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Comparative evaluation of intranasal midazolam, dexmedetomidine, ketamine for their sedative effect and to facilitate venous cannulation in pediatric patients: A prospective randomized study

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ABSTRACT

Background: Sedative premedication has a great role to overcome fear and anxiety and to facilitate easy separation of children from their parents. The current study was designed to compare the effectiveness of intranasal midazolam, dexmedetomidine, and ketamine as sedatives to facilitate the intravenous cannulation before surgery in children.

Methods: The patients were classified into three groups. M group (midazolam), D group (dexmedetomidine), and K group (ketamine), each group received the intranasal drug 30 min before the procedure. The degree of sedation was documented using Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) at baseline and every 10 min till induction of anesthesia. The onset of sedation was documented when reaching MOAA/S of 5. Easiness of venipuncture and the degree of anxiety during parental separation were recorded using 4-point scales (Venipuncture score and Parental Separation Anxiety Scale, respectively).

Results: The cannula insertion was tolerated in the three groups, but the percent of patients in group D showed better conditions for cannula insertion as scored in venipuncture score. Group D showed better sedation level in MOAA/S. The time taken to reach MOAA/S of 4 (venipuncture time) was less in group D.

Conclusion: The study showed that using intranasal midazolam, dexmedetomidine, and ketamine facilitates the cannula insertion at the preoperative period, and they are safe and easy methods for sedation. The three drugs provided a satisfactory child–parent separation. However, intranasal dexmedetomidine provides statistically significant better conditions facilitating cannula insertion.

1. Introduction

Surgery and hospitalization are extremely stressful experiences for both children and their parents. The induction of anesthesia and cannula insertion may be the only negative experiences a child recalls during his procedure [1]. Children can be anxious and fearful at times, making the induction period difficult for both the anesthetist and the children themselves due to vigilant movement and a lack of cooperation [2]. Very anxious children are more likely to develop sympathetic and endocrine system stimulation during the preoperative period, resulting in an increase in heart rate and blood pressure as well as other side effects such as increased analgesic needs, the emergence of delirium, and sleep disturbance [1–3].

If a cannula is already inserted, intravenous induction is a safe, simple, and quick method of induction in pediatric patients. Many recent studies have found that intravenous induction is superior to inhalational induction [1,4,5]. Pediatric intravenous cannulation is technically challenging and may result in psychological issues. Children typically resist any attempts to approach them and make it difficult to insert

a cannula for them. Furthermore, children always resist being separated from their parents in order to be taken to the operating room [1], [4]. Sedative premedications play an important role in pediatric anesthesia, helping patients overcome fear and anxiety associated with cannula insertion and making it easier for them to separate from their parents. There are many routes for administering sedatives that do not require the insertion of a venous line, such as oral, intranasal, intramuscular, and rectal. The intranasal approach is safe and painless, and children tolerate it well, with a comparable onset of action to the intravenous approach [1],[2],[4].

Midazolam is one of the most commonly used sedative premedications in pediatric anesthesia. It is employed in a variety of surgical and nonsurgical procedures. Midazolam is a water-soluble benzodiazepine that works by inhibiting the GABA receptor. It has sedative and anxiolytic properties, which make venous cannulation easier to perform [3,5,6].

Dexmedetomidine has recently become widely used in pediatric sedation. It is a highly selective alpha 2 adrenoreceptor agonist. It has a very strong

sedative effect with very little respiratory depression. We use the intranasal route because it is painless, odorless, and tasteless [4,7,8].

Ketamine is a sedative premedication that is commonly used in children. It is an *N*-methyl D-aspartate (NMDA) receptor antagonist that produces sedation, immobilization, and analgesia without causing respiratory depression. It has been used in a variety of ways, most recently intranasal in children [9].

Midazolam, dexmedetomidine, and ketamine have all demonstrated efficacy as sedative premedication. Drugs administered via the intranasal route are rapidly absorbed into the systemic circulation because they do not pass through the portal circulation [8–10]. An idea was assumed that intranasal midazolam, dexmedetomidine, and ketamine would make venous cannulation easier for anesthesiologists, in addition to their sedative premedication effect.

The primary goal of this study was to compare the efficacy of intranasal midazolam, dexmedetomidine, and ketamine in facilitating and decreasing the discomfort of intravenous cannulation before general surgery in children undergoing different minor surgical procedures. The secondary outcomes were identification of the onset of sedation, sedation level at each of 10, 20, and 30 min after the end of the tested drugs administration, the child anxiety score during parental separation, and hemodynamic changes that associated administration of the tested drugs.

2. Patients and methods

This is a comparative prospective randomized study conducted at Ain-Shams University hospitals in Egypt. The study was launched after receiving approval from Ain-Shams' ethical committee (FMASU R 132/2020) and registration on the clinical trial registry (NCT04704622). Written consent was obtained after a thorough explanation of the research concept to the patients' parents/guardians.

The study included 154 children aged 2–9 years who were scheduled for minor elective surgical procedures (45 –60 min) at the pediatric surgery department. Patients were ASA I or II, within normal weight ranges, and refused venous cannulation. The following patients were excluded: any case after parents' refusal, with nasal deformity or pathology, any known case of allergy to the study drugs, obese patients, suspected difficult airway or venous cannulation, maxillofacial malformations, gastroesophageal reflux, patients with renal, liver, endocrine, or cardiac pathology, patients with increased intracranial or intraocular pressure, patients with sleep apnea, and any patient with a preexisting cannula or accepting cannula insertion.

The day before the surgery patients were assessed in the anesthesia clinic. Preanesthetic assessment included surgical and medical history; general examination, airway examination, and systemic examination. Investigations according to the hospital's protocol were conducted. All guardians were constructed to keep the patients fasting 6 h for food and milk and 2 h for clear fluid.

3. Study design

The trial was planned to be a randomized double-blind study, meaning neither the patients, observers (who recorded data), nor attending anesthesiologists were aware of the medicine used. A random number table was used to divide patients into three groups at random.

The first group (*n* = 51) received 0.2 mg/kg of midazolam (Dormicum, 5 mg/5 ml ampoule; F. Hoffman La Roche Ltd., Basel, Switzerland) nasally and was named M group; the second group (*n* = 51) received 1 µg/kg of dexmedetomidine (Precedex, 200 µg/2 ml vial; Abbott, USA) nasally and named D group; and the third group (*n* = 52) received 2 mg/kg of ketamine hydrochloride (ketamine hydrochloride, 500 mg/10 ml vial, HIKMA Pharmaceuticals, Amman-Jordan) nasally and was named K group.

The total dose of the tested sedative drugs for each patient was calculated and withdrawn from the corresponding vial or ampoule via 1 ml syringe and diluted up to 1 ml with normal saline. The syringe was labeled with a number that code its group. In each group, half of the volume of the tested sedative drugs was dripped into each nostril of the patients via syringe over 3–4 min while they were lying supine on the table. The study drugs were administered 30 min before the administration of general anesthesia.

Routine monitoring was used, and all patients were constantly monitored (for heart rate, blood pressure, and oxygen saturation) during the preoperative period until they were transferred to the operation room. Sedation levels were assessed at baseline and then constantly monitored using the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) [11] (Table 1). The onset of sedation was defined as the time when reaching a MOAA/S score of 5.

The time to insert an intravenous cannula was defined as the time required to achieve appropriate sedation, and it is reaching a MOAA/S score of 4. The attending

Table 1. Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S).

Score	Modified Observer's Assessment of Alertness/Sedation scale
6	Appears alert and awake, responds readily to name spoken in a normal tone
5	Appears asleep but responds readily to name spoken in a normal tone
4	Lethargic response to name spoken in a normal tone
3	Responds only after the name is called loudly or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking

anesthetist assigned a 4-point scale to the ease of veni-puncture, grade I; crying, uncooperative not able to start IV line, grade II; withdrawal for painful stimuli but allows to crying, grade III; calm, no-withdrawal, for painful stimuli and IV cannulation, grade IV; asleep – no response to painful stimuli and IV cannulation. The attending anesthetist performed the cannula insertion, and if the cannula was not inserted after three trails, the patient was excluded from the study, and the access was performed by an expert anesthetist.

The degree of the child's anxiety during parental separation was documented and graded using 4-point scale, which is called Parental Separation Anxiety Scale (PSAS) [12]. This 4-point scale is presented in Table 2. Patients with scores of 1 and 2 were deemed successful.

At the time of induction, a MOAA/S score of 1–4 indicated satisfactory sedation, while a score of 5 or 6 indicated unsatisfactory sedation. All patients were induced in the operating room (OR) using the same induction protocol. General anesthesia was induced with 1 mg/kg propofol, and intubation was performed after facilitation with 0.5 mg/kg atracurium. According to our hospital protocol, mechanical ventilation of the lungs was established, and anesthesia was maintained with oxygen, 2% sevoflurane, and incremental doses of atracurium. Ringer lactate maintained an intravenous fluid infusion in accordance with the patient's fluid chart. At the conclusion of the surgery, the residual muscle relaxant was reversed with atropine 0.02 mg/kg and neostigmine 0.05 mg/kg, and tracheal extubation was performed.

After the surgery, all patients were transferred to the PACU and monitored until they achieved an Aldrete score of 9 and were shifted to the word. Any complications that arose during the perioperative period were documented and managed. Expected complications such as a decrease in mean arterial blood pressure of 60 mmHg were treated by increasing fluid infusion, a decrease in pulse rate of 55/min was treated by 0.3 mg atropine, and O_2 saturation less than 95% was treated by increasing the concentration of O_2 to 100%. Any side effects, such as delayed recovery, nausea, and vomiting, were documented and treated accordingly.

4. Patient assessment

Demographic data (age, weight, and gender) were collected and compared between groups. The MOAA/S was recorded at baseline and every 10 min until anesthesia was administered. Mean heart rate and mean blood pressure were recorded at six different times: baseline (T1), 10 min after premedication (T2), 10 min after induction of anesthesia (T3), 30 min intraoperative (T4), 1 h intraoperative (T5), and 10 min after extubation (T6) (T6). The venipuncture score, PSAS score, onset of sedation, time of venipuncture, and any complications were all recorded.

5. Sample size

Using PASS11 program for sample size calculation and assuming that 53% of patients in the midazolam group achieved satisfactory sedation by MOAA/S compared to 80% of the dexmedetomidine group (Gupta et al.[2]) setting power at 80% and α-error at 0.05, sample size of at least 47 patients per group was needed. No research work measured the satisfactory sedation of ketamine by MOAA/S, so at least 47 patients were considered enough for this group.

6. Statistical analysis

The Statistical Package for Social Science (SPSS) version 22.0 was used to analyze the data. The quantitative data are presented as mean standard deviation (SD) or median and interquartile range (IQR). The frequency and percentage of qualitative data were used. The following tests were carried out: the one-way analysis of variance (ANOVA) is used to compare the means of several subgroups of a variable. When the ANOVA test is positive, the post-hoc test is used to compare subgroups pairwise. The chi-square (X^2) test of significance was used to compare proportions between qualitative parameters. In nonparametric data, the Kruskal–Wallis test is used to compare several subgroups. The confidence interval was set to 95%, and the acceptable margin of error was set to 5%. As a result, the p-value was determined to be significant as follows: the probability (p-value) of 0.05 was considered significant. p-values of 0.001 were considered highly significant. p-values greater than 0.05 were deemed nonsignificant.

7. Results

One hundred and sixty patients were evaluated for eligibility; as shown in the flow chart, only 150 were analyzed in the study, with 50 patients in each group (Figure 1). The demographic characteristics of all patients are displayed in Table 3. Patients in the three groups were comparable in terms of age, weight, and gender.

The mean of heart rate values determined by methodology at all six times is shown in Figure 2. At baseline, there was no statistically significant difference in mean heart rate values between the three groups (T1). Comparing M and K groups, the mean heart rates at T3,
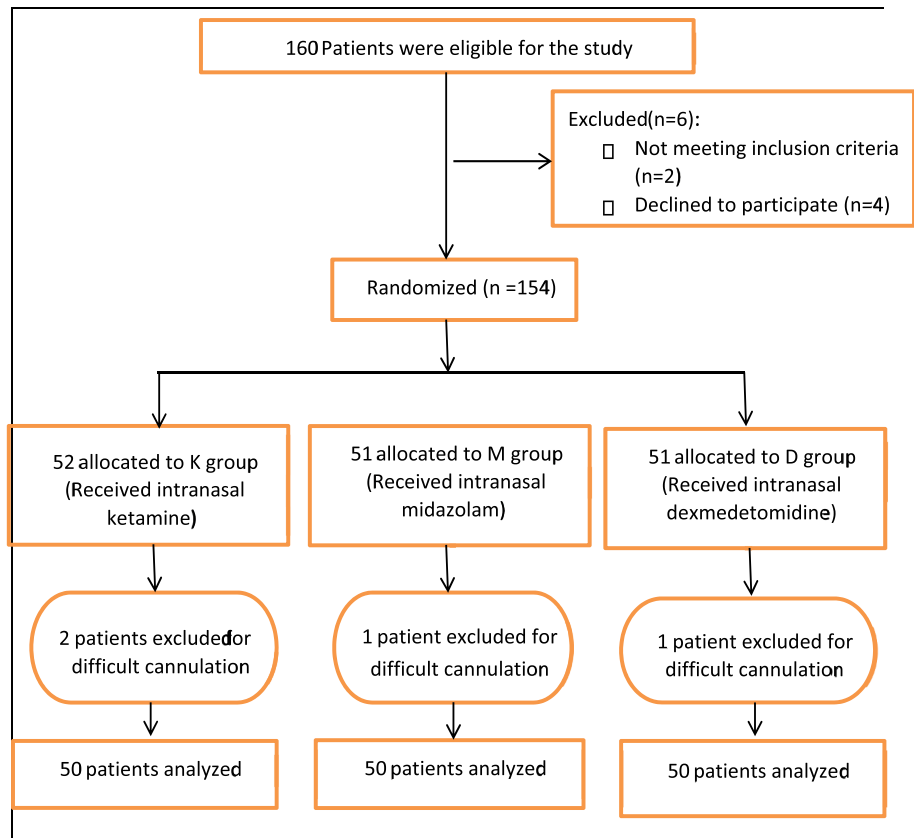
Table 2. Parental Separation Anxiety Scale (PSAS).

Score	Parental Separation Anxiety Scale (PSAS)
1	Easy to separate
2	Sobbing but easy to cease
3	Crying loudly and difficult to stop but without holding the parents and not letting them go
4	Crying loudly and holding the parents and not willing to let them go

Figure 1. Study flow chart.

Table 3. Demographic characteristics of patients in the three groups (data are presented as mean ± SD or number (percent).

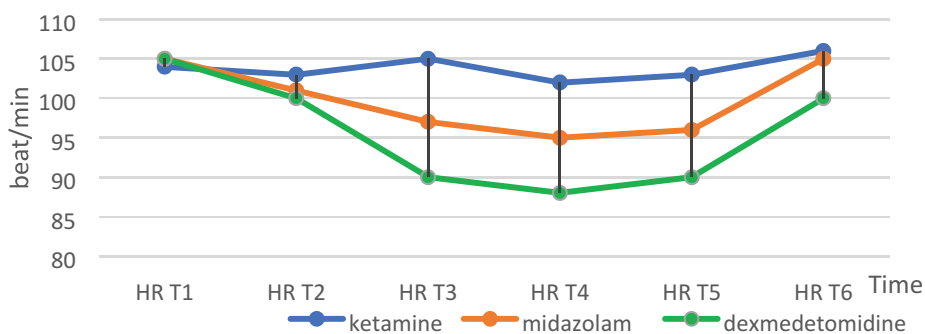|	K group ($n = 50$)	M group ($n = 50$)	D group ($n = 50$)	F	p
Age (years)	5.6 ± 1.99	5.38 ± 2.15	4.88 ± 1.77	1.9	0.15
Weight (kg)	17.36 ± 4.4	16.98 ± 4.28	16.1 ± 3.6	1.2	0.295
Gender (male) percent	26 (52%)	22 (44%)	24 (48%)	$X^2 = 0.6$	0.73

F = ANOVA test, X^2 = chi-square.

Figure 2. Comparison of mean heart rate between the three groups.

T4, T5, and T6 were statistically significantly lower in D group. At T3, T4, and T5, M group had a statistically significant lower score than K group. The mean systolic blood pressure (SBP) values at all six times determined in methodology are shown in Figure 3. The mean SBP values at T2, T3, T4, T5, and T6 were lower in D and M groups compared to K group, but only statistically significantly lower in D group at T3 and T4. However, no episodes of bradycardia or hypotension were observed in any of the three groups.

In the three groups, the baseline MOAA/S was comparable. The MOAA/S values recorded at 10, 20, and 30 min after drug instillation were significantly lower in D group when compared to K and M groups. At 30 min, all the three groups achieved a satisfactory sedation level (MOAA/S < 4) (Table 4).

In terms of cannula insertion, two cases in K group, one case in M group, and one case in D group failed to insert the cannula and were thus excluded from the study. Figure 4 depicts the percentage of patients in
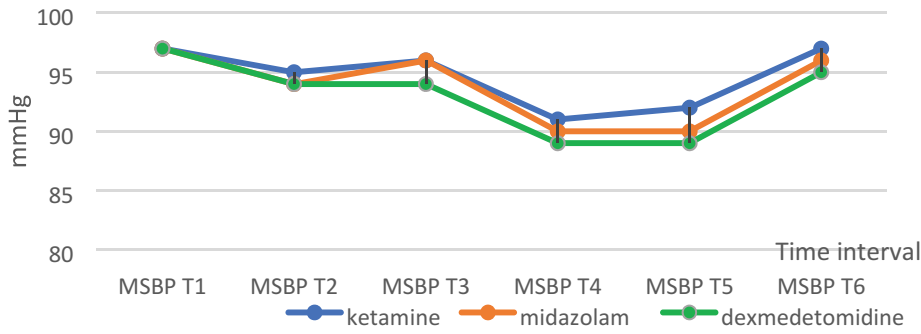
Figure 3. Comparison of mean systolic blood pressure (MSBP) between the three groups.

Table 4. Modified Observer's Assessment of Alertness/ Sedation scale (MOAA/S) values (data are presented as median (interquartile range).

	K group	M group	D group	F	p value
	(n = 50)	(n = 50)	(n = 50)		
MOAA/S baseline	6 (6–6)	6 (6–6)	6 (6–6)	0.44	0.8
MOAA/S 10 min	5 (5–5)	5 (4–5)	4 (4–5)	32.04	<0.001
MOAA/S 20 min	4 (3–4)	3 (3–4)	2 (2–3)	81.8	<0.001
MOAA/S 30 min	3 (3–4)	3 (2–3)	2 (2–2)	76.2	<0.001

F = Kruskal–Wallis test.
p value < 0.05 means statistically significant.

each group based on their venipuncture grade at the time of cannula insertion. According to the chi-square test, the percentage of patients in the D group with scores III and IV was significantly higher than in the K and M groups.

All three groups of patients received a good parent separation scale. D group had a substantially greater percentage of children with a child–parent separation score of grade 1 than M and K groups. The start of sedation occurred sooner in D group compared to M and K groups, and the differences were statistically significant. The time needed to attain the sedation score decided to insert the cannula (time of venipuncture) was less in D group compared to the other two groups and was statistically significant, and in the M group was substantially lower than K group (Table 5).

8. Discussion

The induction of anesthesia and cannula placement may be the only unpleasant memories a youngster has of his medical treatment. Midazolam, dexmedetomidine, and ketamine have all demonstrated efficacy as sedative premedication. The three medicines have demonstrated an easy and quick method of analgosedation [13,14]. The intranasal approach is an effective and safe mode of drug administration, the three medicines when administered intranasally have been found to produce good sedation [13–15]. The primary goal of this study was to determine the ease of intravenous cannulation in children undergoing different minor surgical procedures while under the influence of the study medications (ketamine, midazolam, and dexmedetomidine). The secondary outcomes were to evaluate the degree of drowsiness, the start of sedation, the child's reaction to parental separation, and hemodynamic changes with the research medications employed.

The current study found that cannula insertion was tolerated in all three medications, although the percentage of patients in D group with venipuncture ratings of III (56%) and IV (24%) were considerably greater than those in K and M groups. In research comparing intranasal dexmedetomidine and intranasal ketamine, Gyanesh et al. [15] found that patients in the dexmedetomidine group had higher venipuncture ratings
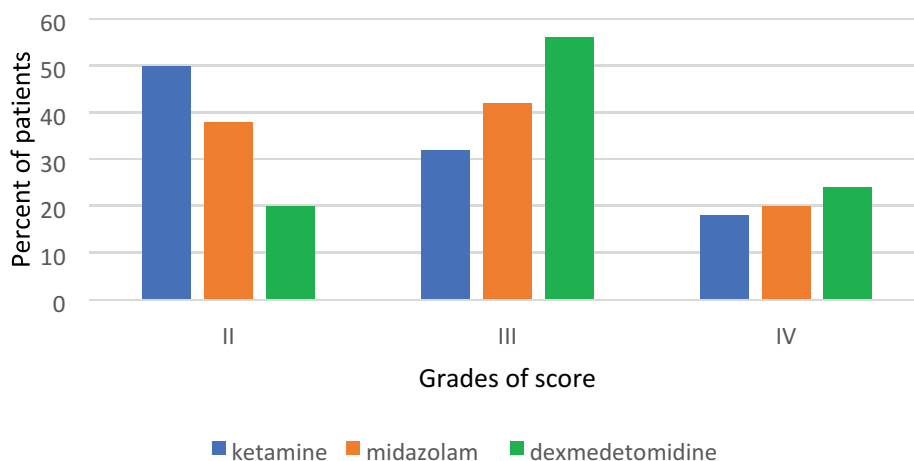

Figure 4. Percent of patients' grades in venipuncture score.

Table 5. Comparison of onset of sedation, time of venipuncture, and percent of PSAS grade I (data are presented as mean ± SD or percent).

	K group	M group	D group	F	p value
	(n = 50)	(n = 50)	(n = 50)		
Onset of sedation (min)	10.72 ± 1.43	10.2 ± 1.09	7.2 ± 1.12 $^{€ ¥}$	120.57	<0.001
Time of venipuncture (min)	17.5 ± 1.88	16.26 ± 1.4 ¶	11.42 ± 1.5 $^{€ ¥}$	199.5	<0.001
PSAS grade I (percent)	22 (44%)	35 (70%)	39 (78%)	X^2 = 13.76	0.008

¶ post-hoc test sig between K and M, € post-hoc test sig between K and D, ¥ post-hoc test sig between M and D. p-value < 0.05 means statistically significant.
F = ANOVA test, X^2 = chi-square, PSAS = Parental Separation Anxiety Scale.

than those in the ketamine group, which supports our findings. However, the difference was not statistically significant, which might be attributed to their study's use of a different venipuncture score. Narendra and colleagues [9] investigated intranasal midazolam and intranasal ketamine and discovered that 40% and 30% of the people in M and K groups, respectively, scored grade III in venipuncture scores, which was comparable to our findings. The current study concurred with Ghai and his colleague [8], who tested oral midazolam with intranasal dexmedetomidine and discovered that D group performed substantially better than M group in venipuncture score findings.

In our investigation, the D group had considerably lower sedation levels on the MOAA/S scale than groups M and K and intranasal ketamine and discovered that 40% and 30% of the people in groups M and K, respectively, scored grade III in venipuncture scores, which was comparable to our findings. The present study agreed with Ghai and his colleague [8], who compared oral midazolam with intranasal dexmedetomidine and found that group D was significantly better than group M in their venipuncture score results.

In our study, it was noticed that the D group showed a significantly better sedation level by MOAA/S scale than M and K groups. However, within 30 min, all patients had reached a sufficient degree of sedation before anesthetic induction. These findings agreed with prior research [16–18].

It was discovered that the D group's start of sedation was substantially sooner than the other two groups (M and K) in the current study, and the M group was also significantly earlier than the K group. Similar studies have been done, and their findings are congruent with ours [9,19–21]. In contrast to our findings, Lang et al. [13] found no difference in the onset of sedation between dexmedetomidine and midazolam, which can be attributed to their larger sample size.

In the current study, D group had a shorter venipuncture time than M and K groups, while M group had a shorter time than K group. These findings were consistent with prior research [8,9].

In the current investigation, it was discovered that intranasal dexmedetomidine provided more acceptable parental separation than midazolam and ketamine. Suvvari and colleagues [22] determined in their study that intranasal dexmedetomidine gives a superior sedation score and parental separation score than intranasal ketamine. In addition, Abdel-Ghaffar et al. [17] found that inhaled dexmedetomidine performed better than nebulized ketamine and midazolam in terms of PSAS. In a study comparing intranasal dexmedetomidine to oral midazolam in children undergoing dental operations, Sathyamoorthy et al. [23] discovered that intranasal dexmedetomidine had a greater success rate in parental separation.

In terms of hemodynamic alterations, the D group had a considerably lower mean heart rate and systolic blood pressure than the M and K groups. It was not, however, clinically significant because no patient required care. Many studies had shown similar results [13], [16], [20], [23,24].

9. Study limitation

One of the main issues in the present study was that there were no similar researches conducted to assess the ability of the study drugs to facilitate cannula insertion as the main point of research for better comparison.

10. Conclusion

Our study found that utilizing intranasal dexmedetomidine, midazolam, and ketamine in the preoperative period facilitates cannula placement and is a safe and simple way of sedation and decreases the child–parent separation anxiety. On the other hand, intranasal dexmedetomidine provides statistically significant better conditions facilitating cannula insertion.

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