA.] Antagonism of rocuronium was accomplished with up to 5 mg neostigmine combined with atropine up to 2.5 mg. In the PACU, morphine was given if additional pain medicine was requested.

All patients were interviewed at 2 h, 6 h, 24 h, and 48 h post-op and questioned about nausea, vomiting, retching, and pain (VAS 0 to 10). At 48 hours, satisfaction was assessed on a 0-100 mm visual analog scale from 0= very dissatisfied to 100= most satisfied imaginable.

Result

PONV risk factors, intraoperative fentanyl administration, neostigmine dose, IV fluid administered, and morphine administered postoperatively were all similar between groups. The global rate of nausea including all patients in all three groups was 35% and vomiting 19%.

Both P6 acustimulation + dexamethasone and tropisetron + dexamethasone prevented PONV better than dexamethasone alone. The group rates of PONV during the first 24 hours post-op were:
• P6 acustimulation group 28%
• tropisetron group 26%
• dexamethasone alone group 50%

The need for rescue antiemetic administration was similar between groups. Patient satisfaction was also similar between groups. The length of PACU stay was statistically significantly different between groups, but the difference was only 5 minutes.

Conclusion

Transcutaneous electrical stimulation at the P6 point combined with dexamethasone resulted in antiemetic prophylaxis similar to that of tropisetron with dexamethasone and better than dexamethasone alone.

Comment

Stimulating a point on the surface of the skin, a la acupuncture, may seem strange to us in the west. To my knowledge we don’t have a scientific foundation to explain it. I’ll admit, these types of things seem very
strange to me, and I’m slow to accept them without very good reason. But, at the same time I have to remind myself of the number of perfectly good drugs for which the mechanism of action is “unknown,” yet, we know from long experience that they work.

I’ve taken notice of PONV studies employing acupuncture, acupressure, or skin surface electrical stimulation at the P6 point for many years now. Early on, studies involving P6 point stimulation were of poor quality, and I gave them little attention. The reason I kept reading these studies was that I’d been working at a free-standing surgery center where an inexpensive skin surface electrical stimulation device was available to place over the P6 point to prevent PONV. The thing looked like a cheap wristwatch and the current it gave off barely felt like a tickle. I laughed at it. I didn’t believe it worked. But the women who used them said they worked, and they wanted them again when they came back for their next surgery!!!

In more recent years, studies involving P6 stimulation have had scientifically solid methods, and many have shown the effectiveness of P6 point stimulation for preventing PONV. I took note of this study because it went head-to-head with a 5-HT3 antagonist and produced results that were roughly equal. Since I highly doubt they are acting by the same mechanism, this makes me think that P6 stimulation may have a place in a multimodal approach to PONV prevention. We all know that for patients at high risk for PONV we need every “mode” we can get.

This study does have its limitations. The largest in my mind is that the 5-HT3 antagonist they compared P6 stimulation to, tropisetron, is one that none of us have experience with since it is not available in the USA. So, yes, it’s in the same class as ondansetron, granisetron, and dolasetron, but does it work? On the other hand, there were a lot of good things about the study. The doses of fentanyl and morphine that patients in each group got were very, very similar, so opioids probably didn’t bias the results. Likewise, the median dose of neostigmine the women received for reversal of rocuronium was only 2 mg, and overall the dose ranges were also similar between groups. At 2 mg we wouldn’t expect neostigmine to bias the rate of PONV. All in all, the methodology of this study was sound.

So here is my urging. We know there are high-risk patients in whom we need to do more to prevent PONV. Electrical stimulation at the P6 point would seem to have incredibly low risk, and there are studies that absolutely show a benefit. Consider setting aside the whole Eastern pseudo-medicine how can it possibly work if we don’t understand how it works thing and give it a try. See for yourself if it helps your high-risk patients. In the mean time, we here at Anesthesia Abstracts will continue to be on the lookout for studies that can provide solid scientific evidence. Studies like this one.

Michael A. Fiedler, PhD, CRNA

Other abstracts and comments about P6 stimulation to prevent PONV:


Temporal trends in anesthesia-related adverse events in cesarean deliveries, New York State, 2003–2012

Guglielminotti J, Wong CA, Landau R, Li G

Abstract

Purpose The purpose of this study was to describe the frequency of anesthesia-related and non-anesthesia-related adverse events after cesarean delivery in New York state between 2003 and 2012.

Background Cesarean delivery is the most common surgical procedure performed in the USA. Compared to vaginal delivery, anesthesia and non-anesthesia-related adverse events have been found to be higher after cesarean delivery, especially unplanned cesarean section. Neuraxial anesthesia is recommended to reduce the risk of adverse events with cesarean delivery. Unfortunately, we are seeing increasing number of advanced maternal age parturients, who tend to have higher rates of comorbid diseases. These factors increase the risk of complications and adverse events after unplanned cesarean deliveries. This study sought to examine the temporal trends in anesthesia and non-anesthesia-related adverse events after cesarean delivery in New York from 2003 to 2012.

Methodology This was a retrospective review of all cesarean delivery discharge records between 2003 and 2012 included in the New York State Inpatient Database. Data was collected on demographic characteristics and anesthesia and non-anesthesia adverse events, both major and minor. Anesthesia-related adverse events were grouped into the following categories:
- pulmonary
- cardiac
- central nervous system
- related to anesthetic drugs
- other
- unspecified systemic
- related to neuraxial anesthesia & local anesthetics

Non-anesthetic complications included:
- acute myocardial infarction or ischemia
- acute heart failure
- acute respiratory failure
- deep vein thrombosis
- disseminated intravascular coagulation
- acute renal failure
- sepsis or septic shock
- stroke

Major events were defined as an adverse event with an associated risk of death or cardiac arrest greater than 1%.

Result There were 785,854 discharges indicating a cesarean delivery. The cesarean delivery rate increased from 29% in 2003 to 35% in 2009 (P < 0.0001), and then remained stable until 2012. The
rate of planned cesarean deliveries increased 21%, and the rate of unplanned cesarean deliveries increased 17% (P < 0.0001 for both). The age and rate of comorbidity increased significantly over the study period. There was a 13% increase in the proportion of women over 40 years old (P < 0.0001), and the proportion of women with at least one comorbid condition increased 9% (P < 0.0001).

Of these 785,854 discharges, there were 5,715 discharges with at least one anesthesia-related adverse event (rate = 730 per 100,000). There were a total of 11,093 adverse events recorded in these 5,715 discharges; a median of 2 adverse events per discharge. There were 7,040 non-anesthetic complications (890 per 100,000) and 266 cardiac arrests or deaths (cardiac arrest rate = 22 per 100,000; death rate = 23 per 100,000). The overall rate of anesthesia-related adverse events decreased 25% (P < 0.0001). This rate of decrease was seen for planned (34% decrease; P < 0.0001) and unplanned cesarean deliveries (16%; P < 0.0001). The decrease was observed in rural and urban hospitals, as well as those with residency programs. The rate of anesthesia-related adverse events decreased to a greater extent for major events compared to minor events (43% vs. 23%; Figure 1).

The rate of general anesthesia for cesarean delivery decreased from 7.5% in 2003 to 6% in 2012 (P < 0.0001). While the rate of general anesthesia significantly decreased for unplanned cesarean deliveries from 9.1% in 2003 to 6.3% in 2012 (P < 0.0001), the rate remained the same for planned deliveries (5.7% in 2003 and 5.6% in 2012, P = NS).

The rate of anesthesia-related adverse events in cesarean deliveries performed under general anesthesia remained stable during the study period (P = NS). However, the rate of anesthesia-related adverse events in cesarean deliveries performed under neuraxial anesthesia decreased 25% (P < 0.0001; Figure 2).

Major anesthesia-related adverse events accounted for 5.7% of all adverse events; women who experienced a major anesthesia-related adverse event were 17.9 times more likely to have suffered a cardiac arrest or death. The most common causes of major adverse events during cesarean delivery included:

- pulmonary complications (2.9%)
- cardiac complications (1.9%)
- central nervous system complications (0.5%)
- adverse event related to anesthesia drugs (0.4%)

Minor anesthesia-related adverse events accounted for 94.3% of all events. Ninety-six percent (96%) of minor adverse events after neuraxial anesthesia were a post-dural puncture headache.
In contrast, non-anesthesia complication rates increased 47% from 2003 to 2012 (P < 0.0001; Figure 1). This increase was seen regardless of the cesarean delivery being planned (36% increase) or unplanned (57% increase; both P < 0.0001). The rate of disseminated intravascular coagulation increased 78%, and the rate of kidney failure increased 127% (P < 0.0001).

**Conclusion**

Major anesthesia-related adverse events accounted for 5.7% of all adverse events. Overall, anesthesia-related adverse events in cesarean delivery decreased 25% in New York state; however, anesthesia-related adverse events during cesarean delivery under general anesthesia did not change. The decrease in anesthesia-related adverse events paralleled the increased use of regional anesthesia for cesarean section.

**Comment**

These study results demonstrate that our obstetric patients are getting older and sicker. These factors most likely contributed to the increased rate of cesarean delivery and non-anesthesia related complications. Fortunately, obstetric anesthesia care for patients undergoing cesarean delivery has gotten safer. A major reason for this is the increased use of neuraxial anesthesia. However, the investigators found that rates of anesthesia-related adverse events after general anesthesia did not change between 2003 and 2012. Furthermore, the rate of adverse events in 2012 was double for patients who required general anesthesia compared to neuraxial anesthesia for cesarean delivery.

The reasons for this are multifactorial; it could be that when general anesthesia is required it is typically either because an emergency cesarean delivery is needed in the face of an ineffective or absent epidural or time to do a spinal. Also, because we have gotten so good with neuraxial anesthesia, our experience with administering general anesthesia has decreased. The results demonstrating an increased rate of disseminated intravascular coagulation are probably due to increased rates of hemorrhage we are seeing either before or during cesarean delivery. Hemorrhage cases will most likely require general anesthesia.

So what can we do to reduce complications (both anesthesia and non-anesthesia) in cesarean delivery? The key is good communication and teamwork. First, I think we need to be proactive and maintain close communication with our obstetricians, midwives, and nurses to identify and come up with a plan for high-risk women prior to admission. For example, this may require inter-disciplinary meeting between anesthesia, obstetrics, pathology, interventional radiology, etc., to come up with the safest plan to manage a patient with...
a known placenta accreta. If you have not already started, you should develop an interdisciplinary team to implement the **Maternal Safety Bundle for Obstetrical Hemorrhage**. You should also have difficult airway equipment available in the immediate vicinity of your obstetric operating rooms (i.e., video laryngoscopy, supraglottic airways, etc.). If you come up with a safe anesthetic plan, make sure your fellow anesthesia providers are aware of the plan if you will not be on duty the day the patient is scheduled for delivery. When in trouble, call for help!

**Dennis Spence, PhD, 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, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Dexmedetomidine as a Rapid Bolus for Treatment and Prophylactic Prevention of Emergence Agitation in Anesthetized Children

Anesth Analg 2015;121:1308-15
Hauber JA, Davis PJ, Bendel LP, Martyn SV, McCarthy DL, Evans MC, Cladis FP, Cunningham S, Land RS, Campbell NF, Tuchman JB, Young MC

Abstract

Purpose The purpose of this study was to determine if 0.5 µg/Kg dexmedetomidine given as a rapid bolus five minutes before the end of ear, nose, and throat surgery (ENT) reduced the incidence of emergence agitation in pediatric patients.

Background Emergence agitation in pediatric patients may result in patient or provider injury, as well as increased length of stay and utilization of staff resources. The incidence of emergence agitation after administration of sevoflurane ranges from 10% to 80%. Numerous medications have been evaluated, including midazolam, opioids, propofol, and clonidine. More recently, dexmedetomidine, an α2-adrenoreceptor agonist with sedative, anxiolytic, and analgesic properties, has been used to reduce emergence agitation in pediatric patients. However, there is no Food and Drug Administration approved indication for dexmedetomidine in pediatric patients. This study sought to examine if a rapid bolus of 0.5 µg/Kg dexmedetomidine at the end of surgery reduced Emergence Agitation.

Methodology This was a prospective, double-blind, randomized, controlled trial of 400 pediatric patients, ASA I to III, aged 4 years to 10 years undergoing tonsillectomy with or without adenoidectomy, with or without ear tube placement. Patients were randomized to either receive 0.5 µg/Kg (4 µg/mL concentration) dexmedetomidine as a rapid bolus five minutes before the end of surgery or to a saline control group.

The anesthetic technique was standardized. No preoperative sedation was administered, and all patients underwent an inhalation induction with sevoflurane, nitrous oxide, and oxygen. Propofol 2 mg/Kg was administered to facilitate intubation. Dexamethasone 0.5 mg/Kg and morphine 0.1 mg/Kg were administered after the start of the surgery. At the end of the surgery, IV ondansetron 0.1 mg/Kg was administered. Five minutes prior to completion of the surgery, the study medications were administered based on the patient’s group assignment. All anesthesia providers, nurses, and research staff were blinded to group assignment. Immediately prior to administration, the heart rate and blood pressure were recorded (baseline), then every one minute for five minutes, and upon arrival in the post anesthesia care unit. Emergence Agitation was evaluated upon arrival in the PACU using the Pediatric Anesthesia Emergence Delirium scale (0-20 scale; >12 defined as Emergence Agitation). Pain and Emergence Agitation were treated with up to three doses of 0.5 µg/Kg fentanyl. If the patient still appeared to be in pain or...
experiencing Emergence Agitation, then dexmedetomidine 0.5 µg/Kg was administered.

Sample size calculation and statistical analysis were appropriate. The investigators hypothesized that administration of this dose of dexmedetomidine would reduce the incidence of Emergence Agitation by 50%. A P value < 0.01 was considered significant.

Result There were 195 patients in the dexmedetomidine group and 198 in the saline group. There were no significant differences in age (average 6 years), gender (50:50 male: female), or weight. Baseline hemodynamic parameters were similar.

The administration of dexmedetomidine reduced the risk of Emergence Agitation compared to saline (relative risk = 0.56 [95% CI, 0.46-0.68], P < 0.0001; Figure 1). Heart rate was significantly lower in the dexmedetomidine group at all time points (P < 0.01). A comparison of heart rate and blood pressure measurements in the two groups is presented in Figure 2. PACU length of stay was similar in patients enrolled at the main hospital in the dexmedetomidine and saline groups (76 min vs. 73 min, P =NS) but was approximately 10 minutes longer in patients enrolled at the outpatient surgery center (39 min vs. 30 min, P < 0.0001). A significantly lower percentage of patients in the dexmedetomidine group required postoperative fentanyl in the PACU (48% vs. 73%, P < 0.0001). There was a trend towards fewer patients in the dexmedetomidine group experiencing an adverse event (9% vs. 17%, P =NS). For example, seven patients in the saline group experienced a laryngospasm compared to zero in the dexmedetomidine group.
Conclusion  Dexmedetomidine 0.5 µg/Kg given as a rapid bolus five minutes before the end of surgery reduced the incidence of Emergence Agitation in pediatric patients aged 4 years to 10 years undergoing ear, nose, and throat surgery. The results demonstrated this dosing regimen had minimal effects on hemodynamics. The results also suggest dexmedetomidine may reduce adverse events such as laryngospasm.

Comment
Emergence Agitation is a common phenomenon in pediatric patients, especially after ear, nose, and throat surgery (e.g., tonsillectomy). Emergence Agitation is not only potentially harmful to the patient and staff; it can be disturbing for parents to see if they are allowed in the PACU. So it is nice to see research being done to address this problem.

The results demonstrated this dosing regimen was safe and effective at reducing Emergence Agitation when compared to saline. One would expect, as the investigators found, that the heart rate will be lower after administration of dexmedetomidine, and that there will be a slight increase in blood pressure transiently after its administration. Otherwise, the hemodynamic responses were very similar to saline. While dexmedetomidine was effective in decreasing Emergence Agitation, it did prolong the PACU length of stay in the investigators’ outpatient surgery center. No difference was found in their hospital setting. There could have been other factors in the hospital setting that impacted the length of stay (i.e., bed availability) or staffing issues. Outpatient surgery centers tend to be faster paced, turn and burn facilities, and as this study found, dexmedetomidine increased the length of stay by about 10 minutes. I am not sure if this is clinically significant, but it could possibly be if you consider staffing costs. However, so is the treatment of Emergence Agitation with opioids and the attendant side effects.

If it was my child, I would be willing to spend a few more dollars to keep them calm in the recovery room.

Dennis Spence, PhD, 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, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Pharmacology

**Prophylactic administration of ondansetron in prevention of intrathecal morphine-induced pruritus and post-operative nausea and vomiting in patients undergoing caesarean section**

Koju RB, Gurung BS, Dongol Y

**Abstract**

**Purpose** The purpose of this study was to assess the effectiveness of IV ondansetron administered before spinal morphine injection on subsequent pruritus and PONV.

**Background** Spinal (subarachnoid) anesthesia is frequently used for cesarean section as well as lower abdominal and lower body procedures. Adding preservative-free morphine to the local anesthetic in a subarachnoid block provides long-lasting postoperative pain relief. However, subarachnoid morphine results in a high incidence of both pruritus (60% to 100% in peripartum women) and PONV (60% - 80%). Pruritus is generally most noticeable in the patient’s face, neck, and upper body. Nalbuphine (Nubain), propofol, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDS), antidopaminergic drugs, and ondansetron have each been used to treat spinal morphine-induced pruritus. None have produced consistent relief from opioid-induced pruritus. Minimizing the dose of subarachnoid morphine does decrease the associated pruritus.

**Methodology** This was a prospective, double-blind, placebo-controlled study of ASA physical status I & II parturients scheduled for cesarean section with spinal anesthesia using a combination of local anesthetic and morphine. Women with a skin disorder or a preexisting condition that predisposed them to pruritus were excluded from the study. Subjects were randomized to an ondansetron group (N=25) or a placebo group (N=25). The ondansetron group received 4 mg ondansetron IV 30 minutes before administration of subarachnoid local anesthetic and morphine while the placebo group received an equal volume of IV saline. Neither the patients nor the anesthesiologists performing the anesthetic knew which group a patient was in. All spinal anesthetics were administered at the L3-4 or L4-5 interspace with a 25 gauge Quincke needle. All spinals were dosed with 11.5 mg hyperbaric bupivacaine and 0.2 mg morphine.

Following administration of the spinal anesthetic, pruritus and PONV were assessed every 15 minutes for 4 hours and then at 8 hours and 24 hours postoperatively. Pruritus was classified as follows:

- 0 = no pruritus
- 1 = mild pruritus
- 2 = moderate pruritus
- 3 = severe pruritus

Likewise, PONV was classified as:

- 0 = no nausea or vomiting
- 1 = mild nausea
- 2 = intense nausea
- 3 = vomiting
Result  The ondansetron and placebo groups had no significant demographic differences. When pruritus occurred, it began in slightly less than three hours in both groups. The duration of pruritus was also similar in both groups at 13 h to 14 h. However, the incidence of pruritus was 16% (4 women) in the ondansetron group vs. 88% (22 of 25 women) in the placebo group (P <0.001). The severity of pruritus experienced was also greatly reduced in the ondansetron group. The worst pruritus in the ondansetron group was “moderate” and only affected 16% of women, while 84% of women in the ondansetron group had no pruritus at all. The placebo group was much different with 8% of women experiencing moderate pruritus and 80% mild pruritus.

No patient in either group vomited. No patient in either group experienced intraoperative or postoperative hypotension. Nausea occurred in 8% of ondansetron patients vs. 56% of placebo patients (P <0.001). The severity of nausea was also greatly reduced in the ondansetron group. In the ondansetron group, 92% of women had no nausea at all vs. 48% of the placebo group. Mild or intense nausea occurred in 8% (4% mild, 4% intense) of the ondansetron group vs. 52% (36% mild, 16% intense) of the placebo group (P <0.001).

Conclusion  Ondansetron 4 mg IV administered 30 minutes before performance of a spinal block with bupivacaine and morphine significantly reduced the incidence and severity of both pruritus and nausea compared to placebo.

Comment  I used to do pain rounds on post-C section women who had received neuraxial morphine. While the pruritus numbers in this placebo group look a little low to me, the nausea numbers in the placebo group look pretty familiar. We always had a problem with pruritus in these women. Over the years there have been a number of studies looking for a way to get these pruritus and nausea numbers down in spinal morphine patients because spinal morphine provides...
such good pain relief. While some studies were better than whatever they were comparing against, none ever made me think, “There, the problem is solved—all we have to do is ...” This study had a simple, appropriate methodology, and a proper analysis; the results show the greatest reduction in both pruritus and nausea I ever remember seeing. What is different about this study than all the others? The only thing I see is that they gave the ondansetron 30 minutes before they did the spinal with morphine. Maybe that is the “aha” we’ve been looking for. In any case, given the extremely low risk, it is well worth trying.

Michael A. Fiedler, PhD, CRNA
Pharmacology

Effects of Sugammadex on Incidence of Postoperative Residual Neuromuscular Blockade: A Randomized, Controlled Study

Br J Anaesth 2015;115:743–51

Abstract

Purpose The purpose of this study was to determine whether or not sugammadex reduced the incidence of residual neuromuscular block upon arrival in the PACU compared to reversal with neostigmine. A secondary outcome was the time from administration of sugammadex or neostigmine and readiness to leave the operating room.

Background Nondepolarizing neuromuscular blocking drugs are commonly used during general anesthesia and are associated with known postoperative respiratory complications such as:

• hypoxemia
• atelectasis
• impairment of pharyngeal muscles
• reduced ventilatory response to hypoxia
• postoperative respiratory failure
• endotracheal reintubation
• increased duration of PACU stay
• unplanned ICU admission
• pneumonia

Studies suggest that residual neuromuscular block is present in between 20% and 60% of patients when they arrive in the PACU. Even in patients who had only a single dose of an intermediate-acting neuromuscular blocking drug, residual neuromuscular block was present in 45% of patients upon PACU arrival in one study. Since the introduction of intermediate-acting nondepolarizing blockers, the risk of residual PACU paralysis has probably actually increased.

Respiratory complications are among the most common postoperative complications, second only to wound infections. Any postoperative respiratory failure is associated with poorer patient outcomes, longer hospital stay, and, like all complications, an increased cost of care. Research is showing us that postoperative respiratory complications of many types are associated with residual neuromuscular block.

While perhaps relatively rare, postoperative respiratory complications have been calculated to be associated with a 90 x increase in mortality.

Monitoring the depth of neuromuscular block during general anesthesia helps to limit the total dose of paralyzing drug administered during the case. Monitoring the depth of neuromuscular block immediately before administration of a pharmacologic antagonist helps determine the dose of antagonist needed to restore full skeletal muscle strength. Monitoring the depth of neuromuscular block after administration of a pharmacologic antagonist allows the anesthetist to assess the success of restoration of neuromuscular function. This is especially important since anticholinesterase drugs,
such as neostigmine and pyridostigmine, cannot restore adequate muscle strength if too much nondepolarizing neuromuscular blocking drug remains in the patient. Furthermore, the effects of neostigmine are reduced by about 25% one hour after administration, so it is possible for the effects of the neuromuscular blocking drug to return if it has not been eliminated before the neostigmine starts to wear off.

Unlike anticholinesterase drugs, sugammadex, approved by the US Food and Drug Administration (FDA) in November 2015, can antagonize any clinical level of neuromuscular block caused by rocuronium or vecuronium. It does this by encapsulating the rocuronium/vecuronium molecules, functionally removing them from circulation. One molecule of sugammadex encapsulates one molecule of rocuronium. On a mg per mg basis, about 4 mg of sugammadex are needed to encapsulate every 1 mg of rocuronium (200 mg for each 55 mg rocuronium).

Methodology  This was a prospective, randomized, partially blinded study. Patients were randomly assigned to receive either sugammadex or neostigmine for antagonism of rocuronium neuromuscular block. Anesthesiologists were not blinded to the patient’s group assignment, but the patient and those assessing the outcomes were blinded to patient group assignments. The study included adults undergoing elective abdominal surgery with general anesthesia and nondepolarizing neuromuscular block. Patients were excluded for the following reasons (partial list):

- suspected difficult intubation
- neuromuscular disorder
- planned ICU admission
- planned overnight PACU stay

The dose of sugammadex administered and the choice of rocuronium as the nondepolarizing neuromuscular blocking drug were the only aspects of the general anesthetic that were controlled by study protocol. General anesthesia and neostigmine doses were at the discretion of the anesthesia provider and commonly included propofol, fentanyl, and sevoflurane. All patients received maintenance doses of rocuronium during the case. Monitoring of neuromuscular block during the general anesthetic with the quantitative TOF-Watch acceleromyograph was available, but the anesthesia provider was free to monitor neuromuscular block or not at their discretion. If the TOF-Watch was used to monitor depth of paralysis, the results were recorded in the computerized anesthesia record and available for analysis during the assessment phase of the study.

Neuromuscular block was categorized as “moderate” or “deep” for the purposes of assigning the proper dose of sugammadex. “Moderate” block was a Train-of-4 count of 1 to 3 twitches. “Deep” block was a Train-of-4 count of 0 with a post-tetanic-count of 1 or more. For patients in the sugammadex group, “moderate” block was antagonized with 2 mg/kg sugammadex. “Deep” block was antagonized with 4 mg/kg sugammadex. In the neostigmine group anesthesiologists followed their usual practices. No more than 5 mg neostigmine was administered. When patients arrived in the PACU, a quantitative Train-of-4 ratio was measured with a TOF-Watch.
acceleromyograph neuromuscular blockade monitor to assess for residual neuromuscular block. Residual neuromuscular block was defined as a Train-of-4 ratio of <0.9. [Editor’s Note: This definition of residual block follows the most up-to-date recommendations. The older definition was a Train-of-4 ratio of <0.7.] A secondary outcome measured was the time from antagonism of neuromuscular block with sugammadex or neostigmine until the patient was ready to leave the operating room.

A blinded data collector assessed each patient for any evidence of a complication related to residual neuromuscular block. These assessments were performed in the PACU, during the first postoperative day, and at seven days post-op.

Result Completed data collection included 74 patients in the sugammadex group and 76 patients in the neostigmine group. Intraoperative, quantitative neuromuscular block monitoring with the TOF-Watch was used for 87% of patients. In these patients from both groups, there was no median difference in the depth of block before reversal. However, in 42% of sugammadex patients and 32% of neostigmine patients, reversal was administered with no monitoring of depth of paralysis or with the presence of “deep” neuromuscular block. The dose of neostigmine administered was left to the discretion of the anesthesia provider. On average, neostigmine patients received 0.052 mg/kg (52 µg/kg) neostigmine, or 3.6 mg neostigmine in a 70 Kg patient. Upon arrival in the PACU, 33 patients had residual neuromuscular block. All 33 patients with residual block were in the neostigmine group; thus, 43% of neostigmine patients had residual neuromuscular block. No sugammadex patients had residual neuromuscular block upon arrival in the PACU (P<0.0001). Furthermore, 10.5% of patients in the neostigmine group (8 patients) even had residual neuromuscular block by the old criteria of Train-of-4 ratio ≤0.7. On average, the sugammadex group was ready to leave the OR four minutes faster than the neostigmine group.

“Adverse Events” occurred at a similar rate in both groups. They were mostly judged to be “mild” or “moderate” in severity. However, 10% of patients in both groups had a “serious” adverse event, none of which involved respiration and each of which were unlikely to have been related to the study drug (e.g., gastrointestinal bleeding). There was an exception to this, however; two neostigmine patients had clinically significant skeletal muscle weakness judged to be related to the study drug. One of these cases involved re-paralysis 60 minutes after neostigmine administration in a patient who had received a total of

![Figure 1. Residual Block](image-url)
150 mg vecuronium during anesthesia. During analysis the investigators judged that in fully one-third of the neostigmine group, reversal of the nondepolarizing relaxant was attempted in a manner contrary to normally accepted practice. Either reversal was attempted without first assessing the depth of paralysis, or if depth of paralysis was assessed the patient was still deeply paralyzed with a Train-of-4 count of 0 or 1 twitch. There was no skeletal muscle weakness in any sugammadex patient. Also, there was no evidence of allergic reaction in sugammadex patients.

**Conclusion**

No patients who received sugammadex had residual neuromuscular block upon arrival in the PACU. Forty-three percent of patients who received neostigmine had residual neuromuscular block upon arrival in the PACU. In some cases this residual block was quite profound.

**Comment**

This study makes me want to write a comment that is way too long so I’m going to hit just a couple points. I accept the fact that those of you who know me are laughing.

This study was conducted at a major, big name, east coast USA hospital. So imagine my surprise that 33% of the time, expert anesthesia providers were using neostigmine incorrectly. Either they were trying to reverse a block with no idea how deep the block was (no neuromuscular block monitoring) or they were trying to reverse a block that they knew was too deep to reverse, like 0 twitches on a Train-of-4. Another surprise to me was the average dose of neostigmine used, only 0.052 mg/kg or about 3.6 mg in a 70 Kg patient. (Some patients got only 0.017 mg/kg, 1.2 mg in a 70 Kg pt, or even less.) Given the fact that 43% of neostigmine patients arrived in the PACU with residual neuromuscular block, these were not winning strategies.

In my judgment, there are two primary reasons why these practices might have seemed acceptable. First, this is admittedly the way we taught reversal of neuromuscular block in the 1980s, 1990s, and 2000s when we thought that residual block of 30%, or a Train-of-4 ratio of 0.7, was safe and good enough. Second, intermediate-acting nondepolarizing relaxants like vecuronium, rocuronium, and atracurium are so much easier to antagonize that their use has bred some complacency. Believe me, when all we had were metubine, pancuronium, and d-tubocurarine we were very, very conservative about patients regaining full skeletal muscle function before we extubated them. But, we now have clear research that shows us that residual neuromuscular block greater than 10%, or a Train-of-4 ratio <0.90, is associated with a number of adverse respiratory events that we didn’t used to think had anything to do with residual paralysis; adverse events that place patients at risk. To further complicate things, we cannot assess a Train-of-4 ratio with the twitch monitors we’ve used for decades because we can’t visually determine if the fourth twitch is at least 90% as big as the first twitch in a Train-of-4. We need quantitative accelerometric block monitors to be able to do that. Bottom line, we must immediately revise our thinking about monitoring and antagonizing neuromuscular block in every patient we paralyze if we are going to eliminate the complications of residual neuromuscular block.
The second big thought I take away from this and many other studies is just how big a deal sugammadex can be. Sugammadex works completely differently than anticholinesterases. Neostigmine and similar drugs simply increase the amount of acetylcholine (ACh) at the neuromuscular junction in hopes that ACh will get to the receptor instead of the muscle relaxant. Sometimes that works; sometimes it doesn’t. In contrast, think of sugammadex like a sponge that soaks up rocuronium or vecuronium, not other muscle relaxants, and removes them from the body in a state where they can’t cause paralysis. That is why no one in the sugammadex group had any residual neuromuscular block. This drug has the potential to almost eliminate complications due to residual neuromuscular block overnight ... if we use it correctly.

Michael A. Fiedler, PhD, CRNA

Other studies about Residual Neuromuscular Block available in Anesthesia Abstracts:


NOTE: For those statistically inclined it should be noted that the 95% confidence interval for the odds ratio of residual neuromuscular block with sugammadex vs. neostigmine included 0.00 (0.00 to 0.06). A most unusual finding.
Residual neuromuscular block in the elderly: incidence and clinical implications

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Abstract

Purpose The purpose of this study was to compare the incidence of residual neuromuscular blockade in the young (18 years to 50 years old) and elderly (70 years to 90 years old). A secondary purpose was to evaluate the effect of age on adverse events after extubation in patients with residual neuromuscular block (TOF <0.9).

Background Older patients have higher rates of perioperative morbidity and mortality. Decline in organ function may impact the pharmacology of anesthetic agents in older patients. Several studies have demonstrated that elderly patients have higher rates of Residual Neuromuscular Block after administration of nondepolarizing neuromuscular blocking agents. Residual Neuromuscular Block in the elderly is associated with muscle weakness, upper airway obstruction, hypoxemia, unpleasant symptoms, and prolonged PACU stay. This study examined the incidence and severity of Residual Neuromuscular Block in young vs. old patients.

Methodology This was a prospective, observational study. Inclusion criteria were ASA I to III patients undergoing elective surgery under general anesthesia which required the administration of nondepolarizing neuromuscular block. Patients were excluded if they took medications that impaired neuromuscular transmission, had severe renal insufficiency (creatinine >2.0 mg/dL), or had severe hepatic dysfunction (LFTs >50% normal values).

Patients were assigned to a “young” group (18 years to 50 years old) or an “old” group (70 years to 90 years old). The two cohorts were examined for the presence of Residual Neuromuscular Block (TOF ratio <0.9) both within groups and between groups.

A standardized anesthetic was administered to all patients. Anesthesia was induced with propofol, lidocaine, fentanyl, and rocuronium 0.6 mg/Kg and maintained with sevoflurane, fentanyl, and rocuronium titrated to Train-of-4 of 2 to 3 twitches. A qualitative peripheral nerve stimulator was used. The site of monitoring was left up to the anesthesia provider (ulnar nerve or facial nerve). Anesthesia providers were instructed to avoid administration of neuromuscular blockers 30 minutes prior to the end of surgery and to administer reversal at the end of the case with neostigmine 50 µg/mL and glycopyrrolate at completion of wound closure. At the conclusion of surgery up to 2 mg of hydromorphone was administered based on the discretion of the anesthesia provider.
On arrival to the PACU, a TOF-watch was used to quantify the Train-of-4 ratio. Residual Neuromuscular Block was defined as a TOF ratio <0.9. Moderate Residual Neuromuscular Block was a Train-of-4 ratio between 0.7 and 0.9. A Train-of-4 ratio < 0.7 was defined as severe Residual Neuromuscular Block. Within ten minutes of arrival in the PACU and again 20 minutes later, patients were evaluated for signs and symptoms of Residual Neuromuscular Block. Data was collected on demographics and perioperative data, including oxygen saturations and pulmonary complications. This included, for example, presence of atelectasis or pneumonia on a chest radiograph. A P value < 0.01 was considered significant.

**Result**

There were 150 patients in the young group and 149 in the old group. As expected, patients in the old group had more comorbidities. The following compares the old group vs. the young group:

- ASA III: 46% vs. 7%
- obstructive sleep apnea: 11% vs. 7%
- chronic renal insufficiency: 9% vs. 0%
- arrhythmia: 13% vs. 3%
- thyroid disease: 23% vs. 11%
- diabetes: 14% vs. 3%

Between groups, no differences were seen in the:

- total rocuronium administered
- frequency of rocuronium administration within last 45 minutes of procedure
- Train-of-4 count at time of reversal
- time from administration of neostigmine to extubation
- total neostigmine dose

The investigators did not present differences in opioid use between the two groups.

The rate of Residual Neuromuscular Block (Train-of-4 < 0.9) was significantly greater in the old group; 57.7% vs. 30% (P < 0.001). The rate of moderate and severe Residual Neuromuscular Block was also significantly greater in the old group (P < 0.01; Figure 1). Significantly more oxygen desaturations to 90%-94% occurred in the old group (38% vs. 17%, P <0.001). Old group patients also had higher rates of pulmonary complications during their hospital stay (15% vs. 2%, P < 0.001). Patient reports of general weakness were similar in the old group (72%) and young group (58%) on PACU admission (P = NS). However, 20 minutes after admission the old group reported significantly greater weakness; 60% vs. 36%. (P < 0.001). Time until PACU discharge readiness was 5 minutes longer in the old group (P = NS). But time until actual discharge was 14 minutes longer in the old group (P < 0.001).

Next the investigators stratified the groups based on the presence or absence of Residual Neuromuscular Block (Figure 2). Overall, demographic and clinical characteristics were similar within each cohort. However, rates of obstructive sleep apnea were significantly higher in the...
young group with Residual Neuromuscular Block while sleep apnea rates were similar in the old group with and without Residual Neuromuscular Block (Figure 2). Patients in the young group with Residual Neuromuscular Block received significantly more rocuronium during their surgery (60 mg vs. 50 mg, P < 0.01) and within the last 45 minutes of surgery (29% vs. 6%, P < 0.001). No differences were seen in the old group with regards to rocuronium administration.

The rate of oxygen desaturation during PACU transport in patients with Residual Neuromuscular Block vs. those without residual block was significantly higher in both the young group (22% vs. 1%, P < 0.001) and old group (30% vs. 3%, P < 0.001). In patients with Residual Neuromuscular Block in the PACU vs. those without residual block the frequency of oxygen desaturation to 90%-94% was significantly higher in both the young group (33% vs. 11%, P < 0.001) and old group (52% vs. 19%, P < 0.001). The rate of pulmonary complications was similar in the young group with and without Residual Neuromuscular Block (4% vs. 1%) but was higher in the old group with Residual Neuromuscular Block (21% vs. 8%; P=NS). Rates of self-reported general weakness were greater in the young group with Residual Neuromuscular Block on admission (91% vs. 44%, P < 0.001) and 20 minutes later (76% vs. 19%). Likewise in the old group with Residual Neuromuscular Block on admission (97% vs. 38%, P < 0.001) and 20 minutes later (90% vs. 19%, P < 0.001).

**Figure 2. Comparison of TOF ratio**

Note: OSA = Obstructive Sleep Apnea, ROC = Rocuronium, RNMB = Residual Neuromuscular Blockade. Rates of OSA and rocuronium administration (ROC) within 45 minutes of the end of surgery were significantly higher in those patients in the young group with residual neuromuscular blockade (P < 0.01).

**Conclusion**

Patients 70 years old to 90 years old have higher rates of residual neuromuscular blockade on arrival to the PACU. Higher rates of Residual Neuromuscular Block are associated with more frequent adverse events in both young and old patients.

**Comment**

I do not think the results of this study are surprising to anyone - residual neuromuscular blockade is unfortunately still fairly common despite increased awareness raised by the Anesthesia Patient Safety Foundation. Rates of Residual Neuromuscular Block are also higher in older patients. Residual neuromuscular blockade was associated with more frequent desaturations and pulmonary complications in the older patients. These higher rates occurred
despite all patients receiving reversal at the end of the surgery. To me these results speak to the need for increased availability of quantitative monitors to monitor the TOF ratio. Current recommendations are only to extubate with a TOF >0.9.

Unfortunately, these devices are expensive; therefore, we still have to rely on our qualitative monitors. Steps you can take are to: (1) be judicious in your use of muscle relaxants; (2) limit when possible the administration of muscle relaxants in the last 45 minutes of surgery; (3) always use reversal agents; (4) verify full reversal (Train-of-4 with 4 out of 4 twitches with sustained tetanus plus clinical signs); and (5) be especially vigilant in patients with comorbidities that place them at increased risk for complications, for example sleep apnea, renal failure, or obesity.

There are some limitations to these results. The investigators should have used multivariate regression analysis to control for group differences that could have affected the outcomes. Specifically, patients in the older cohort had higher rates of obstructive sleep apnea (10.7% vs. 6.7%) and diabetes (14.1% vs. 3.3%). Additionally, patients in the younger group with residual neuromuscular blockade had significantly higher rates of obstructive sleep apnea (13.3% vs. 3.8%). Nonetheless, I still believe these results are important and speak to the need to rely on the tips I suggested above.

Dennis Spence, PhD, CRNA