MIDAZOLAM-SPARING APPROACH FOR NEONATAL SEDATION:

A SYSTEMATIC REVIEW

A Major Paper Presented

by

Amanda M. Moran

Approved:

Committee Chairperson _____ _____
(Date)

Committee Members _____ _____
(Date)

_____ _____
(Date)

Director of Master's Program _____ _____
(Date)

Dean, School of Nursing _____ _____
(Date)

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Abstract

Neonates are in a very vulnerable state, as they adjust to their new environment and experience a period of significant physiological and psychological developmental changes. Therefore, it is important to keep in mind the role this vulnerability plays in the pharmacokinetics of administered medications due to the immaturity of the neonate's developing brain and hepatic function. Properly sedating this population, without over sedating them, can become problematic. The commonly used drug, midazolam, in higher doses, can lead to hypotension and decreased cerebral blood flow to an already underdeveloped cerebral vascular supply, resulting in decreased oxygenation of the brain and potential neurologic injury, principally in the form of periventricular leukomalacia (PVL). There is evidence that the alpha-2 agonist dexmedetomidine could be a safer sedation option, but it is not currently approved by the FDA for neonate use. This systematic review examines the current literature to determine if dexmedetomidine showed superiority to midazolam as a primary mechanism for neonatal sedation while appearing to provide a safer profile. This systematic review used PRISMA as a framework guideline. A literature review was conducted and data was collected in table form. A cross-study analysis was created to compare the results of these studies, which showed that midazolam in fact alters hemodynamics in neonates and had the potential to cause neurologic injury. The results urge further research to gain FDA approval of dexmedetomidine in the neonatal population and to form established guidelines for anesthesia provider reference.

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Midazolam-Sparing Approach for Neonatal Sedation: A Systematic Review

Background/Statement of the Problem

The term neonate refers to an infant in its first twenty-eight days of life or one month after birth. Neonates are in a very vulnerable state, as they adjust to their new environment and experience a period of significant physiological and psychological developmental changes (Anand & Hall, 2006). Therefore, it is important to keep in mind the role this crucial developmental period plays in altering the pharmacokinetics of administered medications due to the immaturity of the neonate's developing brain and hepatic function. The pharmacokinetics of a drug is how the drug is absorbed, distributed, broken down and metabolized, and how it is disposed of or eliminated by the body. The reduced activity of the enzymes of the CYP450 system, in particular, creates a decreased rate of clearance of drugs that depend on key enzymes for metabolism and elimination. In reference to midazolam, a benzodiazepine with rapid onset of action and short duration of effect and highly metabolized by CYP3A4, the half-life in a neonate is longer and its clearance rate is lower (Pacific, 2014).

There have been reports of adverse neurological effects associated with the use of midazolam for neonatal sedation (Anand & Hall, 2006). According to Volpe (2001), one of the most commonly occurring of poor neurological outcomes is periventricular leukomalacia (PVL), which is the formation of an ischemic area in the cerebral white matter of the brain caused by a brief period of cerebral hypo-perfusion and decreased oxygenation. The underdeveloped cerebral vasculature of a neonate creates a greater propensity for PVL occurrence. The resulting ischemic lesion acts like a hole in the white matter and can manifest as a variety of symptoms on a wide scale of severity, depending

on location and size. It can take years for symptoms to become evident and can present in the form of spastic motor deficits, cerebral palsy, seizure activity, and cognitive and behavioral deficits that interfere with schooling (Volpe, 2001).

This population is also at a higher risk to develop PVL because of their heightened perception of pain and stress, which can interfere with proper ventilation and perfusion. For this reason, it is vital for the neonate to maintain an appropriate comfort level before, during, and after any procedure to properly ventilate, recover and avoid future psychological and behavioral issues related to stressful experiences during this vulnerable time (Anand & Hall, 2006). The neonate is adjusting to its new environment after leaving the protection of the womb. Therefore, painful procedures are unexpected and can be disruptive to physiological development (Anand & Hall, 2006), leading to the neonate having a heightened sensitivity to painful stimuli that can continue through life (Squillaro et al., 2019).

In attempts to prevent this occurrence, many studies have been done to validate an appropriate comfort measure scale to quantify pain in this population (Beltrammi et al., 2017). An example of one scale is the Premature Infant Pain Profile (PIPP), which is approved for term and preterm neonates using three facial expression items and two physiological items to gauge a procedural pain level experienced by the neonate. The PIPP scale considers variation in heart rate, oxygen saturation, and excessive sedation.

Midazolam, a benzodiazepine, has been used to achieve the level of sedation for neonates deemed adequate by multiple validated comfort scales. Benzodiazepine drugs activate Gamma-aminobutyric acid A (GABA-A) receptors. The endogenous neurotransmitter, GABA, inhibits brain signals from one neuron to another when

connected to the GABA-A receptor. Benzodiazepines also bind to GABA-A receptors on their own site, and have the same effect of blocking nerve impulses, resulting in a sedating, anxiolytic effect with amnesia, and muscle relaxation (Anand & Hall, 2006). Midazolam specifically has a short duration of action and is therefore the chosen benzodiazepine for procedural use.

The problem with midazolam administration is related to its effects on hemodynamics. There is a fine balance between adequate sedation and ineffective comfort management, and the consequence of misjudging either can be developmentally harmful to the neonate (Squillaro et al., 2019). It has been shown that bolus administration of midazolam usually requires higher dosing to reach an adequate level of sedation, as shown in Treluyer et al. (2005), which aimed at improving management of non-painful stress in neonates. This study investigated the most effective dose of midazolam to adequately sedate a neonate for a procedure was the highest dose tested, which was a bolus dose of 200mcg/kg and then a maintenance infusion of 100mcg/kg/hr. However, using a continuous infusion of midazolam to maintain a steady level of comfort can create accumulation of the drug and its active metabolite, alpha1-hydroxymidazolam, due to the decreased rate of metabolism and elimination in the neonate, increasing the chance for adverse effects. Midazolam in higher doses can lead to hypotension and decreased cerebral blood flow to an already underdeveloped cerebral vascular supply, resulting in decreased oxygenation of the brain and neurologic injury, principally in the form of PVL (Volpe, 2001).

Therefore, there is reason to believe that the higher dosing of midazolam necessary to sedate the neonate for uncomfortable procedures is contributing to poor

neurologic outcomes in the form of PVL. The Cochrane Systematic Review reporting on midazolam use for sedation in neonates found controversial data on the neurologic effects of midazolam raising the question of its safety profile in this population (Ng et al., 2017), and the need for the review of better options.

Literature Review

Adequate Sedation of Neonates Requiring Midazolam

Treyluyer et al. (2005) defines an acceptable level of sedation as the patient experiencing an adequate comfort level to effectively ventilate and avoid complications such as pneumothorax and intraventricular hemorrhage (IVH) related to stress. A double-blind study was designed to determine the minimum effective dose of midazolam. The study was approved by a local ethics committee, appropriate exclusion criteria was applied, and written parental consent was obtained for all subjects. Each neonate was designated to a dose unknown by the Neonatal Intensive Care Unit (NICU) providers in order to avoid bias. The researcher concluded that the highest midazolam loading dose of 200mcg/kg had the greatest sedation at the one-hour checkpoint. A continual reassessment method was used during that time to observe for agitation during and following tracheal suctioning. Reduced midazolam clearance and increased half-life of the drug might have contributed to the highest midazolam loading dose being most effective in the short, one-hour window. The neurological problems seen with midazolam in this population did not occur in this study, although the sample was small and the time frame was short. The study did however show the requirement for higher dosing of midazolam for clinical effectiveness. The need for a safe, effective sedation plan for this population is not well addressed with the outcome of this study and requires further testing.

Midazolam Sedation in Correlation to Poor Neurological Outcomes

A systematic review (Ng et al., 2017) was conducted that included three randomized and quasi-randomized controlled trials with a total of 148 neonates, primarily focusing on infants 28 days old or younger receiving an intravenous midazolam

continuous drip for sedation. The need for appropriate sedation for this age group is critical because they often undergo uncomfortable procedures.

The review assessed the adequacy of a midazolam infusion to promote sedation and complications that may arise as a consequence of the infusion such as IVH, PVL, death, increased length of stay in the Intensive Care Unit (ICU), all adverse effects associated with midazolam (Ng et al., 2017). A descriptive analysis for categorical and continuous data was used. Heterogeneity was assessed between trials with forest plots. The fixed-effect model was used for all meta-analyses.

The results revealed that midazolam drips provided a significantly higher level of sedation for these patients as opposed to the dextrose placebo drip. It also showed that patients on the midazolam drips had a significantly longer ICU stay. One of the trials showed that adverse neurological events were significantly higher with a midazolam drip as opposed to a morphine drip. The reviewers considered the trials to be of moderate quality, but found the data to be insufficient to support the use of midazolam drips in this age group. Findings of the review call attention to the safety risks of using a midazolam drip in neonates and the need for further research into alternative and effective sedative agent with an improved safety profile for this population.

Anand et al. (1999) conducted a quantitative, multi-site randomized pilot study focused on preterm neonates and the use of sedation when mechanical ventilation is required. The trial focused on the effectiveness of sedation management in these subjects. The study aimed to find the appropriate sedation for neonates subject to multiple painful procedures after birth and high risk of experiencing acute physical reactions to pain and stress, mainly poor neurological outcomes, such as IVH and PVL (Anand et al., 1999).

The study proposed a three-group intervention with a midazolam drip, morphine drip, and 10% dextrose placebo drip for each group of neonates. Appropriate exclusion criteria were used to select eligible subjects. The study population included 67 out of 170 preterm neonates from nine centers, and each was assigned to the three groups randomly to avoid bias. The researchers used a COMFORT score scale to measure sedation and a Premature Infant Pain Profile (PIPP) scoring system to assess pain through observation before, during and after discontinuation of the drips to compare the three groups along with routine cranial ultrasounds.

Findings from the study revealed poor neurological outcomes defined as neonatal death, severe IVH grade III or IV, and PVL in 24% of neonates in the placebo group, 32% in the midazolam group, and 4% in the morphine group. The researcher concluded that a continuous sedative drip was more effective than the placebo at preventing pain and stress to avoid poor neurological outcomes, but that a midazolam drip was not a good choice as the sedative and recommended further investigation into the use of morphine. The study showed that midazolam use potentially contributed to poor neurological outcomes in this population and raised the question whether midazolam should be used and whether there are other alternative sedative agents more appropriate to consider.

In the randomized controlled trial by Van Alfen-Van Der Velden et al. (2006), the authors focused on preterm infants and the effects of midazolam and morphine infusion on cerebral oxygenation and hemodynamic stability during ventilation. The study population included 10 ventilated preterm neonates who were put on morphine drips and 11 ventilated preterm neonates who were put on midazolam drips. Those enrolled were blindly selected for the midazolam or morphine group to prevent bias.

Patients received loading doses of their respective sedation and were then maintained on a continuous drip of the same drug. The researchers measured changes in oxyhemoglobin and deoxyhemoglobin with the noninvasive method of near-infrared spectroscopy (NIRS), which reflectively shows change in cerebral blood oxygenation, concentration of total hemoglobin and cerebral blood volume. Doppler ultrasound was also used to measure cerebral blood flow velocity. Other continuously monitored measurements included heart rate, mean arterial pressure, arterial oxygenation saturation and transcutaneous pO2 and pCO2. They were analyzed using linear mixed models, which created an easy visual to compare the results and detect change (Van Alfen-Van Der Velden et al., 2006). The above measurements were taken 15 minutes after the loading doses of sedation were administered.

The results showed 50% of both subject groups had decreases in arterial oxygen saturation, transcutaneous oxygen measurement and hemoglobin oxygenation index. The study used a reliable measurement tool and accurately correlated drops in measurements with administration of the medications. A descriptive analysis with longitudinal data analysis using linear mixed models was done, and mean with standard deviation was reported.

Although the small sample size could not demonstrate a relationship between observed changes in cerebral oxygenation and hemodynamics, the clinical findings indicate that these medications result in some changes in ventilated premature infants that require further study for potential harm (Van Alfen-Van Der Veldon et al., 2006). Findings from this study have clinical significance to patient care and strongly support the proposal for further research to consider alternative sedation options.

Dexmedetomidine Safety Profile in Neonates

Dexmedetomidine is an alpha2-agonist that inhibits release of substance P, a neurotransmitter that heightens awareness to pain (Squillaro et al., 2019). By doing so, it provides sedation and analgesia along with an antianxiolytic effect without the side effect of respiratory depression. Dexmedetomidine has not been approved by the Food and Drug Administration (FDA) for use in infants and children and therefore, its use is off-label and depends on results of comparative studies and case reports to guide clinical practice (Squillaro et al., 2019).

Surkov (2019) studied the effects of dexmedetomidine on cerebral perfusion to determine whether it is safe for the developing neonate's neurologic function. Noninvasive, ethically approved methods were used to monitor cerebral hemodynamics. Doppler ultrasound was used to monitor blood flow of the cerebral artery and near infrared spectroscopy (NIRS) was used to measure cerebral oximetry. A statistical analysis of collected data was done and then was examined for normal distribution. The study included a sample size of 205 neonates, all of whom were under the stress of ventilation and all recovering from hypoxic ischemic encephalopathy which had occurred within 72 hours of life. The results showed that dexmedetomidine did not interfere with measures of cerebral perfusion and did not interfere with their recovery back to normal neonatal development and neurologic function. With the risks related to other sedation agents in the neonatal population, such as those seen with midazolam, it is important to test efficacy of other drug options and create a safety profile to promote transition of the usual standard of care to include additional safe options for sedation.

Conclusion

In summary, there is reason to believe that use of midazolam in the neonatal population may be unsafe, and other effective sedative agents should be sought after. There is evidence that dexmedetomidine could be a safer option for this population. In Squillaro et al. (2019), a multimodal approach to neonatal sedation was used with the focus on delivery of an opioid-sparing technique. The results of dexmedetomidine use showed that perioperative sedation was achieved with decreased adverse effects. Can a midazolam-sparing approach accomplish the same results, without risking an uncontrolled pain and stress response in the neonatal population? The FDA has not approved dexmedetomidine for use in neonates, despite the current off-label use. This warrants further investigation into whether dexmedetomidine should be considered for authorization by the FDA in neonates.

Theoretical Framework

According to Polit and Beck (2017), every study has a theoretical framework, whether it is based on a theoretical model or a conceptual model. A theory is “an abstract

generalization that explains how phenomena are interrelated" (Polit & Beck, 2017, p.184) and takes at least two concepts and forms a relationship that the theory is bringing relevance to and forming a hypothesis about. A conceptual model is a less formal means of organizing phenomena than a theory. Theories and conceptual models guide the researcher to an understanding of why a phenomena occurs (Polit & Beck, 2017, p. 186). Theories and models of nursing practice have been formulated over the years to help create a basis for nursing science.

Looking through many of the commonly used frameworks, it is evident that most are formed from a middle range theory, which is most conducive to the types of phenomena within this scope of clinical practice, such as decision making, stress, comfort, health promotion and unpleasant symptoms (Polit & Beck, 2017). This type of theory is also most favorable for empirical testing, which requires direct and indirect observation for both qualitative and quantitative analysis of a phenomenon.

Despite the usefulness of using a theoretical framework to guide nursing research, a systematic review will be most fitting for this review because of the need to compare and evaluate the results of randomized control trials (RCTs). Completed RCTs conducted by Chysostomou (2014) and Dilek (2011) pilot the use of dexmedetomidine in the neonatal population. Completed RCTs conducted by Mayorga (2018) and O'Mara (2012) do the same, while also showing a direct comparison to midazolam. Research investigations with vulnerable populations, such as neonates, are difficult given the many ethical considerations surrounding their participation. Therefore, it is best to analyze current RCTs and design a systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is most appropriate to organize this

review because it serves as a guideline for systematic classification of primary studies. The PRISMA method is composed of a twenty-seven-item checklist (Appendix A) with a four-phase flow diagram (Appendix B) to summarize evidence properly and "reduce the risk of flawed reporting" (Moher, 2009, p. 37). It begins with a solid, clear title and flows from the abstract to the introduction, methods, results, discussion and finding sections respectively while noting all important subcategories within these main sections. It is not an assessment tool but rather a "reporting guidance" (Moher, 2009, p. 3).

A systematic review is a collation of empirical evidence to answer a specific research question (Moher, 2009). The PRISMA method guides an author through a series of steps of a systematic review while conducting a research study. First, one must identify records through database searching and other sources, remove duplicates, and then screen and exclude irrelevant records. Full text articles must then be assessed for eligibility and biased influence and excluded if necessary. From there, included studies can be used to develop a qualitative and potentially quantitative synthesis to make recommendations.

For conducting the systemic review of the proposed research plan, the PRISMA model will maintain organization and best ensure all steps are adequately covered while analyzing the results of the study.

Methodology

Research Question

Does a midazolam-sparing approach to sedation with the use of dexmedetomidine decrease the risk for adverse neurological outcomes in neonates undergoing uncomfortable procedures?

Inclusion/Exclusion Criteria

The proposed inquiry is a systematic review of experimental randomized control trials. The included studies focus on neonates less than 28 days old receiving procedural sedation primarily with the use of dexmedetomidine. Articles were excluded if not written in English. Studies with a patient sample greater than 28 days old were excluded. When analyzing results, data must have been taken from a large enough sample size to compare adequately.

Search Strategy

The search strategy for the proposed study was taken from the Cochrane Neonatal Review Group's Neonatal Standard Search Strategy (Cochrane, 2019). Data from studies was retrieved through search engines such as PubMed, Google Scholar and Cochrane's Library. Cochrane's strategy gives suggested search words for best outcomes specifically for randomized controlled trials conducted in the field of neonatology. The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist (Cochrane, 2019). Filters include the keywords neonate, drug therapy trial and dexmedetomidine. Other studies were found by searching through reference lists included in this review for potential cross-references.

Critical Appraisal Tool

To assess scientific quality of studies, the appraisal tools used were the Critical Appraisal Skills Programme (CASP) tools, which rate the quality of evidence in RCTs and systematic reviews. Randomized control trials and systematic reviews make up the top two levels of quality on the evidence pyramid, and therefore were mostly used for data collection. The CASP tools have a checklist method to assess an RCT or a systematic review (Appendix C) that helps determine if the study is of good quality to obtain results from.

Data Collection/Cross Analysis

Any studies that were found through above searches were reviewed independently to analyze for data. Bias was also assessed based on guidelines of Cochrane's Handbook for Systematic Reviews of Interventions, which includes screening for blinding of participants and selective reporting in studies to assess quality of results. Any comparison of vital signs obtained through the RCTs in studies used were analyzed in relation to sedation interventions in a summary chart. Sedation and pain levels assessed through valid measurement scales were also analyzed through a chart to better show comparisons across the RCTs. Any neurological complications or deaths reported in studies had to address if the cause was sedation related, whether from effect of the drug itself or the result of unsafe sedation and inadequate pain management.

Table 1 – *Data Collection Tool 1*

Study Title	Authors	Sample	Methodology	Results	Limitations

Table 2 – *Data Collection Tool 2*

Dexmedetomidine dose	Vital sign Analysis (BP, HR, Oxygen saturation)	Adverse Events Reported/Safety Assessment	Adequate Sedation Reported via an appropriate scale	Relevance To Clinical Practice

The data collected was then cross analyzed into a third table to compare results across studies. This table identified the author of the study and addressed the consensus on vital sign changes in relation to hemodynamics and oxygenation with dexmedetomidine along with reports of adequate sedation in neonates reported with appropriate scale.

Table 3- *Cross Study Analysis*

Author of study	Changes in BP and HR with dexmedetomidine	Changes in Oxygenation with dexmedetomidine	Dexmedetomidine Efficacy in Sedating the neonatal population

Dissemination of Results

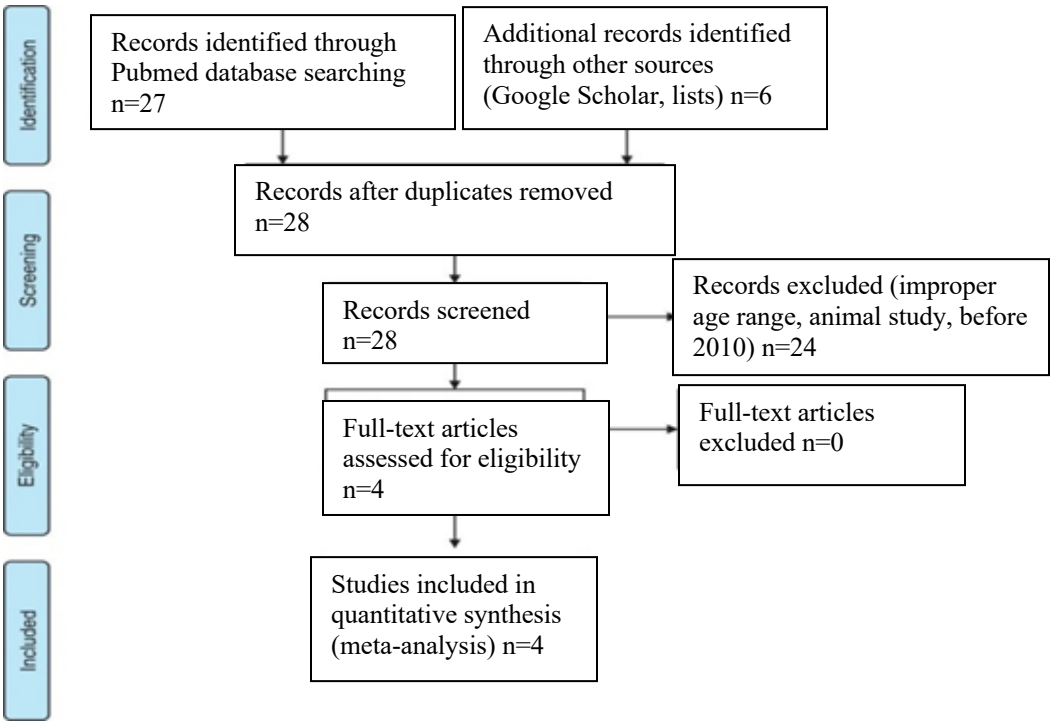
The results of the systematic review will be presented to faculty of the Rhode Island College School of Nursing and other graduate nursing students during an electronic poster presentation event, and the completed academic paper will be posted on the Rhode Island College library digital commons.

Results

Data Collection

The PRISMA flow diagram was used as the tool to organize the search for appropriate articles used in this systematic review. The databases used were PubMed, Google Scholar and Cochrane Library along with analysis of reference lists. With search words "dexmedetomidine, neonate, and drug therapy trial," there were 27 results from PubMed, 6,970 results from Google Scholar and 0 results from Cochrane Library. Results prior to the year 2010 were excluded and then duplicate articles were removed. The remaining articles were screened for appropriate age range (some used wider age range than strictly 28 weeks or under) and were excluded if the study included animal testing results. The full-text articles of the four remaining studies were then assessed and chosen for this review (Figure 1).

Figure 1*PRISMA Flow Diagram*



A Phase II/III Multicenter safety, efficacy, and pharmacokinetics study of dexmedetomidine done by Chrysostomou et al. (2014) assessed 42 intubated, mechanically ventilated neonate patients from 28 weeks to 44 weeks gestational age. Each patient was given a loading dose of dexmedetomidine over 10-20 minutes followed by an infusion for 6-24 hours. Doses ranged from a 0.05mcg/kg loading dose with a 0.05mcg/kg/hr maintenance, a 0.1mcg/kg loading dose with a 0.1mcg/kg/hr maintenance, and a 0.2mcg/kg loading dose with a 0.2mcg/kg/hr maintenance. Based on the Neonatal Pain, Agitation, Sedation Scale, 5% of patients scored greater than a 3 and 8% required more sedative medication. Monitoring of vital signs, including blood pressure (BP), heart rate (HR) and oxygen saturation, showed a decrease in the patients' BP and HR by approximately 12-14%, but no instance of respiratory depression. There were 56 adverse events reported, with only 3 related to dexmedetomidine including diastolic hypotension, hypertension, and significant agitation. None of the adverse events were serious enough to require discontinuation of dexmedetomidine. A limitation of this study is the sample size, but with this vulnerable population, it is hard to acquire large samples due to difficulty gaining consent and ethical dilemmas in consenting neonates (Appendix D).

A prospective chart study done by Dilek et al. (2011) assessed preliminary experience with dexmedetomidine in 16 full term neonates born at 37 weeks gestation or more and less than 29 days old who underwent general anesthesia with sevoflurane and dexmedetomidine for abdominal surgery in a university hospital between October 2008 and March 2009. Each patient was given 1mg/kg of ketamine on induction and infused 1mcg/kg of dexmedetomidine over the first 10 minutes followed by a dexmedetomidine maintenance infusion of 0.5-0.8mcg/kg/hr until the end of surgery. Patients were

adequately sedated for the duration of surgery 2.3 +/- 0.9 hours with only three cases requiring one ketamine bolus of 1mg/kg for either a 20% increase in SBP or 20% increase in HR. No subsequent doses were required. No patient required a sevoflurane concentration greater than 0.2%. There were no reports of hypotension, hypertension, bradycardia, hypoxia or respiratory depression. Mild hypothermia was observed without related adverse event. Patients were all reported as extubated after surgery with satisfactory breathing and appropriate neurological responses including crying and eye opening. Exclusions for this study included presence of major congenital malformation, birth weight less than 1000 grams, previous opioid for any reason including for cesarean section under general anesthesia, hemodynamic instability before the indication of tracheal intubation and refusal of parents to enroll the neonate in the study. This resulted in a small sample population. This study showed that the initial dose of dexmedetomidine with maintenance dose 0.5mcg/kg/hr as an adjuvant to low concentration of sevoflurane maintained a stable HR and BP under surgical stimulation. Larger studies are needed to further evaluate efficacy and safety in this population (Appendix E).

A prospective study done by Matorga-Buiza et al. (2018) compared 53 neonates born at a health institute from January 2016 to February 2018 who were to receive intranasal dexmedetomidine for MRI to a historical group of 40 babies born the 2 years before dexmedetomidine introduction, who received midazolam as their first-line drug. All 53 neonates were given intranasal dexmedetomidine 3mcg/kg with rescue midazolam dose if needed. The median time for the dexmedetomidine group to achieve adequate sedation for MRI was 10 minutes after dose, and median time to arousal was 59 minutes. Twenty seven patients did not require midazolam and 25 patients required one

midazolam dose. In the historical midazolam group that had received midazolam prior to MRI, all 40 required additional midazolam doses (12 required 1 additional dose, 14 required 2 and 14 required 3.) In the dexmedetomidine group, 7 neonates had a brief, self-resolving desaturation (only 1 of these had received dexmedetomidine alone, the other 6 had required 1 midazolam bolus.) In the historical midazolam group, 2 neonates had apnea requiring positive pressure ventilation. There were no recorded cases of bradycardia. None of the adverse events reported required intervention. The study did not report the bolus midazolam dose that was given. It shows dexmedetomidine as useful for procedural sedation for MRI, but does not show efficacy with higher levels of procedural stimulation (Appendix F).

A retrospective, observational case-control study done by O'Mara et al. (2012) assessed 48 premature neonates requiring mechanical ventilation between January 2005 and May 2010 where 24 neonates received standard therapy fentanyl for sedation and 24 neonates received dexmedetomidine. Half of the patients started with 0.5mcg/kg bolus doses of dexmedetomidine. Every patient received maintenance of 0.3mcg/kg/hr with 0.1mcg/kg/hr increases twice a day based on elevated sedation scores requiring >3 doses of adjuvant sedation in 12 hours. The mean infusion rate was 0.6mcg/kg/hr (highest required rate was 1.2mcg/kg/hr.) Those in the dexmedetomidine group required less adjunctive sedation and had more days free of additional sedation in comparison to the fentanyl group and duration of mechanical ventilation was shorter. There was no difference in hemodynamics between the two groups. Dexmedetomidine decreased mechanical ventilation duration, decreased amount of chest x-rays needed by 50% compared to the fentanyl group, and a significantly smaller percent of patients required

dexamethasone dosing for ventilator weaning. No adverse events were associated with dexmedetomidine use. Limitations of this study include small sample size and the inability to assess long term neurologic outcomes in these patients until more time has transpired. However, dexmedetomidine was reported as potentially neuroprotective (Appendix G).

Critical Appraisal

All four studies were critically appraised using the CASP checklist.

In the study by Chrysostomou et al. (2014), 9 out of 11 of the questions were answered as "yes." The efficacy and safety of dexmedetomidine in the neonate population was the focused issue. The assignment of patients to dexmedetomidine doses was randomized, and all patients were accounted for at the end of the trial. The groups were treated equally, effects of intervention were reported and can be applied to the local population. It appears the benefit of dexmedetomidine use outweighs harm. The only "no" in the CASP checklist was applied to the question related to randomized treatment, because all patients received the same treatment, and because the study personnel were not blind, but rather used criteria based on their sedation scale on whether to use a higher dose or not (Appendix I).

In the study by Dilek et al. (2011), the focus was to assess adequate sedation of dexmedetomidine in neonates with 9 out of 11 "yes" checks on the list. The study was not blind, as it was a prospective chart study. All participants included in the study were screened using exact criterion and had no reason for exclusion. The same treatment was given to every participant, based on certain criteria for subsequent boluses. All patients

were accounted for at the end of the study. Results can be applied to local population and show benefit to dexmedetomidine use in neonates (Appendix J).

In the study done by Mayorga-Buiza et al. (2018), the focus was to compare a midazolam-sparing approach with dexmedetomidine to midazolam use with neonates. The same 9 out of 11 “yes” checks were seen on the CASP list. This is because most of the studies with neonates are not blind, and have a specific set of guidelines that personnel must follow (Appendix K).

The last study by O’Mara (2012) had 10 out of 11 “yes” checks on the CASP list because of previously stated reasons. There was benefit found to use of dexmedetomidine in the neonate population compared to fentanyl (Appendix L) that will be discussed below.

Summary and Conclusions

This systematic review was intended to determine if dexmedetomidine use in the neonatal population was a safe and efficacious primary sedation mechanism to spare the use of midazolam. Dexmedetomidine is not approved by the FDA for use in neonates because of the difficulty to study this population and perform ethically-approved trials. The four studies reviewed determined that dexmedetomidine could be used to adequately sedate a neonate who is mechanically ventilated or undergoing an uncomfortable procedure. As shown in Table 3 (Appendix H), where the four studies (Chrysostomou et al., 2014; Dilek et al., 2011; Matorga-Buiza et al., 2018; O'Mara et al., 2012) were cross analyzed, dexmedetomidine adequately sedated the studied neonates according to an appropriate sedation scale with minimal need for subsequent sedation. In all instances where subsequent sedation was required, there was only need for a one-time dose of an adjuvant medication, which is drastically less than the required additional doses needed when primarily sedating with midazolam.

In all four studies, there was minimal hemodynamic instability noted with dexmedetomidine. With the doses studied, the majority of the trials showed no significant alteration to heart rate or blood pressure, the most being a reported 10% decrease in both from baseline that was not harmful. All studies showed no changes to oxygenation or signs of respiratory depression. One study showed a couple of self-resolving instances of oxygen desaturation (Matorga-Buiza et al., 2018), but these were linked to patients who had received one-time doses of an adjuvant medication other than dexmedetomidine.

In conclusion, dexmedetomidine has been shown to have neuroprotective properties in the neonatal population. Despite small sample sizes, which is often the case

for trials regarding neonates, dexmedetomidine's performance was consistent and warrants a serious consideration by the FDA to approve its use and to establish guidelines for administration in this population. This will give providers an alternate primary mechanism for sedation and the ability to spare midazolam use for neonatal patients.

Recommendations and Implications for Advanced Nursing Practice

The neonatal population requires extra close attention to detail and diligence when it comes to what drugs are being administered and the dosing. As an anesthesia provider, one must protect this vulnerable population by providing adequate sedation and analgesia. This is to decrease the likelihood of adverse effects that come from being exposed to a traumatic experience early in life. At the same time, it is important to not over sedate with drugs and dosing that will alter hemodynamics significantly and subsequently affect perfusion to developing areas of the brain, interfering with normal development.

This review supports a midazolam-sparing approach to neonatal sedation. It reports dexmedetomidine as an adequate alternative with neuroprotective properties, despite the lack of approval by the FDA at this time. As its use in younger populations becomes more popular, further studies and research will contribute to the evidence and support FDA approval and an established set of administration guidelines for dexmedetomidine dosing as the primary mechanism for sedation of the neonatal population.

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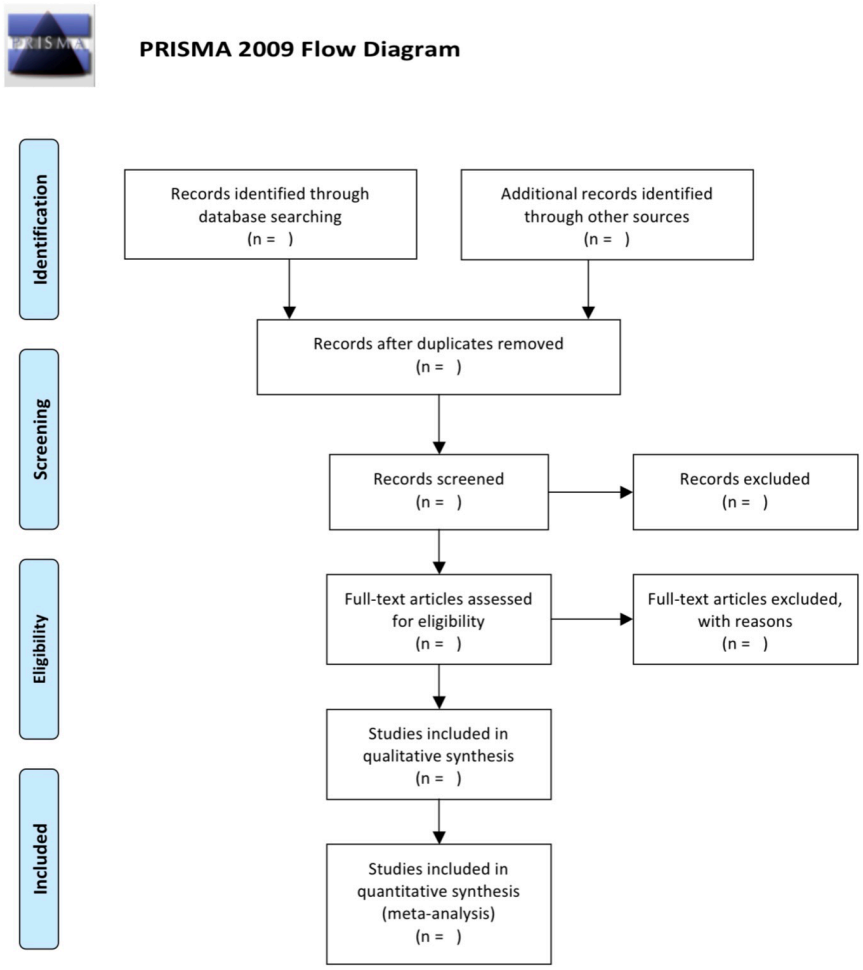
Appendix A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

By Moher et al., 2009

Appendix B



By Moher et al., 2009

Appendix C

	11 Questions	Yes	Can't Tell	No
1	Did the trial address a clearly focused issue?			
2	Was the assignment of patients to treatments randomized?			
3	Were all the patients who entered the trial properly accounted for at its conclusion?			
4	Were patients, health workers, and study personnel 'blind' to treatment?			
5	Were the groups similar at the start of the trial?			
6	Were the effects of intervention reported comprehensively?			
7	Was the precision of the estimate of the treatment effect reported?			
8	Can the results be applied in your context? (Or to the local population?)			
9	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?			
10	Were all clinically important outcomes considered?			
11	Are the benefits worth the harms and costs?			

By Critical Appraisal Skills Programme, 2017

Appendix D

Chrysostomou, C., Schulman, S., Castellanos, M. H., Cofer, B., Mitra, S., Garcia da Roche, M., Wisemandle, W. & Gramlich, L. (2014). A phase II/III, multicenter, safety, efficacy, and pharmacokinetics study of dexmedetomidine in preterm and term neonates. *The Journal of Pediatrics. 164*(2), 276-282. https://doi.org/10.1016/j.jpeds.2013.10.002

Table 1

Study Title	Authors	Sample	Methodology	Results	Limitations
A Phase II/III Multicenter, Safety, Efficacy, and Pharmacokinetic Study of Dexmedetomidine in Preterm and Term Neonates	Chrysostomou, Schulman, Castellanos, Cofer, Mitra, Garcia da Rocha, Wisemandle, Gramlich	42 intubated, mechanically ventilated patients from 28 weeks gestational age to 44 weeks	Phase II/III, open-label, multicenter center, efficacy and pharmacokinetic trial	Based on the Neonatal Pain, Agitation, Sedation Scale, 5% patients scored >3 and 8% required more sedation. 5% of adverse events were related to dexmedetomidine. No serious events/hemodynamic changes requiring discontinuation of dexmedetomidine	Size of study

Table 2

Dexmedetomidine dose	Vital sign Analysis (BP, HR, Oxygen saturation)	Adverse Events Reported/Safety Assessment	Adequate Sedation Reported via an appropriate scale	Relevance to Clinical Practice
Escalation of dosing 0.05mcg/kg loading dose and 0.05mcg/kg/hr maintenance; 0.1mcg/kg and 0.1mcg/kg/hr; 0.2mcg/kg and 0.2mcg/kg/hr;	HR and BP decreased by approximately 12-14%, no	56 AEs, 3 AEs r/t dexmedetomidine (diastolic hypotension, hypertension, and significant agitation), 0	Neonatal Pain, Agitation, Sedation scale, NPASS	Study provides pivotal multicenter efficacy, safety and PK data.

Loading doses over 10-20 min, infusion over 6-24 hours	respiratory events	AEs requiring discontinuation		

Appendix E

Dilek, O., Yasemin, G. & Atci, M. (2011). Preliminary experience with dexmedetomidine in neonatal anesthesia. *Journal of Anaesthesiology Clinical Pharmacology. 27*(1), 17-22. Retrieved at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146151/

Table 1

Study Title	Authors	Sample	Methodology	Results	Limitations
Preliminary Experience with Dexmedetomidine in Neonatal Anesthesia	Dilek, Yasemin, Atci	16 full term neonates born at 37 weeks gestation or more and less than 29 days old who underwent general anesthesia	Prospective chart study of full term neonates who underwent general anesthesia with sevoflurane and dexmedetomidine for abdominal surgery in a University Hospital between October 2008 and March 2009. Plan in place for specific changes in SBP and HR.	Patients were adequately maintained for the duration of surgery 2.3 +/- 0.9 hours with 3 cases requiring a one-time ketamine bolus 1mg/kg for either 20% increase in SBP or HR. No subsequent doses required. No HD instability or respiratory depression. Patients were all reported as extubated after surgery with satisfactory breathing and appropriate neurological responses including crying and eye opening.	Exclusions included presence of major congenital malformation, birth weight less than 1000 grams, previous opioid for any reason including for cesarean section under general anesthesia, hemodynamic instability before the indication of tracheal intubation and refusal of parents to enroll the neonate in the study. This resulted in a small sample population.

Table 2

Dexmedetomidine dose	Vital sign Analysis (BP, HR, Oxygen saturation)	Adverse Events Reported/Safety Assessment	Adequate Sedation Reported via an appropriate scale	Relevance To Clinical Practice
1mg/kg of ketamine on induction and 1mcg/kg infused for first 10 minutes followed by maintenance 0.5-0.8mcg/kg/hr infusion until end of surgery	This dose obtained hemodynamic stability and effective anesthesia.	No reported hypotension, hypertension, bradycardia, hypoxia and respiratory depression. Mild hypothermia observed without related adverse event.	Three patients needed supplemental ketamine doses only once (meaning their SBP and/or heart rate had increased greater than 20% from baseline levels.) No patient required more than 0.2% sevoflurane concentration.	This study showed that this initial dose of dexmedetomidine with maintenance dose 0.5mcg/kg/hr as an adjuvant to low concentration of sevoflurane kept stable HR and BP under surgical stimulation. Larger studies are needed to further evaluate efficacy and safety in this population.

Appendix F

Mayorga-Buiza, M. (2018). Intranasal dexmedetomidine, as midazolam-sparing drug, for MRI in preterm neonates. *Pediatric Anesthesia.* https://doi.org/10.1111/pan.13454

Table 1

Study Title	Authors	Sample	Methodology	Results	Limitations
Intranasal dexmedetomidine, as midazolam-sparing drug, for MRI in preterm neonates	Mayorga-Buiza, Rivero-Garvia, Gomez-Gonzalez, Marquez-Rivas	53 neonates	Prospective study with comparison to a historical group of 40 babies born the 2 years before dexmedetomidine introduction who received midazolam as first-line drug.	27 patients did not require midazolam and 25 patients required 1 midazolam dose. In the historical midazolam group that had received midazolam prior to MRI, all 40 required additional midazolam doses (12 required 1, 14 required 2 and 14 required 3.)	Article did not divulge the bolus midazolam dose that was given. This study shows dexmedetomidine as useful for procedural sedation for MRI, but does not show efficacy with higher levels of stimulation.

Table 2

Dexmedetomidine dose	Vital sign Analysis (BP, HR, Oxygen saturation)	Adverse Events Reported/Safety Assessment	Adequate Sedation Reported via an appropriate scale	Relevance To Clinical Practice
Intranasal dexmedetomidine 3mcg/kg with rescue midazolam dose if needed	In the dexmedetomidine group, 7 neonates had a brief, self-resolving desaturation (only 1 of these had received dexmedetomidine alone, the other 6 had required 1 midazolam bolus.) In the historical midazolam group, 2 neonates had apnea requiring positive pressure ventilation. No recorded cases of bradycardia.	No adverse events requiring intervention reported in the dexmedetomidine group.	Median time for dexmedetomidine group to achieve adequate sedation for MRI was 10 minutes after dose, median time to arousal was 59 minutes.	Dexmedetomidine spares the use of midazolam in the neonate population with very low risk of respiratory adverse events and potential neuroprotective properties.

Appendix G

O'Mara, K., Gal, P., Wimmer, J., Laurence Ransom, J., Carlos, R., Dimaguila, M., Davanzo, C. & Smith, M. (2012). Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature neonates. *Journal of Pediatric Pharmacology and Therapeutics. 17*(3), 252-262. https://doi.org/10.5863/1551-6776-17.3.252

Table 1

Study Title	Authors	Sample	Methodology	Results	Limitations
Dexmedetomidine Versus Standard Therapy with Fentanyl for Sedation in Mechanically Ventilated Premature Neonates	O'Mara, Gal, Wimmer, Ransom, Carlos, Dimaguila, Davanzo, Smith	48 premature neonates requiring mechanical ventilation	Retrospective, observational case-control study in a level III neonatal intensive care unit where 24 neonates received fentanyl and 24 received dexmedetomidine.	Those in the dexmedetomidine group required less adjunctive sedation and had more days free of additional sedation in comparison to the fentanyl group and duration of mechanical ventilation required was shorter.	Small sample size, inability to assess long term neurologic outcomes in these patients until more time has transpired.

Table 2

Dexmedetomidine dose	Vital sign Analysis (BP, HR, Oxygen saturation)	Adverse Events Reported/Safety Assessment	Adequate Sedation Reported via an appropriate scale	Relevance To Clinical Practice
Half of the patients started with 0.5mcg/kg bolus doses of dexmedetomidine. Every patient received maintenance of 0.3mcg/kg/hr with 0.1mcg/kg/hr increases twice a day based on elevated sedation scores requiring >3 doses of adjuvant sedation in 12 hours. Mean infusion rate was 0.6mcg/kg/hr (highest required rate was 1.2mcg/kg/hr.)	There was no difference in hemodynamics between the two groups.	Reported as potentially neuroprotective. No adverse events associated with dexmedetomidine use.	Patients in the dexmedetomidine group required less adjuvant sedation.	Dexmedetomidine decreased mechanical ventilation duration, decreased amount of chest x-rays needed by 50% compared to the fentanyl group, and a significantly smaller percent of patients required dexamethasone dosing for ventilator weaning.

Appendix H

Table 3

Cross Study Analysis

Author of study	**Changes in BP and HR with dexmedetomidine**	**Changes in Oxygenation with dexmedetomidine**	**Dexmedetomidine Efficacy in Sedating the neonatal population**
Chrysostomou et al (2014)	Decrease in BP and HR 12-14%	No respiratory depression	8% required more sedation
Dilek et al (2011)	No noted decrease in BP or HR	No respiratory depression	3 out of 16 cases required a one-time subsequent sedation bolus for 20% increase in SBP or HR
Matorga-Buiza et al (2018)	No reported changes	7 patients had a brief, self-resolving desaturation (only 1 of these patients had received dexmedetomidine alone) compared to the midazolam group, where 2 had apnea requiring positive pressure ventilation	Compared to midazolam only group (all 40 required additional midazolam doses), in the dexmedetomidine group, 27 required no further sedation and 25 required one single midazolam dose.
O'Mara et al (2012)	No hemodynamic differences noted	Mechanical ventilation for dexmedetomidine group vs fentanyl group was shorter.	Those in dexmedetomidine group compared to fentanyl group required less adjunctive sedation

Appendix I

Chrysostomou, C., Schulman, S., Castellanos, M. H., Cofer, B., Mitra, S., Garcia da Roche, M., Wisemandle, W. & Gramlich, L. (2014). A phase II/III, multicenter, safety, efficacy, and pharmacokinetics study of dexmedetomidine in preterm and term neonates. *The Journal of Pediatrics. 164*(2), 276-282. https://doi.org/10.1016/j.jpeds.2013.10.002

	11 Questions	**Yes**	**Can't Tell**	**No**
1	Did the trial address a clearly focused issue?	X		
2	Was the assignment of patients to treatments randomized?			X
3	Were all the patients who entered the trial properly accounted for at its conclusion?	X		
4	Were patients, health workers, and study personnel 'blind' to treatment?			X
5	Were the groups similar at the start of the trial?	X		
6	Aside from the experimental interventions, were the groups treated equally?	X		
7	Were the effects of intervention reported comprehensively?	X		
8	Was the precision of the estimate of the treatment effect reported?	X		
9	Can the results be applied in your context? (Or to the local population?)	x		
10	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	X		
11	Are the benefits worth the harms and costs?	X		

Appendix J

Dilek, O., Yasemin, G. & Atci, M. (2011). Preliminary experience with dexmedetomidine in neonatal anesthesia. *Journal of Anaesthesiology Clinical Pharmacology. 27*(1), 17-22. Retrieved at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146151/

	11 Questions	Yes	Can't Tell	No
1	Did the trial address a clearly focused issue?	X		
2	Was the assignment of patients to treatments randomized?			X
3	Were all the patients who entered the trial properly accounted for at its conclusion?	X		
4	Were patients, health workers, and study personnel 'blind' to treatment?			X
5	Were the groups similar at the start of the trial?	X		
6	Aside from the experimental interventions, were the groups treated equally?	X		
7	Were the effects of intervention reported comprehensively?	X		
8	Was the precision of the estimate of the treatment effect reported?	X		
9	Can the results be applied in your context? (Or to the local population?)	x		
10	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	X		
11	Are the benefits worth the harms and costs?	X		

Appendix K

Mayorga-Buiza, M. (2018). Intranasal dexmedetomidine, as midazolam-sparing drug, for MRI in preterm neonates. *Pediatric Anesthesia.* https://doi.org/10.1111/pan.13454

	11 Questions	Yes	Can't Tell	No
1	Did the trial address a clearly focused issue?	X		
2	Was the assignment of patients to treatments randomized?			X
3	Were all the patients who entered the trial properly accounted for at its conclusion?	X		
4	Were patients, health workers, and study personnel 'blind' to treatment?			X
5	Were the groups similar at the start of the trial?	X		
6	Aside from the experimental interventions, were the groups treated equally?	X		
7	Were the effects of intervention reported comprehensively?	X		
8	Was the precision of the estimate of the treatment effect reported?	X		
9	Can the results be applied in your context? (Or to the local population?)	x		
10	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	X		
11	Are the benefits worth the harms and costs?	X		

Appendix L

O'Mara, K., Gal, P., Wimmer, J., Laurence Ransom, J., Carlos, R., Dimaguila, M., Davanzo, C. & Smith, M. (2012). Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature neonates. *Journal of Pediatric Pharmacology and Therapeutics. 17*(3), 252-262. https://doi.org/10.5863/1551-6776-17.3.252

	11 Questions	Yes	Can't Tell	No
1	Did the trial address a clearly focused issue?	x		
2	Was the assignment of patients to treatments randomized?	x		
3	Were all the patients who entered the trial properly accounted for at its conclusion?	x		
4	Were patients, health workers, and study personnel 'blind' to treatment?			x
5	Were the groups similar at the start of the trial?	x		
6	Aside from the experimental interventions, were the groups treated equally?	x		
7	Were the effects of intervention reported comprehensively?	x		
8	Was the precision of the estimate of the treatment effect reported?	x		
9	Can the results be applied in your context? (Or to the local population?)	x		
10	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	x		
11	Are the benefits worth the harms and costs?	x		