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Abstract

This review examines the use of intravenous dexmedetomidine in the role of decreasing or preventing emergence delirium in pediatric patients undergoing ambulatory surgery. The included randomized controlled trials evaluated the administration of dexmedetomidine, whether as a bolus, infusion, or in combination, and its effectiveness in preventing or reducing emergence delirium. The analysis scales for emergence delirium varied between studies, and it was noted that multiple scale components overlapped with pain scale components used in the trials. It has also been noted that differentiating between pain and emergence delirium can be challenging for clinicians (Somaini, Engelhardt, Fumagalli & Ingelmo, 2016). To address this challenge, both the prevalence of pain and emergence delirium were assessed. Variations between studies included the administration of premedication, surgical procedure performed, and other pharmacological agents administered during the perioperative period. Eleven of the twelve trials demonstrated that dexmedetomidine decreased the incidence of emergence delirium when compared to the use of a placebo and eight studies reported decreased pain scores. Thus, it can be suggested that dexmedetomidine is an adequate pharmacological option to help prevent the incidence of emergence delirium and pain, regardless of whether the two outcomes are tied together. However, it is imperative that further research be performed to establish the most effective time during the perioperative period dexmedetomidine should be administered. In addition, further research must be performed to establish a dose that allows for the prevention of emergence delirium, but not at an expense of the increased discharge time.

Introduction

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that results in decreased norepinephrine release and ultimately provides sedative and analgesic effects without causing respiratory depression (Nagelhout & Plaus, 2014). The onset of intravenous dexmedetomidine is 5 to 10 minutes, with a peak effect of 15 to 20 minutes and a duration, which is dose dependent, of 60 to 120 minutes. Once within the blood stream, it is metabolized by the hepatic system and excreted by the kidneys. Dexmedetomidine is used in multiple clinical settings, some of which include the intensive care unit for sedation or in the operating room for conscious sedation. Over the recent years, researchers have investigated the role of dexmedetomidine in the prevention of emergence delirium (ED) in pediatric patients. The care of pediatric patients requires the anesthetist to consider different aspects of their care than those when caring for adults in the operating room; one of these considerations is that children are more likely to experience ED than their adult counterparts (Lerman, 2017). Therefore, it is important that the anesthetist is aware of the current literature surrounding the prevalence of ED and the options available to treat the phenomenon.

ED, also called emergence agitation or excitation, has been described as "a mental disturbance that consists of confusion, hallucinations, and delusions manifested by inconsolable crying, disorientation, nonpurposeful restlessness, involuntary physical activity, and thrashing about in bed" (Mukherjee et al., 2015, p. 24). It has also been named as a component of early-postoperative negative behavior (e-PONB) (Somaini et al., 2016). Pain is the other component of e-PONB. When considering these two components, there is always a possibility that they may overlap in presentation or that they may be independent of each other. This information has

promoted the study of dexmedetomidine in the prevention of ED as it provides both sedative and analgesic qualities, which may help to alleviate one or both components of e-PONB.

The incidence of ED has been linked to several risk factors. Pain, as mentioned, is one component of e-PONB and is a risk factor for ED (da Silva, Braz and Módolo, 2008). Patients who present with ED do not always undergo a procedure that involves pain and, therefore, any pediatric patients undergoing anesthesia should be considered at risk for ED. Age has also been determined a risk factor. Lerman (2017) isolates two to six years of age, otherwise known as "preschool-aged" children, where 30 to 50 percent of patients in this age group will experience ED. Overall, it has been found that the incidence of ED decreases with an increase in age. Da Silva, Braz and Módolo (2008) explain "the cause of the increased incidence in this group appears to be that their emotional lability is exacerbated when faced with a stressful situation in an unfamiliar environment" (p.108). The authors also explain that children who are anxious and impulsive as well as less sociable are at increased risk for ED. Therefore, clinicians should have a heightened awareness when caring for patients in this age group and to prepare for the possibility of ED.

Parental presence is a commonly discussed topic when addressing pediatric anesthesia. According to Da Silva, Braz and Módolo (2008), there has not been any proven connection between parental presence with induction of anesthesia and the prevention of ED. However, it was found that patients who experienced a "traumatic separation from their parents on the way to the operating room" (p. 109) had increased negative postoperative behavior, including an increase in the incidence of ED. Therefore, the authors suggest parental presence remains intact as it may facilitate a smoother transition and create a safer environment for the child.

Another risk factor discussed is the anesthetic regimen chosen. Inhalational anesthetics,

including sevoflurane, desflurane, and isoflurane, have been found to have a higher incidence of ED than the use of intravenous anesthetics such as propofol. The mechanism for this has not been established at this time. Interestingly, the length of exposure to these anesthetics does not increase or decrease the incidence of ED (Lerman, 2017). At this time, inhalational anesthetics are commonly chosen as the anesthetic of choice and, therefore, discussing medications that can attenuate or decrease the incidence of ED is important.

Certain long-term effects of ED are still under investigation. However, it is important that the anesthetist recognizes those that have been well established. ED can cause parental anxiety and, therefore, can reduce parental satisfaction (Somaini et al., 2016). Also, research suggests the potential for altered behavioral patterns 30 days postoperatively in the pediatric population. Short-term effects of ED are often obvious and distressing for the patients, caregivers and clinicians. Research has shown that in the short-term period ED can cause injury to the patient and unintentional removal of intravenous catheters. Somaini et al. (2016) also state accidental removal of "drainages, or dressing and may require extra nursing care, additional time in recovery room, and supplemental sedatives or analgesic drugs" (p. 378). Thus, ED is an important part of postoperative management that clinicians should address and aim to prevent.

The anesthetist must also consider that pediatric patients undergoing ambulatory surgery are discharged on the day of surgery. This results in a postoperative recovery period in the hospital that is shorter than those patients who are admitted. Parents must feel confident taking their child home, and an occurrence of ED may make this process challenging. Additionally, children undergoing ambulatory surgery who experience ED may require additional pharmacological intervention that could delay discharge (Sato, Shirakami, Tazuke-Nishimura, Matsuura, Tanimoto & Fukuda, 2010). Sato et al. explain that clinicians should "try to prevent

ED in order to provide efficient and high-quality care that is a positive experience for patients and their parents" (p. 675). Clearly, a smooth recovery that is satisfactory to the patient, their family, and the clinician is important after ambulatory surgery. Research thus far has suggested that dexmedetomidine may be helpful in reducing ED and, therefore, the use of dexmedetomidine in pediatric patients undergoing ambulatory surgery to reduce the incidence of ED will be examined.

Methods

A total of twelve randomized controlled trials were chosen that were obtained from Pubmed, SpringerLink, ScienceDirect and MEDLINE databases. Studies were excluded that included patients undergoing surgical procedures that were not ambulatory surgeries. The keywords used to for the search included the following: "dexmedetomidine", "emergence delirium", "ambulatory surgery" and "pediatrics". If patients did stay overnight in the hospital, but the surgical procedure was one that could be performed in an ambulatory setting, it was still included. Patient ages ranged from less than a year to fourteen years of age with an average age of 3.7 years. The only route of dexmedetomidine administration was intravenous, all studies that included intranasal or oral dexmedetomidine were excluded.

Once the twelve articles were chosen, the incidence of ED was assessed. Another measure examined in the randomized controlled trials was the incidence of pain in the postoperative period. As mentioned, Somaini et al. (2016) state that although pain and ED are assessed on different scales, there are overlapping clinical components of the scales used. ED was examined using different scales throughout the randomized controlled trials. Seven of the twelve studies used the Pediatric Anesthesia Emergence Delirium (PAED) scale and three of these seven also used a modification of the 4-point scale. The 4-point scale, overall, includes

assessment of agitation ranging from calm to combative, excited or disoriented (Sato et al., 2010). In comparison, the PAED scale assesses eye contact, purposefulness of actions, awareness, consolability and restlessness. The other five studies used only a modification of the 4 point-scale. Pain was assessed using the children and infants postoperative pain scale (CHIPPS), the face, leg activity, cry, consolability (FLACC) scale, the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and the visual analog scale (VAS).

Literature Review

Multiple different study models were used throughout the 12 studies, but all were reproducible, well controlled trials conducted in ambulatory surgical patients. The articles will be reviewed dependent upon the time dexmedetomidine was administered in the perioperative period. The studied three periods of administration are immediately after the induction of anesthesia, during the maintenance of anesthesia or during the emergence of anesthesia.

Six of the twelve randomized controlled trials administered dexmedetomidine within the anesthesia induction time frame. All studies, with the exception of the study by Bong, Lim, Allen, Choo, Siow, Teo and Tan (2014), demonstrated that dexmedetomidine resulted in a decreased incidence of ED. In the double-blinded randomized controlled trial performed by Sato et al. (2010), 81 children, ages 1-9, were compared in two different groups: one received intravenous dexmedetomidine 0.3mcg/kg over 10 minutes after induction and another received a placebo. The surgical procedures performed were of comparative length, acetaminophen or diclofenac was given for pain control, and the inhaled agent sevoflurane was used as the main anesthetic. The four-point assessment tool was used to identify ED. The authors found that there was a significant reduction in ED in those that received dexmedetomidine. Pain scores, using the

CHIPPS, were also found to be significantly lower in the dexmedetomidine group.

Similar results were found in the study performed by Asaad, Hafez, Mohamed and El-Mahgoup (2011), where 90 patients, ages 5-10, undergoing inguinal hernia, hydrocele or circumcision procedures less than 60 minutes in duration, were randomly assigned into three different groups. One group received intravenous fentanyl 1mcg/kg, another received intravenous dexmedetomidine 0.15mcg/kg and the last received intravenous saline after the induction of anesthesia. Sevoflurane was used as the main anesthetic and a caudal block was used for pain control. The study also used the four-point scale for the assessment of ED and the CHIPPS for pain. The results demonstrated that the incidence of postoperative ED in the dexmedetomidine and fentanyl groups decreased significantly when compared to the saline group. The dexmedetomidine group was also found to have a significant reduction in pain scores when compared to a placebo. There was, however, not a significant difference between the use of dexmedetomidine and fentanyl.

Contrary to what Assad et al. (2011) concluded, a study by Patel et al. (2010) found that dexmedetomidine was superior to fentanyl in decreasing the incidence of ED. The study compared 122 patients, 2-10 years of age, undergoing tonsillectomy and adenoidectomy procedures. Sevoflurane was used as the main anesthetic and acetaminophen was given for pain control. A major difference between the two studies was the timing and dosage of dexmedetomidine. In the study by Patel et al., the dexmedetomidine group was given a bolus dose of dexmedetomidine 2mcg/kg after induction, which was followed by an infusion of 0.7mcg/kg/hr until five minutes before the end of surgery. The fentanyl group received fentanyl 1mcg/kg during induction. From that point on, both groups received fentanyl boluses to maintain pain control throughout the procedure with use of a strict protocol. When compared to the

fentanyl group it was found that the incidence of ED and the opioid requirement was significantly reduced in the dexmedetomidine group. Interestingly, the initial dosage of fentanyl was the same in both the study by Patel et al. and the study by Assad et al., thus demonstrating that a larger bolus dose of dexmedetomidine, followed by an infusion, may be more effective in reducing the incidence of ED and improving pain control.

The incidence of ED was assessed using both the Cole 5-point scale and the PAED scale (Patel et al., 2010). The authors discuss the validity of the PAED scale, stating that although it is "the only validated rating scale for emergence delirium" (2010, p. 1009), it had to be modified and cross referenced with the Cole 5-point scale. The authors justified this by explaining that the PAED scale rates children, that are still asleep under anesthesia, with higher numbers due to their inability to make eye contact and lack of purposeful movement. Therefore, in conjunction with the PAED scale, the authors used the 5-point Cole scale to ensure their results did not become skewed from modifying the PAED scale to fit sleeping patients.

Lili, Jianjun and Haiyan (2012) conducted a study that also examined the effect of dexmedetomidine on the incidence of ED by providing a bolus dose at the start of the intraoperative period. Of note, in comparison to the dose given by the previous studies discussed, the dose was larger at 0.5mcg/kg over 10 minutes. All patients underwent vitreoretinal surgery and received sevoflurane as the main anesthetic. Pain scores were not provided or discussed in the study. Using a variation of a PAED scale, which closely resembles a four-point scale, the incidence of ED was significantly diminished in the dexmedetomidine group.

He, Wang, Zheng and Shi (2013) also found similar results by providing a larger dose of dexmedetomidine during the beginning of the intraoperative period. This was similar to the study Lili et al. (2012) performed, where the control group received saline and the dexmedetomidine

group received dexmedetomidine 0.5mcg/kg at induction. However, He et al. had an additional dexmedetomidine group, which received dexmedetomidine 1mcg/kg at induction. Thus, through their study there was a direct comparison of two different dexmedetomidine doses with a control saline group. The study included 87 patients, ages 3-7, undergoing procedures less than 60 minutes in length with sevoflurane as the main anesthetic. The study found that in comparison to the control group, dexmedetomidine in both groups significantly reduced the incidence of ED, but when comparing the dexmedetomidine dose of 0.5mcg/kg to 1mcg/kg there was no significant difference. Therefore, the study concluded that dexmedetomidine can be effective independent of the dose in the range of 0.5-1mcg/kg. Pain control for the procedure was provided with regional and local anesthesia in all groups and no difference between pain scores was observed.

Another study that supports the use of dexmedetomidine in the prevention of ED, given in the beginning of the intraoperative period, was performed by Song et al. (2016). In the study there was one control group and three intravenous dexmedetomidine groups that received three different doses: 0.25mcg/kg, 0.5mcg/kg or 1mcg/kg, over 10 minutes during induction. Pain was assessed using the FLACC scale. The study demonstrated significant pain score reduction in the patients receiving dexmedetomidine 0.5mcg/kg and 1mcg/kg. The incidence of ED was assessed with a 4-point scale and a PAED scale, which found that dexmedetomidine decreased the incidence of ED in all the groups receiving it, but more so at a dose of 1mcg/kg in comparison to the other doses. This study suggests that an increased dose of dexmedetomidine yields a dose-dependent decrease in the incidence of ED. This contradicts the result found by He et al. (2013), which found that there was not a dose-dependent decrease in the incidence of ED with dexmedetomidine.

In contradiction to the results discussed thus far, the study by Bong et al. (2014) found that dexmedetomidine did not reduce the incidence of ED when compared to a placebo and propofol. The study examined 120 patients, ages 2-7, undergoing magnetic resonance imaging (MRI) procedures. The dexmedetomidine group received dexmedetomidine 0.3mcg/kg after the induction of anesthesia, which was compared with two other groups, one which received 1mg/kg of propofol prior to emerging from anesthesia and another that received saline as a control group. Pain was not a factor in this study because a MRI procedure does not result in postoperative surgical pain. It was found that both dexmedetomidine and propofol did not reduce the incidence of ED using the PAED scale. The results presented oppose those found in the study by Sato et al. (2010), where both studies used the same dose for procedures that were similar in length. Comparatively, Sato et al. used a 4-point grading scale, whereas Bong et al. used the PAED scale, which may explain the variance in results.

The studies discussed above administered a bolus of intravenous dexmedetomidine during or just after the induction of anesthesia. As mentioned, the study by Patel et al. (2010), demonstrated a decrease in ED with a bolus dose of dexmedetomidine during the induction of anesthesia that was followed by an infusion throughout the intraoperative period. Three more studies included in this literature review administered dexmedetomidine comparably and all were found to have a decrease in the incidence of ED. One of these studies was performed by Chen, Jai, Liu, Quin and Li (2013), which examined 78 patients, ages 3-7, undergoing strabismus surgery. In this study there were three different groups and all received sevoflurane as the main anesthetic. One group received a bolus of dexmedetomidine 1mcg/kg followed by an infusion of 1mcg/kg/hr, another group received ketamine 1mg/kg followed by an infusion of 1mg/kg/hr, and the last received saline as a control group. Using the PAED scale, it was concluded that both the

administration of dexmedetomidine and ketamine reduced the incidence of ED. Using the

CHEOPS, pain incidence was also significantly lower in both the ketamine and

dexmedetomidine groups when compared to the placebo group. However, there was no

significant difference seen between the administration of ketamine or dexmedetomidine in the

incidence of pain or ED.

Another study that administered dexmedetomidine similarly to Patel et al. (2010) was

conducted by Kim, Kim, Yoon and Kil (2014), which had two different study groups consisting

of 40 patients, 1-5 years of age, undergoing ambulatory orchiopexy or hernioplasty surgery. One

group received saline and the other received a dexmedetomidine 0.1mcg/kg bolus over 10

minutes, followed by an infusion of 0.1mcg/kg/hr until the end of surgery. Sevoflurane was used

as the main anesthetic. Using a four-point scale to assess the incidence of ED, the authors found

that dexmedetomidine decreased the incidence of ED significantly without delaying the patient's

discharge from the hospital. Also, using the CHEOPS, pain scores were significantly lower 30

minutes postoperatively, but otherwise were comparable. That being said, all patients received a

caudal block for pain control, which could explain why pain scores were not significantly lower

overall.

In support, Meng et al. (2012) found comparable results, but included 120 patients, 5-14

years of age in their study, which was an older population than any other study in this literature

review. Also in deviation from the majority of the other studies examined, all subjects in the

study received midazolam preoperatively. The average age was 7-8 years, a four-point scale was

used to assess the incidence of ED, and the VAS was used to measure pain incidence. There

were three study groups: one that received saline, another that received dexmedetomidine

0.5mcg/kg followed by an infusion of 0.2mcg/kg/hr, and the last that received dexmedetomidine

1mcg/kg followed by an infusion of 0.4mcg/kg/hr. VAS scores were significantly decreased in both of the groups receiving dexmedetomidine in a dose-dependent fashion, meaning those in the dexmedetomidine group with the higher dose had lower pain scores up until 10 minutes after extubation. It was found that the higher dose dexmedetomidine group, when compared with the placebo group, had a reduced incidence of ED only at the time of extubation. Aside from this brief period, there was no significant difference between the placebo and the study groups that received dexmedetomidine.

Another time dexmedetomidine can be administered in the perioperative period is prior to the emergence from anesthesia. Ali and Abdellatif (2013) performed a study on 120 patients, 2-6 years of age undergoing adenotonsillectomy. Sevoflurane was used as the main anesthetic and a four-point scale was used to assess the incidence of ED. In the study, one group received dexmedetomidine 0.3mcg/kg, the second received propofol 1mg/kg and the third received saline, all 5 minutes before the end of surgery. Similarly, to the study by Meng et al. (2012), all patients were given midazolam preoperatively. It was found that dexmedetomidine was significantly more effective in decreasing the incidence and severity of ED, whereas propofol showed no significant difference when compared to the saline group. Pain was measured using the CHEOPS and it was found that pain was significantly reduced in the dexmedetomidine group compared to those in the propofol and the placebo group as well.

An additional study that administered dexmedetomidine during the end of the intraoperative period was performed by Makkar, Bhatia, Bala, Dwivedi and Singh (2015). The study included 110 patients, 2-8 years of age, undergoing a surgical procedure less than 60 minutes in length. Desflurane, another type of inhalational anesthetic, was used. Patients either received dexmedetomidine 0.3mcg/kg 15 minutes before the end or surgery or propofol 1mg/kg

5 minutes prior to the end of surgery. Pain control was provided with a caudal block. With the use of the PAED scale, it was found that dexmedetomidine significantly reduced the incidence of ED. Propofol also helped to decrease the incidence of ED, but not as extensively as dexmedetomidine. It was also found that dexmedetomidine and propofol significantly increased sedation in the postoperative period, demonstrating that with an increased emergence time the incidence of ED decreases.

Discussion

The literature reviewed concluded that in eleven of the twelve randomized controlled trials, dexmedetomidine significantly reduced the incidence of ED compared to a placebo. This is important as it allows clinicians to make an evidenced-based decision to administer dexmedetomidine in the prevention of ED. As mentioned, dexmedetomidine has many benefits as it provides analgesia and sedation without causing respiratory depression. In light of these findings, the studies also revealed important characteristics of dexmedetomidine administration that the clinician must consider when giving the medication. First, it has been shown to have a biphasic effect on blood pressure (BP), which manifests with an initial increase in BP and then a subsequent decrease in both BP and heart rate (Song et al., 2016). Kim et al (2014) note that "the most common hemodynamic effects of dexmedetomidine are bradycardia and hypotension, which are attributed to central α_2-agonist properties" (p. 214). Multiple studies did affirm this conclusion, but all hemodynamic effects were within normal parameters, meaning within 20 percent of the patient's baseline, and did not require pharmacologic intervention. Nevertheless, Kim et al. do advise caution to the clinician administering dexmedetomidine because of the possibility of hemodynamic changes. Given this information, it is vital that the clinician always considers the hemodynamic status of each patient prior to dexmedetomidine administration.

A second point of caution to consider prior to the administration of dexmedetomidine is the functional status of a patient's hepatic system. dexmedetomidine undergoes hepatic metabolism using N-methylation, N-glucuronidation and the CYP2A6 enzyme (Lerman, 2017). If a child has liver impairment and cannot adequately metabolize dexmedetomidine, the duration of action may be significantly prolonged. In this scenario, the administration of dexmedetomidine must be questioned as a delayed discharge could result from the increased duration of action.

Sedation in the postoperative period, even in the patient with adequate liver function, can be observed after the administration of dexmedetomidine. This effect is not unexpected as one of the uses of dexmedetomidine administration is for sedation (Lerman, 2017). Therefore, a clinician must ask himself or herself whether the administration of dexmedetomidine could prolong the time to awakening and increase the length of stay. This is important to address as the purpose of ambulatory surgery is to discharge the patient as soon as safely possible. Therefore, the length of stay after dexmedetomidine administration was examined to provide clinicians with this vital information. All studies included did examine the time it took for the sedation from dexmedetomidine to diminish in the operating room and/or the PACU. It was found that the majority of the studies, with the exception of the study by Lili et al. (2012), did have an increase in the sedation period after the end of the surgery. These studies also found that there was a significantly lower incidence of ED in these groups. With this information, one could draw the comparison between an increased emergence time and the decreased incidence of ED. Interestingly, this coincides with the evidence presented by Makkar et al. (2015), which stated that a prolonged emergence time had an inverse relationship with the incidence of ED.

To further support this, Bong et al. (2015), which was the only study that concluded dexmedetomidine did not reduce the incidence of ED, supports the idea that increased emergence

time decreases ED. The authors state, "the only predictor of emergence delirium was a short time to regain consciousness whereby, for every additional minute of wake-up time, the odds of emergence delirium were reduced by 7%" (p. 399). With this information the clinician can conclude that, the sedative effects that cause a slower wakeup may not be a negative as it could reduce the incidence of ED.

As mentioned above, discharge time from the hospital is important in ambulatory surgery. Of the included studies, nine evaluated discharge time from the PACU. Eight of the nine studies did not find any significant prolongation in PACU stay. Chen et al. (2013) was the only study that found an increase in PACU stay, which could be a result of the dosing used in the study. The study was only one of three studies, out of the 12 studies, that administered a bolus of dexmedetomidine, followed by an infusion. The infusion of dexmedetomidine was 1mcg/kg/hr, which was higher than the other two groups that ran infusions throughout the case. Due to the fact that there is not an established dose or time of dexmedetomidine administration that will decrease the incidence of ED, the above information could suggest that possibly a smaller dose for an infusion could allow for faster PACU discharge. This is not able to be determined, though, by the presented research and will require further exploration. However, the information does suggest an inverse relationship between the incidence of ED and the initial wake-up time after the discontinuation of anesthesia.

In addition to the use of dexmedetomidine, a multitude of studies have been published assessing different pharmacological options in the prevention of ED. One of the medications that has been suggested to prevent ED is fentanyl. Fentanyl is an opioid, which works by binding to opioid receptors, including the Mu, Kappa and Delta receptors (Nagelhout & Plaus, 2014). This binding causes a decrease in the release of neurotransmitters and inhibits the transmission of pain

signals. As mentioned, pain has been established as a component of e-PONB and Lerman (2017) points out that fentanyl provides analgesic qualities and has been found to decrease the incidence of ED in some studies.

In the literature reviewed, two of the 12 studies compared the use of dexmedetomidine with fentanyl. As mentioned, the study by Patel et al. (2010) demonstrated that dexmedetomidine significantly lowered the incidence of ED and required less postoperative pain rescue management when compared to fentanyl. In contrast, Assad et al. (2010) found that there was no significant difference in the incidence of ED between the fentanyl and DEX groups, but that patients in the fentanyl group had significantly less pain postoperatively than those in the dexmedetomidine group. The study by Patel et al. provided a higher dose of dexmedetomidine than the study by Assad et al., which could have provided less sedation and pain control and yielded to the equivalent ED prevention between the fentanyl and dexmedetomidine groups.

Another medication compared with the use of dexmedetomidine was propofol. Propofol works on the gamma-aminobutyric acid receptor, which when bound causes an influx of chloride ions, hyperpolarizing the cell and ultimately causing sedation by inhibiting neuronal transmission (Nagelhout & Plaus, 2014). Propofol has been found to reduce the incidence of ED (Lerman, 2017). That being said, the studies that compared the use of propofol and dexmedetomidine in the presented literature demonstrate conflicting results. First off, Ali and Abdellatif (2013) found that propofol and dexmedetomidine decreased the incidence of ED when compared to a placebo, but that overall dexmedetomidine provided the greatest reduction in the incidence of ED. In addition, Makkar et al. (2015) found that dexmedetomidine decreased the incidence of ED more when compared to propofol and a placebo. Propofol did, however, provide a decrease in the incidence of ED when compared to the placebo. Bong et al. (2015) found conflicting results with

these two studies, concluding that neither propofol nor dexmedetomidine provided a significant decrease in the incidence of ED when compared to a placebo.

Further research will need to be performed to directly compare the use of propofol and dexmedetomidine in the reduction of ED, but the two studies discussed do suggest that dexmedetomidine is superior to propofol for this purpose. Another medication examined was Ketamine in the study performed by Chen et al. (2013). Ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist, which causes dissociative anesthesia and analgesia (Nagelhout & Plaus, 2014). It was found that ketamine and dexmedetomidine equally reduced the incidence of ED and pain scores. According to Lerman (2017) ketamine has been shown in multiple studies, either as a bolus or infusion, to be effective in reducing the incidence of ED. Interestingly, propofol is the only medication compared with the use of dexmedetomidine that does not have any analgesic qualities. Further research will be needed to conclude whether complete prevention of pain is necessary to completely prevent ED, but from the discussed comparisons, it appears it is a major component.

Limitations

The reviewed literature presented multiple limitations that will need to be addressed in the future to strengthen this body of evidence. One is that anesthetic regimens were not identical throughout all the randomized controlled trials. For example, two of the twelve studies, performed by Meng et al. (2012) and Ali et al. (2013), preoperatively administered the anxiolytic medication midazolam. Nevertheless, the results paralleled the majority of the other studies reviewed by concluding that they did support the use of dexmedetomidine in the prevention of ED. Another variance among studies was that two inhalation anesthetic agents, desflurane and sevoflurane, were used as the main anesthetic. According to Lerman (2017), the incidence of ED

is similar with the use of sevoflurane, desflurane and isoflurane. Therefore, it is unknown at this time how these factors impact the discussed results and, in turn, prevent concluding if the use of one inhalation agent over the other is more effective.

Along with different pharmacological regimens used for the anesthesia provided, the patient ages also varied throughout the literature reviewed. The ages ranged from less than 1 year to 14 years old, and 10 of the 12 studies had average patient ages less of than 5 years. As mentioned, ED has been found to have the highest incidence in preschool-aged children and the incidence decreases with an increase in age (Lerman, 2017). It may be suggested, then, that future research should focus on preschool aged children. However, children go through major cognitive, social and perceptual changes during years of development, such as the development of time orientation and the ability to focus (Malarbi, Stargatt, Howard and Davidson, 2011). Therefore, the range of ages in the literature reviewed may be considered a strength as not all children are at the same cognitive, social and intellectual levels. Thereby, providing a large patient age range demonstrates that dexmedetomidine could work for children throughout different stages of development.

Ambulatory surgery was the concentration of the reviewed literature, but within that umbrella the type of surgical procedure, surgeon, operating room and recovery room staff as well as the facility itself varied between the randomized controlled trials. This causes difficulty when comparing the literature as compensation for these variances is not possible. The types of surgery performed in the literature included strabismus and vitreoretinal surgeries, tonsillectomies and adenoidectomies, MRI procedures, hernia repairs and many more elective ambulatory procedures. Most procedures were performed in under an hour or less, but it is obvious that each one yields different postoperative recovery considerations. Expected pain postoperatively is one

major difference between the procedures performed. It is clear that an MRI procedure itself does not cause pain, whereas a tonsillectomy does cause significant postoperative pain. Therefore, each procedure will require different pain medications and the choice of these medications can change the postoperative course. For example, opioids may have been used for a tonsillectomy and can cause respiratory depression and sedation. In comparison, hernia repair patients could have received a caudal block and, therefore, do not require any opioids that could cause postoperative sedation and impact the incidence of ED. This is one example that demonstrates how the procedure performed requires different postoperative medication, which could vary the incidence of ED and create challenges when comparing the included literature.

Along with the pharmacological variances required throughout the procedures, it is also vital to mention the impact postoperative pain has on the incidence of ED. As mentioned, postoperative pain and agitation are the two components of PONB (Somaini et al., 2016). Therefore, differentiating between the two in regards to the causative factor of ED is critical. In patients receiving a caudal block or those undergoing a MRI procedure, the incidence of pain is negated. Therefore, one must recognize that pain does not always need to be present for ED to occur. As multiple studies have suggested, including the study by Sato et al., inhalational agents have been linked as a causative factor for ED and patients receiving these must always be considered at risk for ED (2010).

It has also been found that certain procedures result in an increased incidence of ED. For example, otorhinolaryngological procedures, such as tonsillectomies and adenoidectomies, have an increased incidence of ED (da Silva, Braz, and Módolo, 2008). In addition to the variation between procedure types, the facilities and staff varied between the randomized controlled trials. It is unknown what the environment was in the operating room or PACU during the emergence

of anesthesia for the study participants. However, it is suggested that waking the child in a non-stimulating, silent environment without physical or emotional stimulation may be helpful in reducing the incidence of ED. It is unknown whether the studies that determined dexmedetomidine administration decreased the incidence of ED provided a non-stimulating environment and, therefore, make it not possible to compare that aspect of the research.

Another weakness that is important to mention is that varying scales to assess ED and pain were used in the studies. The use of different scales creates a discrepancy when attempting to compare the incidence of ED, calling for further studies to be performed with the use of a validated, consistent scale to allow for complete comparison between studies. Creation of the PAED scale occurred after the use of the four-point scale in hopes of constructing a more accurate assessment tool. Somaini et al. (2016) point out that the PAED scale is the only validated scale that is used. However, according to Malarbi et al. (2011), validity issues still exist. This includes a high-false positive rate and that the components of the scale can be confused with pain, hunger and distress.

In conjunction, Makkar et al. (2015) also point out that a sedated patient can receive a high PAED score. This would be because points are given to patients who have a lack of eye contact, purposeless actions or unawareness. If a patient has not fully awoken from their sedated state, or falls asleep after emerging from anesthesia, they will display these characteristics. Clearly, a clinician would be aware of this, but the scale does not compensate for the fact that a clinician can differentiate between a sleeping or sedated patient versus a patient who is actively awake and experiencing these characteristics of ED. The authors point out that to be able to accurately assess ED using the PAED scale, one must also assess sedation using a validated scale and exclude those patients that are determined to be sedated. Only Makkar et al. used a sedation scale

to compare to the PAED scale used, therefore calling into question whether patients in other included studies were sedated, received a high PAED score and were categorized as having ED. This explanation demonstrates the problems with the use of different scales and again, demands the need for a solidified, validated scale that addresses the issues discussed.

Conclusion

As previously mentioned, the included randomized controlled trials administered dexmedetomidine at different times and at different doses throughout the intraoperative period. This creates a discrepancy when comparing the literature, but with that being said, all studies except for one demonstrated that dexmedetomidine decreased the incidence of ED when compared to a controlled placebo. Therefore, it does demonstrate that dexmedetomidine is effective in decreasing the incidence of ED. At this time in clinical practice, it is at the discretion of the clinician to evaluate each patient and procedure to decide upon a dose and time for dexmedetomidine administration. To support the clinician and to allow for complete evidenced-based practice, further research will be required to establish when and how much dexmedetomidine should be administered to be most effective. Furthermore, it will be important for additional research to determine to what extent pain has on the incidence of ED, which could be accomplished by the creation of new analysis scales that incorporate, but also differentiate, the characteristics of sedation, pain and ED.

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