Use of Esmolol During Induction of General Anesthesia to Reduce Opioid Drug Usage - A Review of the Current Literature and Creation of an Educational Module for Anesthesia Providers

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Abstract

Intubation is required for many surgical procedures, for which the standard is direct laryngoscopy. Direct laryngoscopy results in a sympathetic outflow which may be attenuated with multiple medications, such as esmolol or opioids. Due to the current culture and the inexpensive cost of the opioid fentanyl, providers are more likely to utilize it to minimize this response despite its negative side effects, such as nausea and vomiting. Esmolol is a superior alternative to opioids for prevention of the sympathetic response to direct laryngoscopy for several reasons. A review of the literature suggests esmolol is both a historic and more effective agent for preventing the sympathetic outflow caused by direct laryngoscopy. With the nationwide narcotic shortage, esmolol administration may be a simple solution to better utilize medicinal resources, avoid the negative side effects associated with fentanyl, and slow down consumption of the dwindling supply of narcotics. Education is a method of affecting change. A thirty-minute PowerPoint presentation was provided to 19 students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University on September 27, 2018 to increase the knowledge base on the use of esmolol during induction of general anesthesia to reduce opioid drug usage. An identical ten question test was administered to 19 students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University both before and after the PowerPoint presentation. The Statistical Package of Social Sciences program was used to analyze the results of the pre- and post-tests. The tests strategically contained multiple choice questions, to allow for quantitative interpretation. This method identified a clinically significant improvement in the knowledge base of esmolol use during induction of general anesthesia to reduce opioid drug usage.

Table of Contents

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Hemodynamic changes with direct laryngoscopy are undesirable. High-risk patients, such as those with cardiac compromise, increased intracranial pressure, or increased intraocular pressure, are especially at risk for the negative sympathetic outflow effects caused by direct laryngoscopy (Siddiqui, Katznelson, & Friedman, 2009). For example, direct laryngoscopy may cause dysrhythmias or even cardiac arrest in the patient with cardiac compromise (Lewis & Swerdlow, 1964).

Hemodynamic changes are normally attenuated with potent painkillers like fentanyl or other opioids, but in this time of opioid crisis, alternatives are desired to keep the patient safe. Examples of opioid interventions include hydromorphone, morphine, alfentanil remifentanil, and sufentanil, but the most common alternative is the administration of intravenous fentanyl during induction of general anesthesia. (Casserly & Alexander, 2018). Fentanyl is a synthetic opioid agonist. When compared to morphine it has a faster onset and shorter elimination half-life, and it is 100 times more potent when administered intravenously (Nagelhout & Plaus, 2014).

Opioid utilization is not without consequence. Perioperative narcotic use may result in additive effects of other sedating agents, urinary retention, respiratory depression, apnea, decreased peristalsis, constipation, nausea, vomiting, increased intraocular pressure with hypoventilation, bradycardia, chest wall rigidity, itching, acute opioid tolerance, and opioid addiction (Food and Drug Administration, 2018). Despite the shortage and risk factors of opioids, anesthesiologists, certified registered nurse anesthetists, and student registered nurse anesthetists commonly use fentanyl during induction because they are withheld from alternatives during their education and training. Since fentanyl is metabolized through the liver and excreted

through the kidneys, it should only be used in patients with healthy kidneys and livers (Casserly & Alexander, 2018). However, this is not the case in all scenarios since narcotic alternatives have limited research studies.

There is a national narcotic shortage of fentanyl (FDA, 2018). An effective alternative to fentanyl is esmolol, a short-acting selective beta 1 receptor blocker with fast onset, used commonly for intraoperative tachycardia, postoperative hypertension, and myocardial ischemia episodes (Helfman, Gold, DeLisser, & Herrington, 1991). It decreases sympathetic outflow caused by laryngoscopy (Mavri et al., 2015). Furthermore, the cost of fentanyl can be between $0.68 to $1.28 per unit and the cost of esmolol is about $0.69 per unit, so the drugs are extremely similar in price point ("Fentanyl: Drug information," 2018).

Using esmolol, instead of a narcotic, may help decrease the opioid shortage and allow the provider to use narcotics strictly for surgery related pain prevention and treatment. Its administration in place of an opioid avoids the side effects of the opioid utilization (Fentanyl: Drug information, 2018; Casserly & Alexander, 2018). Several studies agree it is more effective at preventing an increase in systolic, diastolic, and mean arterial blood pressures in the surgical patient undergoing direct laryngoscopy (Mavri et al., 2015; Hanci et al., 2013; Vucevic, Purdy, & Ellis, 1992).

Problem Statement

Opioids including fentanyl are routinely utilized to abate sympathetic outflow caused by direct laryngoscopy. Opioids have untoward side effects and utilization should be limited to preventing and treating surgery-related pain (Casserly & Alexander, 2018). According to Berterame et al. (2016), worldwide use of opioids doubled from 2001. This

increased utilization has led to the current national opioid shortage, and this shortage of opioids is affecting patient care. If esmolol is utilized in place of opioids, opioid use may decrease, conceivably preserving scarce supply for pain prevention and management. Further education is necessary to facilitate and expand the use of esmolol for direct laryngoscopy in 19 students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University.

Project Questions

The authors of this scholarly project support the use of esmolol to prevent of the sympathetic outflow caused by direct laryngoscopy and seek to answer the following question. Will a presentation of a 30-minute education module via PowerPoint increase the knowledge base regarding esmolol administration for attenuation of the sympathetic outflow caused by direct laryngoscopy in 19 students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University?

Literature Review and Synthesis

A review of the literature demonstrated an association with direct laryngoscopy and the activation of the sympathetic nervous system. This activation of a sympathetic discharge included elevations in heart rate and blood pressure for a period of 5 to 10 minutes, peaking in one minute (Chopra, Gupta, & Lone, 2017). Direct laryngoscopy and intubation also cause dysrhythmias, and the stimulation of intubation may lead to adverse outcomes (Siddiqui et al., 2009). In a different study, negative outcomes associated with the sympathetic stimulation of direct laryngoscopy included myocardial infarction, increased intracranial pressure, elevated intraocular pressure, and stroke (Hagberg, Georgi, & Krier, 2005). Because sympathetic

stimulation caused by direct laryngoscopy can result in a heart attack, sympathetic stimulation must be attenuated. If a heart attack is to occur, readmission rates are high. According to Dharmarajan et al. (2015) patients who experience a myocardial infarction have one-year hospital readmission rates of 49.9 % and death rates as high as 25.1%.

It has been noted that esmolol, when compared to fentanyl, is more effective at reducing the sympathetic outflow after direct laryngoscopy. This claim has been repeatedly supported since the early 1990s. An example of one of these early studies was conducted by Helfman, Gold, DeLkser, and Herrington (1991). Helfman et al. (1991) conducted a study comparing the sympathetic reduction rates of esmolol, fentanyl, and lidocaine. The dosages for this study were 200 mg of lidocaine, 200 mcg of fentanyl, and 150 mg of esmolol. Additionally, the study utilized patients that were classified as American Society of Anesthesiologist (ASA) class two through four. In other words, each patient underwent a physical assessment to determine his or her body's level of systemic disturbance. The patient was able to be included in the study if they had a mild, severe, or threatening systemic disease. However, moribund patients who had a history of cardiac arrest, asthma, or that were on beta-blocker therapy, were excluded. According to Helfman et al. (1991), patients' heart rates increased by 18% with esmolol, 37% with fentanyl, and 51% with lidocaine. Since Helfman's study identified that esmolol resulted in the lowest sympathetic outflow, it was concluded that esmolol was the best agent in attenuating sympathetic response due to laryngoscopy (Helfman et al. 1991).

Consequently, other researchers began focusing their efforts on the effectiveness of esmolol. For example, similar to Heffman's (1991) study, Feng et al. (1991) compared the effects of lidocaine, fentanyl, and esmolol as well as a control group of no intervention. This study presented the occurrence of tachycardia with direct laryngoscopy in only 15% of the

patients who received esmolol. On the other hand, tachycardia occurred in 85% of the patients who were in the control group, 75% of the patients who received lidocaine, and 55% of the patients who received fentanyl. In addition, Feng et al. (1996) found that hypertension (defined as a systolic blood pressure greater than 180) occurred in only 20% of the patients who received esmolol, while hypertension occurred in 80% of the patients in the control group, 70% of the patients that received lidocaine, and 40% of the patients who received fentanyl. In conclusion, Feng et al. (1991) claimed that esmolol was more effective than fentanyl and lidocaine because it resulted in a lower risk of tachycardia and hypertension.

According to Varma, Aparanji, and Uma (2015), laryngoscopy can cause the average heart rate to increase by 66% and the baseline blood pressure to be increased by 45%. These alarming statistics consequently purport Varma et al.'s (2015) study to identify the superior agent (fentanyl or esmolol) for attenuating sympathetic outflow. This study utilized patients that were classified as ASA class one through two. In other words, patients whose systemic disturbance were life-threatening and were at high risk during intubation were excluded. The measured variables consisted of blood pressure, heart rate, diastolic pressure, systolic pressure, and mean pressure to quantify the sympathetic response. The control group consisted of observing a patient's sympathetic response due to direct laryngoscopy without an intervention. Evidently, they found that in the absence of intervention, heart rate, blood pressure, diastolic pressure, systolic pressure, and mean pressure increased during direct laryngoscopy by as much as 42.6%. They also established that 2 mcg/kg of fentanyl decreased the measured parameters (heart rate, blood pressure, diastolic pressure, systolic pressure, and mean pressure) better than the control group. This was exemplified when the control group experienced a rise in systolic blood pressure of 19.2% and the fentanyl group had a 12.9% increase. However, the patients who were given

esmolol were noted to have a 6.2% increase of the sympathetic response (Varma et al. 2015). The data also demonstrated that esmolol cause an increased heart rate of 16.4% fentanyl resulted in a 26.2% heart rate increase (Varma et al., 2015). Therefore, Varma, Aparanji, and Uma (2015) concluded that administration of esmolol 2 mg/kg resulted in superior attenuation of the sympathetic response when compared to both fentanyl and the control group.

Additionally, Gupta & Tank (2011), conducted a study comparing esmolol, fentanyl, and normal saline for attenuation of the sympathetic response caused by laryngoscopy. For this study, they selected patients that were ASA class 1 or 2 and they also measured heart rate, systolic and diastolic blood pressures. Patients were excluded from this study if they had a history of difficult intubation, cardiac history, or chronic obstructive pulmonary disease. Normal saline was the control group for this study, while the other two groups where administered esmolol 2 mg/kg or fentanyl 2 mcg/kg three minutes before laryngoscopy (Gupta & Tank 2011). The study was able to demonstrate that the sympathetic response was successfully attenuated with esmolol over fentanyl as this was evidenced by reductions in heart rate and mean arterial pressure (Gupta & Tank 2011).

According to Gogus, Akan, Serger, and Baydar (2014), laryngoscopy caused catecholamine release. Releasing catecholamine resulted in an increased oxygen consumption of the heart muscle which then led to a reduced supply of oxygen to the coronary arteries. Gogus et al. (2014) compared the reduction rates of the sympathetic response caused by esmolol, fentanyl, and dexmedetomidine. The study's population consisted of patients who were considered class one through two of ASA. Therefore, just like most other studies, patients who had a cardiac history, pulmonary disease, were a high risk of difficult intubation, or had diabetes, were excluded from this study. The following variables were measured after each patient underwent

direct laryngoscopy: blood pressure, heart rate, diastolic pressure, systolic pressure, and mean pressure. Gogus et al. (2014) observed that the intervention of dexmedetomidine (an alpha 2 adrenergic receptor agonist)1 mcg/kg was the most effective in preventing tachycardia. However, esmolol was still superior to fentanyl in lowering the risk of tachycardia. Most importantly, esmolol 2mg/kg was found to be more effective at the prevention of spikes in diastolic pressure, systolic pressure, and mean arterial pressures.

Marvi et al. (2015) conducted a study comparing the efficacy of dexmedetomidine, fentanyl, and esmolol on prevention of the sympathetic outflow caused by laryngoscopy and intubation. To quantify sympathetic outflow caused by direct laryngoscopy heart rate, systolic pressure, diastolic pressure, and mean arterial blood pressure was measured at the following times: prior to induction, prior to intubation, and then 1, 2, 4, and 10 minutes post intubation (Marvi et al., 2015). Marvi et al. found that in ASA 1 and ASA 2 patients, esmolol was superior to fentanyl and dexmedetomidine in reducing systolic, diastolic, and mean arterial blood pressure response post direct laryngoscopy.

Tolerance and substance abuse due to opioid consumption have been a concern in North America within the past 20 years. This is evidenced by an estimated 27,500 admissions to health care facilities due to opioid overdose in the United States (Boyer, 2012). According to Dart et al. (2015), deaths caused by prescription opioids peaked over 16,000 in 2010 in the United States. In attempts to reduce opioid prescriptions in 2012, Canada replaced opioid prescriptions with fentanyl (Fischer, Russell, Murphy, & Kurdyak, 2015). This reduced OxyContin's use by 50% but caused fentanyl dependency to increase. Canada's fentanyl prescriptions increased by 500% within the last 10 years, which makes Canada the highest consumer of fentanyl in the world (Fischer et al., 2015). As a result, the number of fentanyl-related opioid deaths in British

Columbia increased from 12 to 575 deaths per year (Fischer et al., 2018). Both Boyer (2012) and Fisher et al. (2015) agreed that desensitization of opioid receptors causes patients to require higher doses of opioid over time. Higher concentrations of fentanyl cause bradycardia, nausea, vomiting, skeletal muscle rigidity, and fatal respiratory depression (Casserly & Alexander, 2018).

According to the literature, fentanyl is a synthetic opioid of the phenylpiperidine family (Boyer, 2012). Fentanyl's primarily works on the mu opioid receptors found in the thalamus, amygdala, dorsal root ganglion, and gastrointestinal tract (Boyer, 2012). When mu receptors are stimulated, G-proteins become activated. As a result, the cAMP production and calcium influx are decreased while potassium efflux is increased (Boyer, 2012). Fentanyl has an onset of 5 to 15 minutes, peaks in 20 to 30 minutes, and has an elimination half-life of 2 to 4 hours (Nagelhout, 2014; FDA, 2018). Fentanyl is metabolized in the liver by CYP3A4, CYP2D6, and CYP2B6 enzymes and then eliminated through the bile and kidneys (Boyer, 2012). Side effects of fentanyl include changes in a patient's peristalsis, sedation, dizziness, urinary retention, nausea, vomiting, respiratory compromise, pruritus, hypotension and high potential for substance abuse (Nagelhout, 2014). Due to the side effects of fentanyl, additional interventions like increased administration of antiemetics, stool softeners, and vasopressors may be required (Stanley, 2014). However, most of these side effects are not encountered with the administration of esmolol (Lexicomp, 2018).

Therefore, the literature focused on supporting the use of esmolol as an effective alternative for narcotics like fentanyl. Esmolol is a selective Beta-1 receptor blocker, class II antiarrhythmic that prevents hemodynamic changes following laryngoscopy and its commonly accepted dose is 1.5-2 mg/kg (Lexicomp, 2018). It is commonly used to prevent or treat

supraventricular tachycardia and emergency hypertension. Esmolol does not increase the risk of stroke and has a safe drug profile. It is a historically safe agent to administer, even to septic patients (Du, W., Wang, X., Long, Y., & Liu, D.-W., 2016).

In conclusion, the literature's data presents esmolol as superior to fentanyl for various reasons after direct laryngoscopy. Esmolol proved to be more effective in the reduction of the sympathetic outflow response. In other words, esmolol prevented more spikes in diastolic, systolic, and mean arterial pressures than fentanyl for mild to severe classified patients. Esmolol also presented the lowest risk of tachycardia and hypertension. Therefore, the studies support esmolol as an effective alternative for fentanyl when attempting to reduce the sympathetic outflow caused by direct laryngoscopy.

Contribution and Dissemination/Justification

There is a knowledge gap regarding the administration of esmolol to attenuate the sympathetic response caused by direct laryngoscopy. After an extensive literature review, an educational module was prepared to increase the knowledge base of esmolol administration to abate the sympathetic response to laryngoscopy. This educational module along with a pre- and post-test was disseminated to 19 students of the graduating class of 2019 of the Nurse Anesthesia Program at AdventHealth University during the clinical conference course in Fall of 2018.

Project Aims

Anesthesia providers should be experts in the common medications administered during the induction of general anesthesia. This includes the knowledge of alternative medications methods for the prevention of a sympathetic response due to direct laryngoscopy. The authors of this scholarly project identified a gap in the knowledge base regarding alternative medications utilized during the induction of general anesthesia. The independent variable was the educational

module of esmolol for preventing the sympathetic outflow during direct laryngoscopy. The dependent variable was a change in mean scores of the pre- and post-test. The aim was to increase the knowledge base of esmolol administration for attenuation of the sympathetic response in 19 of students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University. This project was implemented during the Fall 2018 clinical conference course, on September 27, 2018. To identify if the aim was met, the investigators evaluated for an increase in mean test scores, with the traditional significance level ($p \leq 0.05$).

Project Methods

This study's research subjects included 19 students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University (the planned sample size was 23 students, but only 19 made inclusion criteria). The study took place in a classroom at AdventHealth University. Recruitment was not necessary, because the students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University were required to take this course. Inclusion criteria included the participant being a student of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University, arriving at class on time, voluntarily signing the consent, completion of the pretest, presence for the educational module (PowerPoint presentation and discussion), and completion of the posttest. Students who failed to meet any of the inclusion criteria were excluded from participation.

Consent was voluntarily obtained via a signed waiver prior to implementation of data collection. A pretest was administered to the subjects before the educational presentation was given. Following the 30-minute PowerPoint presentation, an opportunity for questions was

presented. Upon completion of the presentation, the students were given a post-test to evaluate the knowledge base after the presentation.

To maintain confidentiality the pre- and post-test were placed in an envelope together, with a number between 1-23 (same number written on both tests) and the envelopes were randomly distributed throughout the class. The number was necessary so the same student took the same numbered pre- and post-test to afford the ability to test base knowledge before and after the presentation. There were no identifiers, allowing the subjects to remain anonymous. Data collection was stored on a flash drive without any identifying information. The information was destroyed by deleting the contents of the flash drive upon completion of the study. Only the investigators and Dr. Roy Lukman (the chair of the scientific review committee) had access to the data. Dr. Roy Lukman was given data access to complete quantitative statistical analysis on the test data. Dr. Roy Lukman then determined if a clinically significant increase in test scores was obtained, to evaluate whether an increase in knowledge was met.

Timeline

The topic proposal and partner submission were due on May 11, 2018. The PICOT question was synthesized on May 18, 2018. The partners submitted their request for time off for capstone work, within the suggested time frame (by May 23, 2018). The timeline and Scholarly Project Mentor Email thread was due on May 23, 2018. The Scholarly Project Proposal was due May 28, 2018. The ADU CITI modules, completed by individual partners, were due May 30, 2018. The proposal score was less than 90%, so a mandatory writing center appointment was attended. Written proof of appointment attendance was due June 11, 2018. The revised proposal, with edits from the writing center, was emailed to the Mentor and Chair by June 14, 2018. The

proposal must be revised with edits from the Mentor and Chair. On June 29, 2018, a Revised Project Mentor- Approved Proposal, Scholarly Project Concept/Plan Approval (signed by the Project Mentor), and AdventHealth University (AHU) Scientific Review Committee (SRC)/Institutional Review Board (IRB) application form were due. After the Nurse Anesthesia Program (NAP) Scholarly Project Approval form has been approved and signed by the NAP faculty, the partners completed the Scholarly Project Application form on July 6, 2018. The SRC review was finalized on July 18, 2018. Changes requested by the SRC were implemented on September 11, 2018. IRB approval was granted on September 10, 2018. Mentor approval and signature of the Scholarly Project Presentation Approval form was obtained September 20, 2018. The Scholarly Project Presentation Approval Form was uploaded to Canvas on September 24, 2018. The final PowerPoint was approved on September 24, 2018. The Scholarly Project was presented to 19 of the students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University on September 27, 2019. Data collection was subsequently initiated, and post-implementation data was collected on the day of the presentation. The Scholarly Project data was analyzed on October 19, 2018. The final PowerPoint was submitted November 24, 2018. The completed copy of the Trimester 2 Scholarly Project form was submitted on November 27, 2018.

Data Collection Plan

After obtaining permission from the ADU SRC and IRB to conduct research, the project was implemented on September 27, 2018. The data was collected in the form of the pre- and post-test from the test subjects. The tests were identical and marked with an identifying number and placed in an envelope. The identifying number was not linked to the participant, but served to identify that the pre- and post-test were taken by the same individual. The test was comprised

of ten multiple choice questions about fentanyl and the use of esmolol to abate sympathetic outflow caused by direct laryngoscopy. The investigators collected the pretest prior to the educational module, and the posttest was collected post the educational module. There were 4 exchanges with the participants of the study including the dissemination of the pre-and posttest, the collection of the pretest, execution of the educational module, and collection of the posttest. The data was then collected and organized. Next, the data was quantitatively analyzed by Dr. Roy Lukman.

Evaluation Plan

The effectiveness of the educational module was determined by evaluation of mean scores from pre-and post-test. The IBM Statistical Package of Social Sciences program was utilized for quantitative interpretation of the data. A paired samples t test was conducted and resulted with a t value of -8.931 with an associated $p < 0.001$. This analysis identified a statistically significant increase in average test scores between the PreTest and Posttest. Therefore, the educational module, on average, did increase the knowledge base of the 19 participants.

Results and Findings

Nineteen out of an eligible 22 (n=19) of the students of the graduating class of 2019 of the Nurse Anesthesia Program of AdventHealth University participated in the study. The participants were all registered nurses with the same level of anesthesia school education. The participants all met the inclusion criteria of arriving at class on time, signing consent, taking the Pretest, participating in the educational module and taking the Postest. The three students unable to stay for the educational module were excluded from the study. To determine if an improvement in knowledge base of esmolol administration for attenuation of the sympathetic

response, a paired-samples t-test was performed to analyze the average difference of scores between the PreTest and PostTest. Analysis of the data resulted in a mean PreTest score of 35.7895 % and a mean PostTest score of 85.2633% , a t value of -8.931 and $p < 0.001$. The educational module resulted in a statistically significant increase in average test score on use of on the use of esmolol during induction of general anesthesia to reduce opioid drug usage.

Limitations and Conclusion

Limitations of this study included the small sample size. Convenience sampling was utilized, so the subjects of the study were the investigator's classmates. Unfortunately, this limited the number of potential participants to 22 subjects. The original target sample size was unobtainable due to the limited number of participants that were present. Only 19 participants were present and signed the consent, and completed both the pre- and post-test. A larger sample size would have produced more accurate results in the learning outcomes and reduced the margin of error. The educational module was presented in the late afternoon after the participants completed a full day of clinicals. The timing of the project implementation, late afternoon after a clinical day, may have impacted the ability to stay engaged and process the material being presented due to participant fatigue. If the project implementation occurred at a time the participants were more rested, engagement and attention may have been improved, therefore leading to a further increase in the knowledge base of the use of esmolol in place of opioids for direct laryngoscopy, resulting in better post-test scores. The post-test was administered immediately after the PowerPoint presentation, with a time limit of about 10 minutes. The time limit may have restricted the participants' ability to thoroughly analyze each question, which may have negatively affected post-test scores. Regardless of these limitations, post-test scores were higher

than the pretest scores, demonstrating an improvement in the knowledge base among the participants. In conclusion, this presentation could be used in conjunction with other studies to fill gaps in knowledge among SRNA of future cohorts.

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Appendix A

ADU NAP SCHOLARALY PROJECT – INFORMED CONSENT FOR PARTICIPATION

We are two MSNA students in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU), the principal investigators (PIs). We are doing a Scholarly Project called *Use of Esmolol During Induction of General Anesthesia to Reduce Opioid Drug Usage - A Review of the Current Literature and Creation of an Educational Module for Anesthesia Providers*. This project is being supervised by a member of the Nurse Anesthesia Program faculty member. This faculty member will not participate in recruitment or retention of research participants. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to increase knowledge base of esmolol administration for attenuation of the sympathetic response to direct laryngoscopy.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address questions on the basics of esmolol administration to prevent sympathetic stimulation during direct laryngoscopy. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately an hour.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Your participation in this study is voluntary. You may choose to not to participate. The decision to participate or not participate in this research study is completely up to you. If you choose not to participate your refusal to participate in this research study will involve no penalty or loss of benefits to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw inform the PIs of your wishes.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don’t anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge about esmolol administration for attenuation of the sympathetic response to direct laryngoscopy.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. The tests will be assigned a number to ensure the pre and post-test is taken by the same individual, but no identifying information will be labeled on the tests, to maintain confidentiality of assessments. The investigators will randomly administer the identical pre and post-tests. Data will be stored on a flash drive without any identifying information. This information will be deleted post analysis of the data in Fall of 2018. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 60 minutes of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. You do not have to participate in this research study and choosing not to participate in this study will not involve any penalty or loss of benefit to you. The decision to participate or not participate in this research study is completely up to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw from the study informed the PI of your wishes. The investigators will be happy to answer any questions you have about the project. If you have any questions or concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

_____ **Date** _____

Participant Signature/ Participant Name (PRINTED LEGIBLY)

_____ **Participant Name (PRINTED LEGIBLY)**

Appendix B

Pre- and Post-test

1. According to the literature the appropriate intubating dose for esmolol to attenuate the sympathetic response due to laryngoscopy is?

a) 0.5-1 mcg/kg

b) 0.5- 1 mg/kg

c) 1-2 mcg/kg

d) 1-2 mg/kg

2. The appropriate time when esmolol should be administered is _____

a) immediately before intubation

b) 1.5- 3 minutes prior to intubation

c) immediately post intubation

d) 30 seconds to 1 minute prior to intubation

3. The following are contraindications to esmolol administration except _____& _____. (Pick two).

a) asthma

b) pulmonary hypertension

c)1st degree heart block

d) hypertension

e) decompensated heart failure

4) Approximately, the cost of a prefilled syringe of esmolol (100 mg) is?

a) $5

b) $10

c)$15

d) $30

5. At the cellular level, esmolol specifically is a _____ receptor blocker?

a) NMDA

b) Alpha 1- Selective

c) Beta 2- Selective

d) Beta 1-Selective

6) When discussing pharmacodynamics an anesthesia provider should know esmolol is metabolized by _____ ?

a) Glucuronidation

b) CYP 450 enzymes

c) Pseudocholinesterase

d) red blood cell esterases

7) The typical onset of esmolol is _____ and the duration of action is _____ minutes.

a) 1-2 minutes, 10-30 minutes

b) 10 minutes, 5-10 minutes

c) 2-10 minutes, 10-30 minutes

d) 2-10 minutes, 30 -60 minutes

8) Esmolol is _____ % protein bound.

a) 20

b) 55

c) 70

d) 15

9) Select all that apply laryngoscopy is associated with all of the following except

a) increased intraocular pressure

b) tachycardia

c) HTN

d) hypotension

e) increased ICP

10) Fentanyl's detrimental side effect include

a) increased peristalsis

b) tachycardia

c) respiratory depression

d) skeletal muscle flaccicity

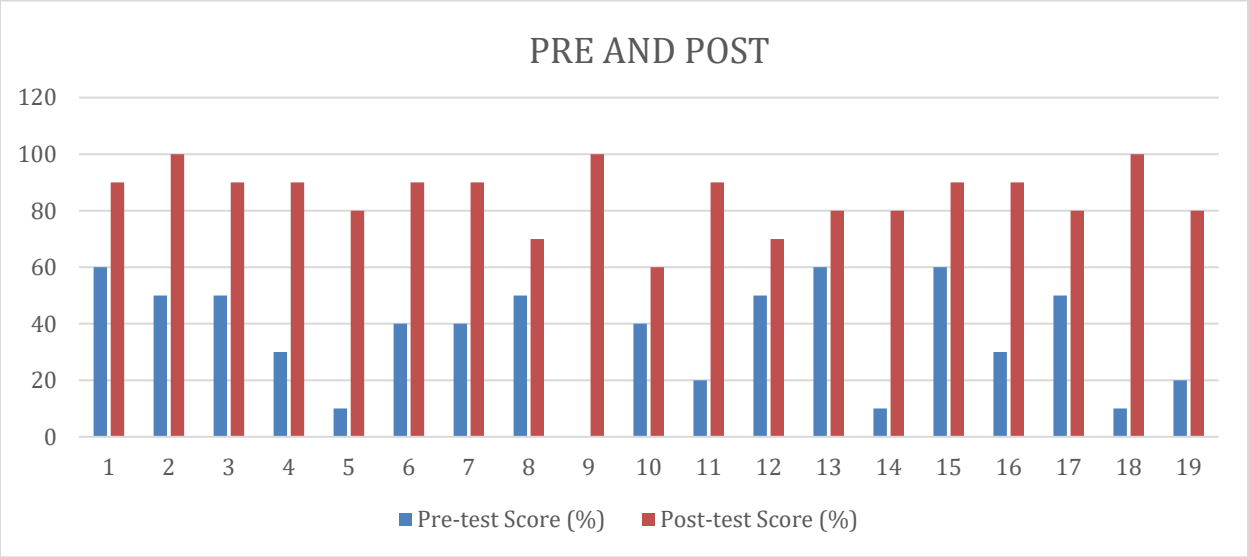
Appendix C

Pre-Test and Post Answer Key

1) **D**
2) **B**
3) **A&D**
4) **B**
5) **D**
6) **D**
7) **C**
8) **B**
9) **D**
10) **C**

Appendix D

Table 1



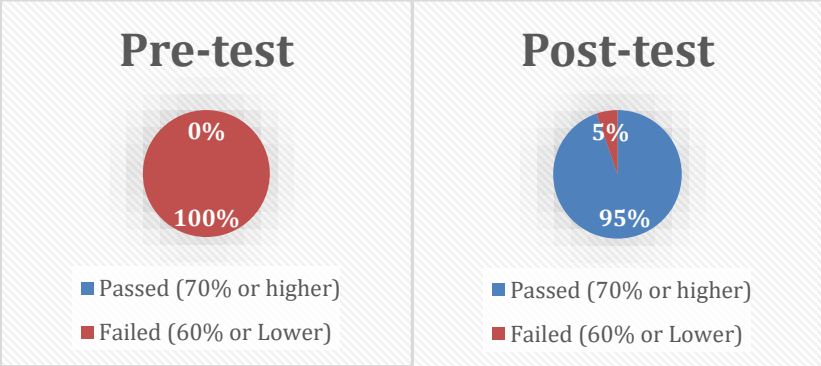


Table 2

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PreTest	35.7895	19	19.23994	4.41395
	:PostTest	85.2632	19	10.73334	2.46240

Table 3

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PreTest - :PostTest	-49.47368	24.14624	5.53953	-61.11180	-37.83557	-8.931	18	.000

Appendix E

A. (2018, May 09). Quand l'anesthésiste reproche l'intubation difficile du patient au chirurgien. Retrieved September 2018, from https://www.journal-anesthesie.com/quand-lanesthesiste-reproche-lintubation-difficile-du-patient-au-chirurgien/

Use of Esmolol During Induction of General Anesthesia to Reduce Opioid Drug Usage

Gustavo Velazquez BSN, RN
&
Jonelle Weagraff BSN, RN
Project Mentor
Jesenia Torres MSN, CRNA
Project Chair
Dr. Manuel Tolosa DNAP, CRNA

Objectives

- Identify the efficacy of esmolol during the perioperative period
- Identify esmolol's role in reducing perioperative opioid use
- Identify patient populations that may benefit from esmolol administration
- Identify key pharmacology of esmolol and fentanyl

Problem Statement

- Currently opioids are routinely used to abate sympathetic outflow
- Opioids have untoward side effects and utilization should be limited to preventing and treating surgery-related pain
- Worldwide use of opioids in the U.S. has doubled since 2001 leading to a national crisis
- National shortage of opioids
- Use of esmolol instead of fentanyl opioid usage may decrease

(Berterame et al. 2016; Food and Drug Administration, 2018; Gupta, S., & Tank, P. 2011)

Tachycardia (n.d.). Best Tachycardia GIFs | Find the top GIF on Gfycat. Retrieved September 8, 2018, from https://gfycat.com/gifs/search/tachycardia

Clinical Experience

- Neurosurgical
- Endoscopy

Potential Risks of Laryngoscopy

- Dysrythmia
- **Hypertension**
- Myocardial Ischemia
- Myocardial Infarction
- Hypoxia
- **Tachycardia**
- Hypercapnea
- Laryngospasm
- Bronchospasm
- **Increased intracranial pressure**
- Increased intraocular pressure

(Siddiqui, Katznelson, & Friedman, 2009)

Esmolol Pharmacology

Esmolol Hydrochloride Injection. (2018). Retrieved September 8, 2018, from https://www.medpluspro.com/esmolol-hydrochloride-injection.html

- Mechanism of Action
  - Competitively blocks response to beta-1- adrenergic stimulation
- Protein Bound
  - **55%**
- Onset
  - IV- 2-10 minutes
- Duration of Action
  - 10-30 minutes
- Metabolism
  - **red blood cell esterases**

Esmolol may benefit those with:

- History of stent placement
- Multi-vessel disease
- Heart Failure
- Elevated ICP
- History of Glaucoma
- Hypertension
- Epilepsy or seizures
- Acute head injury
- Cardiomyopathy
- Valvular disease
- Heart disease
- Pulmonary HTN
- Renal Failure
- Hydrocephalus
- Subdural Hematoma
- Epidural Hematoma

Mechanism of Action of Esmolol

- Class II antiarrythmic agent
- Competitive **beta 1 adrenergic blocker**, with little to no beta 2 blockade This decreases the force and rate of heart contractions
- Lacks intrinsic sympathomimetic activity and membrane stabilizing activity

(Lexicomp, 2018)

Beta 1 receptors

- Of the beta receptors in the myocardium, 75 % are beta 1
- By **blocking beta 1 receptors** esmolol reduces heart rate, contractility , and conduction speed

(Nagelhout & Plaus, 2014)

Additional benefits of Esmolol Usage

- Meets the day of procedure beta blocker administration requirement for patients who prescribed beta blockers
- May reduce anesthetic requirements

(Asouhidou & Trikoupi, 2015)

Clinical Uses for Esmolol

- Hypertension and tachycardia prevention and treatment
- Treatment of thyrotoxicosis or pregnancy induced hypertension
- Reduction of sympathetic response of electroconvulsive therapy

(Lexicomp, 2018)

Table 19-4

Possible Explanations for Cardioprotective Effects Produced by Perioperative β-Adrenergic Receptor Blockade

Decreased myocardial oxygen consumption and demand
Less stress on potentially ischemic myocardium owing to decreased heart rate and myocardial contractility
Attenuation of effects of endogenous catecholamines
Redistribution of coronary blood flow to ischemic areas
Increased coronary blood flow owing to increased diastolic time
Plaque stabilization owing to decrease in shear forces
Cardiac antidysrhythmic effects
Antiinflammatory effects (?)

(Stoelting, Hillier, Stoelting, 2006)

Table 19-1

Comparative Characteristics of β-Adrenergic Receptor Antagonists

	Propranolol	Nadolol	Pindolol	Timolol	Metoprolol	Atenolol	Acebutolol	Betaxolol	Esmolol
Cardiac selectivity	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Partial agonist activity	No	No	Yes	No	No	No	Yes	No	No
Protein binding (%)	90–95	30	40–60	10	10	5	25		55
Clearance	Hepatic	Renal	Hepatic Renal	Hepatic	Hepatic	Renal	Hepatic Renal	Hepatic Renal	Plasma hydrolysis
Active metabolites	Yes	No	No	No	No	No	Yes		No
Elimination half-time (h)	2–3	20–24	3–4	3–4	3–4	6–7	3–4	11–22	0.15
First-pass hepatic metabolism (estimate) (%)	75	Minimal	10–15	50	60	10	60		
Blood level variability	+ + + +	+	+ +	+ + +	+ + + +	+	+ +		
Adult oral dose (mg)	40–360	40–320	5–20	10–30	50–400	50–200	200–800	10–20	
Adult intravenous dose (mg)	1–10		0.4–2	0.4–1	1–15	5–10	12.5–50		10–80 IV 50–300 μg/kg/min

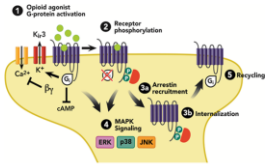
+, minimal + +, modest + + +, moderate + + + +, marked.

(Stoelting, Hillier, Stoelting, 2006)

Fentanyl Pharmacology

West Ward Pharmaceutical 00641602410. (2018). Retrieved September 8, 2018, from https://mms.mckesson.com/product/624328/West-Ward-Pharmaceutical-00641602410

- Mechanism of Action
  - Mu opioid receptor agonist
  - Inhibits the response to substance P
- Onset
  - 30 seconds – 1 minute
- Duration of Action
  - half life 2-4 hours
- Metabolism
  - Primary metabolic pathway is conjugation in the liver (Cytochrome P450)



Al-Hasani, R., & Bruchas, M. (2011, December 01). Molecular Mechanisms of Opioid Receptor-dependent Signaling and Behavior. Retrieved September 8, 2018, from http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1934470

Mechanism of Action

Clinical uses of Fentanyl

- Analgesia
- Blunt circulatory response to painful stimulation
- Provide surgical anesthesia
- Intrathecal analgesia
- Transdermal analgesia

Fentanyl's side effects should limit use exclusively for pain prevention and treatment.

- Abdominal pain
- Headache
- Fatigue
- Dizziness
- Nervousness
- Hallucinations
- Dyspnea
- **Respiratory Depression**
- Hypoventilation
- Apnea
- Urinary retention
- Diarrhea
- Nausea
- Constipation
- Dry mouth
- Somnolence
- Asthenia

(Lexicomp, 2018)

Fentanyl Side Effects Continued

- Constipation
- Biliary colic
- Delayed gastric emptying
- Enhance tone of pyloric sphincter, ileocecal valve and anal sphincter
- Narrowing or closure of sphincter of Oddi
- Nausea and vomiting
- Stimulation of CTZ
- Miosis
- Skeletal muscle rigidity "Chest wall rigidity"

(Lexicomp, 2018)

Literature Review

- Direct association with direct laryngoscopy and activation of the sympathetic nervous system
- Laryngoscopy can cause the average heart rate to increase by 66% and the baseline blood pressure to increase by 45%
- Elevations in heart rate and blood pressure for a period of 5-10 minutes peaking in 1 minute
- Sympathetic stimulation is associated to higher risk of myocardial infarction, increased ICP, increased IOP, and stroke

(Chopra, Gupta, & Lone, 2017; Hagberg, Georgi, & Krier, 2005; Varma, Aparanji, and Uma, 2015)

Literature Review

Fentanyl

- Side effects
  - altered patient's peristalsis
  - sedation
  - dizziness
  - urinary retention
  - ileus
  - nausea
  - vomiting
  - respiratory compromise
  - pruritus
  - hypotension
  - substance abuse

Esmolol vs Fentanyl

- Fentanyl administration may require
  - Anti-emetics
  - Stool softeners
  - Vasopressors

(Lexicomp, 2018)

A Comparative Study of Efficacy of Esmolol and Fentanyl for Pressure Attenuation of Intubation During Laryngoscopy and Endotracheal intubation

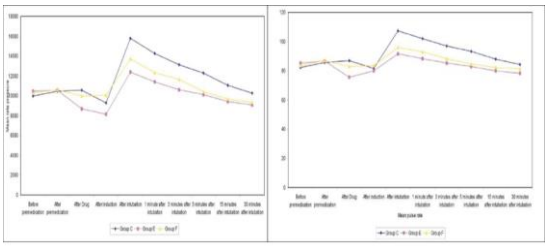
Methods

Intervention:

- **Group C**; Normal Saline was given
- **Group E**: **Esmolol 2mg/kg** IV **3 minutes before laryngoscopy**
- **Group F**: Fentanyl 2mcg/kg IV 3 minutes before laryngoscopy

- Results

(Gupta & Tank, 2011)



Blood pressure Heart Rate

(Gupta & Tank, 2011)

A Comparative Study of Efficacy of Esmolol and Fentanyl for Attenuation of Intubation Response During Laryngoscopy

Methods

Intervention:

- **Esmolol 2mg/kg** IV **three minutes before intubation**
- Fentanyl 2mcg/kg IV three minutes before intubation
- Control group: no drug was given

Results

(Varma, Aparanji, & Uma, 2015)

The Comparison of the Effects of Dexmedetomidine, Fentanyl and Esmolol on Prevention of Hemodynamic Response to Intubation

Methods

Intervention:

- **Group I**; Dexmedetomidine with infusion 1mcg/kg in 10 minutes
- **Group II**: Fentanyl 2mcg/kg IV 2 minutes before laryngoscopy
- **Group F**: **Esmolol 2mg/kg** IV **2 minutes before laryngoscopy**

- Results

(Gogus, Akan, Serger, & Baydar, 2014)

Esmolol Hydrochloride Injection. (2018). Retrieved September 8, 2018, from https://www.medpluspro.com/esmolol-hydrochloride-injection.html

Barriers

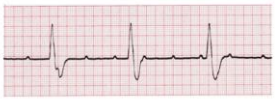
- Side Effects
- Contraindications
- Pricing
- Safety and Efficacy
- Limitations

Side Effects of Esmolol

- Severe Bradycardia
- Hypotension
- Ventricular Arrhythmia
- Heart Failure
- Increase Digoxin levels

(Lexicomp, 2018)

Esmolol Contraindications



Heart Blocks - Third Degree Heart Block. (2018). Retrieved September 8, 2018, from https://ekg.academy/learnekg?courseid=316&seq=7

- Hypersensitivity
- **Decompensated heart failure**
- **Heart block greater than 1st degree (if no a/v pacemaker)**
- Severe sinus bradycardia
- Sick sinus syndrome
- Cardiogenic shock
- IV calcium channel blockers administered recently
- **Pulmonary hypertension**

(Lexicomp, 2018)

Cost

ESMOLOL	FENTANYL
IV solution • 100mg/10ml: $25.60 • ($2.56 per ml)	IV solution • 100 mcg/ 2 ml:$1.75 • ($0.88 per ml)
•Prefilled Syringes • **100mg/10ml: $9.47** • ($0.95 per ml)	

(Lexicomp, 2018)

Safety and Efficacy of Esmolol

- The POISE trial in 2008 found that although the myocardial infarction and myocardial ischemic events decreases with metoprolol administration, stroke rates increased (POISE Study Group, 2008) .
- It is not recommended to begin a beta blocker regimen in a patient without cardiac risk prior to surgery (Mounsey, A., Rogue, J., & Egan, M., 2014).
- Metoprolol is a longer acting beta blocker than esmolol (Lexicomp, 2018).
- Esmolol is a historically safe agent to administer, even with septic patients (Du, W., Wang, X., Long, Y., & Liu, D.-W. (2016).

Limitations To Use

Staff resistance

- Anesthesia Providers
- Pharmacy
- Nursing Staff

Summation

- Esmolol is a better alternative to fentanyl in reducing the sympathetic response to laryngoscopy
- It has fewer side effects than fentanyl, and is a non- narcotic
- It is slightly more expensive than fentanyl, so it should be used for specific patient populations (i.e. those with heart disease, increased intracranial pressure, etc.)

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