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The use of Dexmedetomidine to mitigate perioperative anxiety in pediatric patients receiving general anesthesia: An evidence-based education module

Felipe Ocampo MSN, RN
Florida International University, pocam001@fiu.edu

Valerie J. Diaz DNP, CRNA, APRN, CAPT, USN, NC
Florida International University, vdiaz@fiu.edu

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By

Felipe Ocampo MSN, RN

Supervised By

Valerie J. Diaz, DNP, CRNA, APRN, CAPT, USN, NC

Jordany Gattorno, DNP, CRNA, APRN

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Date:_____

Approval Acknowledged:_____, DNP Program Director

Date:_____

ABSTRACT

Background: When patients need a surgical procedure, the natural reaction is to have a heightened sense of anxiety. This anxiety can be regarded as an unwanted response, as it can affect the patient's perception of the procedure and how pain is experienced. In children, the fear of the unknown and the new can be a traumatizing event in their lives; therefore, it should be considered how practitioners help handle this anxiety and apprehension. Medications such as midazolam and dexmedetomidine are used to help modify this emotion.

Aim: This systematic review aims to investigate the potential benefits of using dexmedetomidine intranasally instead of midazolam to help cope with this preoperative sedation and postoperative emergence in the pediatric population. An education module was also deployed to help improve the current knowledge of certified nurse anesthetists working within the pediatric population.

Results: All 10 studies were randomized controlled trials (RCT) with a minimum level 1C appraisal designation according to the Johns Hopkins research evidence appraisal tool.[11] A total of 828 children were selected for these trials in all parts of the world. The ages ranged from 2-14 years old. Four of the RCTs used comparable levels of sedation compared to the 10 studies when comparing dexmedetomidine and midazolam. Six of the remaining RCTs had better results regarding sedation levels and were recommended by the authors. The statistical analysis between the pre-test and post-test of the education module showed an increase in provider knowledge.

Discussion: The results from 10 RCTs demonstrate that dexmedetomidine is indeed a better preoperative medication for sedation and has the added benefit of analgesic properties to help postoperatively. The drawback is the cost difference when compared to midazolam. The other potential downside is the onset of action time is slower with dexmedetomidine versus midazolam in reaching optimal sedation levels.

Conclusion: The studies' results have been consistent and clear that dexmedetomidine is superior to midazolam for preoperative sedation and postoperative analgesia. The use of dexmedetomidine can help curb unwanted side effects as well such as respiratory depression with midazolam. The movement to change this common practice of midazolam should be done with the sole focus of improving patient experiences and outcomes.

TABLE OF CONTENTS

INTRODUCTION

Problem Identification

In the world of children, fear of the unknown and the unfamiliar poses a problem as practitioners across the country struggle to prepare these pediatric patients for any procedure properly. This fear or anxiety can cause hemodynamic instability, metabolic side effects, increased postoperative pain, and emergence agitation.[1] Various studies have shown that this preoperative anxiety continues after the procedure, as the children require more pain medication and have difficulty with sleep.[2] A vast majority of children undergoing surgery experience mental anguish and stress during the entire period. Several research studies have evaluated the role different factors play in negative behavior manifestation and postoperative anxiety, including parents and children's preoperative anxiety, the history of surgery, preoperative preparation and medication, the anesthetic used, the child's experience in the postoperative care unit, and length of hospitalization.[2]

In addition to the inherent problems when dealing with children, such as separation anxiety and managing parents' expectations, it also comes with choosing medications that can produce the best outcomes. The current situation leaves practitioners limited regarding choices for sedation that do not require an intravenous (IV) or intramuscular (IM) injection. The leading choice has been midazolam, as various routes can be used without the need for any injection. Midazolam, a water-soluble benzodiazepine, improves children's anxiety due to its fast onset, anterograde amnesia anxiolysis, and sedation effects. The problem posed with this choice is the added risk of respiratory depression as associated with all benzodiazepines.

Scope of the Problem

Anxiety is a large predictor of undesirable outcomes postoperatively.[5] The frequency of negative behavioral changes includes aggression, nightmares, and separation anxiety.[5] Also, this

anxiety influences the demand for increased pain control.[6] The lack of control of anxiety now is known to contribute to the alteration of pain neuropathways for children.[6]

Research has shown a correlation of delirium from observing 580 admissions in a pediatric intensive care unit (PICU).[7] The 580 patients over 6 months demonstrated a 43% increase of delirium when administered a benzodiazepine.[7] The routine administration of benzodiazepine proves it could affect a large portion of the population of pediatric patients. Therefore, a further review of these potential adverse side effects should be examined and studied.

Consequences of the Problem

The issue of leaving the routine administration of benzodiazepines as the status quo could alter learning and cognitive behavior.[8] Brain cell death has been shown in animal models when exposed to γ-aminobutyric acid receptor agonists.[8] The developing brain of children is at risk when exposed to these associated drugs. There should be a desire to find less harmful alternatives for the sake of the patients and their families.

The results of 71,996 children study suggest a moderate association between γ-aminobutyric acid receptor agonists exposure and children demonstrating internalizing problems that are not likely due to stable familial confounding factors.[9] Delirium is a prime example that the neurochemistry is potentially being altered. Dexmedetomidine diminishes that effect and carries other benefits when compared to benzodiazepines such as midazolam.

Background

Dexmedetomidine is a drug that has been around since December 1999 and has only grown in acceptance.[3] Dexmedetomidine is a specific alpha 2 adrenoreceptor agonist and a highly selective and potent drug containing both analgesia and sedative effects.[4] Current practices in intensive care and emergency departments have seen the advantages of using dexmedetomidine

as a first-line agent instead of midazolam because it can produce analgesia, cause less respiratory depression, and result in less delirium.[4] Because children are the main focus of this study, these additional benefits are an advantage. Even while under the influence of dexmedetomidine, patients can still interact more clearly as the drug provides a different sedation type of effect compared to benzodiazepines.[4]

PICO

P - Pediatrics **I -** Dexmedetomidine **C -** Midazolam **O -** Reduction of adverse/side effects for sedation

Does dexmedetomidine or midazolam work better to reduce the adverse/side effects of sedation for pediatric patients?

Knowledge Gaps

A large gap of information is missing in respects to the altering effects of benzodiazepines and how it affects the neurochemistry of the child. Clinicians are at a disadvantage with the lack of information that can alter the decision making process. Multiple studies and trials will be required to narrow the amount of low-quality evidence that presently exists.[8] It is necessary to determine how the dose, duration, and frequency of drugs such as dexmedetomidine and midazolam interfere with cognitive and behavioral functions.[8]

Proposal Solution

The use of dexmedetomidine in contrast to midazolam for sedation has comparable effects that are satisfactory for sedation in a wide array of procedures. The proposed study to substitute the two medications will not only allow safer administration and control of the sedation but eliminate the unwanted side effects. These side effects, such as delirium, respiratory depression, laryngospasms, and possible neurotoxicity, can therefore be carefully reviewed and create a new standard of care.

SUMMARY OF LITERATURE

Summary of Evidence

The literature review included 10 RCTs that allowed for a wide variety of patients from different parts of the world. The large sample sizes and consistent findings from the research can lead to a definitive conclusion. The exclusion criteria consisted of eliminating any research that went outside the boundary for the ages of 2-14, children who did not receive any pre-medication, and children that received a combination of sedatives. Studies were also excluded that encompassed results outside of peri-operative sedation, postoperative pain control, and emergence delirium.

The quality of evidence for the RCTs was appraised by using the Johns Hopkins research evidence appraisal tool[11], which allowed for consistent standards in judging the results. All 10 of the studies had a level 1 rating, which indicates the use of randomized controlled trials. The associated letter and subclassification determined how well the research parameters and study results are graded. The selection of this literature review included five Level 1A studies, four Level 1B, and one Level 1C study.

From the 10 RCTs, all the research concluded that dexmedetomidine adequately sedated the children pre-operatively, which allowed for a decrease in separation anxiety.[12,13,14,15,16,17,18,19,20,21] Only one RCT acknowledged that the difference between medications was negligible and recommended the use of midazolam for its lower price point.[20] Two of the RCTs pointed out the prolonged onset of action of dexmedetomidine as a negative to take into account when comparing the two medications.[13,21]

Information Sources and Search Strategy

To meet the standards of systematic reviews, PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) was used as a guideline.[10] The 27-item checklist helps to report and evaluate current research.[10] In doing so, it allows for critical appraisal of interventions

and randomized control trials that have been conducted.[10] The PRISMA tool is invaluable as clinicians further develop and analyze current research.

The databases used to identify the most accurate and relevant research included the use of the Cochrane Database of Systematic Reviews, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Google Scholar, Medline (ProQuest), and PubMed electronic database. The keywords used in the search were dexmedetomidine, midazolam, premedication, (kids or youth or pediatric or children or toddler). The PRISMA flow diagram in Figure 1 helps illustrate the screening process.

Table 1: Database Search Table

Database	**PubMed**	**CINAHL**	**Medline (ProQuest)**	**Cochrane**	**Google**
Boolean Phrase	"Dexmedetomidine" AND "Midazolam" AND "Premedication" AND "Kids" OR "youth" OR "pediatric" OR "children" OR "toddler"	-	-	-	-
Search Results	**58**	**16**	**296**	**89**	**42**

Study Selection and Screening Method with Inclusion/Exclusion Criteria

The study selection was conducted using five databases and Endnote to help filter through duplicates. The Cochrane search yielded 89 results, CINAHL 16 results, PubMed 58 results, Medline 296 results, and Google Scholar 42 results for a total of 501 records. Once the results were input to Endnote, 315 duplicates were identified and removed. The remaining 186 records were then screened for randomized controlled trials (RCT). Once the full-text results were

narrowed down to 39, the leftover records were eliminated due to the lack of similarity to the PICO question, leaving 10 studies to critique.

The inclusion criteria consisted of pediatric children under the age of 14 who were observed in the preoperative setting. These children also had to be given dexmedetomidine or midazolam to compare with each other. The route of administration preference is intranasally to demonstrate how to avoid issues with intravenous catheter insertions. The chosen articles are Random Controlled Trialed (RCT) based; these methods of studies help prevent bias and allow to show a higher quality of evidence. The outcomes in these studies focused on sedation effects, pain control, and emergence delirium post-procedure.

The exclusion criteria consisted of children older than 14 years old and those not given dexmedetomidine or midazolam as premedication before a procedure. If the children were given more than one of the aforementioned drugs, this would also exclude the study as the purpose is to measure the two drugs in direct comparison. Any studies that were not RCT were not considered or any research older than from 2010. The outcomes other than pain control, sedation effect, and emergence delirium were not considered.

Table 2. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Population: • Peri-operative setting; "Premedication" • Pediatric children 2-14 years old Intervention • The use of midazolam or dexmedetomidine in the same study preoperatively • Intranasal route of administration Outcomes: • Effectiveness of sedation preoperatively • Reduced pain postoperatively • Reduced emergence delirium Type of study: • Research studies conducted from 2010 to 2020 • RCTs	Population: • Children younger than 2 years and older than 14 years • Patients who didn't receive "premedication" Intervention: • Any patients receiving midazolam or dexmedetomidine in combination with other sedatives Outcomes: • Anything other than peri-operative sedation, postoperative pain control, and emergence delirium

	Category of research: • Articles prior to 2010

Collection, Analysis, and Data Items

The gathering of research was done methodically in accordance with the Johns Hopkins research evidence appraisal tool.[11] The tool is categorized into five evidence levels, where each classification helps distinguish the articles by the format the authors conducted the research. The Level I classification includes experimental studies, randomized controlled trials (RCT), explanatory mixed-method design, and systemic review of RCTs, with or without meta-analysis.[11] The Level II classification includes quasi-experimental studies, explanatory mixed-method design with a level II quantitative study, a systemic review of a combination of RCTs and quasi-experimental studies, or quasi-experimental studies only, with or without meta-analysis.[11] The levels III and above are considered to be the least reliable of evidence and thus were not used for this review.

In regards to the quality ratings for quantitative studies, there are three alphabetical ordered classifications. The "A" rating signifies a high-quality study that demonstrates consistent, generalizable results, sufficient sample size for the study design, adequate control, definitive conclusions, and consistent recommendations based on fairly comprehensive literature through scientific evidence.[11] The "B" rating is defined as having reasonably consistent results, sufficient sample size for the study, some control, fairly definitive conclusions, and reasonably consistent recommendations based on a fairly comprehensive literature review that includes some reference to scientific evidence.[11] The "C" rating is used when the study demonstrates low quality or significant research design flaws. With inconsistent results, these studies are defined by little evidence, an insufficient sample size for the design, and conclusions that could not be drawn.[11]

The articles that were selected only met the highest of marks as RCTs. The comprehensive search included studies that were most relevant to the PICO question posed. "In

the pediatric population, does dexmedetomidine or midazolam serve as the best medication to reduce adverse and side effects for sedation?" Adhering to these strict guidelines for inclusion and exclusion allowed narrowing the focus of this analysis. It led to 10 studies that favorably mirrored the answer to the PICO question.

Study Characteristics

The 10 studies conducted had a total of 828 participants. From these totals, 397 of the patients were given dexmedetomidine intranasally, 32 patients were administered ketamine, and 399 were given midazolam. The age demographic spread from age 2-14 years old. The research conducted spanned from 2011-2020 while all following a randomized control trial (RCT) format. According to the Johns Hopkins research evidence appraisal tool, the benefit of the RCTs helped establish a minimum of quality to the research, as they were all at a minimum of level 1C.[11] The children in the studies were also from different backgrounds, including countries such as China, India, South Africa, Saudi Arabia, Egypt, and Spain.

Risk of Bias

For this literature review, the Cochrane Handbook Collaboration Tool was used for assessing bias.[22] The 10 research studies were completed as randomized controlled trials (RCTs), thus demonstrating a minimum of a double-blind process through their methods. One of the RCTs by Surendar et al.[19] was completed using a triple-blind method. All of the ten RCTs showed a low risk of bias for random sequence and selective reporting. However, the RCT done by Ghosh et al. had unclear allocation concealment and, therefore, offers a possibility of bias.[22]

THEORETICAL FRAMEWORK

The theoretical framework to be implemented targets the subject group of learners who are certified nurse anesthetists (CRNA). Malcolm Knowles in 1980 developed the popular concept of andragogy and what is now known as the adult learning theory (ALT).[23] The adult learning theory focuses on organizing new ways to help adults learn and retain information. As

people age, the neuroplasticity in the brain declines, where new needs are created for learning.[24] To overcome this barrier, Knowles stipulated that adults need to know why they are required to learn something new and how learning this new information will benefit them specifically.[24] The other main factor is adults also have a tendency to draw from past experiences and knowledge to help form the way they process information.[24]

In following the ALT and using its foundational assumptions on how adults learn, a questionnaire was developed to provoke interest and the internal drive for the participants to learn. A PowerPoint presentation was created to drive the main points of the teaching and encourage change in everyday practice. The participants selected are all graduate-level or clinical doctorate-employed CRNAs. The educational instruction is provided at no cost and is readily available at the convenience of the participant. In the effort to establish the method for this educational intervention, the adult learning theory incorporated the best background to achieve this goal.

METHODOLOGY

Setting

The setting was a full-service children's hospital with seven operating rooms and two procedural rooms located in South Florida. The children’s hospital treats all types of diseases and injuries ranging from minor to complex medical conditions.

Recruitment

The recruitment targeted CRNA alumni from Florida International University that specialized in pediatrics. The participants were identified using the alumni list through the university. The CRNAs were emailed a request to participate in the project.

Participants

The only participants invited to partake in the project were pediatric CRNAs who work in the operating room setting to see through the whole peri-operative process. All other CRNAs that

did not specifically treat pediatric children or worked in a setting other than the operating room were excluded from participation. The entire list of CRNAs that met the inclusion criteria was emailed a pretest and posttest.

Intervention

The intervention was to provide an educational module-based presentation, and a Qualtrics survey was used to help administer pre-and posttesting. The baseline knowledge of the practitioners participating in the lecture was assessed, as well as the likelihood of willing to change practices in respect to sedation for pediatric patients. The presentation should establish a significant enough reason to venture into new protocols for the pediatric population.

The proposed change in practice is first to prepare the patient to have intranasal dexmedetomidine administered 45 minutes prior to induction. According to previous studies, doses of 1-1.5 mcg/kg can be used for optimal sedation scores. Once the patient is calm, placing ECG leads, SPO2, and BP cuff to monitor vitals would occur. The preoperative nurse can also keep an atropine syringe in case of an emergency for bradycardia.

Procedures

The procedure to deploy the educational module began with an informational email requesting for participation. All participants pre-selected from the alumni database at Florida International University had no identifiable information attached to the surveys. The results of the examinations were done anonymously and protected through Qualtrics. A 2-week grace period was given to complete the questions and submitted for the results.

Protection of Human Subjects

The participants included in the surveys were protected by anonymous submission of results. The Qualtrics system allowed for anonymous links and responses for the pretest and posttest. This anonymity protected survey participants.

RESULTS

The educational module had 5 CRNA participants (n = 5) who completed 100% of the pretest and posttest. This allowed for no changes in the demographics and had no attrition for those who took part in the education. The participants race consisted of four Hispanics (*n* = 4; 80%) and one Caucasian (*n* = 1; 20%). The sex of the participants were three males (*n* = 3; 60%) and two females (*n* = 2; 40%). The majority included CRNAs in the 30-39 age range (*n* = 3; 60%) and the remaining in the 40-49 age range (*n* = 2; 40%).

Table 3: Demographic Characteristics

Demographics	n (%)
Total Participants	5 (100%)
Age	
<30 years	0
30-39	3 (60%)
40-49	2 (40%)
>60	0
Gender	
Male	3 (60%)
Female	2 (40%)
Ethnicity	
Hispanic	4 (80%)
Caucasian	1 (20%)

Pretest Knowledge

From the 5 CRNAs' pretest answers, there was a demonstration that an opportunity existed to increase their knowledge base through the module. The first question in regards to factors that influenced children's anxiety pre-operatively were all answered incorrectly (0%). The

next three questions asked what receptors midazolam and dexmedetomidine worked on as well as which drugs could be used for sedation and pain. All five CRNAs answered those three questions correctly (100%). The majority of the CRNAs also had some difficulty in answering question items regarding to the side effects of midazolam and dexmedetomidine. The main problem was the lack of knowledge that midazolam, although rare, has a possibility of causing a laryngospasm, only one CRNA answered it correctly (20%). The next question in the survey was about which main factor was a predictor for post-operative outcomes, and all the CRNAs answered this correctly (100%). The following question, answered correctly by 40% of the CRNAs, asked what medication was responsible for adverse effects of altered learning and cognitive behavior. Finally, the last question was only correctly answered by one CRNA (20%) in regards to what effects are seen post-operatively due to anxiety before the procedure.

Posttest Knowledge

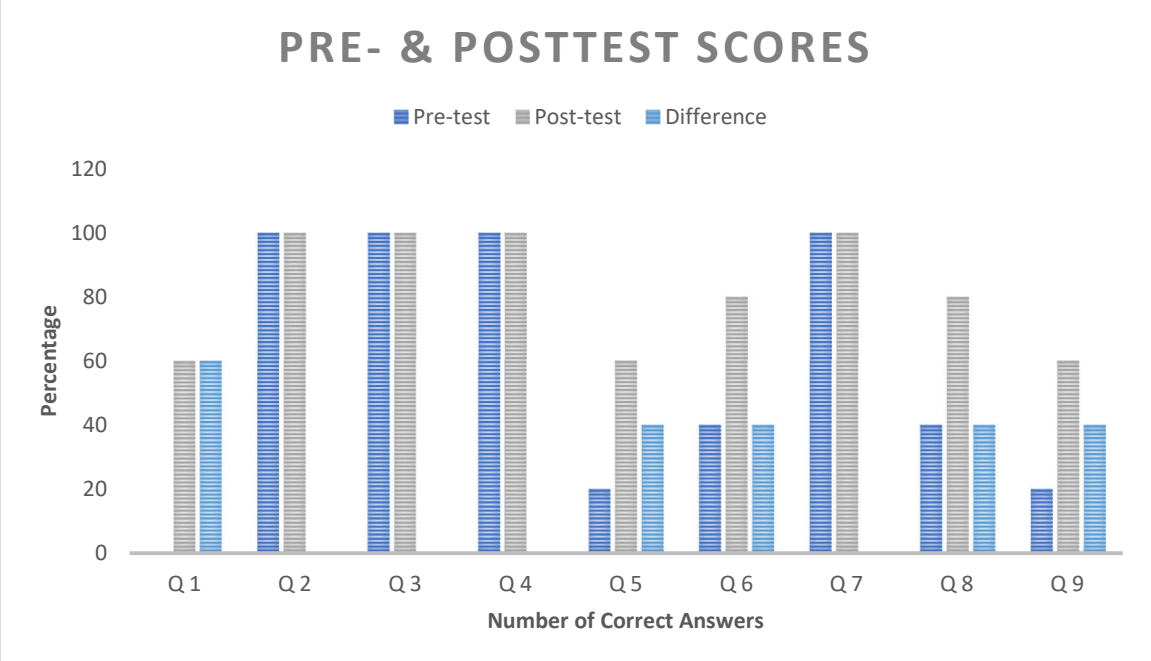
The five CRNAs that participated all completed the posttest after viewing the PowerPoint presentation. This video was played immediately after the pretest. The goal was to see if any new knowledge could be learned for the post evaluation after the video. On the topic of stress factors that play a role in children pre-operatively, there was 60% increase ($n = 3$) in participants who answered this correctly. The question on the side effects of midazolam saw an improvement as $n = 3$; 60% answered correctly in comparison to $n = 1$; 20%. For dexmedetomidine side effects ($n = 4$; 80%) of the participants correctly answered the question. The following item discussed adverse effects on cognitive leaning and behavior of children. There was an increase in correct responses that resulted in $n = 4$; 80%. Finally, the last question on the survey asked about the effects of pre-operative anxiety seen after the procedure. A total of $n = 3$; 60% of CRNAs answered correctly.

Table 4. Difference in Pretest and Posttest Knowledge

Correct Responses	**Pretest**	**Posttest**	**Difference**
1. WHAT FACTORS PLAY A ROLE IN STRESS FOR CHILDREN BEFORE SURGERY? **SELECT ALL THAT APPLY** **A) PARENTS ANXIETY LEVEL** **C) CHILD'S PREVIOUS EXPERIENCE** **D) ANESTHETIC USED**	0%	60%	+60%
2. WHAT MEDICATIONS CAN BE USED FOR BOTH SEDATION AND ANALGESIA? **B) DEXMEDETOMIDINE**	100%	100%	-
3. WHAT RECEPTORS DOES DEXMEDETOMIDINE WORK ON? **D) ALPHA 2**	100%	100%	-
4. WHAT RECEPTORS DOES MIDAZOLAM WORK ON? **A) GABA A**	100%	100%	-
5. IDENTIFY A POTENTIAL ADVERSE EFFECTS FROM MIDAZOLAM IN CHILDREN? SELECT ALL THAT APPLY **A) LARYNGOSPASM** **C) RESPIRATORY DEPRESSION**	20%	60%	+40%
6. WHAT ARE SOME POTENTIAL ADVERSE EFFECTS FROM DEXMEDETOMIDINE? SELECT ALL THAT APPLY **A) BRADYCARDIA** **B) HYPOTENSION** **C) HYPERTENSION** **D) DRY MOUTH**	40%	80%	+40%

7. WHAT IS A SIGNIFICANT PREDICTOR OF UNDESIRABLE OUTCOMES POST-OPERATIVELY? **C) ANXIETY**	100%	100%	-
8. WHICH MEDICATION CAN HAVE ADVERSE EFFECTS OF ALTERED LEARNING AND COGNITIVE BEHAVIOR? **D) MIDAZOLAM**	40%	80%	+40%
9. WHAT ARE SOME EFFECTS OF PRE-OPERATIVE ANXIETY SEEN POSTOPERATIVELY? SELECT ALL THAT APPLY **A) INCREASED REQUIRED AMOUNTS OF PAIN MEDICATION** **B) EMERGENCE AGITATION**	20%	60%	+40%

Figure 1.



DISCUSSION

Anxiety in children has been linked as a significant influence on postoperative complications. These complications include increased postoperative pain, hemodynamic fluctuations, metabolic disarrangement, and emergence agitation.[1] The goal for all team members who are involved for taking care of children through the surgical experience is to produce the best safe outcomes for the patients. The focus of these outcomes presents an opportunity to acknowledge the potential negative effects of maintaining traditional methods of preoperative sedation. The family of benzodiazepines has demonstrated these unwanted side effects not only affect short-term but potentially long-term health as well with neurological changes to learning and cognitive behavior.[8]

The solution is to try to employ the use of dexmedetomidine when possible, instead of the commonly used midazolam. The benefits of better sedation and relief of anxiety results in avoiding the large number of negative outcomes benzodiazepines can produce. The barriers to employ this method vary from institution in respects to timing and costs of the medications. As a result, discussions should take place amongst hospital leadership on how to make these changes conceivable. The research available demonstrates dexmedetomidine as the better medication for most patients preoperatively. The knowledge gap on long-term effects of benzodiazepines for children is of concern and should be a driving force to implement change.

Finally, there are circumstances where drugs such as midazolam are needed. Children with autism, behavioral problems, and teenagers can present challenges where the faster onset of the medication outweighs the potential risks of midazolam. Each medication has its pro and cons but hopefully will be used when appropriately called for.

IMPLICATIONS

The future of anesthesia is always evolving as more research and new drugs enter the market. The long-term impact of our current medications on children still has not been well established. In continuing with the status quo, we are unnecessarily exposing children to

medications that can be avoided. As of 2020, dexmedetomidine not only causes better sedation but reduces the risks of altering learning and cognitive behavior.[5] GABA agonists have been linked to brain cell death in animal models, yet no human studies have been conducted.[5,25]

This sample of current CRNAs demonstrates an opportunity for quality improvement in daily practice. Current practitioners should have the choice in how they practice to advocate for the patient. If more practicing CRNAs can be made aware of the benefits and reduction of detrimental risks, then practitioners can get to be one step closer to achieving safer anesthesia. Better sedation that is established can help throughout the whole perioperative experience for the children.

CONCLUSION

The studies' results have been consistent and clear that dexmedetomidine has been comparable if not better than midazolam for preoperative sedation and postoperative analgesia. The use of dexmedetomidine can help curb unwanted side effects that can greatly affect children such as respiratory depression and possible laryngospasms with midazolam. The movement to change this common practice of midazolam administration should be done when advantageous for the patient. This is the sole focus of improving patient experiences and outcomes.

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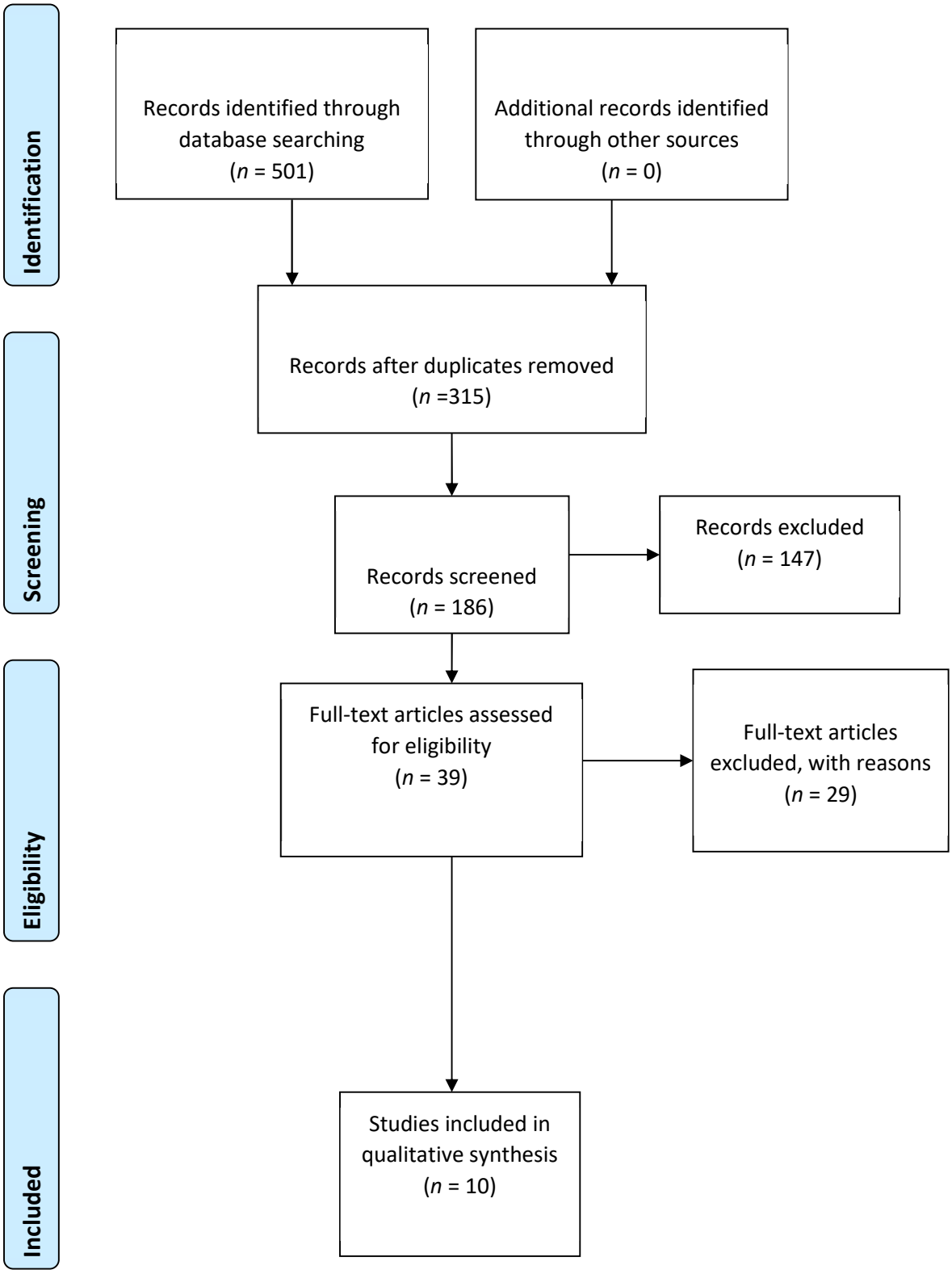
APPENDIX A: PRISMA Flow Diagram

Figure 1:



APPENDIX B: MATRIX TABLE

Table 5. Studies Included in Appraisal

Title Authors (Year) Citation	Design/ Method	Sample/ Setting	Major Variables Studied and Their Definitions	Measurement & Data Analysis	Findings	Results & Conclusions	Appraisal Worth to Practice Level
The comparison of dexmedetomidine and midazolam premedication on postoperative anxiety in children for hernia repair surgery *Du Z, Zhang Y, Qu S, Song Z, Wei SW, Xiang Z, Guo QL* (2019) Citation #12	Design: RCT Method: To determine the effects of premedication on postoperative anxiety	90 patients Age (6-11) *n* = 45 received an intravenous infusion of dexmede-tomidine *n* = 45 received an intravenous infusion of midazolam Setting: Hunan Children's Hospital Hunan, China	Group D = dexmede tomidine Group M = midazolam	Numerical rating scale (NRS)=Patient satisfaction Modified Yale Preoperative Anxiety Scale =(m-YPAS)21	Scores of 23.5-30 indicate no or mild anxiety, whereas scores >30 indicate severe anxiety (Group M Baseline=27.88 ± 3.34 ;5 min post admin 29.29 ± 4.34) (Group D Base line= 28.15 ± 6.38; 5 min post admin= 32.71 ± 9.99)	Dexmede tomidine effectively lowered separation anxiety along with pain and agitation postoperatively	Level 1A

Intranasal dexmedetomidine versus intranasal midazolam as pre-anesthetic medication in pediatric age group undergoing adenotonsillectomy *Bassem BS, Tharwat A, Ghobrial H, Elfawal S* (2020) Citation # 13	Design: RCT Method: To compare effects of premedication to reduce anxiety and sedation level prior to surgery	48 patients ASA 1 Age (3-7) (*n* = 24) intranasal dexmede-tomidine (*n* = 24) received intranasal midazolam University Hospitals Cairo, Egypt	Group D received intranasal dexmede-tomidine Group M received intranasal midazolam	Modified Observers Assessment of Alertness/Sedation Scale =(MOAA/S) Anxiety Scale Child Separation Scale	Sedation score in dexmedetomidine group is 2.53 ± 0.74; in midazolam group is 3.69 ± 0.87	The midazolam group at the 10 min and 20 min had better sedation compared to the dexmede-tomidine group. The intranasal dexmede-tomidine was more effective at the 30- and 45- min mark.	Level 1A
Efficacy of intranasal dexmedetomidine versus oral midazolam for paediatric premedication *Lakshmi K, Kumar A, Panikkaveetil R, Vasu B, Rajan S, Nair S* (2017) Citation # 14	Design: RCT Method: To determine the effects of premedication for sedation and separation anxiety	60 Patients ASA 1-2 Age (2-12) (*n* = 30) Intranasal dexmede-tomidine (*n* = 30) Intranasal Midazolam	Group A= Midazolam Group B= dexmede-tomidine	Numerical rating scale for sedation, behavior	Sedation scores at induction. Group A- Scores <4= 23.3% ; Scores >5= 76.7% Group B- Scores <4=83.3%; Scores >5= 16.7%	Initially, Group A (midazolam) had better sedation scores. In the end, intranasal dexmede-tomidine at a dose of 1 µg/kg had better sedation scores when compared to midazolam orally.	Level 1B

		Amrita University Karala, India					
Preanesthetic medication in children: A comparison of intranasal dexmedetomidine versus oral midazolam *Ashraf M, Abdul Kader M, Maher A* *(2011)* *Citation #15*	Design: RCT Method: To compare effects of premedication to reduce anxiety and sedation level prior to surgery	120 patients Age (4-12) (*n* = 60) Intranasal dexmede-tomidine (*n* = 60) Oral Midazolam	Group D received intranasal dexmede-tomidine Group M received oral midazolam	Yale preoperative anxiety scale (YPAS) Sedation level was analyzed with a six point sedation scale; It was changed from the original (MOAA/S)	Sedation score baseline in dexmedetomidine group is 5.86 ± 0.14; in midazolam group is 5.92 ± 0.08 Transfer to OR for Group D = 2.94 ±1.37 Group M = 3.99 ±1.58	Children premedicated with intranasal dexmede-tomidine had better sedation and lower anxiety when compared to oral midazolam	Level 1B

A Comparative Evaluation of Intranasal Dexmede-tomidine & Intranasal Midazolam for Preoperative Sedation in Children *Ghosh A, Das A, Mukherjee M, Begum, S* *(2020)* *Citation #16*	Design: RCT Method: To compare effects of premedication to reduce anxiety and sedation level prior to surgery	90 Patients ASA 1 & 2 Age (2-8) (*n* = 42) Intranasal dexmede-tomidine (*n* = 48) Intranasal Midazolam RG Kar Medical College Kolkata, India	Group A = dexmede-tomidine Group B = midazolam	Ramsay Sedation Scale & Observer Pain Scale	Satisfactory sedation for group A at induction=93%; Satisfactory sedation at induction for Group B= 60%	Intranasal Dexmede-tomidine has a better sedative and analgesic effect when compared to midazolam	Level 1A
Comparison of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery *Singla D, Chaudhary G, Dureja J, Mangla M* *(2015)*	Design: RCT Method: To compare effects of premedication to reduce anxiety and sedation level prior to surgery	Patients 60 ASA 1 Age (3-10) (*n* = 30) Intranasal dexmede-tomidine (n=30) Intranasal	Group D= dexmede-tomidine Group M= midazolam	Modified Observers Assessment of Alertness/Seda tion Scale (MOAA/S) Four-point Parental Separation	Sedation for Group M at 20 min post administration= 3.53±1.14 Group D at 20 min= 2.93 ± 1.143	Premedication with intranasal dexmede-tomidine decreased anxiety, and allowed for improved parent separation and mask acceptance versus intranasal midazolam	Level 1A

Citation # 17		Midazolam Bhagat Phool Singh Govt Medical College and Hospital for Women Haryana, India		Anxiety Scale (PSAS)			
Pre-anesthetic medication with intranasal dexmedetomidine and oral midazolam as anxiolytic. A clinical trial *Linares Segovia B, García Cuevas I, Ramírez Casillas J, Guerrero Romero I, Botello Buenrostro R, Monroy Torres X, Ramírez Gómez* *(2014)* *Citation #18*	Design: RCT Method: To compare effects of premedication to reduce anxiety and sedation level prior to surgery	108 Patients Age (2-12) (*n* = 52) Intranasal dexmede-tomidine (*n* = 56) Oral Midazolam	Group A= pre-anesthetic medication with oral midazolam and intranasal placebo Group B=intranasal dexmede-tomidine and placebo orally	Modified Yale scale for anxiety	Anxiety in dexmedetomidine group at 60 minutes had P-values *(p* = .001); at induction (p =.04); at recover *(p* = .0001)	Children premedicated intranasal dexmede-tomidine had better sedation and lower anxiety when compared to oral midazolam	Level 1B

A comparative evaluation of Intranasal Dexmedetomidine, Midazolam and Ketamine for their sedative and analgesic properties: A Triple Blind Randomized Study *Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G* *(2014)* *Citation #19*	Design: RCT Method: Comparing Intranasal (IN) Dexmedetomidine, Midazolam and Ketamine in producing moderate sedation	84 Patients ASA 1 Age (4-14) (*n* = 21) Intranasal dexmede-tomidine dose 1µg/kg (*n* = 21) Intranasal dexmede-tomidine dose 1.5µg/kg (n=21) Intranasal Midazolam (n=21) Intranasal Ketamine	Group D_1= dexmede-tomidine dose 1µg/kg Group D_2= dexmede-tomidine dose 1.5µg/kg Group M= midazolam Group K= Ketamine	Measured through behavior and vital signs	Sedation satisfaction – Dexmedetomidine at dose 1µg/kg= 19 (90.5%) dexmede-tomidine dose 1.5µg/kg = 20 (95.2%) Intranasal Midazolam= 15(71.4%) Intranasal Ketamine= 16 (76.2%)	Determined all 3 drugs were suitable for sedation pre-operatively with dexmede tomidine having the most success	Level 1C

Premedication with intranasal dexmedetomidine, midazolam and ketamine for children undergoing bone marrow biopsy and aspirate *Mostafa MG, Morsy KM* *(2012)* *Citation #20*	Design: RCT Method: Comparing Intranasal (IN) Dexmedetomidine, Midazolam and Ketamine in producing moderate sedation	96 patients ASA 2 Age (2-8) (*n* = 32) Intranasal dexmede-tomidine (*n* = 32) Intranasal Midazolam (*n* = 32) Intranasal Ketamine	Group D= dexmede-tomidine Group M= midazolam Group K= Ketamine	4-point sedation scale 4-point child-parent separation scale	Sedation score at 20 min; Midazolam = 2.21 ± 0.70 Ketamine= 2.41 ± 0.68 Dexmedetomidine = 2.10 ± 0.71	All three drugs demonstrated adequate sedation but the authors recommend midazolam for the lower price point	Level 1 A
Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation *Sheta SA, Al-Sarheed MA, Abdelhalim AA*	Design: RCT Method: To compare effects of premedication to reduce anxiety and sedation level prior to surgery	72 patients ASA 1&2 Age (3-6) (n=36) Intranasal dexmede-tomidine	Group D= dexmedetomidine Group M= midazolam	*Awaiting full article	Sedation scores Group D =77.8%; Group M= 44.4% At (P = 0.002).	Intranasal dexmede-tomidine is a superior drug for sedation but has prolonged time onset of action	Level 1B

	(*n* = 36)
(2014)	Intranasal
	Midazolam
Citation # 21	

Office of Research Integrity FIU | FLORIDA INTERNATIONAL UNIVERSITY
Research Compliance, MARC 414

MEMORANDUM

To: Dr. Yasmine Campbell
CC: Felipe Ocampo

From: Maria Melendez-Vargas, MIBA, IRB Coordinator **Date:** April 6, 2021

Protocol Title: "The use of Dexmedetomidine to mitigate perioperative anxiety in pediatric patients receiving general anesthesia: 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-21-0122 **IRB Exemption Date:** 04/06/21 **TOPAZ Reference #:** 110246

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

Welcome to the QI project!

Pretest and Posttest Questionnaire:

The use of Dexmedetomidine to mitigate perioperative anxiety in pediatric patients receiving general anesthesia: An evidence-based education module

INTRODUCTION

The primary aim of this QI project is to improve the knowledge of dexmedetomidine for perioperative anxiety in pediatric patients receiving general anesthesia.

You will be presented with information on medications to treat perioperative anxiety and asked to answer some questions about it. Please be assured that your responses will be kept completely confidential.

The study should take you around five minutes to complete, and you will receive no incentive for your participation. Your participation in this research is voluntary. You have the right to withdraw at any point during the study, for any reason, and without any prejudice. If you would like to contact the Principal Investigator in the study to discuss this research, please e-mail Felipe Ocampo Pocam001@fiu.edu

By clicking the button below, you acknowledge that your participation in the study is voluntary, you are 18 years of age, and that you are aware that you may choose to terminate your participation in the study at any time and for any reason.

Please note that this survey will be best displayed on a laptop or desktop computer. Some features may be less compatible for use on a mobile device.

Questionnaire

1. **What factors play a role in stress for children before surgery? Select all that apply**
   A) Parents anxiety level
   B) Location of operative site
   C) Child's previous experience
   D) Anesthetic used
   E) Length of hospitalization

2. **What medications can be used for both sedation and analgesia?**
   A) Midazolam
   B) Dexmedetomidine
   C) Propofol
   D) Tylenol

3. **What receptors does dexmedetomidine work on?**
   A) GABA A
   B) GABA B
   C) Alpha 1
   D) Alpha 2

4. **What receptors does midazolam work on?**
   A) GABA A
   B) GABA B
   C) Alpha 1
   D) Alpha 2

5. **Identify a potential adverse effects from midazolam in children? Select all that apply**
   A) Laryngospasm
   B) Bradycardia
   C) Respiratory depression
   D) Nausea

6. **What are some potential adverse effects from dexmedetomidine? Select all that apply**

   A) Bradycardia
   B) Hypotension
   C) Hypertension
   D) Dry mouth

7. **What is a significant predictor of undesirable outcomes post-operatively?**

   A) Sex of the patient
   B) Height

C) Anxiety

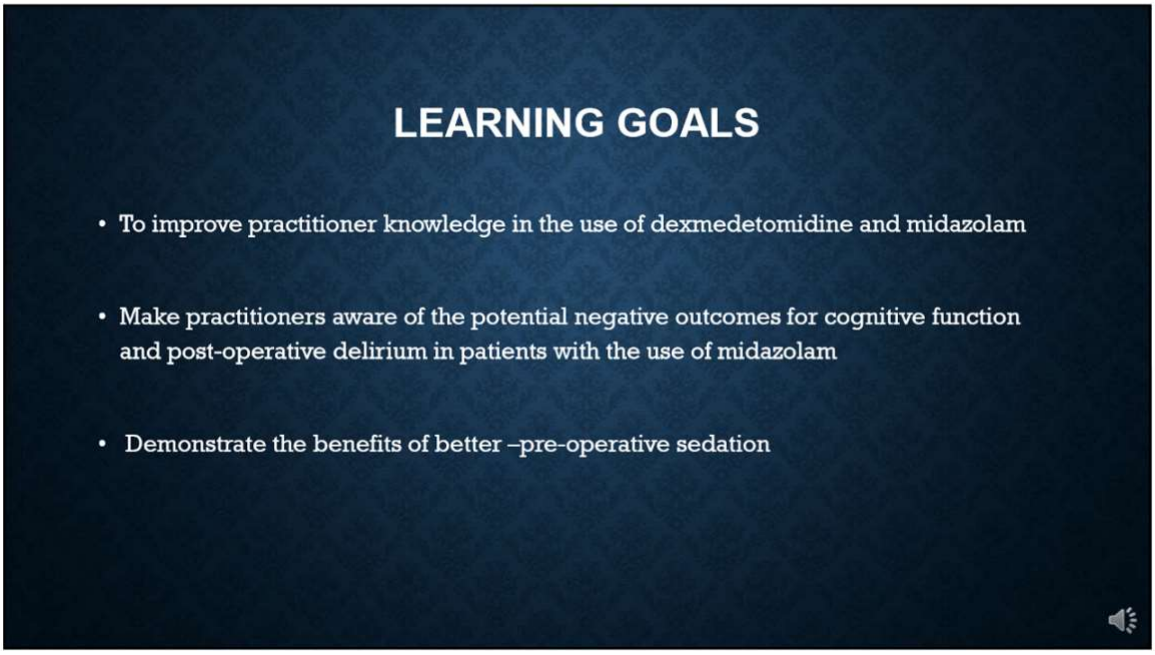
8. Which medication can have adverse effects of altered learning and cognitive behavior?

A) Ketamine
B) Fentanyl
C) Dexmedetomidine
D) Midazolam

9. What are some effects of pre-operative anxiety seen postoperatively? Select all that apply

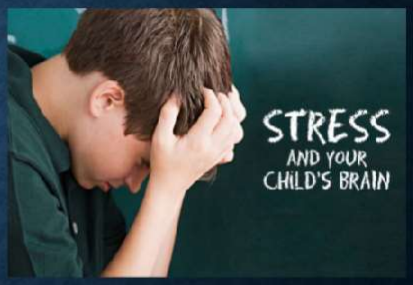
A) Increased required amounts of pain medication
B) Emergence agitation
C) Decreased hunger
D) Nausea


THE USE OF DEXMEDETOMIDINE TO MITIGATE PERIOPERATIVE ANXIETY IN PEDIATRIC PATIENTS RECEIVING GENERAL ANESTHESIA: AN EVIDENCE-BASED EDUCATION MODULE
Felipe Ocampo BSN, RN, CCRN
Dr. Valerie Diaz DNP, APRN, CRNA
Nicole Wertheim College of Nursing and Health Sciences
Department of Nurse Anesthetist Practice
Florida International University


LEARNING GOALS
• To improve practitioner knowledge in the use of dexmedetomidine and midazolam
• Make practitioners aware of the potential negative outcomes for cognitive function and post-operative delirium in patients with the use of midazolam
• Demonstrate the benefits of better –pre-operative sedation

DESCRIPTION OF THE PROBLEM

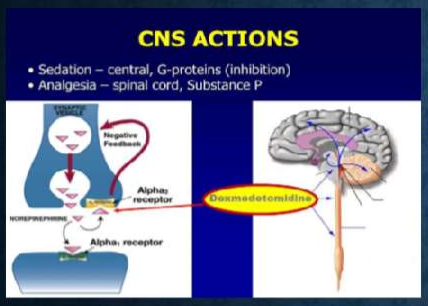
- Pre-operative fear or anxiety can cause hemodynamic instability, metabolic side effects, increased postoperative pain, and emergence agitation [2]
- Common drug of choice is midazolam for sedation and amnesia
- Short term and long term side effects of midazolam can be worse than the stress



BACKGROUND

- **Benzodiazepines Mechanism of Action:** Midazolam exerts its effect at the gamma-aminobutyric acid (GABA) receptor-chloride ionophore complex in the central nervous system (CNS). [3]
- Leads to an increase in the opening of chloride channels, membrane hyperpolarization and increases the inhibitory effect of GABA in the CNS. [3]
- Midazolam may also interfere with the reuptake of GABA, thereby causing accumulation of GABA in the synaptic cleft. [3]
- Midazolam mechanism of action is due to activation of alpha-1 subunits of GABA-A receptors whereas anxiolytic effect is due to alpha-2 subunit activity. [4]

BACKGROUND



- **Options to midazolam ?** Answer – *dexmedetomidine* which is a specific alpha 2 adrenoreceptor agonist, and a highly selective and potent drug, containing both analgesia and sedative effects
- **Why dexmedetomidine ?** Answer- Provides better sedation versus midazolam, includes analgesic component and avoids respiratory depression along with delirium.[5,6]

IMPLICATIONS

- Routine administration of benzodiazepines as the status quo could alter learning and cognitive behavior.[5] Brain cell death has been shown in animal models when exposed to γ-aminobutyric acid receptor agonists.[5] The developing brain of children is at risk when exposed to these associated drugs.
- The results of 71,996 children study suggest a moderate association between γ-aminobutyric acid receptor agonists exposure and children demonstrating internalizing problems that are not likely due to stable familial confounding factors.[6]
- Delirium is a prime example that the neurochemistry is potentially being altered. Dexmedetomidine diminishes that effect and carries other benefits when compared to benzodiazepines such as midazolam.

RECOMMENDATIONS

- New research for the lack of high-quality studies in general anesthetics for children. With out proper safety data in children an ethical dilemma arises in the decision making process.
- Research can help identify vulnerable periods in brain development, which can compare the cognitive outcomes in children who underwent the same procedure with the same anesthetic agent at different ages.

WHAT TO CHANGE

- The need to change the common practice of midazolam administration.
- Limiting midazolam to situations for
    i. older children
    ii. autistim
    iii. behavioral problems
- Use dexmedetomidine in the pre-operative setting intranasally to provide better sedation.

INTERVENTIONS

- Prepare patient to have intranasal dexmedetomidine administered 45 minutes prior to induction
- Doses of 1-1.5 mcg/kg can be used for optimal sedation scores
- When patient is calm place ECG leads, SPO2 and BP cuff to monitor vitals
- Keep atropine syringe ready in case of emergency for bradycardia

CONCLUSIONS

- The studies' results have been consistent and clear that dexmedetomidine is superior to midazolam for preoperative sedation and postoperative analgesia.
- The use of dexmedetomidine can help curb unwanted side effects such as
  - Respiratory depression
  - Post-operative delirium
  - Potential altered neurochemistry
- The use of dexmedetomidine can also allow for better mask acceptance on inhalational induction
- The movement to change this common practice of midazolam should be done with the sole focus of improving patient experiences and outcomes.

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