2021

An Educational Module for the Utilization of Dexmedetomidine in Patients Undergoing One Lung Ventilation During Thoracic Lung Surgeries to Enhance Oxygenation

Robert M. Dillon
Florida International University, rdill008@fiu.edu

Valerie Diaz
Florida International University, vdiaz@fiu.edu

Steve Khavandegaran

An Educational Module for the Utilization of Dexmedetomidine in Patients Undergoing One Lung Ventilation During Thoracic Lung Surgeries to Enhance Oxygenation

A DNP Project Presented to the Faculty of the
Nicole Wertheim College of Nursing and Health Sciences

Florida International University

In partial fulfillment of the requirements
for the Degree of Doctor of Nursing Practice

By

Robert Dillon, MSN, RN

Supervised By

Valerie J. Diaz, DNP, CRNA, APRN, CAPT, USN, NC
Steve Khavandegaran, MSN, CRNA, APRN

Approval Acknowledged: _____, DNA Program Director

Date: _____

Approval Acknowledged: _____, DNP Program Director

Date: _____

TABLE OF CONTENTS

ABSTRACT

Background: During lung surgeries, one-lung ventilation (OLV) produces severe ventilation and perfusion abnormalities that can delay patient recovery. Recent articles suggest that Dexmedetomidine may have protective effects on the lungs when hypoxic conditions exist and may improve hypoxic pulmonary vasoconstriction. Additional literature review is needed to confirm the reproducibility of these findings and generate evidence-based practice recommendations regarding the usage of Dexmedetomidine as an anesthesia adjunct during one-lung ventilation.

Aim: This literature review aims to assess the best randomized control trials (RCTs) available regarding the benefits of Dexmedetomidine (DEX) coadministration during one-lung ventilation for pulmonary surgeries. By analyzing current evidence, the authors strive to introduce recommendations for anesthesia professionals that will reduce the prevalence of hypoxia and ventilation/perfusion abnormalities during pulmonary surgeries.

Study Selection: Seven RCTs, totaling 419 subjects, were included in this literature review and selected based upon their inclusion of adult human participants undergoing general anesthesia with one-lung ventilation for pulmonary surgeries, written in the English language, from 1999 to 2020, published in scientific/peer-reviewed journals and available for download from the CINAHL, Medline, and EMBASE databases

Results: Six of the seven RCTs reviewed reported improved oxygenation amongst the group receiving Dexmedetomidine compared to the control; however, only four studies could establish statistical significance. One article observed a reduction in PaO2 in the DEX group that did not achieve statistical significance. After distribution of the literature review via an online educational module, the number of anesthesia providers “very likely” to implement DEX coadministration during OLV increased between the pre-test (n=2) and post-test (n=4).

Conclusion: Current evidence suggests that Dexmedetomidine coadministration with Propofol or inhalational anesthetic agents during one-lung ventilation will improve oxygenation intraoperatively. The mechanisms through which these benefits occur remains a debate and should be the focus of future research. After receiving a virtual module on the evidence gathered, more anesthesia providers indicate they are “very likely” to incorporate Dexmedetomidine during these types of surgery, signifying willingness to implement evidence-based practice changes.

Keywords: one-lung ventilation, lung isolation, single lung ventilation, hypoxic pulmonary vasoconstriction, oxygenation, lung surgery, precedex, Dexmedetomidine, anesthesia

INTRODUCTION

Description of Problem

In 2020 there were approximately 228,820 new cases of lung cancer diagnosed in the United States alone.[1] Lung cancer is the second most common type of cancer in both men and women, and each year more people die from lung cancer than colon, breast, and prostate cancers combined. [1] Non-small cell lung cancer accounts for 85% of all lung cancer diagnoses and over half of people with this condition die within one year of discovery.[2] Because of the aggressive nature of this disease, early surgical intervention is recommended as the standard of care.[2]

Although frequently performed, lung surgeries are not without complications. Following thoracic surgeries, patients frequently experience complications from atelectasis, pneumonia, atrial fibrillation, and require chest tube placement for several days.[3] Failure to optimize respiratory function and control pain are the two most significant risk factors for postoperative complications that increase the length of stay[3]; therefore, research should focus on these areas to improve patient outcomes. In 2008, a video-assisted thoracoscopic (VATS) lobectomy cost approximately $20,316, which may also highlight a significant financial incentive to reduce length of stay and decrease insurance expenditures for lung surgeries.[4] The prevalence of minimally invasive VATS procedures has increased five-fold within the last decade;[5] therefore, it is imperative to identify anesthesia techniques that improve oxygenation and reduce pain during these procedures to minimize recovery times for these patients.

Background

Surgical procedures involving the lungs, such as pneumonectomies, lobectomies, segmental wedge resections, and VATS, require the operative lung to remain motionless during surgery. Forcing the lung to remain still for surgery naturally creates a problem with maintaining oxygenation; therefore, anesthetists must be familiar with how to respond to the physiological changes that occur during these procedures. Specific anesthetic techniques, known as lung isolation or one-lung ventilation (OLV), utilize special endobronchial tubes to allow a patient to

breathe through one lung while the other lung is held still for surgery. While the operative lung lies motionless and no longer participates in gas exchange, a hypoxic environment may persist and inflammatory changes within the lungs may occur that ultimately delay the patient's postoperative recovery.

Natural protective mechanisms, such as hypoxic pulmonary vasoconstriction (HPV), exist to counteract these problems during one-lung ventilation by constricting pulmonary blood vessels so that more blood flows to the oxygenated lung.[6] Shifting pulmonary blood flow to areas of the lungs that are better ventilated allows for more diffusion of oxygen into the bloodstream and ultimately improves oxygen delivery to organs and tissues. The preservation of hypoxic pulmonary vasoconstriction is important for maintaining normal oxygenation during lung surgeries; however, several of the most common anesthetic agents used to provide hypnosis and limit responses to surgical stimulation can impair HPV. Anesthesia providers must understand how to develop an appropriate plan of care which provides sufficient anesthesia while also implementing steps to preserve HPV and improve oxygenation during these surgeries.

Anesthetic interventions to prevent desaturation during OLV primarily revolve around ventilation strategies, maintaining hemodynamic stability, and titration of anesthetic medications to preserve HPV.[7] Volatile anesthetic agents (VAAs) Desflurane, Isoflurane, and Sevoflurane, as well as the intravenous medicine Propofol, are commonly used for maintenance of anesthesia during lung surgeries; however, several studies suggest that both VAAs and Propofol inhibit the protective effects of hypoxic pulmonary vasoconstriction in a dose-dependent manner.[8] When medications inhibit HPV during one-lung ventilation, the pulmonary vasculature allows more blood flow towards the hypoxic surgical lung. This blood supply misses out on the opportunity to pick up oxygen from ventilated alveoli and participate in gas exchange, thus reducing the overall oxygen concentration within the systemic circulation. The pressing need to preserve HPV, improve intraoperative oxygenation, and provide adequate pain control to improve patient

outcomes warrants the search for an anesthetic modality free from the limitations of current anesthetic practices.

The use of Dexmedetomidine (DEX) as part of a balanced anesthetic technique has gained popularity recently because of the drug's ability to provide sedation and anxiolysis without depressing respiratory drive.[9] While the effects of alpha 2 agonists on heart rate and blood pressure are well known, research detailing DEX's impact on the pulmonary vasculature is scarce and has produced variable results.[8] Animal studies propose that Dexmedetomidine may provide bronchoprotective effects and decrease histamine-induced bronchoconstriction; however, a clear gap in knowledge exists as to how these results may translate into clinical practice.[10]

Dexmedetomidine is FDA approved for short-term sedation with mechanical ventilation or for sedation of non-intubated patients during surgical procedures.[11] DEX is valuable as an anesthetic adjunct, yet it is still underutilized in many clinical settings. The findings of the aforementioned animal studies have sparked recent interest in evaluating Dexmedetomidine's mechanism of action on the inflammatory response of the lungs seen during stressful or hypoxic conditions, such as those encountered during one-lung ventilation. A handful of studies have explored whether Dexmedetomidine is responsible for preserving HPV during one-lung ventilation or if DEX's bronchoprotective effects only occur due to anesthesia sparing effects of the primary agent. Currently, there is a lack of evidence-based guidelines, quality improvement plans, or hospital-based protocols utilizing this application of Dexmedetomidine; therefore, this scholarly project seeks to evaluate current literature regarding the relationship between Dexmedetomidine and pulmonary oxygenation during lung surgery and measure the willingness of anesthesia providers to implement evidence-based practice change based upon our literature review findings.

Objectives of Literature Review

Developing a clinical question to focus research is an essential component of conducting a literature review. The PICO mnemonic often used in evidence-based medicine is helpful to

guide literature reviews and focuses the scope of research on including a specific population (P), intervention (I), comparison (C), and outcome of interest (O).[12] This literature review focuses on investigating whether the coadministration of Dexmedetomidine (I) in patients undergoing one-lung ventilation for lung surgeries (P) will improve oxygenation (O) in comparison to patients who receive only Propofol or VAAs for anesthetic maintenance. This literature review will then be utilized to create an educational module for anesthesia providers with the intent of delivering helpful information to influence the incorporation of evidence-based research into the plan of care for patients undergoing one-lung ventilation during thoracic lung surgeries. A pre-test post-test designed implementation strategy utilizing Qualtrics surveys will be executed to determine the effectiveness of the educational module.

METHODOLOGY OF LITERATURE REVIEW

Search Strategy

A search of the CINAHL, MEDLINE/Proquest, and Embase electronic databases was conducted to capture a comprehensive view of current evidence regarding the administration of Dexmedetomidine during one-lung ventilation. Key search terms were identified to build the search phrase ("one-lung ventilation" OR "lung isolation" OR "single lung ventilation" OR "hypoxic pulmonary vasoconstriction" OR "thorac*") AND ("Precedex" OR "Dexmedetomidine"), which was utilized in all three databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was then implemented to facilitate screening and critically appraise each article utilized in the review.

Study Selection and Screening of Evidence

Appendix A illustrates that the CINAHL database initially yielded 54 results from the search phrase mentioned above. Filters were applied to screen results to academic journal articles written in English and published after 1999, when Dexmedetomidine first gained FDA approval.[11] After filters were applied, 52 articles were available for appraisal. The Medline

database yielded 375 results initially, but after filters were applied to screen results to peer-reviewed journals, written in English and published between 1999 and 2020, only 109 articles in the MEDLINE/Proquest database remain available for appraisal. Lastly, Embase retrieved 630 results, with 336 remaining after screening for journal articles in English with publication dates between 1999 and 2020. A total of 497 articles resulted from all three databases, and after duplicates were removed, 428 articles remained for appraisal.

Titles and abstracts of the remaining article were reviewed for relevance to the population, intervention, comparison, and outcomes of interest for this project. A total of 413 articles were excluded based on the inclusion/exclusion criteria detailed in Appendix B, leaving 15 articles for full-text review. After full-text review of the 15 remaining articles, two were excluded for data sections written in languages other than English, three were rejected for having non-human participants, and three were excluded because they did not contain relevant comparisons. Seven articles remained and therefore were utilized for analysis of the clinical problem and data comparison. A PRISMA diagram (Appendix D) illustrates the article selection process, while the synthesis matrix (Appendix C) helps to categorize the data that was collected and identify the quality of articles chosen, based upon the Johns Hopkins Evidence Level and Quality Guide.

RESULTS OF LITERATURE REVIEW

Oxygenation Levels

Six out of the seven articles reviewed reported higher oxygenation measurements amongst the Dexmedetomidine group than their control.[13-18] Four studies demonstrated that the differences in oxygenation levels between groups were statistically significant, suggesting higher oxygenation due to Dexmedetomidine administration.[14,15,17,18] One article observed a reduction in arterial oxygenation (PaO_2) amongst the DEX group in comparison to the control, although this result was not statistically significant.[16]

Timing of Effects

Two studies measured arterial blood gas values every 10 minutes after the initiation of one-lung ventilation.[17,19] The first study suggested that the 30-minute mark may be a pivotal moment for mediator release during OLV, as the most significant changes in PaO2 and pulmonary shunt fraction (Qs/Qt) were observed at this time mark.[17] This same study also reported that Dexmedetomidine administration was associated with a statistically significant decrease in pulmonary shunting across all time intervals, indicating that Dexmedetomidine plays a beneficial role in reducing shunting after the initiation of OLV.[17] Although not statistically significant, patients in the second study, receiving 0.5mcg/kg/hr of Dexmedetomidine, showed persistent improvements in PaO2 from 20-50 minutes after OLV compared to the other groups.[19] Two other studies, which recorded ABGs at baseline, 30 min, and 60 min after the initiation of OLV, reported improvements in oxygenation amongst the dexmedetomidine group at both the 30 and 60 minute mark.[15,18] The findings from these four studies demonstrate that the most significant effects of Dexmedetomidine are observed around the same time that hypoxic pulmonary vasoconstriction is initiated, thus signifying that DEX may play a role in the preservation or augmentation of HPV.

Dexmedetomidine and Inhalational Anesthetics

Five of the seven studies included in the literature review tested the effects of Dexmedetomidine coadministration with volatile anesthetic agents by comparing a DEX infusion to a control group receiving saline.[13,14,16-18] Four of these five studies utilizing inhalational anesthetics observed improvements in oxygenation as a result of Dexmedetomidine infusion.[13,14,17,18] Two of the studies, one utilizing Desflurane and the other using Isoflurane, suggest that the improvement in oxygenation amongst the DEX group might be due to an anesthetic-sparring effect.[13,16] The authors speculate that because volatile anesthetic agents are known to inhibit hypoxic pulmonary vasoconstriction, the coadministration of Dexmedetomidine allowed a reduction in the total concentration of VAAs administered and thus prevented the adverse effects

of inhaled anesthetics on HPV.[13,16] One study, maintaining anesthesia with Sevoflurane, reported that there was no significant decrease in Sevoflurane concentration administered between the Dexmedetomidine and control group; therefore, the improvement in oxygenation seen in the DEX group must be related to the inherent mechanisms of Dexmedetomidine and not due to an anesthetic-sparing effect.[18] A study utilizing Isoflurane and measuring levels of oxidative species and nitric oxide throughout Dexmedetomidine administration in OLV also suggests that DEX has an inherent anti-inflammatory property that protects pulmonary functioning, improves oxygenation, and maintains hypoxic pulmonary vasoconstriction.[17]

Dexmedetomidine and Propofol

In this review of current literature, two studies compared the effects of Dexmedetomidine administration on oxygenation in patients receiving intravenous Propofol as the primary anesthetic agent.[15,19] Both studies observed an improvement in oxygenation in at least one of their groups receiving Dexmedetomidine, although one study reported the effects were not statistically significant and only observed in the group receiving an intermediate dose (0.5mcg/kg/hr) of Dexmedetomidine.[19] The authors of the same study proposed that Dexmedetomidine infusion did not significantly decrease the amount of Propofol needed to maintain adequate depth of anesthesia, thus the mechanism of Dexmedetomidine's improvements in oxygenation is not related to an anesthesia-sparing effect.[19]

The second article reviewed involved a novel experiment seeking to highlight the effectiveness of nebulized Dexmedetomidine on oxygenation levels and measurements of pulmonary compliance during OLV.[15] This article was included in the review of current literature despite the nebulized route of administration of Dexmedetomidine because research regarding dexmedetomidine and propofol coadministration in the setting of OLV for thoracic surgeries is noticeably limited. In this study, nebulized Dexmedetomidine resulted in statistically significant improvements in oxygenation, shunting, and lung compliance during OLV compared to the control group, which was observed amongst all Dexmedetomidine dosages (0.5mcg/kg-

2mcg/kg).[15] Despite the administration of nebulized Dexmedetomidine decreasing propofol requirements, the authors hypothesize that the dexmedetomidine groups' improvement in oxygenation and pulmonary mechanics is related to both an attenuation of pulmonary inflammatory factors and reduction of propofol dose administered.[15]

Dose-Dependent Effects

Only two studies in this review explicitly tested for a dose-dependent relationship between Dexmedetomidine and the drug's effects on oxygenation.[15,19] One study, utilizing nebulized Dexmedetomidine, found doses of 0.5mcg/kg, 1mcg/kg, and 2mcg/kg to produce statistically significant improvements in oxygenation and pulmonary shunting in comparison to a normal saline placebo.[15] A second study revealed that dexmedetomidine increases PaO2 after a loading dose of 1mcg/kg IV and continuous infusion of 0.5mcg/kg/hour, but not with continuous infusions of 0.3mcg/kg/hour and 0.7mcg/kg/hour.[19] Improvements in oxygenation observed in this second study were not statistically significant,[19] and it should be noted that the two studies in this review that explicitly tested for dose-dependent relationships were also the two studies that utilized Propofol as the primary anesthetic agent.

All studies with inhalational anesthetic agents that reported improvement of oxygenation following DEX infusion utilized a bolus of 1mcg/kg over 10 minutes, followed by a continuous rate of 0.5mcg/mg/hour or greater.[13-15,17,18] The only study that reported decreased PaO2 amongst the DEX group compared to the control administered Dexmedetomidine at a continuous rate of 0.3mcg/kg/hr.[16] These results amongst both the Propofol and volatile anesthetic studies suggest a dose-dependent relationship exists and a loading dose of 1mcg/kg of Dexmedetomidine over 10 minutes followed by an infusion of at least 0.5mcg/kg/hr should be administered to produce improvements in oxygenation.

DISCUSSION OF LITERATURE REVIEW

Summary of Evidence

Kernan et al. observed an improved in PaO_2/FiO_2 ratio, a measurement of oxygenation, when Dexmedetomidine was co-administered with Isoflurane, but because the results were not statistically significant, the authors hypothesized that the reason for this improvement might be due to Dexmedetomidine's ability to limit the dose of Isoflurane rather than a mechanism produced by Dexmedetomidine itself.[13] Volatile anesthetic agents are known to inhibit hypoxic pulmonary vasoconstriction; thus, reducing the total concentration of these agents could theoretically be the mechanism for improvements in oxygenation and pulmonary shunting.[13] Xia et al.'s original study in 2013 showed that Dexmedetomidine administered with a loading dose of 1mcg/kg over 10 minutes and maintained with a continuous infusion of 0.7mcg/kg/hour produced statistically significant reductions in pulmonary shunting (Qs/Qt%) and improvements in arterial oxygen pressure (PaO_2).[14] The measurement of both oxygenation and shunt fraction allowed the authors to establish that Dexmedetomidine does indeed play a role in preserving hypoxic pulmonary vasoconstriction and reducing pulmonary shunting. However, only a hypothesis of the mechanism was described.

A follow-up study by Xia et al. in 2015 expanded on the 2013 research and measured levels of nitric oxide (NO) and reactive oxygen species superoxide dismutase (SOD) and malondialdehyde (MDA), in addition to PaO_2 and shunt fraction, in an attempt to highlight Dexmedetomidine's impact on oxidative stress and pulmonary vasodilation during one-lung ventilation.[17] Xia and colleagues found a significant decrease in MDA, an inflammatory factor associated with oxidative stress, and a significant increase in nitric oxide, a potent vasodilator.[17] These findings were able to confirm that the improvement in oxygenation seen with Dexmedetomidine infusion during OLV is related to the drug's ability to reduce oxidative stress, improve hypoxic pulmonary vasoconstriction, decrease shunt fraction, and increase PaO2; not just as a byproduct of decreased Isoflurane concentration.[17]

Finally, a study by Lee and colleagues confirmed the benefits of Dexmedetomidine coadministration with Sevoflurane during OLV, as their research demonstrated significant increases in both oxygenation and airway compliance amongst the DEX group.[18] These results endorse that there are inherent mechanisms of Dexmedetomidine responsible for improvements in oxygenation during one-lung ventilation beyond the simpler anesthetic-sparing effect theory speculated by other studies.[18]

Limitations of Literature Review

As with most scientific research, several limitations exist within this review of current literature. The primary limitation of this review is the exclusion of articles written in languages other than English, such as Chinese and Arabic, based on the primary investigator's language of origin. The limited number of English articles combined with the inability of the research team to translate articles written in different languages into valid data points for this literature review means that potentially valuable findings may have been missed. Additionally, this literature review only included articles that were peer-reviewed or published within academic journals. This lack of consideration for grey literature and expert opinions potentially exposes our findings to publication bias.

A second limitation of our research involves the variability of DEX dosing amongst the studies included. This literature review only found two studies that explored the dose-dependent relationship of Dexmedetomidine's effects on oxygenation, and from these two studies, only one study found a statistically significant result.[15] The two studies that explored a dose-dependent relationship used Propofol as their control anesthetics; therefore, no statistically significant data was uncovered regarding DEX dosing and inhalational anesthetics, despite the majority of articles utilizing inhalational anesthetic agents as their primary agent. Future research is needed to establish dosing recommendations for Dexmedetomidine coadministration during one-lung ventilation that will elicit the drug's beneficial effects.

The third limitation of this literature review lies within the participant selection and methodology of the included studies. All seven articles included in this review are single-center randomized control trials.[13-19] Despite RCTs being Level 1 evidence on the Johns Hopkins Evidence Level and Quality Guide, multicentered studies conducted by multiple groups of researchers might have produced greater generalizability of results and diversity in the sample population. Four of the seven studies included ASA I and II participants.[14,15,17,19] Two of the seven included up to ASA III participants[16,18] and no studies allowed ASA IV. Five studies explicitly excluded participants with severe underlying comorbidities such as heart, liver, or kidney disease and substance abuse or psychiatric disorders.[14-17,19] Only one study focused on patients with a diagnosis of COPD, which is commonly found in patients with smoking history or lung cancer, and who are likely to need thoracotomies.[18] Although 419 participants were included amongst the seven studies, the lack of research on patients with significant comorbidities that are reflective of the general population requiring thoracic lung surgery may limit the generalizability of these findings or have artificially overestimated the beneficial results.

Recommendations for Future Research

Future research regarding the effects of Dexmedetomidine on oxygenation during one-lung ventilation is certainly needed. The mechanism of how DEX improves oxygenation during OLV is under-researched and often attributed to an anesthetic-sparing effect of the primary agent.[13,16] Only one of the seven studies reviewed proposed a direct biochemical mechanism of action for the results seen within their study.[17] Two of the seven studies concluded that Dexmedetomidine must have an inherent ability to improve oxygenation separate from anesthetic-sparing effects but were unable to suggest how this is accomplished.[15,18] A more detailed investigation into the dosing of Dexmedetomidine to achieve desired improvements in oxygenation might also be explored, especially when co-administered with inhalational anesthetics.

Limitations of this current review need to be addressed in future research to produce more generalizable results for the typical population that requires one-lung ventilation and lung surgery. Patients with significant cardiovascular, pulmonary, and renal comorbidities may receive the most benefit from strategies to improve intraoperative oxygenation and therefore should be involved in future research studies. Barriers to future literature reviews, such as language, can be reduced by including researchers from multilingual backgrounds within the research team.

METHODOLOGY OF QUALITY IMPROVEMENT

Setting and Recruitment

The setting for the implementation of this educational module was within the Broward Health system, specifically amongst the employees of the Anesco group, which provides anesthesia services to patients in Broward County, Florida. Broward Health Medical Center is a 716 bed, Level 1 trauma facility and the largest medical center in Broward County, offering virtually every medical and surgical specialty. MD and CRNA anesthesia providers at this location frequently care for high acuity patients, classified as ASA 3 and 4, and frequently utilize one-lung ventilation during pulmonary surgeries; therefore, they are an appropriate target audience for this evidence-based educational module. IRB approval from both Broward Health and Florida International University was obtained for the implementation of this module.

Participants were recruited through email lists procured with permission from the Anesco anesthesia group leadership team. Recruitment emails were delivered to CRNA providers containing a brief description of the benefit of the educational module, requirements for their participation, and the anticipated time commitment. Incorporating this information into the initial recruitment letter was designed to foster participation by addressing potential barriers. An anonymous Qualtrics link to the pre-test, post-test, and the educational module was also included in the recruitment email, allowing participants' information to remain confidential at all times as no personally identifiable information was collected, in agreement with the IRB-approved

protocol. Participants were allowed three weeks to complete the educational session and the pre/post-test knowledge surveys.

Intervention

An educational module summarizing the findings from our review of current literature regarding the use of Dexmedetomidine to improve oxygenation during one-lung ventilation was created utilizing Microsoft PowerPoint and published with voice-over content. A quasi-experimental pretest-posttest survey design was then incorporated using the Qualtrics online survey platform to administer a questionnaire to a convenience sample of CRNAs working within the Broward Health system via email. CRNAs were given a pre-test survey to assess baseline knowledge of Dexmedetomidine, variables affecting hypoxic pulmonary vasoconstriction, and the frequency of which they utilize Dexmedetomidine for thoracic lung surgeries. Once the pre-test was completed, the CRNAs were instructed to review an educational PowerPoint presentation disseminating the beneficial findings of a current literature review on Dexmedetomidine's role in improving oxygenation during lung surgeries requiring one-lung ventilation. CRNAs were then asked to complete the post-test Qualtrics questionnaire. A control group was not established for this study design, and the educational module represents the intervention that was implemented to manipulate CRNA's knowledge of Dexmedetomidine's ability to alter oxygenation during hypoxic conditions.

Data Collection

The Qualtrics platform was used for the collection of data from the pre/post-test questionnaires. Qualtrics data was then downloaded onto a password-protected laptop, where data was manually compared to identify if a change in the knowledge or behaviors of CRNAs occurred after watching the educational module. The data was then input into Microsoft Excel to develop graphic comparisons of the pre and post-test results so that generalizations and comparisons could be visualized.

Protection of Human Subjects

Institutional Review Board (IRB) approval was obtained from Florida International University and the Broward Health IRB for this study protocol as a means to protect the rights and safety of all participants (Appendices E and F). An informational message describing the study and the risks and benefits of participation was presented to all Broward Health CRNAs before launching the questionnaires and modules. Participation in the educational module was completely voluntary, and subjects were notified that they were free to withdraw from participation at any time. A randomized numerical digit was provided to each participant at the beginning of the survey to protect the anonymity of participants throughout the implementation of the educational module. The results of all questionnaires were stored securely on a password-protected laptop. Only the principal investigator had access to these responses, thus ensuring security, anonymity, and data privacy. Lastly, the authors of the study had no financial interests to disclose pertaining to the development or implementation of the study

RESULTS OF QUALITY IMPROVEMENT

Participant Demographics

A total of five participants completed the evidence based-educational module by viewing the presented content and answering the pre-test and post-test surveys. The participant demographics are displayed in Table 1 below. The majority of the participants were female (n=3, 60%), as opposed to male (n=2, 40%), with most participants identifying their age as between 30-49 years old (n=3, 60%). Other participants reported age groups 18-29 (n=1, 20%) and 50-69 (n=1, 20%). There were no participants reporting age as 70 years or greater (n=0, 0%). A diverse population of participants was observed, with Hispanic (n=2, 40%) being the largest lineage of respondents, followed by Caucasian (n=1, 20%), African American (n=1, 20%), and Other (n=1, 0%). No participants claimed Asian ethnicity (n=0, 0%). Lastly, participant level of experience was assessed by asking “How many years have you been administering anesthesia?”, which

produced the following results: 0 - 2 years (n=2, 40%), 3 - 5 years (n=1, 20%), 6 - 10 years (n=1, 20%), and 10+ years (n=1, 20%).

Table 1. ***Pre-Test/Post-Test Participant Demographics***

Demographics	**N (%)**
Total Participants	5 (100%)
Gender	
Male	2 (40%)
Female	3 (60%)
Age	
18-29	1 (20%)
30-49	3 (60%)
50-69	1 (20%)
70+	0 (0%)
Ethnicity	
Hispanic	2 (40%)
Caucasian	1 (20%)
African American	1 (20%)
Asian	0 (0%)
Other	1 (20%)
Experience	
0-2yrs	2 (40%)
3-5yrs	1 (20%)
6-10yrs	1 (20%)
10+yrs	1 (20%)

Pre-Test Knowledge and Opinions

Current knowledge of Dexmedetomidine, HPV, and anesthetic management of lung surgeries requiring one-lung ventilation was assessed by asking participants to answer a pre-test survey. The complete pre and post-test survey can be found in Appendix G, while a summary of

the number of the participants who answered correctly is displayed in Table 2. The indications for OLV (n=5, 100%), physiology of HPV (n=5, 100%), and mechanisms of action for Dexmedetomidine (n=5, 100%) were well understood at baseline as evidenced by all participants answering correctly. The mechanism of how DEX is able to improve oxygenation during OLV, however, was poorly understood at baseline amongst participants (n=2, 40%), which indicated an opportunity for learning to occur. Operative complications associated with OLV (n=3, 60%), significant risk factors affecting recovery after OLV (n=4, 80%), and anesthetic agents associated with HPV inhibition (n=3, 60%) were correctly reported by only a fraction of the participants prior to viewing the module, signifying a need for education. Pre-test willingness to implement the coadministration of Dexmedetomidine during pulmonary surgeries requiring one-lung ventilation was as follows: somewhat unlikely (n=1, 20%), somewhat likely (n=2, 40%), and very likely (n=2, 40%).

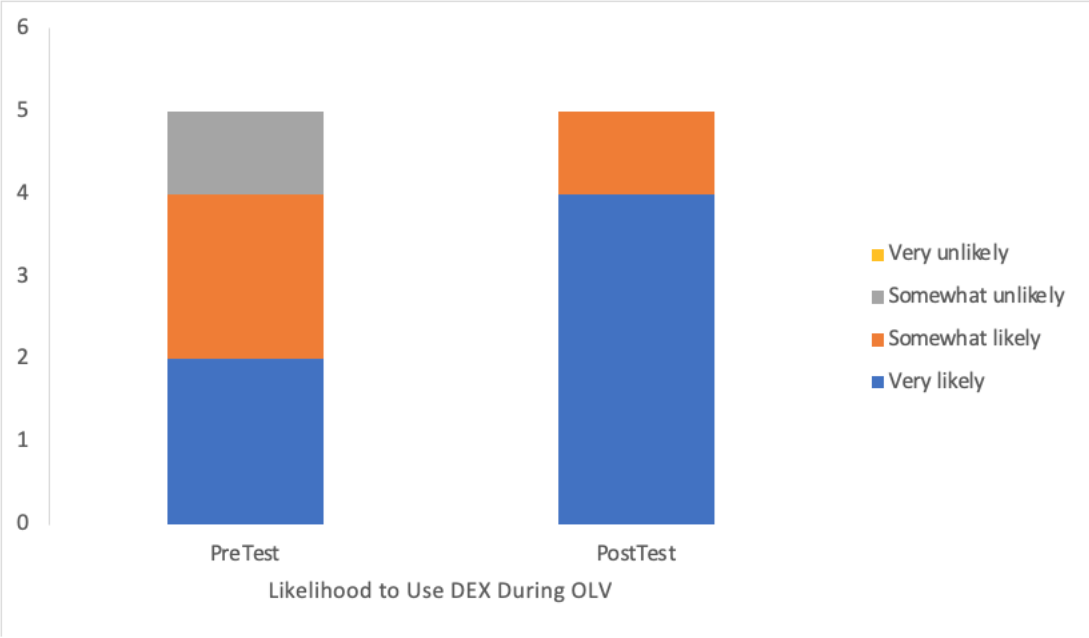
Table 2. Difference in Pre- and Post- Test Knowledge

Questions	***Pre-Test***	***Post-Test***	***Difference***
1. One lung ventilation (OLV) is required during many ____ procedures to optimize surgical conditions:	***100%***	***100%***	***0***
2. What are the two most significant factors that delay recovery after OLV?	***80%***	***100%***	***20%***
3. OLV is associated with which intraoperative complications?	***60%***	***60%***	***0***
4. Hypoxic pulmonary vasoconstriction (HPV) is an adaptive mechanism unique to the pulmonary vasculature that allows for:	***100%***	***100%***	***0***
5. Which anesthetic agent is known to inhibit HPV when administered in high concentrations?	***60%***	***80%***	***20%***
6. Dexmedetomidine is an:	***100%***	***100%***	***0***
7. The coadministration of Dexmedetomidine with volatile anesthetic agents or Propofol during OLV can:	***100%***	***100%***	***0***
8. The proposed mechanism through which Dexmedetomidine improves oxygenation and preserves HPV during one-lung ventilation is by:	***40%***	***80%***	***40%***

Post-Test Knowledge and Opinions

As expected, more participants were able to correctly identify the mechanisms through which DEX improves oxygenation and preserves HPV during OLV after viewing the educational intervention (n=4, 80%) than at baseline (n=2, 40%). A greater number of participants were also able to identify risk factors that delay recovery after OLV (n=5, 100%) and recall anesthetic agents associated with HPV inhibition when administered in high concentrations (n=4, 80%) on the post-test survey. These findings suggest that learning occurred after the information was presented within the educational module. Additionally, the number of providers that reported they were "very likely" (n=4, 80%) to adopt the evidence-based intervention after viewing the presentation doubled from pre-test (n=2, 40%), suggesting that a meaningful clinical practice change may occur as a result of the teaching. Figure 1, below, further illustrates these described changes in provider willingness to utilize the coadministration of Dexmedetomidine in future pulmonary surgeries requiring one-lung ventilation.

Figure 1. Difference in Pre- and Post- Test Willingness to Adopt Intervention



DISCUSSION OF QUALITY IMPROVEMENT

Implications for Advanced Practice Nursing

As the number of intrathoracic procedures for the diagnosis and treatment of lung cancer continues to rise, the need for continued research and evidence-based practice will continue to follow. The utilization of one-lung ventilation for optimal operating conditions produces a highly abnormal physiological state which is often not tolerated for long periods amongst healthy individuals, let alone patients suffering from years of smoking and pulmonary pathologies associated with lung cancer, such as COPD or emphysema. Advanced practice nurses involved with the management of anesthesia for these procedures must be acutely aware of all possible interventions available to optimize pulmonary function and recovery.

The outcomes of this review of current literature support adopting Dexmedetomidine coadministration with either Propofol or volatile anesthetic intraoperatively to preserve hypoxic pulmonary ventilatory mechanisms, as well as improve oxygenation and facilitate postoperative recovery. The results of our pre and post-test questionnaire suggest that learning did indeed occur via this virtual presentation and that this teaching style may be utilized to implement clinical practice changes in the future. The willingness of providers to implement the evidence-based practice changes addressed within this presentation doubled between the pre and post-test questionnaire (Figure 1), suggesting an opportunity for organizational practice change moving forward.

Limitations

Limitations of this project include the small sample size and difficulty with participant recruitment. Despite the survey deployment to the entire email list obtained from the target anesthesia group, most invitations to participate in the survey remained unused. Only five participants contributed to the findings presented in this project; therefore, our results are underpowered and unable to ensure reliability or generalizability. In order to achieve greater participation in the future, multiple recruitment avenues should be attempted. Unfortunately, face-

to-face reminders and other in person prompts to increase participant recruitment were unable to be utilized due to COVID-19 social distancing mandates imposed at the time of this educational module's distribution.

CONCLUSION

Four out of seven studies in the literature review observed a statistically significant improvement in oxygenation amongst patients receiving Dexmedetomidine during one-lung ventilation;[14,15,17,18] therefore, the coadministration of Dexmedetomidine may be considered an appropriate intervention to reduce the degree of hypoxia seen in lung surgeries. If maintaining oxygenation and preventing inflammatory changes in the lungs during surgery can lead to improved postoperative outcomes and reduce hospital length of stay, then it becomes even more imperative for anesthesia providers to learn about the benefits of Dexmedetomidine coadministration. The number of research articles available on this topic, however, remains limited; therefore, further research into the mechanism of action through which Dexmedetomidine might preserve hypoxic pulmonary vasoconstriction is certainly needed. As the prevalence of lung surgeries continues to rise, research and education regarding the anesthetic management of these complicated patients must also persist.

This educational module demonstrated the ability to facilitate learning virtually as evidenced by improved scores in the pre and post-test surveys. This educational module also demonstrated the ability to influence anesthesia provider willingness to implement evidence-based practice changes; thus, signifying that virtual learning, despite recruitment concerns, retains the potential to ignite meaningful clinical practice change. Our project supports the continued utilization of virtual learning platforms because of their potential to bridge the research to practice gap and quickly disseminate best evidence-based practices to local, national, and global audiences.

REFERENCES

1. Key statistics for lung cancer. American Cancer Society website. https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Accessed October 3, 2020.
2. Zappa C, Mousa SA. Non-small cell lung cancer: Current treatment and future advances. *Transl Lung Cancer Res*. 2016;5(3):288-300. doi:10.21037/tlcr.2016.06.07
3. Lee SH, Lee CY, Lee JG, Kim N, Lee HM, Oh YJ. Intraoperative Dexmedetomidine improves the quality of recovery and postoperative pulmonary function in patients undergoing video-assisted thoracoscopic surgery: A CONSORT-prospective, randomized, controlled trial. *Medicine*. 2016;95(7), 1-8. doi:10.1097/MD.0000000000002854
4. Lacin T, Swanson S. Current costs of video-assisted thoracic surgery (VATS) lobectomy. *J Thorac Dis*. 2013;5(S3), S190-S193. doi:10.3978/j.issn.2072-1439.2013.07.13.
5. Phillips JD, Bostock IC, Hasson RM, et al. National practice trends for the surgical management of lung cancer in the CMS population: An atlas of care. *J Thorac Dis*. 2019;11(4), S500-S508. doi:10.21037/jtd.2019.01.05.
6. Lumb AB, Slinger P. Hypoxic pulmonary vasoconstriction: physiology and anesthetic implications. *Anesthesiol.* 2015;122:932-946.
7. Kitabjian L, Bordi S, Elisha S, et al. Anesthesia case management for video-assisted thoracoscopic surgery. *AANA J*. 2013;81(1)65-72.
8. Huang SQ, Zhang J, Zhang XX, et al. Can Dexmedetomidine improve arterial oxygenation and intrapulmonary shunt during one-lung ventilation in adults undergoing thoracic surgery? A meta-analysis of randomized, placebo-controlled trials. *Chin Med J (Engl)*. 2017;130(14), 1707-1714.
9. Watt KM, Walgos J, Cheifetz IM, Turner DA. Dexmedetomidine for transport of a spontaneously breathing combative child. *Pediatr*. 2012;130(3):e690-e694. doi:10.1542/peds.2011-3397.

10. Groeben H, Mitzner W, Brown RH. Effects of the alpha 2- adrenoceptor agonist dexmedetomidine on bronchoconstriction in dogs. *Anesthesiology*. 2004;100(2):359-363.
11. Highlights of prescribing information: Dexmedetomidine. FDA website https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021038s021lbl.pdf. Accessed October 20, 2020.
12. Cook DA, West CP. Conducting systematic reviews in medical education: A stepwise approach. *Med Educ*. 2012;46:943-952. doi:10.1111/j.1365-2923.2012.04328.x
13. Kernan S, Rehman S, Meyer T, Bourbeau J, Caron N, Tobias JD. Effects of Dexmedetomidine on oxygenation during one-lung ventilation for thoracic surgery in adults. *J Minim Access Surg*. 2011;7(4):227-231.
14. Xia R, Yin H, Xia ZY, Mao QJ, Chen G, Xu W. Effect of intravenous infusion of Dexmedetomidine combined with inhalation of Isoflurane on arterial oxygenation and intrapulmonary shunt during single-lung ventilation. *Cell Biochem Biophys*.
15. Xu B, Gao H, Li D, Hu C, Yang J. Nebulized dexmedetomidine improves pulmonary shunt and lung mechanics during one-lung ventilation: A randomized clinical control trial. *PeerJ*. 2019;8:e9247. doi:10.7717/peerj.92472013;67:1547-1550.
16. Asri S, Hosseinzadeh H, Eydi M, Marahem M, Dehghani A, Soleimanpour H. Effect of Dexmedetomidine combined with inhalation of Isoflurane and oxygenation following one-lung ventilation in thoracic surgery. *Anesth Pain Med.* 2020;10(1):e95287.
17. Xia R, Xu J, Yin H, et al. Intravenous infusion of dexmedetomidine combined isoflurane inhalation reduces oxidative stress and potentiates hypoxia pulmonary vasoconstriction during one-lung ventilation. *Mediators Inflamm*. 2015;2015:238041. doi:10.1155/2015/238041.
18. Lee SH, Kim NK, Lee CY, Ban MG, Oh YJ. Effects of Dexmedetomidine on oxygenation and lung mechanics in patients with moderate chronic obstructive pulmonary disease

undergoing lung cancer surgery. *Eur J Anaesthesiol*. 2016;33:275-282. doi:10.1097/EJA.0000000000000405

19. Gu Z, Yang J, Xin L, Xu J, Yang Y, Wang Z. Dose-dependent effects of Dexmedetomidine during one-lung ventilation in patients undergoing lobectomy. *Int J Clin Exp Med.* 2017;10(3):5216-5221.

APPENDIX A: DATABASE SEARCH

Table 1. **Database Search**

Database	Keywords & concepts	Filters applied
CINAHL	(“one lung ventilation” OR “lung isolation” OR “single lung ventilation” OR “hypoxic pulmonary vasoconstriction” OR “thorac*”) AND (“Precedex” OR “Dexmedetomidine”)	Initial # of Results: 54 Filters Applied: • Academic Journals • English Language • Published 1999-2020 # of Results after filters: 52
MEDLINE (ProQuest)	(“one lung ventilation” OR “lung isolation” OR “single lung ventilation” OR “hypoxic pulmonary vasoconstriction” OR “thorac*”) AND (“Precedex” OR “Dexmedetomidine”)	Initial results: 375 Filters Applied: • Peer reviewed • English Language • Publication date: 1999-2020 Results after filters: 109
Embase	(“one lung ventilation” OR “lung isolation” OR “single lung ventilation” OR “hypoxic pulmonary vasoconstriction” OR “thorac*”) AND (“Precedex” OR “Dexmedetomidine”)	Initial results: 630 Filters Applied: • Academic Journal Articles • English Language • Publication date: 1999-2020 Results after filters: 336

APPENDIX B. INCLUSION AND EXCLUSION CRITERIA

Table 2. Inclusion and Exclusion Criteria

Inclusion	Exclusion

Population:
• Adult human participants
Type of Procedures:
• Thoracic surgeries involving the lungs
Anesthetic Management:
• One lung ventilation under general anesthesia
Intervention/Comparison
• Dexmedetomidine in combination with VAAs or Propofol compared to control group receiving only VAAs or Propofol and no dexmedetomidine
Primary Outcomes
• Direct measurements of oxygenation
  ○ (ex: ABGs, PaO2, SpO2, PaO2/FiO2 ratio)
• Measurement of HPV and lung compliance
  ○ Shunt fraction (Qs/Qt)
  ○ Pulmonary compliance (Cdyn ml/cmH2O)
  ○ Serum concn of inflammatory mediators
Type of Study:
• English Language
• Randomized placebo-controlled trials
• Publication date 1999-Present
• Published in a scientific journal
	Population:
	• Participants <18 years old
	• Animal studies
	Types of Procedures:
	• Non-surgical procedures (ex. imaging studies, biopsies)
	• Thoracic surgeries of non-lung origin (esophageal repair, mediastinal mass, minimally invasive cardiac procedures etc.)
	Anesthetic Management
	• Non general anesthesia modalities (i.e., regional anesthesia, MAC, etc.)
	• Ventilation modalities other than one lung ventilation (ex. two lung ventilation, spontaneous ventilation, etc.)
	Intervention/Comparisons
	• Studies that did not include the use of Dexmedetomidine
	• Studies that did not include the use of Propofol or VAAs
	• Studies without control group receiving only VAAs or Propofol
	Primary Outcomes
	• Any other outcomes besides measurements of oxygenation, lung compliance, and inflammation
	Type of Study
	• Non-English body of text
	• Publications before 1999
	• Articles without titles or abstracts, or non-scientific journals

APPENDIX C. LITERATURE MATRIX

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results/ Conclusions
Kernan et al., 2011 Key Concept: DEX improved PaO_2 & decreased Desflurane req.	Prospective, Randomized, double-blinded trial Level 1 Evidence Strength: Randomization, double-blinding Weakness: Small sample size, did not reach statistical significance	• Tertiary care, University-based hospital • 19 adult patients undergoing thoracic surgery requiring OLV (9 DEX, 10 Placebo) • No differences in demographical data between groups reported	• During inhalational anesthesia with Desflurane, patients were randomized to either receive Dexmedetomidine (0.3mcg/kg bolus followed by 0.3mcg/kg/hr infusion) or saline placebo. • PaO2/FiO2 ratio measured	• Three arterial blood gas samples to examine levels of oxygenation (1) 10 min after anesthetic induction during two lung ventilation, (2) after 10 min of OLV, and (3) 15 minutes after study drug bolus while continuous infusion being administered	ABG #1 - Two lung ventilation • DEX group PaO_2/FiO_2 ratio 387 +/- 124 • Placebo PaO_2/FiO_2 ratio 363 +/- 107 ABG #2- One lung ventilation • DEX group PaO_2/FiO_2 ratio 194 +/- 99 • Placebo PaO_2/FiO_2 ratio 188 +/- 70 ABG #3- One Lung ventilation with DEX vs placebo administration • DEX group PaO_2/FiO_2	• No difference in oxygenation was seen between the groups during two-lung ventilation (ABG#1) and one lung ventilation prior to administrations of Dexmedetomidine (ABG #2). • Although it did not reach a statistical significance, level of oxygenation, expressed as PaO_2/FiO_2 ratio, was greater during one lung ventilation in patients receiving dexmedetomidine (188 +/- 115) compared to the placebo (135 +/- 80). • With the administration of DEX, there was a decrease in the expired concentration of Desflurane required to maintain a bispectral index of 40-60, when compared to the control group (4.5 ± 0.8% versus 5.1 ± 0.8%) • The improved oxygenation with Dexmedetomidine may have resulted from the direct

					ratio 188 +/- 115 • Placebo PaO_2/FiO_2 ratio 135 +/- 80	effects of Dexmedetomidine on HPV or more likely because of the anesthetic sparing effects of Dexmedetomidine, which allowed for decrease in concentration of Desflurane, thus lessening its effects on HPV.[13]

Xia et al., 2013 Key Concept: DEX improves PaO_2 & decreased shunting, less Isoflurane req.	Randomized control trial Level 1 Evidence Strength: Randomization, Large sample size, Achieved statical significance in multiple data points, Exhaustive data collection across multiple time periods Weakness: High # of drop outs due to SpO2 or BIS	• 60 ASA I-II patients aged 18-70 years old, weighing 43-73kg, height 151-175cm, with no serious underlying heart, lung, liver, or kidney disease undergoing OLV during elective thoracic surgery • No statistical significance between demographics of groups • 10 cases were withdrawn from the study when SpO2 was observed <90% and OLV was discontinued, 5 cases were withdrawn due to BIS values	• All patients were randomly divided into two groups • 30 adults received isoflurane + saline bolus & drip, 30 adults received isoflurane + DEX (1.0 mcg/kg bolus over 10 min followed by 0.7mcg/kg/hr continuous infusion) • All patients received continuous infusion remifentanil 0.1-0.2 mcg/kg/min and isoflurane 1.0-2.0% keeping BIS value 40-60 • PaO_2 & Qs/Qt ratio measured	• Five arterial blood gas samples were collected: (1) after 15 min of two lung ventilation (TLV-15), (2) after 10 min OLV (OLV-10), (3) after 20 min OLV (OLV-20), (4) after 30 min OLV (OLV-30), (5) after 40 min OLV (OLV-40).	ABG #1 TLV-15min • DEX group PaO_2 452+/-83.2 mmHg; QS/QT (%) 12.5 +/- 2.5 • Placebo group PaO_2 460.5+/-89.5 mmHg; QS/QT (%) 11.7 +/- 1.5 ABG #2 OLV-10min • DEX group PaO_2 257.8 +/-69.7 mmHg; QS/QT (%) 30.4 +/- 2.5 • Placebo group PaO_2 225.5 +/-89.5 mmHg; QS/QT (%) 38.7 +/- 1.7 ABG #3 OLV-20min • DEX group PaO_2 197.5 +/-64.3 mmHg; QS/QT (%) 24.4 +/- 2.5 • Placebo group PaO_2 169.2 +/-71.3 mmHg;	• After the initiation of OLV, PaO2 starts to decrease significantly in both groups ($P<0.05$) down to a valley at the 30-minute mark, then begins to rise at the 40-minute mark due to the role of HPV. • During OLV, PaO2 was significantly higher in the DEX group in comparison to the control group ($P<0.05$). • Qs/QT, a measure of pulmonary shunt describing the percentage of blood that reaches the left side of the heart without picking up oxygen, was significantly lower in the DEX group than the control group across all intervals during OLV ($P<0.05$). • Qs/QT ratio is typically 2-5% during normal breathing, about 10% after general anesthesia, and 40-50% during OLV,[14] but with the infusion of DEX, maximum Qs/QT ratio with OLV was 30.4 +/- 2.5 % at the 10 min mark and significantly lower than control group 38.7+/-1.7% ($P<0.05$). • This study confirms that intravenous Dexmedetomidine along

		outside of the control range			QS/QT (%) 31.5 +/- 2.0 ABG #4 OLV-30min • DEX group PaO_2 182.6 +/- 72.2 mmHg; QS/QT (%) 24.5 +/- 3.5 • Placebo group PaO_2 152.3 +/- 69.4 mmHg; QS/QT (%) 30.7 +/- 2.8 ABG #5 OLV 40min • DEX group PaO_2 205+/- 83.2 mmHg; QS/QT (%) 23.1 +/- 2.5 • Placebo group PaO_2 170.8 +/- 89.5 mmHg; QS/QT (%) 27.5 +/- 1.9	with isoflurane inhalation during OLV can significantly reduce the drop in arterial oxygen pressure, reduce the degree of increased intrapulmonary shunting, and reduce isoflurane dose, while also confirming safety and feasibility of DEX infusion in OLV.

Xu B, Gao H, Li D, Hu C, Yang J., 2019 Key Concept: Neb DEX, improves PaO_2, improves pulmonary compliance, decreases shunting, and decreased Propofol req.	Randomized control trial Level 1 Evidence Strength: Randomization, Measurement of dynamic compliance, Achieved statistical significance Weakness: Feasibility of nebulized DEX	• Hospital-based study • 128 patients, ASA I &II, aged 20-80yrs old, height 150-180cm, with no previous allergic rxn to DEX and no serious cardiovascular, liver, kidney, neuropsychiatric, or drug dependence disorders undergoing elective thoracoscopic surgery • Randomly divided into 4 groups: Placebo/Saline Dex 0.5mcg/kg Dex 1mcg/kg Dex 2mcg/kg • No statistically significant differences	• After bronchial intubation but prior to initiation of OLV, patients received different doses of nebulized DEX in 5 mL (0.5mcg/kg, 1mcg/kg, 2mcg/kg) or 5mL of 0.9% saline placebo. • OLV was initiated 15 min after bronchial intubation, and anesthesia was maintained with IV infusion of Propofol and cisatricurium, titrating propofol infusion to	• Arterial Blood gas samples were taken: (1) 15 min after bronchial intubation during two lung ventilation (TLV), after 30 mins (2) and 60 mins (3) of OLV, and (4) 15 min after reinstitution of two lung ventilation • Dynamic compliance was also calculated at the same intervals	ABG #1 -TLV 15min PaO2 (mmHg) • Placebo- 431.8 +/- 54.3 Dex 0.5 - 435.8 +/- 44.1 Dex 1 - 424.4 +/- 38.7 Dex2 - 423 +/- 53.3 Qs/Qt (%) • Placebo- 9.9 +/- 2.2 Dex 0.5 - 9.8 +/- 1.2 Dex 1 - 9.4 +/- 2.0 Dex2 - 9.7 +/- 2.3 Cdyn (ml/cmH2O) • Placebo- 43.4 +/- 7.1 Dex 0.5 - 42.8 +/- 6.0 Dex 1 - 42.2 +/- 5.3 Dex2 - 41.5 +/- 4.3 ABG #2 -OLV 30min PaO2 (mmHg)	• This study found that at the 30 and 60-minute OLV ABG, statistically significant increases in PaO2 were observed amongst all DEX groups in comparison to the control ($P<0.05$) • Statistically significant improvement in dynamic compliance was also observed amongst all DEX dosages (0.5mcg/kg-2mcg/kg) at the 30 and 60-minute OLV mark ($P<0.05$). • Statistically significant reductions in pulmonary shunting (Qs/Qt) were observed with 1mck/kg and 2mcg/kg nebulized DEX groups and the 30 & 60-minute OLV interval, in comparison to the placebo group. • Nebulized Dexmedetomidine improved oxygenation not only by reducing intrapulmonary shunting but by also improving lung compliance during OLV. The administration of nebulized DEX also decreased propofol requirements and avoided significant hemodynamic instability, validating the feasibility of

		existed between demographics of each group	maintain bispectral index 40-50, • PaO_2, Qs/Qt ratio, and dynamic compliance (Cdyn) measured		• Placebo- 168.6 +/- 43.6 Dex 0.5 - 217.9 +/- 43.5 Dex 1 - 242.5 +/- 60.8 Dex2 - 262.7 +/- 53.6 Qs/Qt (%) • Placebo- 30.4 +/- 2.3 Dex 0.5 - 30.0 +/- 3.0 Dex 1 - 24.6 +/- 2.2 Dex2 - 22.6 +/- 2.5 Cdyn (ml/cmH2O) • Placebo- 21.0 +/- 2.8 Dex 0.5 - 26.7 +/- 2.4 Dex 1 - 26.4 +/- 2.6 Dex2 - 26.9 +/- 3.2 ABG #3 -OLV 60min PaO2 (mmHg) • Placebo- 178.5 +/- 41.3 Dex 0.5 - 255.6 +/- 47.0	utilizing nebulized DEX to improve oxygenation during OLV. • The authors hypothesize these effects may be related to an attenuation of local inflammation factors that contribute to the hypoxic vasodilator effect of OLV, due to DEX's ability to reduce pro-inflammatory factors. Secondly, DEX may play a direct role in pulmonary artery mechanics by impacting bronchodilation, and also reducing the requirement of Propofol, which has shown to attenuate HPV in a dose dependent manner, thus decreasing the dose of Propofol may lead to the decrease pulmonary shunt and improved HPV.[15]

					Dex 1 - 282.1 +/- 54.6 Dex2 - 298.6 +/- 38.4 Qs/Qt (%) • Placebo- 27.5 +/- 1.4 Dex 0.5 - 27.2 +/- 2.5 Dex 1 - 22.3 +/- 3.6 Dex2 - 26.2 +/- 2.9 Cdyn (ml/cmH2O) • Placebo- 19.7 +/- 2.8 Dex 0.5 - 26.2 +/- 2.4 Dex 1 - 25.5+/- 2.6 Dex2 - 26.2 +/- 2.9	

Asri et al., 2020 Key Concepts: Dex & Isoflurane - No significant differences in PaO2 between groups	Double-blinded, Randomized control trial Level 1 Evidence Strength: Randomization, inclusion of sicker population Weakness: Results conflict with discussion, few data points achieved statistical significance	• University funded study • 42 patients ASA I-III aged 20-60 yrs undergoing OLV and elective thoracic surgery • Excluded participants with liver or kidney dysfunction, end-stage COPD, severe heart block, or uncontrolled HTN • No significant difference identified in baseline demographics and hemodynamic	• General anesthesia provided with inhalational isoflurane; patients randomized into DEX group (DISO) (0.3mcg/kg DEX bolus IV over 10 min + infusion 0.3mcg/kg/hr) and saline bolus (NISO) with infusion group • Isoflurane titrated to BIS of 40-60 • Remifentanyl titrated to hemodynamic stability • PaO2 measured	• Arterial Blood gas sampling occurred at 10 min after induction of anesthesia but before OLV (T1), 10 minutes after starting OLV (T2), and after 60min of OLV (T3)	ABG #1 - 10min TLV PaO2 • DISO 172.6 +/- 111 • NISO 176.6 +/- 124 ABG #2 - 10min OLV PaO2 • DISO 102.5 +/- 56 • NISO 149.9 +/- 104 ABG #3 - 60min OLV • DISO 118.4 +/- 54 • NISO 122.6 +/- 71	• Shifting from two lung ventilation to one lung ventilation decreased PaO2 in both groups • The reduction in PaO2 in the dexmedetomidine group was greater than the control group, although not statistically significant. • The authors suggest that the trivial increase in the PaO2 of the DISO group between the 10 & 60 min OLV ABGs could be attributed to DEX administration lessening the dose of Isoflurane needed to maintain adequate depth of anesthesia, b/c volatile agents are associated with inhibition of HPV and increased intrapulmonary shunting[16]

Xia et al., 2015 Key Concepts: DEX improved PaO_2 due to mediator release	Randomized control trial Level 1 evidence Strength: Randomization, large sample size, frequent intervals of measurement, valuable parameters measured, statistical significance achieved Weakness: High # of drop outs due to SpO2 or BIS	• Government funded, single institution-based study • 60 male patients 40-60yrs old, ASA I &II, 50-73kg, 151-175cm, undergoing elective thoracic surgery were included in this study • Exclusion criteria included kidney disease, liver dysfunction, ischemic heart disease, substance abuse and neuro or psychiatric disorders. • A total of 11 participants (6 from the control and 5 from DEX) group were	• Participants were randomized into two groups • 30 patients received DEX infusion (1mcg/kg/hr bolus over 10 min, followed by 0.7mcg/kg/hr infusion), • 30 patients received a similar volume normal saline bolus over 10 min, followed by infusion. • All patients received remifentanil 0.1-0.2 mcg/kg/min gtt and 1.0-2.0% isoflurane titrated to BIS 40-60 • PaO2 and Qs/Qt ratio	• Arterial Blood gas samples were taken: (1) after 15 min of two lung ventilation (TLV-15), (2) after 10 mins of OLV, (3) after 20 min of OLV, (4) after 30min of OLV and (5) after 40 min of OLV • Plasma SOD and MDA levels were collected at the same intervals as ABGs • Serum Nitric Oxide concn was collected at TLV 15 and OLV 30	ABG #1 TLV-15min • DEX group PaO_2 457.5+/-85.2 mmHg; QS/QT (%) 11.5 +/- 1.8 • Placebo group PaO_2 461.5+/-87.5 mmHg; QS/QT (%) 12.0 +/- 1.1 ABG #2 OLV-10min • DEX group PaO_2 258.6 +/-68.6 mmHg; QS/QT (%) 23.5 +/- 2.9 • Placebo group PaO_2 223.5 +/-89.7 mmHg; QS/QT (%) 28.1 +/- 2.5 ABG #3 OLV-20min • DEX group PaO_2 198.5 +/-68.3 mmHg; QS/QT (%) 25.3 +/- 2.3 • Placebo group PaO_2 165.2 +/-75.3 mmHg;	• Initiation of OLV caused a significant decrease in PaO_2 amongst both groups, lowest value at 30min mark. • The decrease in PaO_2 in the DEX group was less severe than the control group ($P<0.05$). • Qs/Qt % increased significantly in both groups upon the initiation of OLV, peaking at 30 min, but the extent of shunting in the DEX group was significantly less than the shunting experienced in the control group ($P<0.05$) • This study observed the largest changes in PaO2 and Qs/Qt % occurred at the 30 min OLV mark. These results suggested that the 30 min mark of OLV may be a key moment for mediator release.[17] • At TLV 15, there was no significant difference in serum nitric oxide concentration between the two groups. After 30 min OLV, the DEX group had significantly higher levels of Nitric Oxide in comparison to the control group. • These findings support the authors hypothesis that DEX

		excluded from analysis because of bispectral indexes BIS) over the goal value or SpO2 <90% • No significant difference amongst demographics between groups	were measured		QS/QT (%) 30.1 +/- 2.0 ABG #4 OLV-30min • DEX group PaO_2 185.6 +/- 73.2 mmHg; QS/QT (%) 27.1 +/- 2.1 • Placebo group PaO_2 151.3 +/- 68.5 mmHg; QS/QT (%) 27.1 +/- 2.1 ABG #5 OLV 40min • DEX group PaO_2 209.6+/- 85.1 mmHg; QS/QT (%) 23.5 +/- 2.2 • Placebo group PaO_2 171.6 +/- 88.9 mmHg; QS/QT (%) 27.7 +/- 2.0 MDA TLV 15 min • DEX 16.9 +/- 1.7 • Placebo 18.3 +/- 1.7 OLV 30 min	combined with Isoflurane may inhibit oxidative stress (MDA), maintain SOD, and increase Nitric oxide release more than Isoflurane alone, thus reducing pulmonary shunt fraction (Qs/Qt) and improving oxygenation in OLV.[17]

					• DEX 17.5 +/- 1.2 • Placebo 21.0 +/- 1.7 SOD TLV 15 min • DEX 1.9 +/- 0.2 • Placebo 1.9 +/- 0.1 OLV 30 min • DEX 1.8 +/- 0.3 • Placebo 1.6+/- 0.2 NO TLV 15 min • DEX 1.9 +/- 0.3 • Placebo 1.9 +/- 0.4 OLV 30 min • DEX 2.3 +/- 0.3 • Placebo 1.8+/- 0.1	

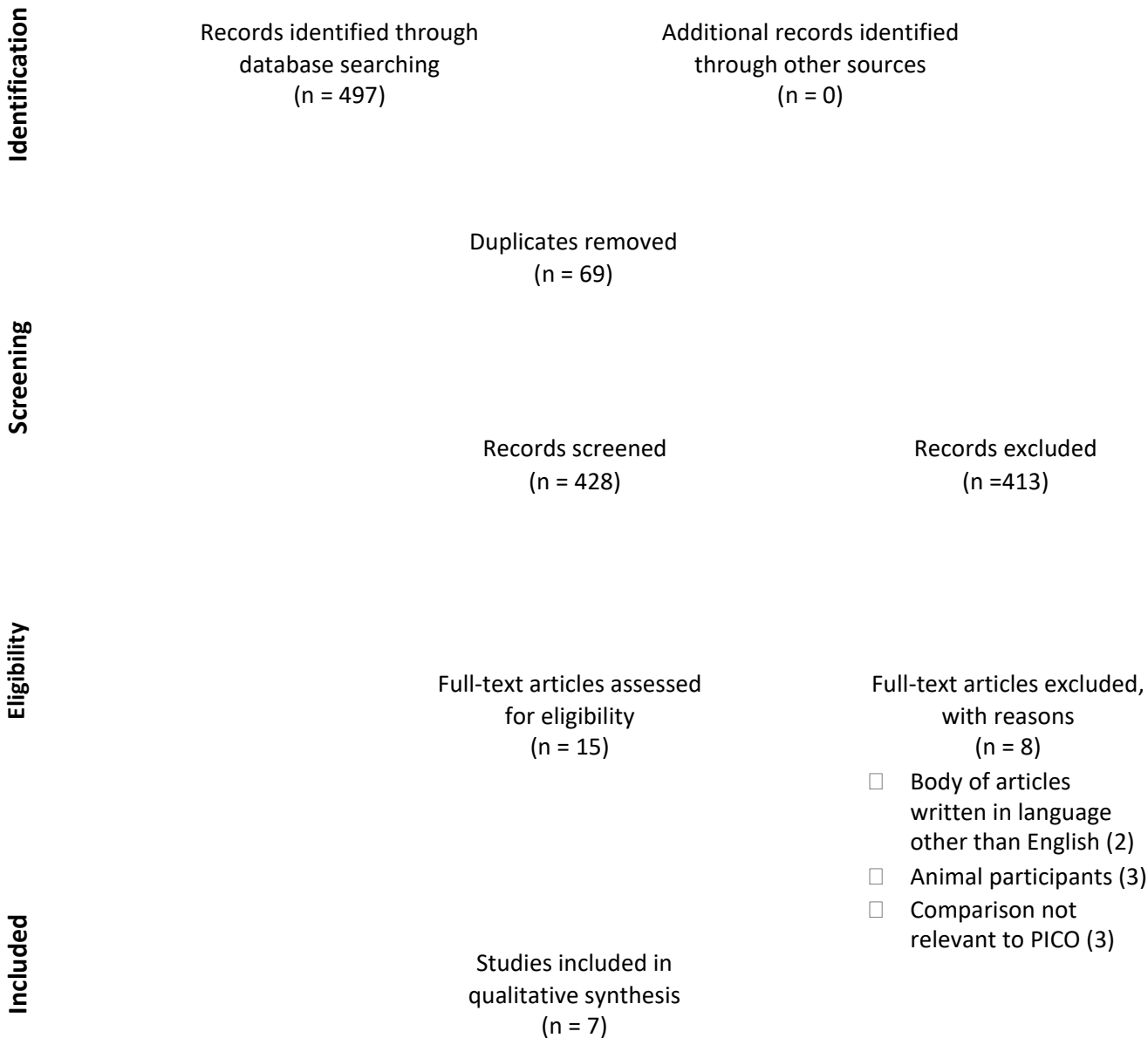
Lee S, Kim N, Chang YL, Ban MG, Oh YJ, 2016 Key Concepts: DEX and Sevoflurane in COPD	Randomized, double-blinded, placebo control study Level 1 Evidence Strength: Large sample size, representative sample population Weakness: Report of primary outcome data in figure format	• Single university hospital • Fifty participants undergoing video-assisted thoracoscopic surgery who have moderate COPD • Men, over 40, ASA II or III, diagnosis of moderate COPD, pre-op FEV1 50-80%	• Participants were randomized into two groups, a DEX and a placebo/ control group (total 25 participants each) • DEX group receives loading dose 1mcg/kg over 10 min, followed by 0.5mcg/kg/hr maintenance infusion, control group received same volume and rate but with 0.9% saline • Titration of Sevoflurane to maintain adequate anesthetic depth of BIS 40-60	• Arterial blood gases were collected at three points in time: (1) 30 min after initiation of OLV, (2) 30 min after DEX infusion during OLV (DEX-30), & (3) 60 min after DEX infusion during OLV (DEX-60) • Primary outcome measured was lung oxygenation expressed via PaO_2/FiO_2 ratio • Secondary outcomes recorded were dynamic compliance, peak airway	PaO_2/FiO_2 ratio 30 min OLV • DEX-30: 27.9kpa +/- 5.8 • Control: 22.5kpa +/- 8.4 60 min OLV • DEX-60: 28.6kpa +/- 5.9 • Control: 21.0kpa +/- 9.9 Peak Airway Pressure (cmH2O) Baseline OLV • DEX group- 22.3 +/- 3.9 • Control group- 22.5 +/- 4.9 30 min • DEX 30: 18.2 +/-3.2 • Control: 23.0 +/- 4.1 60 min • DEX 60: 18.2 +/-2.7 • Control: 21.7 +/- 4.3	• The PaO2/FiO2 ratio was significantly higher in the dexmedetomidine group at the 30- and 60-min mark (P<0.05). • Interesting to note, the end tidal concentrations of Sevoflurane were not statistically different between groups • Dynamic compliance was higher in DEX 30 & DEX 60 group in comparison to the control group (P<0.05) • Plateau airway pressure was significantly lower in the DEX group at the 30- and 60-min marks (P<0.05). • PACU PaO2/FiO2 ration was significantly higher in the DEX group than the control group (p<0.05). • Seven patients in the control group had episodes of SaO2 less than 95% and PaO2/FiO2 less than 40kPa while breathing room air, eventually resulting in ICU admission. Only one patient in the DEX group required care in the ICU • These authors propose that since the concentration of Sevoflurane remained constant between both groups in the study,

				pressure, and hemodynamic parameters. • Respiratory rate and PaO_2/FiO_2 ratio were also recorded 20 min into PACU recovery	Compliance (ml/cm H_2O) Baseline OLV • DEX group- 19.5 +/- 4.9 • Control group- 19.2 +/- 5.2 30 min • DEX 30: 22.5 +/-3.5 • Control: 17.7 +/- 3.4 60 min • DEX 60: 21.4 +/-4.2 • Control: 18.1 +/- 4.6 PACU PaO_2/FiO_2 (kPa) • DEX: 47.5 +/- 7.1 • Control: 42.2 +/- 5.9	Dexmedetomidine is responsible for the increasing the hypoxic threshold in the study group, rather than an inhalational anesthetic-sparing effect.[18]

Gu et al., 2017 Key Concept: Dose dependent effect of DEX infusion, DEX and propofol infusion for maintenance of anesthesia	Randomized control trial, double-blinded, placebo control study Level 1 evidence Strengths: Comparison of different concentrations of DEX Weakness: Small size of comparison groups limits ability to achieve statistical significance, data report is summarized and displayed in figure format	• Urban academic tertiary care hospital • Sixty participants, male and females age 18-80 years old, ASA I & II with no serious heart, lung liver, kidney disorders undergoing elective pulmonary lobectomy surgeries •	• Included 60 participants, randomized into 4 groups: placebo/normal saline group, low dose DEX group (0.3mcg/kg/hr) identified as DEX3, intermediate dose DEX group (0.5mcg/kg/hr) identified as DEX5 group, and high dose DEX group (0.7mck/kg/hr) identified as DEX7 group • After induction of anesthesia and baseline blood sampling was obtained,	• Baseline vitals and ABGs were obtained after induction of anesthesia during two lung ventilation, prior to DEX administration. • OLV was initiated, DEX and saline infusions were administered, and vitals/ABGs were collected at 10-minute intervals for an hour, and after the operation was complete	• Although no statistically significant differences in PaO2 were noted with increasing does of DEX, patients in the DEX 5 group receiving the intermediate dose (0.5mcg/kg/hr) showed persistent improvements in PaO2 from 20-50 minutes after OLV in comparison to the other groups.	• The authors did not observe a decreased propofol requirement with the administration of DEX, however the dose of atropine required to maintain heart rate significantly increased with the DEX7 group. • The group that received an intermittent dose of DEX (0.5mcg/kg/hr) showed better PaO2 values than all other groups between 20 and 50 min of OLV, although this did not reach a level of statistical significance. • The authors propose that an infusion of Dexmedetomidine does not reduce propofol requirements, and that DEX may have dose dependent effects on oxygenation in OLV, but additional studies with larger sample sizes are necessary. [19]

			each DEX group received 1mcg/kg bolus in 10ml of solution, administered over 10 minutes. The saline control received a similar volume of fluid • Adequate anesthetic depth was defined as BIS 40-60, and maintained via propofol titration			

APPENDIX D. PRISMA FLOW DIAGRAM



APPENDIX E. IRB APPROVAL LETTERS

FIU | FLORIDA INTERNATIONAL UNIVERSITY

Office of Research Integrity
Research Compliance, MARC 414

MEMORANDUM

To:	Dr. Yasmine Campbell
CC:	Robert Dillon, Valerie Diaz
From:	Maria Melendez-Vargas, MIBA, IRB Coordinator
Date:	April 7, 2021
Protocol Title:	"Administration of Dexmedetomidine in Patients Undergoing One Lung Ventilation for Thoracic Lung Surgeries to Enhance Oxygenation: An Evidence-Based Education Module"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-21-0132 **IRB Exemption Date:** 04/07/21
TOPAZ Reference #: 110243

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

MMV/em

APPENDIX E. IRB APPROVAL LETTERS

BROWARD HEALTH

Institutional Review Board - Human Research Protections

Broward Health Medical Center
Broward Health Coral Springs
Broward Health Imperial Point
Broward Health North

Salah Foundation Children's Hospital
Broward Health Weston
Community Health Services
Broward Health Physician Group

DATE: 04/28/2021

TO: Robert Dillon, RN

FROM: Broward Health Institutional Review Board

RECORD NUMBER: 2021-057

STUDY TITLE: Administration of Dexmedetomidine in Patients Undergoing One Lung Ventilation for Thoracic Lung Surgeries to Enhance Oxygenation: An Evidence-Based Education Module

RE: NOT HUMAN SUBJECT RESEARCH DETERMINATION

Dear Robert Dillon, RN:

This is to advise you that your project, "Administration of Dexmedetomidine in Patients Undergoing One Lung Ventilation for Thoracic Lung Surgeries to Enhance Oxygenation: An Evidence-Based Education Module " was reviewed on behalf of the Broward Health Institutional Review Board and was declared "not research involving human subjects" based on the definitions provided in the U.S. Department of Health and Human Services Code of Federal Regulations found at 45 CFR 46.102.

Please note, this determination does not absolve the Principal Investigator from complying with other federal, state, or local laws or institutional policies and procedures that may be applicable in the conduct of this project.
This determination applies to your project in the form and content as submitted to the IRB for review. Any variations or modifications to this project involving the participation of human subjects must be approved by the IRB prior to implementing such changes. Please maintain a copy of this determination for your records.

Thank you for submitting your project to the IRB for consideration.

The Broward Health Institutional Review Board – FWA00001248 operates in accordance with the Office of Human Research Protections and U.S. Food and Drug Administration (FDA) regulations. The Broward Health Institutional Review Board complies with the ICH guidelines on Good Clinical Practice (GCP) where they are compatible with the FDA and HHS regulations.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within Broward Health IRB's records.

APPENDIX F. CONSENT FORM

FIU | FLORIDA INTERNATIONAL UNIVERSITY

CONSENT TO PARTICIPATE IN A QUALITY IMPROVEMENT PROJECT

Dexmedetomidine Administration to Improve Oxygenation During One Lung Ventilation:

A Quality Improvement Project

PURPOSE OF THE PROJECT

You are being asked to be in a quality improvement project. The goal of this project is to improve patients' oxygenation during one lung ventilation, by delivering a structured educational intervention targeting anesthesia providers, which highlights the benefits of implementing intraoperative Dexmedetomidine co-administration during pulmonary surgeries.

DURATION OF THE PROJECT

Your participation will require about 20 minutes of your time.

PROCEDURES

If you agree to be in the project, we will ask you to do the following things:

- Complete a pretest and a posttest questionnaire
- Review an educational PowerPoint presentation

RISKS AND/OR DISCOMFORTS

There are no foreseeable risks with you for participating in this project.

BENEFITS

The following benefits may be associated with your participation in this project: An increase in knowledge regarding interventions to improve intraoperative oxygenation and facilitate post-operative recovery for patients undergoing one lung ventilation. The overall objective of the program is to increase the quality of healthcare delivery, improve recovery of our patients, and minimizing complications from pulmonary surgeries requiring one lung ventilation

ALTERNATIVES

There are no known alternatives available to you other than not taking part in this project. However, if you like to receive the educational material given to the participants in this project, it will be provided to you at no cost.

CONFIDENTIALITY

The records of this project will be kept private and will be protected to the fullest extent provided by law. If, in any sort of report, we might publish, we will not include any information that will make it possible to identify you as a participant. Records will be stored securely, and only the project team will have access to the records.

COMPENSATION & COSTS

There is no cost or payment to you for receiving the health education and/or participating in this project.

RIGHT TO DECLINE OR WITHDRAW
Your participation in this project is voluntary. You are free to participate in the project or withdraw your consent at any time during the project. Your withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove you without your consent at such time that they feel it is in the best interest.

RESEARCHER CONTACT INFORMATION
If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Robert Dillon at 813-952-8172, rdill008@fiu.edu or Dr. Valerie Diaz at 305-348-9027, vdiaz@fiu.edu

IRB CONTACT INFORMATION
If you would like to talk with someone about your rights of being a subject in this project or about ethical issues with this project, you may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by email at ori@fiu.edu

PARTICIPANT AGREEMENT
I consent by participating in the survey. I have read the information in this consent form and agree to participate in this project.

Signature: _____ Date:_____

Print: _____

APPENDIX G. PRE-TEST AND POST-TEST SURVEY

FIU | FLORIDA INTERNATIONAL UNIVERSITY

Pretest and Posttest Questionnaire:

Dexmedetomidine Administration to Improve Oxygenation During One Lung Ventilation: An Evidence Based Education Module

INTRODUCTION

The primary aim of this QI project is to improve the knowledge of anesthesia providers pertaining to the administration of Dexmedetomidine in patients undergoing one lung ventilation to improve patient outcomes.

Please answer the question below to the best of your ability. The questions are either in multiple choice or true/false format and are meant to measure knowledge and perceptions on Dexmedetomidine's effects on oxygenation during one lung ventilation (OLV).

PERSONAL INFORMATION

1. **Gender:** Male Female Other_____
2. **Age:** 18-29 30-49 50-69 70 or older
3. **Ethnicity:**

   Hispanic Caucasian African American Asian

   Other_____
4. **Level of Experience:** How many years have you been administering anesthesia?

   Over 10 6-10 years 3-5 years 0-2 years

QUESTIONNAIRE

1. **One lung ventilation (OLV) is required during many _____ procedures to optimize surgical conditions:**
    a. pulmonary
    b. urologic
    c. neurologic
    d. orthopedic
2. **What are the two most significant factors that delay recovery after OLV? (Select 2)**
    a. poor oxygenation
    b. postoperative nausea and vomiting
    c. increased pain
    d. obesity
3. **OLV is associated with which intraoperative complications? (Select 2)**
    a. Wound dehiscence
    b. Atelectasis
    c. Aspiration
    d. V/Q mismatching
4. **Hypoxic pulmonary vasoconstriction (HPV) is an adaptive mechanism unique to the pulmonary vasculature that allows for:**
    a. The redirection of blood flow to alveoli with higher oxygen tension
    b. A reduction in V/Q mismatching during OLV
    c. Increased arterial oxygenation during OLV
    d. All the above
5. **Which anesthetic agent is known to inhibit HPV when administered in high concentrations?**
    a. Sevoflurane

b. Propofol

c. Isoflurane

d. All the above

6. **Dexmedetomidine is an**:

a. Alpha 1 agonist

b. Alpha 1 antagonist

c. Alpha 2 agonist

d. Alpha 2 antagonist

7. **The coadministration of Dexmedetomidine with volatile anesthetic agents or Propofol during OLV can**:

a. Reduce PaO2 but improve HPV

b. Preserve HPV and improve PaO2

c. Improve PaO2 but inhibit HPV

d. Have no effect on PaO2 or HPV

8. **The proposed mechanism through which Dexmedetomidine improves oxygenation and preserves HPV during one lung ventilation is by: (Select 2)**

a. Reducing the dose of Propofol or volatile anesthetic agent administered

b. Inhibiting oxidative stress and increasing nitric oxide concentrations

c. Increasing endorphin release into the CSF

d. Altering serotonin transmission

9. **How frequently do you currently implement the coadministration of Dexmedetomidine when caring for a patient requiring one lung ventilation for pulmonary surgery?**

a. Very frequently

b. Somewhat frequently

c. Rarely

d. Never

10. **How likely are you to adopt the coadministration of Dexmedetomidine during pulmonary surgeries requiring one lung ventilation?**

    a. Very likely

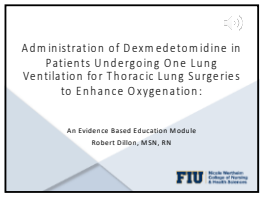
    b. Somewhat likely

    c. Somewhat unlikely

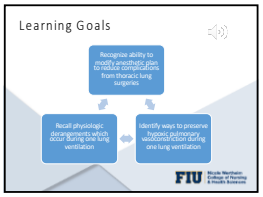
    d. Very unlikely

APPENDIX H. EDUCATIONAL MODULE

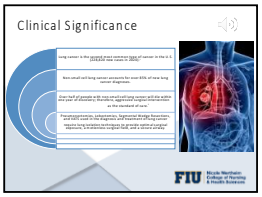
10/18/21



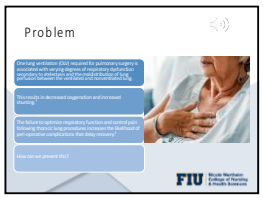
1



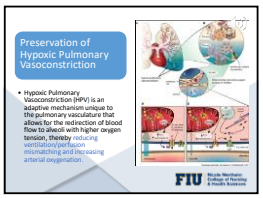
2



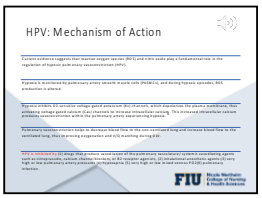
3



4

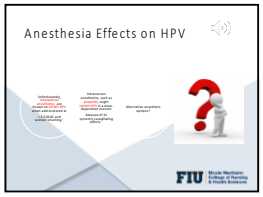


5

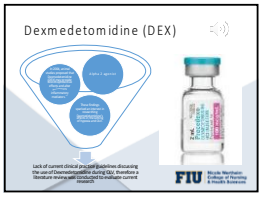


6

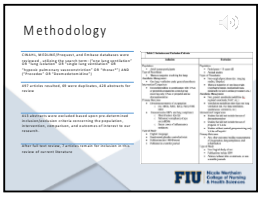
1



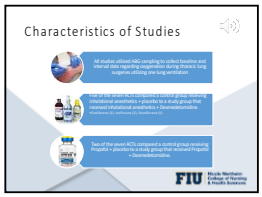
7



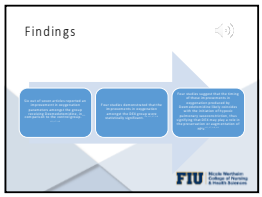
8



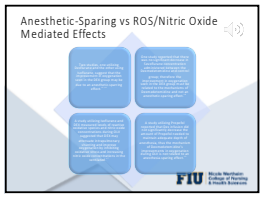
9



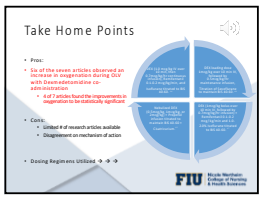
10



11

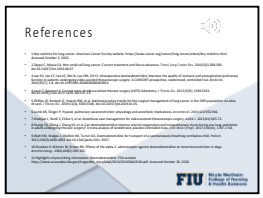


12



13

14



15

2

16

17