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Comparison of Sedative Effects of Two Dose of Oral Ketamine in Pediatric who Undergoing Eye Examination

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Abstract

Background: Ketamine is extensively used for perioperative analgesia, especially in children. It is associated with a high incidence of psychomimetic symptoms and nystagmus, which complicates some procedures including eye examination. In this study, we compared two doses of ketamine as premedication for an eye examination in children.

Methods: This triple-blinded, parallel, 2-group clinical trial included 60 children with ASA (American Society of Anesthesiology) classification I and II, aged 3 to 8 years, who were the candidate of eye examination under generalized anesthesia. They were randomized to receive two different doses of oral ketamine (2 or 4 mg kg^{-1}) as premedication. Sedation level (Ramsay sedation score), nystagmus, hallucination, cardiac rate, and O2 saturation, and the surgeon and nurse satisfaction were evaluated.

Results: The sedation score of ketamine 4 mg kg^{-1} group was significantly higher than the ketamine 2 mg kg^{-1} group (p=0.01). The occurrence of emesis was positively correlated with the dose of ketamine (r=0.26, p=0.04). However, there was no difference in the presence of nystagmus (p=0.15), heart rate (p=0.7), and O2 saturation (p=0.11) between the groups. There was no report of hallucination. The surgeon satisfaction (p=0.78) and the nurse satisfaction score (p=0.29) showed no significant difference between the two doses of ketamine.

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Conclusion: Ketamine at the dose of 4 mg kg^{-1} has greater sedative effects, whereas it is associated with more emesis. Since there is no difference in the satisfaction of treatment staff with anesthesia or other side effects between the two doses, oral ketamine 2 mg kg^{-1} is more preferable as pre-medication in children.

Introduction

Due to the poor cooperation of children for eye examination, examination under anesthesia is required in many eye procedures such as tonometry in glaucoma [1]. General anesthesia and medical procedures can be stressful experience for children which can develop increasing the need for analgesics, delirium and behavioral problems after surgery [2]. Therefore premedication can be helpful in controlling anxiety and separation from parents [3]. Oral ketamine is a good candidate as a premedication for pediatric patients. It is a sedative and analgesic drug which is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist [4]. Ketamine is widely used for short procedures and it is the drug of choice for pediatric sedation, as it has minimal cardiopulmonary and respiratory side effects [5-7]. Nausea and vomiting, excess salivation and lacrimation, double vision, dizziness and sleep problems are some of its side effects [4,8]. Some of ketamine's effects are dose-dependent at anesthetic or sub-anesthetic dose such as intraocular pressure [9], cardiac output [10], oculomotor activity and working memory [11]. Nystagmus is another side effect of ketamine which can make the eye examination challenging. It seems that effect of ketamine on NMDA receptors in the oculomotor nucleus in the brain stem is responsible for nystagmus [12]. Therefore, eye examination under anesthesia with ketamine could be challenging while accompanied by nystagmus, as it causes problems for some examinations [13]. Eventually, we aimed to evaluate existence of nystagmus and other side effects of ketamine among distinct dosages. Herein we compared two different doses of oral ketamine based on sedative efficacy and following complications.

Methods and materials

Subjects

In this triple-blinded, parallel, 2-group clinical trial, 60 children, aged 3 to 8 years, who were candidates for eye examination under generalized anesthesia were randomized to receive two different doses of oral ketamine as premedication. Of patients who came to our center, between January 2017 to December 2018, 60 patients were included in the study. Participants were eligible for inclusion if they met the following criteria's: age between 3 and 8 years; indication for eye examination under general anesthesia; and American Society of Anesthesiologists (ASA) I-II physical status. Exclusion criteria's were: known hypersensitivity or allergy to the study drugs; history of cardiovascular diseases or psychological disorders and history of postoperative vomiting.

Randomization and blinding

Patients were randomly assigned to receive ketamine either at dose of 2 mg kg^{-1} or 4 mg kg^{-1} (single-dose, oral) 30 min before induction of anesthesia, using block randomization with mixing block sizes 4. The size of blocks was not disclosed for minimizing the chance of cracking the code. An investigator with no clinical involvement in the trial prepared a computer random number list for block randomization. Two trained physicians (an anesthesiologist and an ophthalmologist) and a nurse, who was blinded to the randomization method and treatment assignment, collected the data. A blinded investigator to the study groups also analyzed the data.

Interventions and data collection

The patients' demographic data, medical history, and the decision for the examination under anesthesia were recorded at the reception. About 30 min before transferring to the operating room, the participants received oral ketamine at doses of 2 or 4 mg kg^{-1} respectively. Once in the operating room, the sedation level was scored by using the Ramsay sedation score before the induction of general anesthesia. This scale divides the level of sedation into six different categories ranging from severe agitation to deep coma [14]. A blinded ophthalmologist assessed the nystagmus of participants. If the children were restlessness for the physical examination, the second dose of ketamine would be administered.

All of the patients were anesthetized after preoxygenation with the administration of fentanyl (1 µg kg^{-1}) and sevoflurane (5%). After ensuring the sufficient depth of anesthesia, endotracheal intubation was performed and anesthesia was maintained with sevoflurane 3%. Supplemental oxygen (O2) was administered via the tracheal tube (2l/min).

The standard cardiorespiratory monitoring, continuous ECG monitoring, heart rate, mean blood pressure (with 5-minutes intervals), continuous pulse oximetry, capnography, temperature, and nasal end-tidal CO2 were regularly controlled and documented from the beginning of anesthesia.

The patients were then kept at the recovery room (40 to 50 min after administration of ketamine, looking for the presence of nausea and vomiting, and hallucination). Additionally, the postoperative pain was measured as a determinant of surgeon satisfaction with anesthesia by a 9-point Likert scale (ranging from 'no pain' to 'very severe pain'). The satisfaction of recovery nurse with the general condition of the patients were scored using a 5-point Likert scale ('very dissatisfied', 'dissatisfied', 'neither satisfied, nor dissatisfied', 'satisfied', 'very satisfied').

Sample size and statistical analysis

The sample size was calculated using G*power software version 3. Group sample sizes of 30 in each were sufficient to achieve an 80% power to detect a difference of 0.3 (0.1 vs. 0.4) between the group proportions.

Statistical analysis was performed with SPSS version 24 (Chicago, IL, USA). Shapiro-Wilk test was performed to evaluate the normality assumption of continuous variables. T-test was applied for variables with normal distribution. Mann-Whitney U test were used in case that the distribution of data was not normal. Chi-square test was used for qualitative variables and Spearman correlation was used to measure the statistical dependency between the two variables. A P-value < 0.05 was considered significant.

Statement of ethics

The study was performed according the Declaration of Helsinki and the Medical Research Involving Human Subjects [15]. The ethics committee approved the research protocol (Ethics Approval ID: IR.TUMS.FARABIH.REC.1397.005). The law authorizes parent(s) or guardian(s) of any participated child read and

signed the form of informed consent before enrolling in the study. The child's assent was also obtained for participating in research. For this reason, an assent form was read with to or with the child, depending on the child's comprehension and reading abilities.

Results

All of the 60 enrolled patients who were randomized to receive oral ketamine 2 mg kg^{-1} (n=30) or ketamine 4 mg kg^{-1} (n=30) completed the study. The mean age of participants was 4.5±1.4 (3-8) years and the mean weight was 16.05±3.5 (10.17-27.5) kg. Twenty-eight (46.7%) of all participants were female. Both groups were matched regarding patients' parameters including age, sex, or weight (Table 1).

Assessment of sedation level indicates that none of the patients had the Ramsay sedation score of 1 (awake and anxious, agitated, or restless) or 6 (no response to a painful stimulus). Of 30 patients who were treated with ketamine 2 mg kg^{-1}, 13.3% (4 cases), 40% (12 cases), 36.7% (11 cases), and 10% (3 cases), had the Ramsay sedation score of 2, 3, 4, and 5, respectively. In the group that received high dose of ketamine (4 mg kg^{-1}), about 3.3% (1 case), 23.3% (7 cases), 46.7% (14 cases), and 26.7% (8 cases) obtained Ramsay sedation score of 2, 3, 4, and 5, respectively. The participants who were treated with ketamine 4 mg kg^{-1} had significantly higher sedation scores compared to those in the ketamine 2 mg kg^{-1} group (3.96 vs. 3.43; U=299, p=0.01). There was also no difference regarding the presence of nystagmus between the study groups (0 (0%) with low dose ketamine vs. 2 (6.7%) with high dose ketamine; X^2 (1) = 2.06, p=0.15).

The data of vital signs during the general anesthesia showed that there is no significant difference in heart rate (U=424; p=0.7) and O2 saturation (U=349; p=0.11) between the treated groups.

There was no report of hallucination in our patients. Of all participants, 7 (11.66%) and 2 (3.33%) patients had nausea and vomiting and nystagmus, respectively. The incidence of nausea and vomiting was significantly greater with pre-treatment with a high dose of ketamine 1 (3.3%) vs. 6 (20%); X^2 (1) =4.04, p=0.04). Accordingly, the Spearman correlation showed that the occurrence of emesis is positively correlated with the dose of ketamine (r=0.26, p=0.04). Scoring of pain as an indicator of surgeon satisfaction (U=431.5, p=0.78) as well as the nurse satisfaction at the recovery room (U=386, p=0.29) showed no significant difference between the two doses of ketamine (Table 2).

Figure 1: Demographic data of participants.

Characteristics	Ketamine (2 mg kg^{-1}) N=30	Ketamine (4 mg kg^{-1}) N=30	P value
Gender, n (%)			
Female	14 (46.7%)	14 (46.7%)	>0.05
Male	16 (53.3%)	16 (53.3%)	>0.05
Age (year)	4.53 (4 [3-8])	4.46 (4 [3-8])	0.97
Weight (kg)	15.6±3.32	16.51±3.72	0.32

Values are means ±SDs or means (medians [minimum-maximum])
n-noun; kg- kilogram

Figure 2: Clinical characteristics of patients after pre-treatment with ketamine.

Variables	Ketamine (2 mg kg^{-1}) N=30	Ketamine (4 mg kg^{-1}) N=30	P value
Heart rate (beats/min)	109.23 (112 [80-120])	111.06 (110.5 [94-124])	0.7
O2sat (%)	98.4 (98 [97-100])	98.1 (98 [96-100])	0.11
Ramsay sedation score	3.43 (3 [2-5])	3.96 (4 [2-5])	**0.01**
• 1 (Anxious or restless or both)	0	0	
• 2 (Awake and cooperative, orientated and tranquil)	4	1	
• 3 (Awake but drowsy and responding to commands)	12	7	
• 4 (Asleep and brisk response to stimulus)	11	14	
• 5 (Asleep and sluggish response to stimulus)	3	8	
• 6 (Asleep and no response to a stimulus)	0	0	
Nystagmus	0	2	0.15
Nausea/vomiting	1	6	**0.04**
Hallucination	0	0	-
Surgeon's satisfaction (pain)	3.1 (3 [1-6])	3.2 (3 [1-6])	0.78
• 1 (No pain)	2 (6.7%)	4 (13.3%)	
• 2 (Maybe no pain)	8 (26.7%)	7 (23.3%)	
• 3 (Little upset)	5 (16.7%)	5 (16.7%)	
• 4 (pain/little upset)	4 (13.3%)	9 (30%)	
• 5 (Mild to moderate pain)	2 (6.7%)	3 (10%)	
• 6 (Moderate pain)	1 (3.3%)	2 (6.7%)	

• 7 (Moderate to severe pain)	0 (0%)	0 (0%)	
• 8 (severe pain)	0 (0%)	0 (0%)	
• 9 (Vary severe pain)	0 (0%)	0 (0%)	
Nurse's satisfaction	4.5 (5 [2-5])	4.3 (4.5 [2-5])	0.29
• 1 (very dissatisfied)	0 (0%)	0 (0%)	
• 2 (dissatisfied)	1 (3.3%)	1 (3.3%)	
• 3 (neither satisfied nor dissatisfied)	2 (3.3%)	4 (13.3%)	
• 4 (satisfied)	8 (26.7%)	10 (33.3%)	
• 5 (satisfied)	19 (63.3%)	15 (50%)	

Values are means ±SDs or means (medians [minimum-maximum]), n- noun; min-minute; O2sat- O2 saturation

Discussion

In the present study, oral ketamine at both doses of 2 and 4 mg kg^{-1} induced a satisfactory level of sedation for an eye examination in children. While the Ramsay sedation score was significantly higher in ketamine 4 mg kg^{-1} group. Our findings showed that ketamine is associated with minimal cardio-pulmonary effects and good recovery as there was no record of apnea or tachyarrhythmia in both groups. Additionally, there was no difference in heart rate and O2 saturation between the groups. Hallucination was not reported by any of the participants. The presence of nystagmus was not comparable between the study groups; however, nausea and vomiting occurred more frequent in ketamine 4 mg kg^{-1} group. The nurse satisfaction with the recovery process and surgeon satisfaction with anesthesia were optimal with both doses of ketamine and there was no difference between the groups in such scales.

Anesthesia is highly required for frightened children during an eye examination to minimize eye movement. Premedication facilitates child separation from parents and anesthesia process. The oral route is recommended as the ideal route of pediatric premedication [16]. Ketamine is widely used for sedation, induction, and maintenance of general anesthesia. Having satisfactory sedative effect has made ketamine a proper candidate as a premedication in children. It has been shown that ketamine > 0.3 mg kg^{-1} affects consciousness and arousal to a significant degree [8]. Accordingly, a positive correlation is revealed between the increasing dose of ketamine and the level of sedation [5]. Similarly, we found a desirable sedation effect with both doses of oral ketamine while the sedation level was significantly greater with oral ketamine 4 mg kg^{-1} (3.96) vs. oral ketamine 2 mg kg^{-1} (3.43). On the other hand, there has been no significant difference between the sedative effect of 0.5 and 0.75 mg kg^{-1} of intravenous ketamine in adults [16] or 3 and 6 mg $kg^{-1}$of oral ketamine in children [17]. M Stevic et al. reported the Ramsay sedation score of 5 with oral ketamine at the dose of 3.4 mg kg^{-1}in children, which is much higher than our findings with oral ketamine [18]. This difference is due to the co-administration of fentanyl with ketamine and scoring the sedation level after induction of deep anesthesia with propofol.

Ketamine is also a good premedication because of its minimal interfere with respiration. Apnea and laryngospasm occurrence has been reported in only 0.8% and 0.3% of patients, respectively [19]. Here, we did not observe any respiratory depression with either high or low doses of ketamine. Moreover, it has been noted that ketamine could attenuate vital sign depression after propofol administration [20]. Secondary to its property, it also causes a transient increase in heart rate and blood pressure [21]. However, ketamine has been found to minimally affect the cardiovascular system [5-7, 16-17]. Accordingly, our data did not show any tachyarrhythmia with any dose of ketamine.

Other potential features of ketamine include simplicity in administration, rapid onset of action, adequate analgesia, amnesia and immobilization, minimal negative effects on cardiac function, a broad safety margin, and smooth recovery [22]. It has been proved to be adequate for ophthalmological examinations despite the high incidence of nystagmus and diplopia [23]. Additionally, hallucination, delirium, vivid dreams, floating sensation, nausea and vomiting have been reported following the administration of ketamine [8]. However, there are still controversial reports regarding the incidence of ketamine-related side effects.

It has been shown that nystagmus typically appears with high or even sub-anesthetic doses of ketamine presumably by antagonizing the NMDA glutamate receptors of the oculomotor nucleus in the brain stem [12]. A statistically significant higher incidence of nystagmus or diplopia has been found with ketamine comparing with control groups (6.2% vs. 2.6%) (23). Comparing with previous studies, our findings represent the lower incidence of nystagmus (3.33%) following pre-treatment with ketamine (only with 4 mg kg^{-1}). EA Kose et al. showed that nystagmus appeared in 20% and 30% of adult patients who were treated with intravenous ketamine at doses of 0.5 and 0.75, respectively [17]. Şekerci, S et al. found that 13 and 20% of the children anesthetized with oral 3 and 6 mg kg^{-1} ketamine had nystagmus, respectively [16]. M Stevic et al. also revealed the incidence of 49.5% with intravenous ketamine (3.43 ± 1.24 mg kg^{-1}) in children [18]. LE Imbellon et al. reported the occurrence of nystagmus in 55% of adult patients received 0.1-0.25 mg kg^{-1} of dextro-ketamine intravenously. They did not find any association between the increase in the dose of ketamine and the appearance of nystagmus while hallucinations seem to be related to the dose administered [5, 24]. In our study, using the low dose and the high dose of oral ketamine suggests that the appearance of these effects was not dose-dependent so that none of the patients hallucinated and there was no difference in the occurrence of nystagmus between the groups. At doses of 1–3 mg kg^{-1}, more than one-third of patients found to have unsavory dreams or psychosis that may or not be related to hallucination [25]. At lower doses (0.1-0.5 mg kg^{-1}) it may impair some cognitive functions such as attention, memory, reasoning, and thinking [26]. The incidence of hallucination and psychotic symptoms is suggested to be higher in older children [16]. The mean age of our patients is about 4.5, which may explain the zero incidence rates. However, this hypothesis is not extensible to all previous reports as M Stevic et al. reported that 19.4% of

children with the mean age of 3.89 ± 2.92 had hallucinations after injection of ketamine (3.43 ± 1.24 mg kg^{-1}) [18].

There is no increased risk of nausea and vomiting with lower doses of ketamine. Due to its opioid-sparing effects, ketamine has been shown to be associated with a lower rate of postoperative nausea and vomiting [21]. Our findings with the incidence of ketamine-induced nausea and vomiting (20% with ketamine 4 mg kg^{-1} and 3.3% with ketamine 2 mg kg^{-1}) is comparable to that of reported by the previous studies with similar sample size and dosage [16]. Additionally, the current data represent the association of nausea and vomiting with the dose increment. Ketamine- induced emesis is suggested to be modestly associated with increasing age, with a higher incidence (in patients >5 years of age) [27]. We also did not observe any difference in sedation level or adverse effects between the low and high doses of ketamine, which explains the similar surgeon and nurse satisfaction with either dose.

Considering the dose-dependent sedative effect of ketamine, further investigations involving a greater range of dosage and bigger sample sizes are warranted to identify the optimal dose and its association with age, sex, and other characteristics.

Administration of oral ketamine at the dose 4 mg kg^{-1}, 30 min before eye examination, has a greater sedative effect in children. However, this difference did not affect the surgeons' and nurse's satisfaction with anesthesia or recovery time. Additionally, nausea and vomiting is occurred more frequently with oral ketamine 4 mg kg^{-1}, while there is no significant difference in the incidence of other side effects (e.g. the psychomimetic symptoms and presence of nystagmus) between the two doses of oral ketamine. Taken together, ketamine 2 mg kg^{-1} seems to be more favorable.

Main points

- Both dosages of ketamine (2 mg kg^{-1} and 4 mg kg^{-1}) have a satisfactory sedative effect for the eye examination in pediatrics.
- It seems there is no difference in presenting nystagmus as a side effect in two different studied dosages.
- The ketamine dose of 2 mg kg^{-1} seems to be more favorable for sedating children in eye examination procedures.

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