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ANESTHESIA ABSTRACTS

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Pharmacology

Dexmedetomidine for improved quality of emergence from general anesthesia: A dose finding study

Anesth Analg 2017 Dec 29; Epub ahead of print
DOI: 10.1213/ANE.0000000000002763
Aouad, MT, Zeeni C, Al Nawwar R, Siddik-Sayyid SM, Barakat HB, Elias S and Yazbeck Karam VG

Abstract

Purpose The purpose of this study was to determine the optimal dose of dexmedetomidine administered upon surgery completion that would provide the best quality emergence. The goal was to prevent cough, agitation, hypertension, and tachycardia following general anesthesia.

Background Emergence from general anesthesia has been associated with potentially detrimental physiologic changes such as: coughing, agitation, hypertension, tachycardia, bleeding, and shivering, among others. Periextubation cough has the potential to cause postoperative complications, especially when hypertensive episodes need to be avoided or when increases in intraocular or intracranial pressures can occur. Lidocaine, ketamine, opioids, and dexmedetomidine have been previously studied for their ability to prevent or treating the side effects of an agitated emergence from anesthesia. Dexmedetomidine is an option with an attractive side effect profile. As a central alpha-2 agonist, dexmedetomidine encompasses analgesic, sedative, sympatholytic, anxiolytic, and opioid sparing properties without contributing to respiratory depression. Previous studies have suggested intraoperative infusions or boluses of dexmedetomidine at the end of surgery were associated with improved recovery profiles; however, the literature has not produced a consensus as to dexmedetomidine's ability to decrease cough and emergence phenomena. Efficacy and the optimal dexmedetomidine dose are poorly understood.

Methodology The study was a prospective, randomized, double-blind trial. Adult patients scheduled for elective surgery requiring general anesthetics ranging from 1-3 hours were eligible for the study. Patients were excluded from the study if they were obese (BMI >35 Kg/m^2), febrile, pregnant, prescribed anti-depressants, and those with chronic pain who were prescribed opioid medications. Two hundred sixteen patients were selected and randomly assigned to 4 groups: dexmedetomidine 1µg/Kg (Dex 1), 0.5µg/Kg (Dex 0.5), 0.25µg/Kg (Dex 0.25), or Control. Upon surgical completion and discontinuation of general anesthesia, patients received their assigned dose or placebo as a 10 minute IV infusion.

Result Surgical procedures were evenly distributed between the four groups and included: orthopedic, general, gynecological, head and neck, and urological procedures. Both N_2O and sevoflorane end tidal concentrations were 0 at the time of extubation. The incidence of cough at extubation was

Table 1: Events at Extubation				
	Dex 1 µg	**Dex 0.5 µg**	**Dex 0.25 µg**	**Control**
Cough	48%	64%	64%	84%
Increase in SBP	4%	11%	17%	35%
Increase in HR	11%	12%	30%	43%
Systolic < 90	27%	19%	16%	0%
Event at Emergence				
Agitation	33%	34%	33%	72%

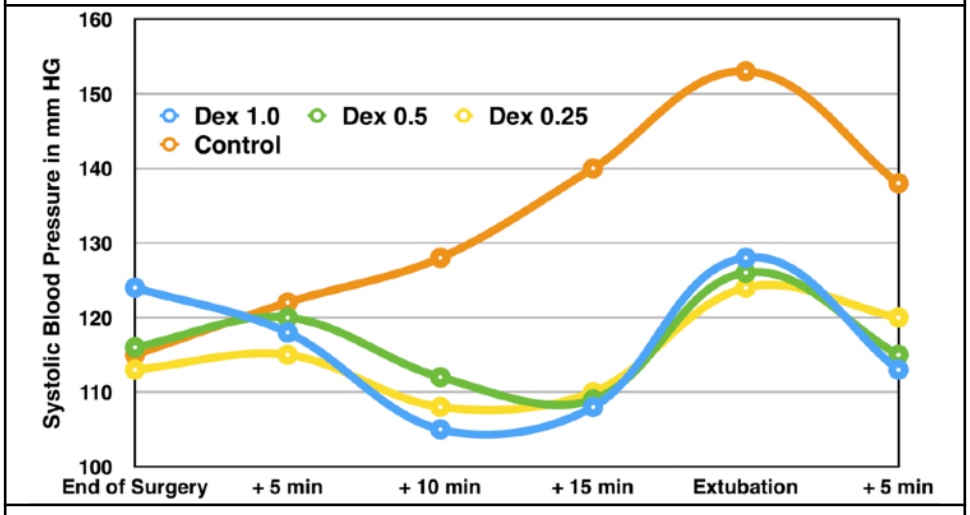
NOTES: Dex = dexmedetomidine, doses in µg/Kg. SBP = systolic blood pressure. HR = heart rate.

lower in all three dexmedetomidine groups compared to the Control group (Table 1). Furthermore, moderate and severe cough in the dexmedetomidine 1 µg/Kg group was reduced by over 60% compared to the control group.

Hypotension (SBP < 90 mm Hg) was found in all dexmedetomidine groups but was not present in the Control group. The magnitude of HR and SBP deviation from baseline during emergence was inversely proportional to the dose of dexmedetomidine delivered. During emergence, the dexmedetomidine groups produced at most a mild elevation of SBP while SBP rose 35% in the control group. On extubation, tachycardia was only present in the Control subjects. Emergence agitation occurred in over 70% of the Control group but only approximately 33% of the dexmedetomidine groups.

There was no variation in sedation scores among the four groups upon arrival to the PACU. PACU hemodynamics were most stable in the

Figure 1: Systolic BP Over Time



NOTES: Dex = dexmedetomidine, doses in µg/Kg. BP = blood pressure.

dexmedetomidine groups. Lastly, PACU length of stay was not statistically different between all groups (Figure 1).

Conclusion Dexmedetomidine 1µg/Kg administered at the end of surgery minimized cough during extubation and considerably reduced moderate and severe coughing. Furthermore, the incidence of emergence agitation was diminished significantly among all dexmedetomidine groups There was no delay in extubation or PACU discharge.

Comment

While dexmedetomidine itself is not new to anesthesia practice, how to fully realize its anesthetic benefits has remained somewhat of a mystery. Probably the biggest reason many of us don't use dexmedetomidine is the fear that emergence, awakening, and discharge times will be delayed. Some feel this cost outweighs the benefits and avoid dexmedetomidine in their anesthetic practice. In my experience, prolonged time to extubation, prolonged PACU stays, and delayed outpatient discharge usually result from either improper dexmedetomidine dosing and/or the timing of administration.

At my clinical institution, the Oral Maxillofacial Surgery (OMFS) team expressed concern over postoperative hematoma formation in their LeFort I osteotomy patients. In collaboration with the Chief of OMFS, I developed an anesthetic protocol which includes a dexmedetomidine 1 µg/Kg infusion. Since implementation of the protocol, rates of tachycardia, hypertension and emergence agitation have been reduced considerably along with the incidence of postoperative hematoma formation.

Ken Taylor, DNP, CRNA

Pharmacology

Incidence of anaphylaxis associated with sugammadex

Anesth Analg 2018;126:1505-8
DOI: 10.1213/ANE.0000000000002562
Miyazaki Y, Sunaga H, Kida K, Hobo S, Inoue N, Muto M, Uezono S

Abstract

Purpose The purpose of this study was to report the incidence of anaphylaxis after sugammadex at a single center in Japan.

Background Sugammadex is a gamma-cyclodextrin that encapsulates the aminosteriod neuromuscular blocking agents rocuronium and vecuronium, thus reversing their effects. The estimated incidence of anaphylaxis with sugammadex is 0.0029%; however, this rate may be underestimated. Therefore, the investigators at this single center in Japan sought to report on the incidence of anaphylaxis after sugammadex.

Methodology This was a retrospective study at the Jikei University School of Medicine, Tokyo, Japan. All surgical cases between September 2012 and August 2015 were evaluated for suspected cases of anaphylaxis based on World Allergy Organization guidelines. Data collected included patient demographics, allergy and surgical history, previous exposure to sugammadex, dose, time from injection to symptoms, symptoms, treatment, time to achieve hemodynamic stability, and any diagnostic tests.

Result There were 6 cases of anaphylaxis out of 15,479 patients who received sugammadex for an incidence of 0.039% (95% CI 0.014%-0.084%). For comparison, there were 8 cases of intraoperative anaphylaxis unrelated to sugammadex out of 23,608 surgical cases for an incidence of 0.033%. The median time from sugammadex administration to symptoms was 1.5 minutes. Five of the six patients had hypotension to a systolic BP < 50 mm Hg; in one case the systolic decreased from 140 to 70 mm Hg. Tachycardia to a heart rate as high as 128 also occurred. Other symptoms included a decreased SpO_2, elevated peak airway pressures (2 of 6 cases), trunk and upper limb uticaria (1 patient), erythema (4 of 6 patients), and cervical and facial edema (1 patient). Treatment generally consisted of small doses of epinephrine 10-100 µg, phenylephrine, fluid bolus, antihistamines, inhaled beta agonists, and hydrocortisone (200 mg). Median time from treatment to resolution of symptoms was 10.5 minutes but took as long as 40 minutes. One patient had an elevated serum tryptase level. One patient required intensive care unit admission, and the other 5 patients were admitted to the ward after the recovery room. No patients experienced major problems or a biphasic reaction.

Conclusion This study suggests the incidence of anaphylaxis after sugammadex is similar to that of the neuromuscular blocking agents succinylcholine and rocuronium.

Comment

While anaphylaxis from anesthetic drugs is uncommon, neuromuscular blocking agents are often the causes of anaphylaxis under anesthesia. The incidence of anaphylaxis after succinylcholine and rocuronium is 0.048% and 0.04%, respectively. This study suggests that the incidence of anaphylaxis after sugammadex may be higher than previously reported, and similar to that of succinylcholine and rocuronium.

Allergic anaphylaxis can be either IgE-mediated (anaphylactic) or non-IgE-mediated (anaphylactoid). Allergic anaphylaxis is a result of degranulation of mast cells or basophils (IgE mediated) leading to the release of histamine, tryptase, carboxypeptidase A and proteoglycans; and activation and synthesis of arachidonic acid metabolites and platelet activating factor and a later release of cytokines. Histamine release leads to vasodilation and increased vascular permeability. Prostaglandins cause bronchoconstriction, pulmonary and coronary artery constriction, and peripheral vasodilatation. Leukotrienes and platelet activating factors contribute to the bronchoconstriction, myocardial depression, and increased vascular permeability. Anaphylaxis signs and symptoms include skin rash, hypotension, tachycardia, wheezing, hypoxemia, and edema.

It is critically important that anesthesia providers quickly recognize anaphylaxis, call for help, and initiate treatment. Use of cognitive aids for perioperative emergencies, such as the Stanford emergency checklists and the Stanford Perioperative Emergency Manual (http://emergencymanual.stanford.edu/) are useful. As soon as symptoms are recognized, the suspected agent should be discontinued and treatment initiated (epinephrine, antihistamines, beta-agonists, fluids, vasopressors, oxygen and airway management as appropriate). This study indicated that symptoms of anaphylaxis occur very quickly after sugammadex administration (less than 2 minutes), and patients with can be stabilized with aggressive treatment within a median of 11 minutes.

Dennis Spence, PhD, CRNA

Pharmacology

Caffeine Accelerates Emergence from Isoflurane Anesthesia in Humans: A Randomized, Double-blind, Crossover Study

Anesthesiology 2018;129:912-920
DOI: 10.1097/ALN.0000000000002367
Fong R, Wang L, Zacny JP, Khokhar S, Apfelbaum JL, Fox AP, Xie Z

Abstract

Purpose The purpose of this study was to test the hypothesis that caffeine administration accelerates emergence from isoflurane anesthesia in healthy humans.

Background Opioids, benzodiazepines, and neuromuscular blockers are accompanied by pharmacologic reversal agents; however, no drug exists to reverse the deep unconsciousness produced by general anesthesia. Genetics, comorbidities and age contribute to inconsistent emergence times from general anesthesia. Following anesthetic emergence, patients' cognitive and psychomotor abilities remain compromised from minutes to hours. Delayed reaction times, memory impairment and poor motor coordination require extended PACU monitoring, increasing the cost of care. Geriatric patients are at increased risk for such delays.

Intravenous infusions of methylated xanthine compounds such as aminophylline, theophylline, and caffeine, hasten emergence from anesthesia. Methylated xanthine compounds increase intracellular cyclic adenosine monophosphate (cAMP) facilitating neurotransmitter release. Elevated cAMP concentrations reverse the inhibition of neurotransmitter release produced by isoflurane anesthesia. Animal studies have shown that IV caffeine elevates cAMP concentrations more effectively than other xanthines. The optimal dose and timing of caffeine administration in humans to accelerate emergence from anesthesia is unknown.

Methodology This was a prospective, double-blind study. Eligible study subjects were healthy males, age 25 to 40 years. Preanesthetic screening, urine toxicology analysis, and electrocardiogram were performed. Those with obstructive sleep apnea, alcohol or drug abuse history, seizures, or head trauma were excluded. The eligible eight participants were subject to two general anesthetic sessions separated by a minimum of 2 weeks time. Subjects were randomized to the order they would receive normal saline or caffeine infusions.

Following a propofol induction, an LMA was inserted. Subjects breathed spontaneously while isoflurane was delivered at an end-tidal concentration of 1.2% for 60 minutes. Ten minutes prior to the discontinuation of isoflurane, the subjects received either an IV infusion of normal saline or 7.5 mg/Kg caffeine.

Test subjects emerged from anesthesia in a tranquil environment without physical stimuli. All subject had

a vigorous gag response as the end tidal isoflurane levels diminished. Upon spontaneous eye opening, verbal commands were given to open their mouth for LMA withdrawal. Time to return of gag reflex, eye opening, and response to verbal commands were recorded. Minute ventilation was measured during emergence. Awakening was defined as the presence of a gag reflex . After awakening subjects indicated how "well" they felt on a visual analog scale and completed two psychomotor tests. These assessments were repeated every 15 minutes for 2 hours following isoflurane cessation.[Editor's Note: for details about the tests used see notes following the comment.]

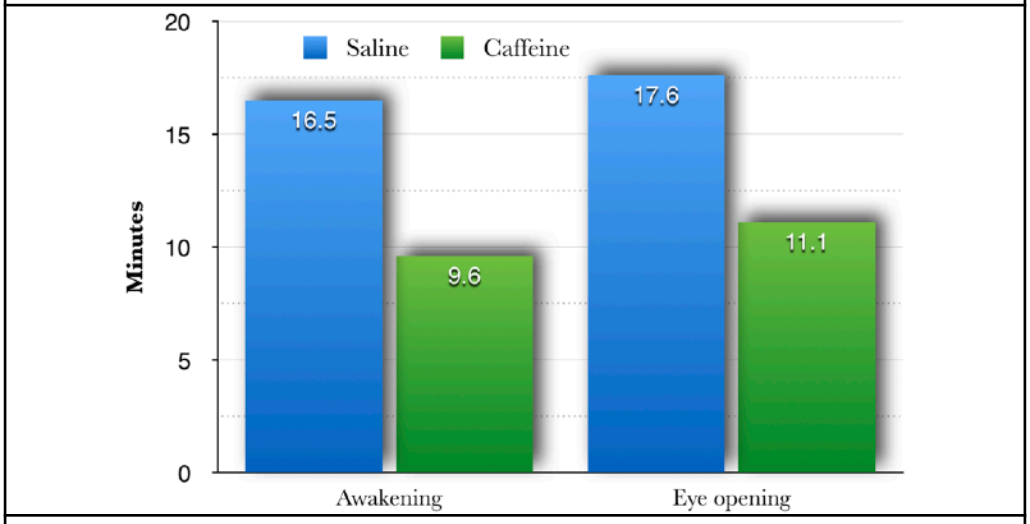
Result There was a significant difference between the saline group and caffeine group in time to emergence, time to eye opening, end tidal isoflurane concentration on awakening, and psychomotor testing. There was a modest improvement in the divided attention task in subjects who received caffeine. There were no differences in HR or mean arterial pressure (MAP). Participants performed similarly in the "feels well" and memory test.

Time to awakening following saline was 16.5 minutes vs. 9.6 minutes following caffeine (P=0.002). This was a 42% reduction in time to awakening. Time to eye opening in the saline group was 17.6 minutes; whereas time to eye opening after caffeine was 11.1 minutes; a mean difference of 6.5 minutes. When test subjects received caffeine, they awakened from anesthesia at 0.33% end-tidal isoflurane compared to 0.21% when they received saline.

Table 1: End-tidal Isoflurane on Emergence	
Saline	0.21%
Caffeine	0.33%

Conclusion Subjects given IV caffeine before isoflurane was turned off awoke 6.9 minutes sooner and at a higher end-tidal isoflurane concentration. Additionally, psychomotor function recovered more quickly following IV caffeine infusion.

Figure 1: Mean Time to Awakening & Eye Opening



Notes: Awakening defined as first gag.

Comment

Initially, I was not impressed with this study and felt it offered little clinical insight. I felt that as anesthesia professionals we have nearly mastered the timing of anesthetic emergence. However, my view began to change as my week of clinical anesthesia progressed and I encountered some patients who awoke more slowly than I would have liked. I experienced a few delayed awakenings when relieving colleagues who used a technique different from my own. I also had a couple patients who were sensitive to anesthetic agents and were "slow to emerge." In these instances, caffeine administration would have been clinically beneficial.

An eight ounce brewed coffee contains 100 mg of caffeine while a 1.5 ounce espresso shot averages 60 mg. At 7.5mg/Kg, a 70 Kg patient would have received 525 mg caffeine. Four hundred mg of caffeine is the safe daily maximum for healthy adults.

We lack a novel reversal agent for general anesthesia and the post anesthesia stupor that periodically follows. This study revealed that after receiving IV caffeine, patients emerged nearly 7 minutes faster and were more coherent. The 42% reduction in time to emergence despite a higher end tidal isoflurane concentration could have tangible clinical impact. I was pleasantly surprised by the lack of tachycardia or hypertension following caffeine administration. Lastly, an expeditious return of psychomotor and cognitive function should translate into a shorter length of stay in the PACU. Additionally, an expedited recovery should increase patient satisfaction. We encounter patients who are truly more sensitive to anesthetic agents causing them to experience prolonged emergence and recovery times. Caffeine administration could be the solution in such scenarios.

Ken Taylor, DNP, CRNA