RESEARCH ARTICLE

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Comparison of Sedation Effect between Midazolam Nebulization and Midazolam - Ketamine Nebulization in Pediatric Ophthalmic Surgery

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ABSTRACT

Background: Pre-anaesthetic drugs are regularly given to children as pharmacological adjuncts to help reduce anxiety and stress before surgery, as well as to soothe separation anxiety from the child's parents and facilitate a smooth induction. Prescription drugs like ketamine and midazolam may be used to sedate children before surgery.

Objectives: The aim of this study is comparison of sedation effect between midazolam nebulization and Midazolam-ketamine nebulization in pediatric ophthalmic surgery farabi eyes hospital in Tehran: A Clinical Trials.

Methods: A total of 50 children, that is, 25 in two groups, underwent the study at Farabi Ophthalmic Hospital during August–October of 2023. Prior, the nebulization standard monitoring (HR, SBP, and SPO_2) was instituted in both groups in setting position. Patients in group M received midazolam inhalation 0.5 mg/kg in 3 cc of distilled water. Group MK received 0.5 mg/kg midazolam and 2 mg/kg ketamin diluted with 2 ml of distilled water. All patients were assessed before receiving the drug and reassessed 15 minutes after nebulization, and (HR, SBP, SPO2), the Ramsay sedation scale, the Parent Separation Anxiety Scale (PSAS), and face mask acceptance were recorded.

Results: The results demonstrated that there are no significant differences in demographic characteristics such as age, sex, and weight between the groups of midazolam and midazolam ketamin. There were no significant statistical differences between the midazolam and midazolam ketamin groups in SPO_2 (P-value = 0.735), HR (P-value =0.526), and SBP (P-value =0.644). Furthermore, the Ramsay Sedation Scale in the midazolam ketamine group was significantly higher than the other group of midazolam (P-value = 0.033). Regarding mask acceptance, the study group had a higher significant relationship with midazolam ketamin when compared to the midazolam group (P-value < 0.001). There was a significant relationship between the study group and parent separation, as the midazolam ketamine group was significantly higher than the group of midazolam (P-value = 0.018).

Conclusions: Overall, our findings suggest that nebulized midazolam-ketamine is a safer and more effective sedative than nebulized midazolam as a nebulizer premedication for patients in pediatrics eye surgery requiring general anesthesia.

Keywords: Sedation, Midazolam, Ketamine, Pediatric, Nebulization.

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INTRODUCTION

All surgeries, as well as the preoperative stage, can be stressful for young children having ophthalmic surgery. This stress might make the child more likely to exhibit uncooperative behavior and result in lasting behavioral changes, including bedwetting, nightmares, and an intense fear of hospitals and medical staff[1]. Premedication plays a crucial role in pediatric anesthesia by alleviating anxiety, reducing vagal stimulation, and preventing postoperative psychological sequel[2]. Consequently, Effective sedation and analgesia may minimize psychological stress, anxiety, and discomfort while increasing patient compliance and satisfaction[3]. Prescription drugs like ketamine and midazolam may be used to sedate children before surgery[4]. Low doses of midazolam and ketamine given through a nebulizer gave positive results in terms of mask acceptance, proper sedation, quick recovery, and few side effects[5]. Premedication to reduce anxiety is an essential concern since excessive anxiety has negative effects on pediatric anesthesia practice. A simple approach with a quick start to effect is intranasal drug administration, which enables the infusion of many different kinds of medications, including midazolam, which is used to sedate children before surgery[6]. Especially in pediatric surgery, ensuring suitable preoperative sedation and anxiolytics is crucial. However, the time it took for intranasal midazolam to start causing drowsiness and reach its peak was much shorter. Children who have not taken any prior medication experience preoperative anxiety a second time as much as those who have. When children are properly pre-medicated and removed from their parents without fear of physical harm, such as a needle insertion, this psychological effect prevents the autonomic reflex, prevents excessive secretion in the airway, eases anxiety, facilitates easy induction of anesthesia, and lowers the dose of general anesthesia. Midazolam usually results in drowsiness with anxiolysis and mild ante-grade amnesia within 10–20 minutes. There are a few studies on the effectiveness of ketamine for pre-medication and sedation in children when administered inhalational with a nebulizer. And our aim is to provide a more effective method of administration of premedication for pediatric patients referring for surgical procedures[7,8]. Comparing the efficacy of nebulized midazolam against nebulized midazolam with ketamine in pediatric eye surgery at Farabi Eye Hospital was the aim of this study.

MATERIAL & METHODS

Study design: In the ophthalmology operating room at Farabi Hospital, this study was carried out from August 2023 to October 2023, with a total of 50 patients recruited. Before anything else, the responsible anesthesiologists in "Tehran City" performed a primary assessment of each patient's anesthetic risk, and the patient's parents verbally agreed to the patient's participation in the study.

In group M: 25 patients, evenly split between the genders, made up the sample size that was taken. In addition, before we start cardiopulmonary monitoring (heart rate, SBP (Systolic Blood Pressure), and SPO_2), the patient keeps resting during the nebulizer in the supine position. Additionally, a 24G IV cannula was implanted. When everything is in working condition, we get the patient ready for inhalation sedation. And beginning sedatives for inhalation, such as midazolam at doses of 0.5 mg/kg coupled with 3cc of distilled water. Following administration, the patient starts close cardiopulmonary monitoring (HR, SBP, and SPO_2) to look for any changes. This includes looking for respiratory depression, if it happened, as well as other symptoms including bradycardia, hypotension, and apnea. These indicators must be constantly monitored throughout the procedure and any changes should be noted.

In group Mk: Furthermore, as this is group M, there are 25 members who were selected at random among them, of both sexes. To begin, a cardiopulmonary monitoring device must be implanted as per Group M instructions. Anesthesiologists must then reassess the patient, and 15 minutes after the nebulization, they must deliver a nebulization of midazolam-ketamine dose 0.5 mg/kg in addition to 2 mg/kg diluted with 2 ml of distilled water. The child is then taken and placed on the OR bed, where all of the cardiopulmonary monitoring equipment is placed to monitor any changes in heart rate, SBP, and SPO_2 once the effects of the midazolam ketamine start to take effect and the patient appears to be relaxed.

We use the Ramsay sedation scale to determine the degree of sedation, which goes as follows and divides the sedation level by sex. The first one was that the patient is anxious, agitated, restless, or both, and for this level give a score of 1, and the second level was that the patient is oriented, cooperative, and tranquil, and for this level give a score of 2, and the third level was that the patient responds to commands only, and for this level give a score of 3, and the fourth level was that the patient exhibits a brisk response to light glabellae tap or loud auditory stimulus, and for this level give a score of 4, and the fifth level was that the patient exhibits a sluggish response to light glabellae tap or loud auditory stimulus, and for this level give a score of 5, and the sixth level was that the patient exhibits no response, and for this level give a score of 6. The RSS was monitored every 5 minutes till it reached the desired score (RSS of 4). After 15 minutes, if the patient didn't reach adequate sedation (RSS of 4), the RSS score will be documented, and standard measures by the anesthesiologist will be taken further[9] and we made use of The Parent Separation Anxiety Scale (PSAS) is a psychological assessment tool used to diagnose social anxiety, obsessive-compulsive disorder, panic disorder/agoraphobia, and other anxiety disorders in children and adolescents aged 8 to 15. This scale contains clinical pictures, and for every clinical picture, we have a PSAS score. For the first clinical picture, if the child separates easily, we give a score of 1, and for the second clinical picture, if the child whimpers but is easily assured (not clinging to parents), we give a score of 2, and for the third

clinical picture, when the child was crying and could not or was difficult to be assured of (not clinging to parents), give a score of 3, and for the last clinical picture, when the child was crying and clinging to parents, give a score of 4[10].

The score of the separation is based on the Parenteral Separation Anxiety Scale after obtaining RSS 4, and we use the behavioral criteria to assess the child, which are divided into four levels: The first level was Excellent = Patient unafraid, cooperative, or asleep, and for this, we gave a score of 1, the second level was Good = Slightly afraid or crying, quiet with reassurance; we gave a score of 2, and the third level was Fair = Moderately afraid and crying, not quiet with reassurance, giving a score of 3. And the last level, poor = crying, needs restraint, gives a score of 4[11]. Face mask acceptance was evaluated after the patient entered the OR 15 minutes after drug administration.

Inclusion criteria: I and II of the ASA; the age of the child (3–7 years); eye surgery with GA (elective). and about the exclusion criteria: dysfunction of the renal or hepatic systems, History of midazolam, ketamine allergy, History of asthma, pre-existing neurologic disease and any patient not reaching RSS 3 within 15 minutes.

Statistical analysis: Excel 2010 for Windows 10 and the Social Sciences module of the Statistical Package for SPSS were used to do the statistical analysis. The percentages, averages, and standard deviations of all research components were extracted and compared in order to find statistically significant differences. For the chi-square test, an independent T-test and paired T-test were used, with a P-value of 0.05 to establish statistical significance used to compare the age, weight, gender, mean heart rate, mean SBP, and mean blood oxygen saturation (SPO_2), RAMSAY score, mask acceptance, and parent separation. All parameters were compared in order to determine the effect of the sedation nebulization method on the important parameters for each patient in this investigation.

RESULTS

The result showed that there are no significant differences in demographic characteristics such as age (P-value = 0.674), weight (P-value = 0.973), and gender (P-value = 0.777) in the nebulization groups of midazolam and midazolam-ketamine Table 1.

There were no significant statistical differences between the nebulization midazolam group and the nebulization midazolam-ketamine combination in SPO2 (P-value = 0.735), HR (P-value =0.526), and SBP (P-value =0.644). There were no significant statistical differences between the nebulization midazolam group and midazolam-ketamin group in the base line, and after 15 minutes in each group, the midazolam group (P-value = 0.369) and the midazolam-ketamin group (P-value = 0.944). There were significant statistical differences in heart rate (P-value<0.001) between the nebulization midazolam group and group midazolam-ketamin at baseline and after 15 minutes in each group. Regarding SBP, both groups had significant statistical differences in the base line, and after 15 minutes, SBP for midazolam (P-value =0.001) and SBP for midazolam-ketamine (P-value = 0.015) Table 2.

The results showed that there were significant statistical differences between the nebulization midazolam group and the nebulization midazolam-ketamin group in the RAMSAY score, and the midazolam-ketamin group was significantly higher than the other group of midazolam (P-value = 0.033) Table 3.

The results of this study showed there were significant statistical differences between the nebulization midazolam group and the nebulization midazolam-ketamine group in the mask acceptance score. The midazolam-ketamine group was more significant than the midazolam group (P-value <0.001) Table 4.

There were significant statistical differences between the nebulization midazolam group and the nebulization

Table 1. Patient Demographic information.

Variable	Group	Group M	Group MK	P- value
Age (years) Mean±SD		5.40±1.00	6.20±1.16	0.674
Weight (kg)Mean±SD		21.52±5.65	21.58±5.64	0 .973
Sex (N, %)	Male	13 (52.0%)	12 (48.0%)	0.777
	Female	12 (48.0%)	13 (52.0%)	

Table 2. Comparison between mean spo2, heart rate, systolic blood pressure for group midazolam and group midazolam-ketamine.

Groups	Group M		Group Mk		P-value
Variable	Base line	15 min	Base line	15 min	
SPO_2 (M±SD)	0.32±1.74* P= 0.369		0.04±2.80* P=0.944		0.735
HR (M±SD)	12.60±12.47** P<0.001		12.68±12.66** P<0.001		0.526
Systolic Blood Pressure (M±SD)	3.40±4.66*** P=0.001		1.76±6.05*** P=0.015		0.644

* Mean Difference and Standard Deviation of SPO2 between Base line and 15 min.
** Mean Difference and Standard Deviation of HR between Base line and 15 min.
*** Mean Difference and Standard Deviation of Systolic Blood Pressure between Base line and 15 min.

Table 3. The result of the Comparison between the two studied groups toward Ramsey score.

Variable	Groups	M GROUP (N, %)	MK GROUP (N, %)	Total	P-Value
1.00	Count % within groups (not Acceptable)	6 24.0%	0 0.0%	6 12.0%	0.033
2.00	Count % within groups (Acceptable Goal)	13 52.0%	17 68.0%	30 60.0%	
3.00	Count % within groups (Great Goal)	6 24.0%	8 32.0%	14 28.0%	

Table 4. The result of the Comparison between the two studied groups toward the score of the mask acceptance.

Variable	Groups	M GROUP (N, %)	MK GROUP (N, %)	P-Value
1.00	Count % within groups (Excellent goal)	4 16.0%	19 76.0%	<0.001
2.00	Count % within groups (Acceptable goal)	9 36.0%	6 24.0%	
3.00	Count % within groups (Fair goal)	12 48.0%	0 0.0%	

Table 5. The results of the Comparison between the two studied groups toward the score of the parent separation.

Variable	Groups	M GROUP (N, %)	MK GROUP (N, %)	P-Value
1.00	Count % within groups (excellent goal)	16 64.0%	24 96.0%	0.018
2.00	Count % within groups (Good goal)	8 32.0%	1 4.0%	
3.00	Count % within groups (Fair goal)	1 4.0%	0 0.0%	

midazolam-ketamine group in the parent separation score; the group of midazolam-ketamine was significant more than the midazolam group (P-value = 0.018) Table 5.

DISCUSSION

Midazolam is a benzodiazepine medication that is commonly used in pediatric patients for preoperative sedation, anesthesia induction, and procedural sedation via oral and intravenous routes. However, nebulized midazolam or midazolam-ketamine has been proposed as an alternative route of administration, particularly in pediatric patients who have difficulty swallowing or fear needles. The purpose of the research is to evaluate the safety and efficacy of nebulized midazolam vs. nebulized midazolam-ketamine in pediatric patients having ophthalmic surgery.

50 pediatric patients, ages 3–7, were taking either nebulized midazolam or nebulized midazolam-ketamine. Our results showed that both nebulized midazolam and nebulized midazolam-ketamine were effective in achieving sedation, with significant statistical variation for the mean systolic blood pressure, mean heart rate, RAMSAY score, parent separation, and mask acceptance level at the 15 minute after administration, where the nebulizer midazolam-ketamine showed a better mean HR value, mean SBP, RAMSAY score, the separation of the parent, and the acceptance of the mask compared to the nebulizer midazolam type.

This research results depend on seven sections that were done by analyzing data, and we discuss these results as below. Preoperatively, we measured the mean HR, mean SBP, and mean SPO_2 with intervals of 0 minutes baseline to 15 minutes. Even though there was a slight difference in the baseline between the two groups, the comparison between the mean HR and the mean SBP in the study by perioperative MSAP and HR was, on the whole, similar between the two groups. After each group's

medication was administered, all of these measures fell in comparison to the baseline 15 minutes later. The mean systolic BP was kept up-to-date for each group's intra- and postoperative periods. The HR was mostly maintained during the treatment, but as it progressed, it dropped below the baseline. There is a study that contradicts the one that was conducted recently by[12]. 108.15±7.8 is the mean of change and standard deviation at baseline to the heart for group M, and the mean and SD was 107.75±7.9 for group MK, and it was not significant. The mean and standard deviation of the heart beat after 15 minutes were 102.23±5.42 for group M, and for group MK, it was 109.48±6.17, and it was a significant result that matches the present study and there is a study that agrees with the current study produced by[13] about group Midazolam's systolic blood pressure, and the result was significant, but the results of the SPO_2 of group Midazolam were no significant.

The study Compared between the two groups regarding the Ramsey score Based on the data analysis of the RAMSAY sedation scale, only 6 children (24.0%) from nebulized midazolam and 0 children from nebulized midazolam-ketamine form had an RSS of 1, which shows a very low percentage of patients who didn't reach an adequate sedation level after the drug administration. 13 children (52.0%) from Group nebulized midazolam and 17 children (68.0%) from Group nebulized midazolam-ketamine reached RSS 2, where the patient is oriented, cooperative, and tranquil, which shows satisfactory sedation level by both forms of drugs. 6 children (24.0%) from nebulized midazolam and 8 children (32.0%) from nebulized midazolam-ketamine reached an RSS of 3, which is also an adequate level of sedation score. If a percentage of patients in both groups are observed, there is a significant difference in sedation level between the nebulized midazolam form and the nebulized midazolam-ketamine form. The present study is also supported and agrees with the study produced by[14] who also discovered that, while no statistical significance was revealed in this trial, ketamine with midazolam appears to be more successful than midazolam alone at controlling the behavior of uncooperative children during medication administration.

The comparison results of the Ramsay Sedation Scale, if considered as a quantitative variable, is the mean sedation score analyzed for nebulizer midazolam and nebulized midazolam-ketamine, respectively, making them almost equal to each other between the two studied groups Compared with the parent separation score.

One of the goals of sedative premedication for children before surgery is to ease parental separation before surgery. Based on our study, the effective sedation via nebulized midazolam-ketamine to make the parental separation had a difference from the nebulized midazolam. Corresponding to our clinical trial data, the Parental Separation Anxiety Scale of patients before surgery has shown an acceptable score for most of the patients. 64.0% of the patients (16 patients) from the nebulized midazolam group and 96.0% of the patients (24 patients) from the group receiving nebulized midazolam-ketamine had an "excellent" score based on the PSAS (Parental Separation Anxiety Scale), which means that most of the patients were unafraid, cooperative, or asleep while being separated from their parents before surgery, and the difference in percentage between the two groups is also unremarkable. 32.0% and 4.0% of the patients had "good" PSAS status with nebulized midazolam and nebulized midazolam-ketamine, respectively. Among all the patients, only one person (4.0%) from Group M was at the "fair" level of the PSAS scale. The P-value of 0.018 in PSAS also states the significant difference between the two groups. There is a study that agrees with the current study and was produced by[15] that the ketamine plus midazolam had excellent PSAS more than midazolam, and the percentage for the MK group was 60%, and for the midazolam, the percentage was 50%, which matches the present results that the MK group had an excellent score for the mask acceptance.

The Mask Acceptance Level Status as "Excellent: Unafraid, cooperative, and accepts mask easily" in our patient groups is followed by 16.0% (4 patients) for group nebulized midazolam and 76.0% (19 patients) for group nebulized midazolam-ketamine, which shows an equal effectiveness of nebulized midazolam and nebulized midazolam-ketamine on mask acceptance. 36.0% and 24.0% of the patients had "acceptable" status for the nebulizer midazolam and the nebulized midazolam-ketamine drug, respectively. Only 48.0% of patients in group midazolam had "fair" mask acceptance status. The p value for mask acceptance is $=<0.001$, which indicates the significance of the difference between nebulized midazolam and nebulized midazolam-ketamine.

These[16] results agree with the current research that a superior proportion and improved clinical profile for premedication were observed in the combination of midazolam and ketamine of MK were 6 (12%) more than the other drug, 22 (44%), a moderate percentage of MK, and at last, 21 (42%), poor results in percentage.

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CONCLUSION

In summary, our results indicate that both nebulized midazolam-ketamine and nebulized midazolam achieve the desired level of sedation. However, nebulized midazolam-ketamine stands out with superior anesthesia mask acceptance, reduced anxiety during parental separation, significantly improved sedation satisfaction, and a quicker onset of sedation compared to nebulized midazolam alone. Consequently, we consider this combined premedication regimen to be a more favorable option**.**

ETHICAL APPROVAL

The ethics committee of the Tehran University of Medical Sciences’ study approved the use of human subjects (IR.TUMS.SPH.REC.1402.118).

CONFLICT OF INTEREST

The authors assert they have no competing interests.

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