

Comparison of oral ketamine and promethazine on preoperative anxiety of children

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ABSTRACT

Introduction: In children, reducing preoperative anxiety is important to ensure proper anesthesia, and induction of appropriate anesthesia can prevent adverse postoperative behavioral changes. Ketamine and promethazine have been used as pretreatment to improve anxiety, but the advantage and comparison of these compounds over each other has not yet been determined.

Methods and materials: This clinical trial study conducted on sixty children were evaluated in 3 groups Received ketamine (n = 20), promethazine (n = 20) controls (n = 20) by available method. children aged 3 to 8 years who have received the desired pre-medication 30 minutes before entering the operating room and their anxiety level upon entering the operating room Has been measured. Statistical analyses were done using IBM-SPSS 25.0. and Chi-square test were used for data analysis.

Results: Sixty children with a mean age of 5.37 years were examined. In the ketamine group 85% of children and in the promethazine group 65% showed reduction in anxiety. Anxiety was higher in the ketamine group than in the promethazine group, but was statistically significant only in the ketamine group (p).

Conclusion and discussion: We found that the use of oral ketamine as a premedication for anesthesia in children is somewhat associated with less anxiety and restlessness in them. Promethazine can also be effective in preoperative sedation in children and there is no significant difference between the two drugs studied.

Keyword: children, ketamine, promethazine, preoperative anxiety, anesthesia

INTRODUCTION

Hospitalization of children, especially for surgeries, is always accompanied by fear and anxiety in them. The child's age and level of understanding is an important factor in the feeling of fear and anxiety before anesthesia and surgery. At a younger age, children often have the anxiety of being separated from their parents [1-6]. At older ages, fear of being naked, fear of incisions, fear of waking up during surgery, fear of postoperative pain, or even fear of death can affect children's minds, which In addition to causing psychological damage, it leads to disruption of the natural course of a safe and successful anesthesia [7].

Inducing a good and calming feeling can improve the undesirable behavioral changes of surgery in children[1]. A wide range of techniques and medications have been used with varying degrees of success in surgery to reduce problems and increase the effectiveness of appropriate anesthesia in children [8-11]. The use of premedication varies according to the underlying medical condition in each child, the length of surgery, how to induce anesthesia, and the degree of anxiety in the child and parents. One of these methods is the use of ketamine, which is thought to reduce stress and anxiety before surgery and is also effective in reducing pain before and after surgery [12, 13[12]]. Ketamine is a versatile anesthetic that acts through complex neural mechanisms as an NMDA receptor antagonist. It produces a strong analgesic effect that is increasingly used for pain management and palliative care [13-16].

Determining effective drug compounds for preoperative anxiety in children can help professionals, including nurses and hospitals, choose the most appropriate solution to control anxiety. Comparison of ketamine combination with other routine sedatives related to anxiety in children has not been done so far, and its study will greatly help to identify and provide new treatment strategies.

In this study, we decided to evaluate the sedative effect of two oral prodrugs, ketamine and promethazine, on children aged 3 to 8 years who are candidates for outpatient surgery.

METHODS AND MATERIALS

Study design: This one-way blind clinical trial study was performed on the children candidates for surgery who referred to Shahid Rajaei Hospital in Tonekabon in mazandaran, Iran from 2019 and 2020. Sixty eligible patients were selected according to the inclusion criteria and entered the study. The effectiveness of drugs on anxiety was evaluated in three groups: ketamine, promethazine and control group. Written consent form for participation in the research plan was consciously signed by his parents.

Inclusion and Exclusion criteria: Inclusion criteria include children 3 to 8 years old in class one or two of American Society of Anesthesiologists (ASA), Parental satisfaction and lack of sensitivity to the drugs. Children with underlying anxiety disorder and children whose parents (one or both)

had underlying anxiety disorder were excluded from the study, and if external anxiety factors in any way affected the sample during the study (In a way that removed it from the conditions equal to other samples) the sample was removed from the study. Children with chronic diseases were also excluded from the research before the study.

Patient and data collection: The sample size was sixty which were randomly divided into 3 groups A, B and C. Group A included children 3 to 8 years of age who received 5 mg/kg of oral ketamine diluted with 20% dextrose to a volume of 0.2cc/kg 30 minutes before entering the operating room. (Ketamine Rotexmedica 50mg/ml - 10ml) Group B included children 3 to 8 years of age who received

1 mg/kg oral promethazine 30 minutes before entering the operating room. (Chemoprozin 5mg/5ml - 60ml syrup) [16] And group C or controls consisted of children who received only 0.2cc/kg of 20% dextrose without any anesthesia 30 minutes before entering the operating room.

The data collection tools in this study is a checklist that qualitatively assesses the level of anxiety and emotional states of the child in the two time periods; before receiving the prodrug or placebo and also 30 minutes after it, upon entering the operating room. To measure anxiety, the VFAS (Visual Facial Anxiety Scale) [17] was used (Fig 1), which categorizes patients into 6 levels of anxiety as follows:







Anxiety Level	None	Mild	Mild-Moderate	Moderate	Moderate-High	Highest
Faces						

Fig 1: A total of 6 facial expressions were designed to reflect differing levels of Anxiety.

Statistical analysis: Data were analyzed using descriptive statistics (mean), independent t-test and chi-square. The Kolmogorov-Smirnov test for normality was performed. SPSS V.25 was used applied for statistical analysis. statistical significance was assessed at the 5% level.

Research ethics: This study was approved on 06/02/2019 in the ethics committee of Islamic Azad University, Tonekabon branch, with the ID: IR.IAU.TON.REC.1398.004. And was registered on 23/9/2020 with the code IRCT20200921048789N1 in the Clinical Trial Registration Center of Iran.

RESULTS

A total of sixty children with their parents participated in this study. Demographic data and the results of measuring preoperative anxiety of study participants are shown in Table 1.

Table 1- Demographic data and the results of measuring preoperative anxiety of study participants

Parameters	Number of patients	Percentage (%)
Sex		
Boys	30	50%
Girls	30	50%
All	60	100
Age (years; mean \pm SD)	5.37 \pm 2.21	

In a group of children who were given ketamine, the mean score of children's anxiety severity and before taking ketamine was 3.35 / 6 and after taking ketamine was 1.40 /

6. In the other group, the mean score of children's anxiety severity before taking this drug was 3.30 and after taking oral promethazine was 2.35 / 6 / 6. In the placebo group, the mean score of pediatric anxiety severity severity of anxiety before placebo 2.25 / 6 and lower than the mean after placebo was 2.80 / 6.

According to Table 2, the anxiety intensity scores of two groups of ketamine and promethazine after taking the oral drug showed a significant decrease ($P < 0.05$). And Anxiety severity score in the placebo group did not change positively and was not significant.

Table 2 - Severity of anxiety, before and after medication and before surgery

Anxiety severity	Before	After	P value
ketamine	3.35 / 6	1.40 / 6	0.00
promethazine	3.30 / 6	2.35 / 6	0.01
placebo	2.25 / 6	2.80 / 6	0.09

According to Table 3, in the group of children who received ketamine, 17 patients (85%) were in the anxiety reduction category. Regarding promethazine, 13 patients (65%) were related to people with reduced anxiety, but fewer than ketamine. Finally, the group received a placebo as a pre-anesthetic drug to reduce anxiety. None of them had a reduction in anxiety and the highest frequency with 14 people (70%) was related to people who did not change their anxiety. According to the results of the statistical test, the groups were significantly different in terms of the severity of anxiety after receiving the drugs ($P < 0.05$).

Table 3 - The effect of ketamine and promethazine on levels of preoperative anxiety in children

Level of anxiety	Ketamine	promethazine	placebo	P-value
Decrease	17 (85%)	13 (65%)	0	
Effectless	2 (10%)	4 (20%)	14 (70%)	0.00
Increase	1 (5%)	3 (15%)	6 (30%)	
Total	20	20	20	

Ketamine and promethazine have a greater effect on reducing preoperative anxiety in children than placebo (Table 4). Comparison data for ketamine and promethazine show that both drugs often reduce preoperative anxiety in children and there is no significant difference between the two drugs in terms of their effect on preoperative anxiety in children 3 to 8 years old. (P value=0.33).

Table 4 - Comparison of the relationship between the groups of anxiety severity

Groups	Ketamine	promethazine	placebo
Ketamine	1	0.33	0.00
promethazine	0.33	1	0.00
placebo	0.00	0.00	1

DISCUSSION

Reducing preoperative anxiety in pediatric patients despite surgery is still a challenging issue. Due to the fact that very few studies have been performed on preoperative anxiety in Iranian children, our study has tried to identify a better and effective drug to reduce anxiety. The use of pharmacological agents in various oral, intravenous, intramuscular and rectal methods can be effective in reducing preoperative anxiety in children and preparing the child to enter the operating room and start surgery. Ketamine is used as a sedative and analgesic, usually as a prodrug in children [18]. Our findings show that oral ketamine was more effective than promethazine in reducing anxiety, but this difference was not statistically significant in the two groups. The two groups showed a significant decrease in the severity of anxiety after receiving the drug orally, and both groups showed a significant difference with the placebo group. Similar studies have shown that ketamine plays an important role in reducing anxiety [19]. The study of A. Paydar et al. showed that the use of oral ketamine as an anesthetic prodrug in surgery of children 2 to 10 years of age is more effective than promethazine syrup [20]. In the study of Akbar Rostaminejad et al., it was found that the use of ketamine as a prodrug of anesthesia reduces the child's excitement, anxiety and fear when separated from parents and causes calm, lack of resistance, not crying and sleeping during bed transfer [21]. In a study by N. Yeganeh et al., in children who received oral ketamine as a prodrug for anesthesia, all findings, including restlessness when separated from parents and when implanting an intravenous catheter, were significantly lower in the case group than the control group [22]. In a study by S. Turhanoilu et al., the use of 8 mg / kg oral ketamine was significantly more effective in calming children than the 4 mg / kg dose. Postoperative recovery was also longer in the group receiving 8 mg / kg oral ketamine [23].

Various findings similar to our study point to the effective and consistent role of ketamine sedatives over other drugs and suggest that ketamine is a reliable combination for reducing preoperative anxiety [19, 24].

The problem of adverse postoperative side effects, such as salivation, nausea, vomiting, and psychiatric complications in sedatives, has limited them as a single choice of pretreatment [25]. We suggest that due to the effective effectiveness of ketamine in future studies, the

combined use of ketamine with other drugs should be considered. In a similar study of intranasal dexmedetomidine with oral ketamine as a preoperative pretreatment in children, they concluded that the combination of 2 mg / kg nasal dexmedetomidine and 3 mg / kg oral ketamine resulted in a process. There are fewer side effects or postoperative complications [25]. In addition, other studies have noted that the combination of ketamine affects the pharmacology of the drug and improves the effect of the drug faster [26, 27].

Oriby reported in 2019 that treatment with intranasal dexmedetomidine 2 µg / kg and oral ketamine 3 mg / kg is a rapid and effective option in reducing anxiety in children undergoing dental rehabilitation compared to midazolam 0.2 mg. They have a better effect on kilograms [24].

The anesthetic and analgesic properties of ketamine are obtained by direct inhibition of N-Methyl-D-aspartate receptors. Confidently analyzing the drug target of ketamine and its metabolites provides important insights into development of new drugs with favorable clinical effects in children [28].

One of the limitations of the study was not examining the role of psychological factors such as the role of parents and environmental factors such as income level and place of residence on children's anxiety. One of the strengths of our research was the sample size.

In general, the most important finding of this study on Iranian children aged 3 to 8 years who were candidates for surgery was that an oral dose of injectable formulation of ketamine or promethazine is effective in rapid sedation and reduction of preoperative anxiety, but this effectiveness in relation to with ketamine was more than promethazine.

CONCLUSION

The findings of the present study showed that use of oral ketamine at a dose of 5 mg / kg is somewhat more effective in reducing preoperative anxiety compared to oral promethazine syrup at a dose of 1 mg / kg as an anesthetic premedication in children 3 to 8 years. However, there is no significant difference between the two groups and according to the facilities and access to the hospital, both drugs can be used.

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