Pediatric Anesthesia and Critical Care Journal 2020;8(2):120-128
doi:10.14587/paccj.2020.19

PACCJ

The effect of dexmedetomidine nebulization as a premedication prior to peripheral intravenous access in pediatric patients and its effect on separation anxiety score and acceptance to intravenous cannulation score

D. M. Bonagua, H. C. Crisostomo, A. G. C. Hernandez, S. E. Brodit

Department of Anesthesiology, St. Luke's College of Medicine, St. Luke's Medical Center, Quezon City, Philippines

Corresponding author: A. G. C. Hernandez, Department of Anesthesiology, St. Luke's College of Medicine, St. Luke's Medical Center, Quezon City, Philippines. Email: agchernandez@stlukes.com.ph

Keypoints

In pediatric anesthesia practice, ease of venous cannulation and parental separation of children from their parents prior to anesthesia remain as an everyday challenge. Inhalation of nebulized Dexmedetomidine (2mcg/kg) is an alternative method of premedication that is relatively easy to set up, non-invasive, produces satisfactory sedative effects, offers an acceptable premedication experience, and less likely to be associated with peri-operative adverse events.

Abstract

Introduction

Sedation in pediatric patients is one of the many challenges in anesthesia practice. Premedication helps facilitate smooth separation from the parents and ease the induction of anesthesia. Dexmedetomidine is a selective α-2 adrenoceptor agonist that provides sedation, anxiolysis and analgesic effects without causing respiratory depression.

Nebulized dexmedetomidine application is a relatively non-invasive, convenient and easy route of administration that is well-tolerated by pediatric patients. Previous studies have established that intranasal dexmedetomidine effectively produced sedation, improved cooperation during invasive procedures such as intravenous cannulation and ameliorated separation anxiety in children with a dose range of 1-2 mcg/kg.

This study was designed to evaluate the effect of dexmedetomidine nebulization as a premedication prior to peripheral intravenous access in pediatric patients and its effect on ease of separation from the parent and acceptance of intravenous cannulation.

Materials and Methods

A total of 52 children, aged 2 to 6 years and American Society of Anesthesiologists' (ASA) physical status classification of I–II, scheduled for elective outpatient diagnostic procedure were randomly allocated to receive either nebulized dexmedetomidine 2mcg/kg (Experimental group) or no interventional premedication (Control group). Sedation state was evaluated every 15 minutes after premedication and behavioral state was assessed during separation from their parents and peripheral intravenous cannulation. The primary endpoint was the acceptance of the venous cannulation and physical separation from the parent.

Results

Both groups were comparable with respect to demographic data (age, gender and comorbidities), weight, duration of procedure and duration of anesthesia. Vital signs were maintained within the normal range in both the groups during the whole peri-operative period, with no

significant statistical difference between the two groups Intravenous cannulation acceptance was statistically significant between the groups, and was satisfactory in 18 patients (69.2%) in the experimental group but only in 6 patients (23.1%) in the control group. Likewise, ease of parental separation was statistically significant between the groups, and was satisfactory in 20 patients (76.9%) in the Experimental group and in 13 patients (50.0%) in Control group.

Conclusion

The use of nebulized dexmedetomidine (2mcg/kg) produces satisfactory sedative effects that facilitate ease of successful intravenous cannulation, ease of children separation from their parents, and is less likely to be associated with perioperative adverse events.

Keywords

Dexmedetomidine, nebulized premedication, pediatric, intravenous cannulation, separation

Introduction

Sedation in pediatric patients is one of the many challenges in anesthesia practice. For any child undergoing a procedure, the preoperative period is the most distressing;[1] especially upon induction of anesthesia.[2] Children may become overly uncooperative at the time of separation from parents, venipuncture, or mask application. Untreated anxiety can lead to difficult induction, increased postoperative pain, greater analgesic requirements, emergence agitation and even postoperative psychological effects and behavioral issues. Despite the many advances in nonpharmacologic interventions, practitioners still rely on sedative premedicants.[3]

The primary goal of premedication in children is anxiolysis, which helps facilitate smooth separation from the parents and ease the induction of anesthesia. Other effects that may be achieved by premedication include amnesia, prevention of physiologic stress, vagolysis, reduction in total anesthetic requirements, decreased probability of aspiration, decreased salivation and secretions, anti-emesis and analgesia.[2] Ideal premedication attributes include prompt onset of action, short duration, simple route of administration that is readily accepted by children, minimal side effects, reliable pain relief, and regulation of autonomic responses.[4]

To date, there is no widely-accepted standard regimen or an ideal route of administration for premedication in children.[2,4] Sedative premedication in children is commonly administered via the oral, rectal, sublingual, and intranasal routes with varying degrees of patient acceptance.[1] Parenteral routes are generally avoided unless an access has previously been sited. Oral administration is well-accepted but has low bioavailability. Rectal administration often causes pain, could lead to expulsion in young children and might not be appropriate for older children. An intramuscular approach is not recommended for children because it is invasive and painful. A more effective route for premedication is transmucosal, including intranasal, sublingual and buccal administration due to the high vascularisation of mucosa and its ability to bypass first-pass metabolism. In young children, compliance with nasal sedation may be more easily attained than oral sedation. The sensation of burning and nasal irritation is a disadvantage of the nasal route, and sneezing or coughing caused by the nasal irritation could reduce the effects of nasal premedication.[2] Inhalation of nebulized drug is an alternative method of administration that is relatively easy to set up, does not require venipuncture, and is associated with high bioavailability of the administered drug.[1]

The use of sedation and analgesia are not without adverse effects as anesthetic agents affect the central nervous and cardiorespiratory systems in a dose-related manner. Midazolam, which causes sedation, anxiolysis and amnesia, is one of the most frequently used premedicants. It has additional beneficial properties, such as anticonvulsant activity, rapid onset and a short duration of action and it reduces postoperative vomiting. However, it is far from an ideal premedicant due to its undesirable effects, which include restlessness, paradoxical reactions, cognitive impairment, postoperative behavioral changes and respiratory depression. Ketamine is another popular premedicant that causes dissociative anesthesia and it has both

sedative and analgesic properties. However, its side effects, such as excessive salivation, nausea and vomiting, nystagmus, hallucination and postoperative psychological disturbances have limited its use. In this regard, dexmedetomidine is unique as it is a highly selective α-2 adrenoceptor agonist that provides sedation, anxiolysis and analgesic effects without causing respiratory depression. Recently, it has been explored extensively in the pediatric population.[3] It has been shown to provide effective sedation in uncooperative children when used as a premedicant prior to anesthetic induction.[5] Additional clinically relevant benefits include reducing the need for rescue analgesia, reducing emergence agitation, postoperative nausea and vomiting and shivering in the postoperative period.[2]

Intranasal dexmedetomidine application is a relatively non-invasive, convenient and easy route of administration.[6] Aside from being easily absorbed through the nasal mucosa, intranasal dexmedetomidine is well-tolerated by pediatric patients due to its lack of taste or pungency. Previous studies have established that intranasal dexmedetomidine effectively produced sedation, improved cooperation during invasive procedures such as intravenous cannulation and ameliorated separation anxiety in children with a dose range of 1-2 mcg/kg not associated with any untoward side-effects. Onset time of sedation was noted to range from 25 to 45 minutes with a median duration of sedative effect of 55 to 100 minutes.[4,6,7] Other published studies using intranasal dexmedetomidine included outcome measures such as sedation score, separation score, ease of induction, face mask acceptance score, hemodynamic changes, analgesia, emergence behavior and adverse events.[1,4-9,11-16] A meta-analysis has provided evidence that intranasal dexmedetomidine provides more satisfactory sedation at parent separation than other intranasal (midazolam, clonidine, ketamine) or oral premedicants (midazolam) with reduced nasal irritation compared with midazolam.[2]

Intranasal administration thru nebulization seems to be a viable route for sedative medication, as it gives tolerable experiences. There will be less mucosal irritation, coughing episodes, hoarseness, and nasal discomfort. As mentioned from previous studies, utilization of atomized spray results in greater diffusion with minimal amount of the drug, less drug loss to the nasopharyngeal area, greater cerebrospinal fluid concentration, better patient tolerability, acceptability, improved clinical effectiveness and satisfaction. Nebulization of dexmedetomidine allows rapid drug absorption as evidenced by bioavailability of 65% through nasal mucosa and 82% through buccal mucosa.[10] A recent study found that children premedicated with inhaled nebulized dexmedetomidine (2 mcg/kg) had more satisfactory sedation scores, higher acceptance of the mask and shorter recovery times than those who received nebulized ketamine (2 mg/kg) or midazolam (0.2 mg/kg). Dexmedetomidine premedication also lowered the incidence of postoperative agitation.[2]

Materials and Methods

This prospective randomized single blind controlled study was approved by the Institutional Ethics Review Committee of St. Luke's Medical Center, Quezon City, Philippines. With a thorough pre-anesthetic evaluation at least a day before the procedure and written informed consent from the parents or legal guardians, pediatric patients scheduled for elective outpatient diagnostic procedures were recruited. Eligible participants were between ages 2 to 6 years old with an American Society of Anesthesiologists' status of I–II. Exclusion criteria were as follows: weight>25kg, BMI>30, known allergy to dexmedetomidine, presence of otorhinological diseases, children with major respiratory and cardiac diseases and procedures lasting more than 1.5 hours. Patients were randomly divided into two equal groups using computer-generated allocation: nebulized dexmedetomidine group (Experimental group) and the no intervention group (Control group). For the experimental group, the primary investigator prepared the dexmedetomidine nebulization (ND) based on weight (2mcg/kg), and diluted in a standardized volume of 0.04mL/kg of normal saline solution in a 3mL syringe. After the first recording of blood

pressure, oxygen saturation and heart rate, the ND solution was administered by the primary investigator. Intravenous cannulation was then attempted on the 30th minute after nebulization under the observance of a data gatherer. For the control group, there was no intervention of ND. All ND materials were concealed from the field of view of the data gatherer essentially blinding the former as to whether the patient under study was given ND or not. The blinded data gatherer then assessed the ease of venous cannulation and parental separation anxiety using four-point behavior scales (Table 1). An Intravenous Cannula Acceptance Scale score of 3 or 4 was classified as an acceptable ease of venous cannulation, whereas scores of 1 or 2 were considered unsatisfactory acceptance of venous cannulation. A Parent Separation Anxiety Scale score of 3 or 4 was classified as an acceptable separation, whereas scores of 1 or 2 were considered difficult separations from the parents.

Table 1. Behavior Scoring Scale

Score	Intravenous (IV) Cannula Acceptance Scale	Parent Separation Anxiety Scale
1	Poor (Terrified and clinging)	Poor (Crying and clinging)
2	Fair (Fear of needle and not assured)	Fair (Crying but not clinging)
3	Good (Slight fear of needle, easily assured)	Good (Whimpers, easily reassured)
4	Excellent (Unafraid, accepts IV cannula readily)	Excellent (Easy separation)

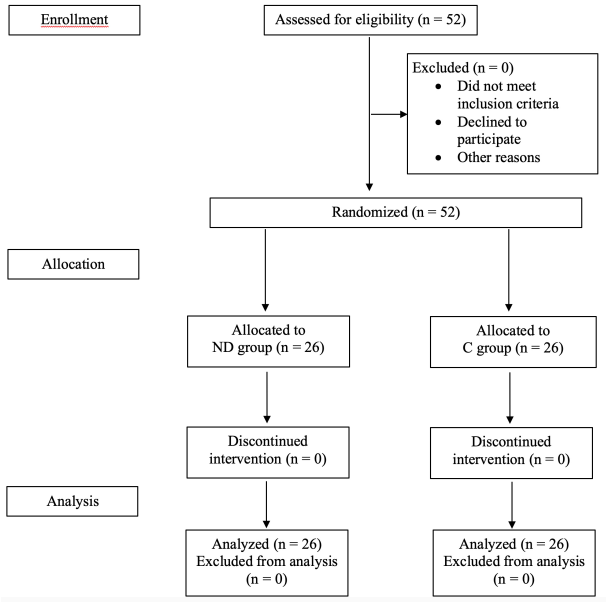
Hemodynamic parameters were recorded by the attending anesthesiologist during the entire process at 15-minute intervals. Development of any drug-induced adverse events such as hypotension, bradycardia, oxygen desaturation, dyspnea or allergic reactions, were monitored. In the scenario wherein an adverse event does occur, emergency medications and materials for cardiorespiratory supportive treatment were prepared and readily available for emergent use. After the diagnostic procedure, the patient was continuously monitored at the post-anesthesia care unit. Outpatient post-anesthetic discharge instructions were given by the anesthesiologist and the contact details of both anesthesiologist and the primary investigator were also given for any concerns related to the anesthesia procedure and research study.

The main outcome measures were the proportion of patient with satisfactory intravenous cannula acceptance scores (scores of 3 or 4 in the Intravenous Cannula Acceptance Scale) and the proportion of patients with satisfactory separation anxiety scores (scores 3 or 4 in the Parent Separation Anxiety Scale). Secondary outcome measures were the mean and standard deviation values of the blood pressure, heart rate and oxygen saturation perioperatively. Sample size calculation was based on the assumption that 59.4% of the treatment group (Experimental group) and 21.9% of the no intervention group (Control group) will achieve satisfactory separation scores, the sample size per group at 80% power and 95% confidence level is 26, or a total of 52. A total of 52 subjects were then enrolled in this study. Raw data were coded, entered and analyzed using the Statistical Package for the Social Sciences (SPSS) software. Descriptive statistics such as percentages, ratios, proportions, means and standard deviation were utilized to objectively illustrate research findings. Chi-Square test and T-test were used for intergroup comparison of categorical and continuous data. The P value at < 0.05 level was used as a reference value to determine statistical significance of the measured outcome scoring.

Results

A total of 52 eligible patients completed the study and were subsequently allocated to 2 groups: the nebulized dexmedetomidine group (Experimental group) and the no intervention group (Control group). All enrolled participants completed the study and were included in the final statistical analyses (Figure 1).

Figure 1. Consort flow diagram



Both groups were comparable with respect to demographic data (age, gender and comorbidities; Table 2).

Table 2. Demographic data

	Experimental Group (n = 26)	Control Group (n = 26)	*P* Value
	n (%)	n (%)	
Age			
2	6 (23.1%)	8 (30.8%)	
3	4 (15.4%)	3 (11.5%)	
4	3 (11.5%)	3 (11.5%)	0.835
5	8 (30.8%)	5 (19.2%)	
6	5 (19.2%)	7 (26.9%)	
Gender			
Male	18 (69.2%)	16 (61.5%)	0.560
Female	8 (30.8%)	10 (38.5%)	
Comorbidities			
Seizure Disorder	5 (19.2%)	2 (7.7%)	0.223
Bronchial Asthma	8 (30.8%)	3 (11.5%)	0.090
G6PD Deficiency	1 (3.8%)	0 (0.0%)	0.313
Lymphoma	0 (0.0%)	1 (3.8%)	0.313
Leukemia	1 (3.8%)	4 (15.4%)	0.158

Mean weight, duration of procedure and duration of anesthesia were comparable as well in both groups (Table 3).

Table 3. Comparison of mean weight, duration of procedure and duration of anesthesia

	Experimental Group (n = 26)	Control Group (n = 26)	*P* Value
	Mean ± SD	Mean ± SD	
Weight	17.69 ± 4.24	18.26 ± 5.9	0.69
Duration of Procedure	28.62 ± 20.86	23.08 ± 17.94	0.309
Duration of Anesthesia	35.77 ± 22.83	27.73 ± 19.89	0.182

There was no statistically significant difference between the two groups with respect to baseline and subsequent readings of systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation at 15-minute intervals (Table 4). Blood pressure, heart rate and oxygen saturation were maintained within the normal range in both the groups during the whole perioperative period.

Intravenous cannulation acceptance and ease of parental separation for both groups are summarized in Table 5. Intravenous cannulation acceptance was statistically significant between the groups, and was satisfactory in 18 patients (69.2%) in the experimental group but only in 6 patients (23.1%) in the control group. Likewise, ease of parental separation was statistically significant between the groups, and was satisfactory in 20 patients (76.9%) in the experimental group and in 13 patients (50.0%) in the control group.

Table 4. Vital signs at different time points

	Experimental Group (n = 26)	Control Group (n = 26)	*P* Value
	Mean ± SD	Mean ± SD	
Systolic Blood Pressure			
Baseline	110.96 ± 10.89	108.69 ± 13.05	0.535
15 minutes	101.23 ± 9.89	100.65 ± 8.93	0.737
30 minutes	100.84 ± 8.11	99.96 ± 10.29	0.227
45 minutes	97.83 ± 8.51	99.75 ± 11.19	0.609
Diastolic Blood Pressure			
Baseline	69.81 ± 11.86	67.54 ±9.05	0.230
15 minutes	63.81 ± 9.54	59.58 ± 8.28	0.680
30 minutes	62.92 ± 7.83	58.32 ± 7.52	0.968
45 minutes	58.83 ± 7.16	56.83 ± 4.90	0.706
Heart Rate			
Baseline	112.31 ± 19.29	109.58 ± 16.74	0.596
15 minutes	108.92 ± 20.22	109.08 ± 17.02	0.357
30 minutes	109.92 ± 20.05	108.40 ± 18.29	0.812
45 minutes	106.83 ± 20.10	108.00 ± 17.86	0.955
Oxygen Saturation			
Baseline	99.62 ± 0.57	99.58 ± 0.47	0.081
15 minutes	99.85 ± 0.37	99.92 ± 0.27	0.085
30 minutes	99.84 ± 0.37	99.92 ± 0.28	0.084
45 minutes	99.83 ± 0.39	99.92 ± 0.29	0.234

Table 5. Number of patients with satisfactory intravenous cannula acceptance and parental separation

	Experimental Group (n = 26)	Control Group (n = 26)	*P* Value
	n (%)	n (%)	
IV Cannula Acceptance Score			
Satisfactory	18 (69.2%)	6 (23.1%)	0.003
Unsatisfactory	8 (30.8%)	20 (76.9%)	
Parental Separation Anxiety Score			
Satisfactory	20 (76.9%)	13 (50.0%)	0.018
Unsatisfactory	6 (23.1%)	13 (50.0%)	

Discussion

An optimal and standardized pre-induction sedation for children remains an elusive goal. A combative and anxious child in the perioperative period is stressful both for

anesthesiologists, caregivers and parents. The manifestation of anxiety may differ in different children and may convey their preoperative anxiety verbally, behaviorally, subtly, or explicitly which makes the induction of anesthesia difficult.[8] Preoperative anxiety in preschool children is particularly distressing.[1] Children in this age group appear to be at highest risk for developing anxiety because those younger are less likely to experience anxiety due to ready acceptance of parental surrogates and response to reassurances like soothing voices, gentle rocking and being held. Older children have relatively more awareness and simple explanations of the procedures that they will undergo and participation in the preparation for induction are usually effective in reducing anxiety.[2,8] Premedication is usually done for pediatric patients to reduce preoperative separation anxiety and postoperative psychological trauma, to help the patient undergo smooth induction of anesthesia, and to ensure perioperative safety.[4] In pediatric population group, ease of venous cannulation and parental separation remain as a challenge for the everyday practice of an anesthesiologist. Sedative agents and their route of delivery have variable efficacy, tolerability, acceptance and safety. Different pharmacological and behavioral interventions have been suggested but no technique or pharmacological agent has been completely satisfactory in this special age group. Selecting the route of sedative drug administration in preschool children is an important task. Different routes of administration have been tried (e.g. intravenous, oral, buccal, rectal and intranasal), with each route having its own advantages and disadvantages. The inhalation route used in this study may offer an alternative mode of administration of sedative premedication that is relatively easy to set up, and does not require an intravenous access or parenteral injection, but is still associated with high bioavailability of the administered drug due to drug absorption occurring directly into the central circulation and bypassing the enterohepatic circulation.[8] We similarly found that the nebulization technique was simple and very convenient for the patients included in this trial. In this study, nebulized dexmedetomidine, an α-2 receptor agonist, at 2 mcg/kg was used. The mechanism of action of dexmedetomidine is unique. The presynaptic activation of α-2A adrenoceptor in the locus ceruleus inhibits the release of norepinephrine and results in the sedative and hypnotic effects. In addition, the stimulation of α-2 adrenoceptors in the descending medullospinal noradrenergic pathway terminates the propagation of pain signals, leading to analgesia. The postsynaptic activation of α-2 receptors in the central nervous system results in a decrease in sympathetic activity, leading to hypotension and bradycardia. At the spinal cord, the stimulation of α-2 receptors at the substantia gelatinosa of the dorsal horn leads to the inhibition of the firing of nociceptive neurons and the inhibition of release of substance P. Also, α-2 adrenoceptors located at the nerve endings play a possible role in the analgesic mechanism by preventing norepinephrine release. The spinal mechanism is the principal mechanism for the analgesic action of dexmedetomidine even though there is clear evidence for both supraspinal and peripheral sites of action. In the peripheral sites, alpha-2 receptors on blood vessels mediate vasoconstriction and inhibit norepinephrine release on sympathetic nerve terminals.[12] In this study, the effect of nebulized dexmedetomidine as a premedicant was assessed mainly by intravenous cannula acceptance and parental separation acceptance scores. Results showed that 69.2% (n=18) of children in the experimental group exhibited satisfactory acceptance of intravenous cannulation as compared to only 23.1% (n=6) in the control group, while 76.9% (n=20) of children in the experimental group exhibited satisfactory acceptance of parental separation as compared to 50% (n=13) in the control group. These results demonstrate that children premedicated with inhaled nebulized dexmedetomidine (2mcg/kg) had more satisfactory intravenous cannulation acceptance and parental separation scores compared with no interventional premedication. Similar results were demonstrated by a randomized trial by Gyanesh et al[13], who compared intranasal dexmedetomidine (1 mcg/kg), ketamine (5 mg/kg), and placebo

(saline) in 150 children between 1 and 10 years undergoing IV placement to facilitate propofol administration for a magnetic resonance imaging. Fewer children in the 2 treatment groups withdrew or fought against IV placement than in the control group ($P < 0.01$), with dexmedetomidine and ketamine premedication being equally efficacious in this regard. The anesthesiologist was satisfied with the cannulating conditions in 90.4% of the dexmedetomidine patients, 82.7% of the ketamine patients, and 21.7% of the control patients. Similarly, a meta-analysis by Peng et al[3] revealed that more children had satisfactory intravenous cannulation following treatment with dexmedetomidine (RD=-0.48, 95% CI: -0.92 to -0.04, p=0.03) versus placebo. However, this analysis was significantly influenced by heterogeneity (I^2=91%). A randomised, double-blind study by Abdel-Ghaffar et al[1] showed similar results as well when they compared nebulized ketamine 2 mg/kg (Group K), dexmedetomidine 2 mcg/kg (Group D), and midazolam 0.2 mg/kg (Group M) as premedication in children aged 3 to 7 years undergoing bone marrow biopsy. Subjects in Group D showed higher medication (P<0.03) and mask acceptance scores (P<0.015) and more satisfactory parental separation anxiety scale (P<0.044). Ambi et al[5] also had similar results when they compared the acceptance behavior of 100 children aged 1 to 12 years who received intranasal dexmedetomidine (1 mcg/kg) prior to the time of parental separation. In their study, significantly more children from the interventional group achieved satisfactory sedation compared to those receiving placebo (62% vs 14.3% respectively, $p < 0.001$). Rajalakshmi et al[12], who evaluated the effects of intranasal dexmedetomidine as a premedicant in pediatric patients undergoing cardiac surgeries, also had similar results. They found that the parent separation score (P value of 0.001) and intravenous cannula acceptance score (P value of less than 0.001) were significant and therefore, on comparison, shows the dexmedetomidine group to have a better sedation, parent separation and intravenous cannula acceptance score compared to the control group who received intranasal saline.

Weerink et al[14] stated that the time of sedation onset for intranasal 1–4 mcg/kg dexmedetomidine was approximately 15 to 45 minutes in healthy volunteers and children, with significant sedation observed for 1 to 2 hours and an elimination half-life of 2.1 to 3.1 hours. In this study, the dose of nebulized dexmedetomidine used was 2 mcg/kg. Similarly Abdel-Ghaffar et al[1] compared the efficacy of nebulized dexmedetomidine at 2 mcg/kg as a sedative premedication administered by nebulizer prior to induction of general anaesthesia in preschool children undergoing bone marrow biopsy and aspiration, and compared it with nebulized ketamine 2mg/kg and nebulized midazolam at 0.2mg/kg. Their study concluded that preschool children premedicated with nebulized dexmedetomidine had more satisfactory sedation, shorter recovery time, and less postoperative agitation than those who received nebulized ketamine or midazolam. Talon et al[15] also used intranasal dexmedetomidine at 2 mcg/kg and compared it with oral midazolam (0.5 mg/kg) as a premedicant in burn children undergoing reconstructive surgery. Their study was carried out on 100 patients and the drug was administered 30 to 45 minutes before induction. They observed that at this dose, dexmedetomidine was more effective than oral midazolam at inducing sleep preoperatively. Yuen et al[6] showed that the onset of action between 1 and 1.5 mcg/kg of intranasal dexmedetomidine was 45 minutes in their study. The crossover trials by Yuen et al[7] evaluated the potential role of intranasal dexmedetomidine as premedication before induction of anesthesia. They described significant sedation occurring at 45 to 60 minutes after intranasal dexmedetomidine (1 to 1.5 mcg/kg) with a peak sedative effect after approximately 90 to 105 minutes. Patterned from these studies, venous cannulation and physical separation from the parent was attempted 30 to 45 minutes after the nebulized dexmedetomidine administration.

Plambech and Afshari[16] showed that hypotension and bradycardia are the most common adverse events

associated with dexmedetomidine and that respiration is only slightly affected. In a similar trend, Rajalakshmi et al[17] found no statistically significant difference between the control group and the nebulized (dexmedetomidine 2 mcg/kg) group with respect to baseline readings of heart rate (P = 0.839), systolic blood pressure (P = 0.132), diastolic blood pressure (P = 0.879) and mean arterial pressure (P = 0.378). However, there was a gradual reduction in heart rate in the dexmedetomidine group, which was statistically significant from the 30th minute until the 45th minute; compared to minimal changes in heart rate in the placebo group throughout the study period. There was also a statistically significant decrease in systolic blood pressure, diastolic blood pressure and mean arterial pressure from the 30th minute until the 45th minute in the dexmedetomidine group when compared with the placebo group. There was no difference between the groups with respect to the respiratory rate and oxygen saturation. Upon comparing nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication in pediatric patient, Zanaty et al[11] found that heart rate and mean arterial pressure values at 30 minutes after administration of premedication were significantly lower in the dexmedetomidine group compared with baseline values. On the other hand, the ketamine and combination groups showed no significant differences between baseline heart rate and mean arterial pressure values and values at 30minutes after administration of nebulization. There were no significant differences in respiration and oxygen saturation values between the 3 groups at 30 minutes after administration of nebulization or during the entire observation period. No patients in the ketamine and combination groups developed hemodynamic instability whereas 2 patients in the dexmedetomidine group developed significant postoperative hypotension and bradycardia.

In contrast, the results of this study showed no statistically significant difference between the experimental and control groups with respect to baseline and subsequent readings of systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation at 15-minute intervals (Table 4). Blood pressure, heart rate and oxygen saturation were maintained within the normal range in both the groups during the whole perioperative period. Bhat et al[8], who used intranasal dexmedetomidine 1 mcg/kg, also showed similar results wherein heart rate and oxygen saturation were maintained in the normal range in both the groups. No episodes of oxygen desaturation, hypotension, and bradycardia were also noted in both groups throughout the trial.

A potential weakness of the study is the choice of scoring system to assess the patients' cooperation. Although this system has been used in several published studies[1,4,7-8,17], it has not been formally validated, and the inter-rater variability has not been established.

Conclusion

In summary, the use of nebulized dexmedetomidine (2mcg/kg) produces sedative effects that facilitate ease of successful intravenous cannulation, ease of children separation from their parents, and is less likely to be associated with peri-operative adverse events. This premedication alternative is thus a reasonable option for use in clinical practice. The nebulized route for premedication in children is underutilized and and further drug combinations and dose finding studies are needed.

References

1. Abdel-Ghaffar H, Kamal S, Sherif F, Mohamed S. Comparison of nebulized dexmedetomidine, ketamine, or midazolam for premedication in preschool children undergoing bone marrow biopsy. Br J Anaesth. 2018; 121(2): 445-452.
2. Dave NM. Premedication and induction of anaesthesia in paediatric patients. Indian J Anaesth 2019;63:713-20.
3. Peng K, Wu S, Li J. Premedication with dexmedetomidine in pediatric patients: a systematic review and meta-analysis. Clinics. 2014 Nov; 69(11): 777-786.

4. Qiao H, Xie Z, Jia J. Pediatric premedication: a double-blind randomized trial of dexmedetomidine or ketamine alone versus a combination of dexmedetomidine and ketamine. BMC Anesthesiol. 2017 Nov; 17:158
5. Ambi U, Joshi C, Ganeshnavar A, Adarsh ES. Intranasal dexmedetomidine for paediatric sedation for diagnostic magnetic resonance imaging studies. Indian J Anaesth. 2012 Nov-Dec; 56(6): 587–588.
6. Yuen V, Hui T, Irwin M, Yao T, Wong G, Yuen M. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. Anaesthesia. 2010 Aug; 65(9): 922-929.
7. Wu X, Hang L, Wang H, Saho D, Xu Y, Cui W, Chen Z. Intranasally administered adjunctive dexmedetomidine reduces perioperative anesthetic requirements in general anesthesia. Yonsei Med J. 2016 Jul 1; 57(4): 998-1005.
8. Bhat R, Santhosh M, Annigeri V, Rao R. Comparison of intranasal dexmedetomidine and dexmedetomidine-ketamine for premedication in pediatrics patients: A randomized double-blind study. Anesth Essays Res. 2016 May-Aug; 10(2): 349-355.
9. Yuen V, Irwin M, Hui T, Yuen M, Lee L. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Anesth Analg. 2007 Aug; 105(2): 374-380.
10. Mason KP and Lerman J. Review article: Dexmedetomidine in children: current knowledge and future applications. Anesth Analg. 2011 Nov; 113(5):1129-42.
11. Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg. 2015 July; 121(1):167-71.
12. Rajalakshmi J, Lokesh Kumar KS. A study to evaluate the effects of intranasal dexmedetomidine as a premedicant in paediatric patients undergoing cardiac surgeries. Egypt J Cardiothorac Anesth 2015;9:17-22
13. Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial. J Anesth. 2014;28:12–8.
14. Weerink M, Struys M, Hannivoort L, Barends C, Absalom A, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017; 56(8): 893-913.
15. Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res 2009; 30:599-605.
16. Plambech, M.Z. and Afshari, A. Dexmedetomidine in the pediatric population: a review. Minerva Anestesiol. 2015; 81: 320–332
17. Rajalakshmi J, Kumar K. A study to evaluate the effects of intranasal dexmedetomidine as a premedicant in paediatric patients undergoing cardiac surgeries. Egypt J Cardiothorac Anesth. 2015; 9(2): 12-22.