A COMPARATIVE STUDY OF INTRAMUSCULAR KETAMINE AND A COMBINATION OF INTRAMUSCULAR DEXMEDETOMIDINE AND KETAMINE AS PREMEDICATION IN PAEDIATRIC ANESTHESIA

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ABSTRACT

Introduction

Preoperative anxiety is an issue of concern in paediatric anaesthesia practice. Forceful transfer of children into the operating room can cause long-term psychological trauma. This clinical study compares intramuscular ketamine and a combination of intramuscular dexmedetomidine and ketamine as anaesthetic premedicants in terms of +anxiolysis, sedation and ease of IV cannulation.

Objectives

To compare the level of preoperative anxiety, sedation and ease of cannulation following premedication between intramuscular ketamine and a combination of intramuscular dexmedetomidine and ketamine.

Methodology

Total of 60 patients belonging to American Society of Anaesthesiologists physical status I-II, in the age group of two to ten years, scheduled for elective surgery under general anaesthesia were included in the study; Group A patients received ketamine 3mg/kg body weight while Group B patients received ketamine 2mg/kg body weight and dexmedetomidine 1mcg/kg body weight intramuscular. The outcome variables were sedation score (Richmond Agitation Sedation Scale), IV cannula acceptance (IV cannula Acceptance Score), and parental separation (Separation Score).

Result

The groups were comparable in patient characteristics and hemodynamic parameters between the groups. Median (IQR) sedation score at 10 min were -1 (-2—0) and 0(-1—1) ($p< 0.001$); mean parental separation scores were 3.76± 0.43 and 3.36±0.55 ($p< 0.001$); IV cannula acceptance score were 3.73±0.44 and 4.53±7.27 ($p= 0.001$) in Group A and Group B respectively.

Conclusion

Combination of dexmedetomidine and ketamine is superior to ketamine alone in terms of sedation at 15 min and ease of IV cannulation but comparable in terms of anxiolysis.

KEY WORDS

Cannulation; Dexmedetomidine; Ketamine; Sedation.

INTRODUCTION

Relieving pre and postoperative anxiety is an important concern for a paediatric anaesthesiologist. Anxiety can lead to distress and makes the control of postoperative pain difficult.[1] Forced induction of anaesthesia may cause personality and behavioral changes in children.[2] Various routes of drug administration are available for premedication. Oral and sublingual preparations are painless, but are slow in onset, have poor bioavailability, and can be spitted out. Rectal preparations can be uncomfortable. Whereas, nasal preparations can be irritating to the patient.[3] Intravenous (IV) administration is painful and incites fear of subsequent contact with healthcare professionals.[4] Intramuscular (IM) medications cause slight pain at the injection site, however easy administration, good bioavailability, and not requiring intravenous access make it a fair option for premedication in a resource-constrained setting. Among various options for intramuscular use, ketamine is an established premedicant. The primary mechanism of action of ketamine appears to be through its NMDA receptor antagonism on the central nervous system (CNS, and spinal cord). Ketamine produces a 'dissociative' anaesthetic state.[5]

Dexmedetomidine is a relatively new selective alpha-2 adrenoceptor agonist and it provides sedation and anxiolysis via receptors within the locus ceruleus and analgesia via receptors in the spinal cord. It is devoid of respiratory depressant effect rendering it potentially useful for anaesthetic premedication.[1] Dexmedetomidine however, as a sole sedative agent has not been uniformly successful for invasive procedures. To overcome some of the pitfalls with dexmedetomidine as the sole agent, its combination with ketamine has been tried.[6]

This study was undertaken to evaluate pre-operative sedative effect, anxiety level changes, ease of child—parent separation of preoperative intramuscular ketamine compared with intramuscular combination of ketamine and dexmedetomidine in children scheduled for surgery under general anaesthesia.

METHODOLOGY

This clinical comparative study was conducted in the elective theatre of BPKIHS, Dharan over the duration of one year from 2017 to 2018.

Ethical approval of this study was obtained from the BPKIHS Institutional Review Committee (IRC no: IRC/1369/018) and informed written consent for the procedure was obtained from the parents of all the eligible patients and assent from the patients whenever possible. Every patient had the right to withdraw from the study at any time.

Children with ASA physical status I and II, aged 2-10 years undergoing elective surgery under general anaesthesia were included. Children with history of allergy or hypersensitivity reaction to dexmedetomidine or ketamine and atropine, children with cardiac arrhythmia, congenital heart disease, active upper respiratory tract infection within 2 weeks, known lung disease or airway abnormalities, seizure disorder and mental retardation were excluded. In addition, children under medications that could provoke seizures, cause hypotension and bradycardia were also excluded from the study.

All together, sixty children were involved 30 children in group A and 30 in group B. Group A children received 3mg/kg ketamine and Group B children received combination of 2mg/kg undiluted ketamine and 1mcg/kg undiluted dexmedetomidine intramuscularly 20 minutes prior to planned induction of anaesthesia via 26 G needle into the gluteal muscle.

All eligible children were evaluated and their parents explained about the nature of the study during preanaesthetic evaluation in the evening prior to the day of the surgery. Informed written consent was obtained. The children were kept nil per oral according to standard paediatric fasting guidelines and premedication was omitted. Baseline systolic and diastolic blood pressure together with heart rate was recorded on the same day in respective wards where the child was admitted. On the day of surgery in the preoperative holding area, each child was assessed for level of sedation using Richmond Sedation Scale, by the investigator responsible for observing the outcome. The baseline pulse rate, oxygen saturation (Spo_2) were noted, and the study solution was administered. Pulse and Spo_2 and the preoperative sedation score was evaluated every 5 min after the study drug was given till induction of anaesthesia. Separation from the parent was evaluated by the separation score described by Venham LL, Gaulin-Kremer E, Munster E, Bengston-Audia D, Cohan J. 7. Availability of oxygen, suction apparatus, self-inflating resuscitation bag, mask, equipment for intubation and drugs for resuscitation were ensured at all times. After observing for 20 min in the preoperative holding area, the child was brought into the operation theatre for induction of anaesthesia and patient monitor was attached. HR, SBP, DBP, MAP and Spo_2 was recorded at 1 min, 3 min and 5 min after induction. Then every 5 min until the end of surgery.

Intravenous cannulation was performed before the induction of anaesthesia in children with satisfactory acceptance score. A four-point evaluation system was used to evaluate the acceptance of the intravenous cannula8. An acceptance score of 3 or 4 was taken as satisfactory. Anaesthesia in children with inadequate sedation was induced inhalationally with sevoflurane in oxygen and their peripheral access was secured by expert hands. After securing the peripheral venous access, injection glycopyrrolate 4mcg/kg was administered IV in all patients. In children accepting intravenous cannulation, induction of anaesthesia was achieved with intravenous bolus of injection propofol 2-4mg/kg and fentanyl 2mcg/kg. After achieving adequate depth of anaesthesia, an appropriately sized laryngeal mask airway (LMA) was inserted using standard technique. Anaesthesia was maintained with 1.0-2.0 MAC end-tidal concentration of sevoflurane in 100% oxygen and intravenous bolus of fentanyl was administered for analgesia as required. Hydration was provided with lactated Ringer's solution was used based on hourly fluid requirements, deficits caused by restriction of food and

fluids, third-space losses according to the surgical procedure. On completion of the surgery, sevoflurane was discontinued and LMA was removed. The requirement of propofol for induction, fentanyl for maintaining analgesia and percentage of sevoflurane required for maintenance was noted. Hypotension was defined as a decrease of systolic blood pressure of more than 20% from the baseline readings and was treated with intravenous fluid bolus of 10ml/kg. Similarly, bradycardia was defined as HR less than 20% of the baseline readings and was treated with IV glycopyrrolate 4mcg/kg. Any complication was managed with the standard hospital protocol. The child was then transferred to the recovery room, where a nurse monitored the child for any complications. Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, whereas vomiting was defined as the forceful expulsion of gastric contents from the mouth.

The main outcome variables were sedation score (Richmond Agitation Sedation Scale), IV cannula acceptance (IV cannula Acceptance Score), and parental separation (Separation Score).

Secondary outcome variables were hemodynamic response during induction; incidence of hypotension and bradycardia; post-operative nausea, vomiting and shivering.

The sample size estimation was based on a previous study 9 which showed 85% patients being adequately sedated in the combination group(intranasal ketamine and dexmedetomidine) and 66% in the other group(ketamine). With a power of 80%, alpha value 0.05 and the percentage of children sedated in each group was taken in consideration and sample size of 23 was calculated to be 23 for each group. To account for the possible drop outs and correct bias the sample size was rounded off at 30 and 30 patients were taken in either group. Proportion, percentage, mean, median, S.D., and interquartile range were calculated for descriptive analysis. Chi-square and independent t-test were applied depending on the data type.

RESULT

All 60 patients completed the study. The demographic parameters including age, sex, height, and weight of the patients in both the groups were statistically comparable.

Table 1: Comparison of minor characteristics between the two groups

Variable		Group A (n=30)	Group B (n=30)	p -Value
Gender	Male	19	17	0.792
	Female	11	13	
Age (years) (Mean ± S.D.)		5.00±2.30	5.26±2.25	0.546
Weight (k.g.) (Mean ± S.D.)		24.81 ±7.46	24±7.30	0.789
A.S.A. I		30	30	-

The anxiety level between the two groups was comparable before the administration of premedication (p = 0.447). After premedication, there was no significant difference in the anxiety level between the two groups except at 0 min after premedication.[1]

Table 1: Age and Gender distribution (Range 4-80 years)

	Timing	RAAS				p-value
		Group A (n=30)		Group B (n=30)		
		Mean ± S.D	Median (IQR)	Mean± S.D	Median (IQR)	
	Baseline	0.77 ± 0.63	1(0—2)	0.63 ± 0.71	1(0-2)	0.447
After premedication	0 min	1.17 ± 0.46	1(0—2)	1.20 ± 0.40	1(0-2)	0.768
	5 min	0.77 ± 0.50	1(0—2)	0.63 ± 0.49	1(0-2)	0.303
	10 min	-1.17 ±0.46	-1(-2—0)	-0.27 ± 0.45	0(-1-1)	<0.001
	15min	-1.17 ± 0.79	-1(-2—1)	-1.43 ± 0.63	-1(-2-1)	0.153
	20 min	-2.3 ± 0.54	-2(-2—0)	-2.47 ± 0.51	-2(-3-0)	0.221

IV cannula acceptance score was significantly higher in Group A compared to group B (p= 0.001). However, the separation score was significantly higher in group B (p= 0.007).

Table 3: Comparison of canula acceptance score among the two groups

	Group A (n=30)		Group B (n=30)		P value
	Mean	S.D.	Mean	S.D.	
IV Cannula acceptance score	3.6	0.49	3.2	0.40	0.001*
Seperation Score	3.36	0.56	3.73	0.40	0.007*

The heart rates at all the other observation points were statistically comparable among the groups (p> 0.05). The baseline mean systolic blood pressure was comparable between the two groups (p> 0.05). However, after induction the systolic blood pressure was significantly higher in group A patients at 1 min, 10 min and 15 min. The mean systolic pressure was comparable at 5 min after induction (p> 0.05). Similarly, mean diastolic blood pressure at 1min and 3 min after induction was significantly higher in group A than in group B (p 0.05). Thereafter, the mean diastolic pressure was comparable between the groups (p> 0.05). MAP was significantly higher in group A than in group B (p= 0.04) 3 min post induction of anaesthesia. Average mean arterial pressure was comparable between the two groups (p> 0.05) at all the other points of measurement.

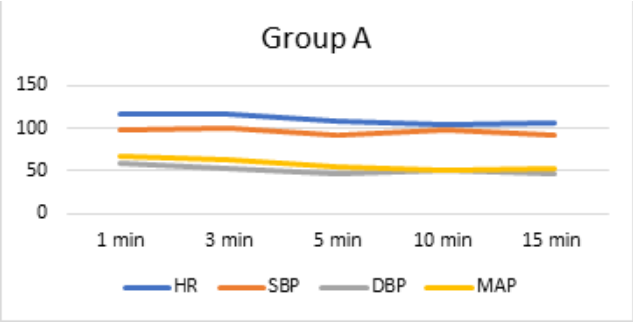
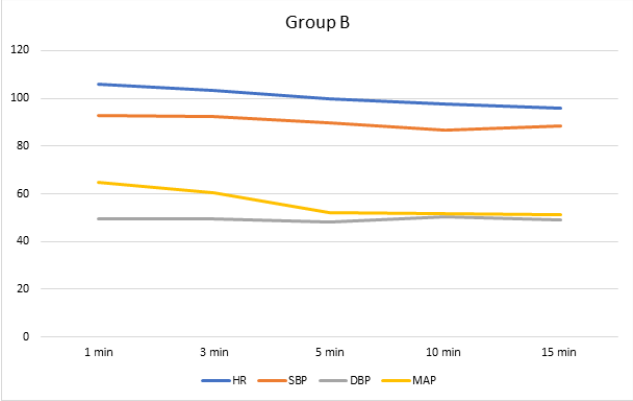


Figure 1: Hemodynamic parameters at different points of measurements noted in Group-A



The mean oxygen saturation values were comparable between the two groups at all time points of measurement ($p>0.05$).

Sevoflurane requirement was significantly reduced in group B as compared to group A and was statistically significant ($p<0.05$) at all time points except 1 min following induction of anaesthesia.

There was no incidence of postoperative nausea and vomiting in any of the groups. Shivering was observed in 2 cases of group A and 2 cases of group B (Table 4)

Table 4: Comparison of adverse events among the groups

Adverse events	Group A	Group B	p-value
Nausea/vomiting	0	0	-
Postoperative Shivering	2	2	1
Any other adverse events	0	0	-

DISCUSSION

The present study did not find any significant difference between the level of sedation in the children undergoing surgery under general anesthesia who received intramuscular ketamine alone. Similar effects, in terms of sedation can be elucidated by the sedative properties of both ketamine as well as dexmedetomidine. However, parental separation was significantly better in the combination group as compared to ketamine alone. Expectedly, ketamine induced delirium could have been attenuated by dexmedetomidine thereby providing a superior parental separation score observed in the combination group. Conversely, anxiolysis in terms of ease of IV cannulation was superior in the ketamine group. This can be construed by the strong analgesic properties of ketamine and a higher dose used in the group.

Previous studies on oral ketamine and intranasal dexmedetomidine have found that the rate of successful venous cannulation was 47%, 68% and 80% with dexmedetomidine, ketamine and the combination groups respectively.[10] The rate of satisfactory parental separation was comparable among the groups. These findings are contrary to the findings of our study where the IV acceptance was better with the ketamine group whereas the combination group had superior outcomes in terms of parental separation. This discrepancy between their findings and ours may also have been as a result of different routes of drug administration and time allowed for premedication.

Yuen VM, Hui TW, Irwin MG, Yuen MK studied intranasal dexmedetomidine in a dose of 0.5 mcg/kg and 1 mcg/kg and oral midazolam 0.5mg/kg for pre-medication in children and concluded that intranasal dexmedetomidine produces more sedation than oral midazolam, but with acceptable cooperation.[1] It is difficult to compare our findings with theirs as we used intramuscular route, a combination of dexmedetomidine and ketamine.

André P Schmidt found that children receiving clonidine or dexmedetomidine preoperatively have similar levels of anxiety and sedation postoperatively as those receiving midazolam on premedication with oral midazolam 0.5mg/kg, oral clonidine 4mcg/kg, or transmucosal dexmedetomidine 1mcg/kg.[11] Our findings are similar to the findings of both the above studies in eliciting the anxiolytic effect of dexmedetomidine. The fact that the time allowed for premedication in our study was significantly less, most likely accounts for the delayed sedation in the combination group of our study.[1,11] Also, we used intramuscular route for premedication, which differs from other routes in terms of bioavailability and further, there are no studies suggesting the equivalent dosing of dexmedetomidine through various routes.

Both intranasal dexmedetomidine and ketamine have been found equally efficacious as a premedicant in children undergoing MRI, with comparable reported anesthesiolgist's satisfaction.[12] It is difficult to compare this study with ours as our study differs from theirs in many respects including use of a different dose and route of drug administration and absence of a placebo group in our study. Further, our study did not compare anesthesiologists' acceptance.

Another study comparing the analgo-sedative effects of oral dexmedetomidine and ketamine reported a delayed onset of sedation with 3mcg/kg and 4mcg/kg of dexmedetomidine relative to ketamine 8mg/kg and 5mcg/kg of dexmedetomidine.[13] Our study differs from this study not only in terms of route of administration but also in dose of the drug used to premedicate the children. Dexmedetomidine alone was not used in our study. Furthermore, we used intramuscular route and a lower dose of the drugs.

Another study reported that a faster sedation with ketamine at 10 min with comparable results at 20 and 30 min respectively.[14] In the study, the effects of intranasal dexmedetomidine 3mcg/kg and ketamine 7 mg/kg was compared for procedural sedation in school aged children undergoing MRI. Again, the route of drug administration and drug dosage used were different from our study. This study used much higher dose of both study drugs as compared to our study. All the above three studies however, found comparable sedation between ketamine and dexmedetomidine, which is similar our own findings.[12,14] We found comparable sedation scores at all time points except at 10 min suggesting a delayed onset of sedation in the combination group. Which is concordant with the findings of Mason KP, Lubisch NB, Robinson F, Roskos R[15] and Ibrahim

M.14 The delayed onset of sedation in our study can be attributed at least partially to the lower dose of dexmedetomidine that we used and also the less time that we allowed for sedation. Though the route of drug administered in their study differed from our study, sedation and anxiolysis were comparable, suggesting intramuscular route being an equally effective alternative for premedication in children in our resource constrained setting where atomisers may not be readily available for intranasal administration of drugs and where securing an intravenous cannula can be difficult and traumatising to a struggling child. Further, there is a paucity of research comparing ketamine and combination of ketamine and dexmedetomidine as pediatric premedicants.

Expectedly, we observed increased heart rate in the children premedicated with only ketamine. In both the groups the heart rate decreased from the baseline and was the least after 20 min of premedication. However, episodes of bradycardia requiring management with atropine were not encountered. This finding is in contrary to the findings of the study by Scheinin H, Jaakola ML, Sjövall S, Ali-Melkkilä T, Kaukinen S, Turunen J. 16 where bradycardia was observed more frequently in dexmedetomidine patients; 20% in those patients who received intramuscular injection of 2.5mcg/kg dexmedetomidine administered 60 min before induction of anesthesia and 33% in those patients who received intramuscular dexmedetomidine 2.5 mcg/kg and intravenous fentanyl 1.5mcg/kg 60 min before induction of anesthesia. Ibrahim[14] also observed bradycardia in two patients premedicated with dexmedetomidine (HR <20% of baseline) but it did not require treatment with atropine. The combination of ketamine with dexmedetomine and use of glycopyrrolate prior to induction of anesthesia may have counteracted the bradycardia caused by dexmedetomidine in our study.

In the same line with our observations, Yuen VM, Hui TW, Irwin MG, Yuen MK[1] also observed significant reduction of heart rate from baseline at 45 and 60 min after administration of dexmedetomidine 0.5mcg/kg and 1mcg/kg which however did not any require treatment.

Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK[12] also found that the heart rate and blood pressure remained similar throughout the procedure and for 3 hr after the completion of MRI in both ketamine and dexmedetomidine group while in the study conducted by Mason KP, Lubisch NB, Robinson F, Roskos R[15] none of the patients given intramuscular dexmedetomidine had bradycardia, hypertension, or oxygen desaturation.

In our study, baseline MAP and DBP were raised in ketamine treated children than in children treated with the combination of ketamine and dexmedetomidine. We attribute this finding to the cardiodepressant action of dexmedetomidine which may have attenuated the rise in blood pressure caused by ketamine. Furthermore, we observed a lesser alteration in hemodynamics in children premedicated with ketamine and dexmedetomidine combination as compared to ketamine alone. The findings of Ibrahim 14 and Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK[12] were in line with our findings.

Also, children premedicated with combination of ketamine and dexmedetomidine had lesser percent of sevoflurane required than those with ketamine alone. It was observed to be statistically significant 3 min after induction of anesthesia and thereafter. Postoperative shivering was observed only in 4 cases, of which 2 were in the ketamine and 2 in the combination group. No other adverse events were observed in our study. Dexmedetomidine is considered a weak antiemetic but ketamine is a known emetogenic therefore, our study showed no incidence of nausea and vomiting in children premedicated with combination of ketamine and dexmedetomidine. Also, the children received intravenous ondansetron which may have attenuated nausea and vomiting postoperatively in both the groups.

CONCLUSION

In conclusion, combination of intramuscular ketamine 2mg/kg and dexmedetomidine 1mcg/kg is a good anxiolytic and sedative comparable with intramuscular ketamine 3mg/kg with superior anxiolysis in terms of parental separation in children and comparable adverse events as compared to ketamine alone. However, intramuscular ketamine has a better anxiolysis in terms of IV cannulation.

LIMITATIONS OF THE STUDY

The major limitation in our study is the short time between administration of premedicant prior to induction of anaesthesia. There was only 20 min before inducing general anesthesia after premedication considering the time constraint and delay in starting the surgery. Had a longer period been allowed, results for sedation could have been different. Similarly, we used intramuscular route which though effective, is not ideal in children. Further we used a quasi experimental design.

REFERENCES

1. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: A double-blinded randomized controlled trial. Anesth Analg. 2008;106(6):1715–21.
2. Weksler N, Ovadia L, Muati G, Stav A. Nasal ketamine for paediatric premedication. Can J Anaesth. 1993 Feb;40(2):119–21.
3. Kalra P. Miller's Anesthesia, Volumes 1 and 2, 7th Edition. 7th ed. Kalra P, editor. Vol. 112, Anesthesiology. The American Society of Anesthesiologists; 2010. 2574–2575 p.
4. Dahlquist LM, Gil KM, Armstrong FD, DeLawyer DD, Greene P, Wuori D. Preparing children for medical examinations: the importance of previous medical experience. Health Psychol. 1986;5(3):249–59.
5. Pai A, Heining M. Ketamine. BJA Educ. 2007 Apr;7(2):59–63.

6. Tobias JD. Dexmedetomidine and ketamine: an effective alternative for procedural sedation? Pediatr Crit care Med a J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2012 Jul;13(4):423–7.
7. Venham LL, Gaulin-Kremer E, Munster E, Bengston-Audia D, Cohan J. Interval rating scales for children's dental anxiety and uncooperative behavior. Pediatr Dent. 1980 Sep;2(3):195–202.
8. Robinson BRH, Berube M, Barr J, Riker R, Gélinas C. Psychometric analysis of subjective sedation scales in critically ill adults. Crit Care Med. 2013 Sep;41(9 Suppl 1):S16-29.
9. 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 Jul;121(1):167–71.
10. 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;17(1):1–7.
11. Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM, Auler JOCJ. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Paediatr Anaesth. 2007 Jul;17(7):667–74.
12. 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 Feb;28(1):12–8.
13. Singh C, Pandey RK, Saksena AK, Chandra G. A comparative evaluation of analgo-sedative effects of oral dexmedetomidine and ketamine: a triple-blind, randomized study. Paediatr Anaesth. 2014 Dec;24(12):1252–9.
14. Ibrahim M. A prospective, randomized, double blinded comparison of intranasal dexmedetomodine vs intranasal ketamine in combination with intravenous midazolam for procedural sedation in school aged children undergoing MRI. Anesth essays Res. 2014;8(2):179–86.
15. Mason KP, Lubisch NB, Robinson F, Roskos R. Intramuscular dexmedetomidine sedation for pediatric MRI and CT. AJR Am J Roentgenol. 2011 Sep;197(3):720–5.
16. Scheinin H, Jaakola ML, Sjövall S, Ali-Melkkilä T, Kaukinen S, Turunen J. Intramuscular dexmedetomidine as premedication for general anesthesia. A comparative multicenter study. Anesthesiology. 1993 Jun;78(6):1065–75.