

## Promethazine hydrochloride reduces children's agitation during ocular examination for trauma

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### Abstract

Examination and intervention are always the causes of agitation, anxiety, and fear in children's lives. This study aimed to investigate the effectiveness of promethazine hydrochloride in reducing children's agitation during the ocular examination for trauma. In this interventional-clinical trial study, a total of 62 children referred to Al-Zahra Ophthalmology Hospital in Zahedan, Iran, were evaluated in two matched groups (case (n = 31) and control (n = 31)) for an initial examination of ocular trauma. Finally, the intervention was performed (giving placebo or promethazine hydrochloride cough syrup 20 minutes before the initial ocular examination at 0.5 mg/kg), and the demographic information form and researcher-made questionnaire modeled on the Cohen-Mansfield Agitation Inventory (CMAI) were completed. The obtained results revealed that the mean scores of physical/aggressive behaviors ( $p < 0.001$ ), physical/nonaggressive behaviors ( $p = 0.013$ ), verbal/aggressive behaviors ( $p < 0.001$ ), and hiding behaviors ( $p < 0.001$ ) were significantly lower in the promethazine hydrochloride-receiving group than the placebo group. These findings demonstrated that promethazine hydrochloride cough syrup facilitated the examination among the pediatric patients who suffered from traumatic ocular injuries. However, further studies in this field need to be carried out through randomized controlled trials.

**Key Words:** Examination, ocular, promethazine hydrochloride, trauma.

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Pediatric patients visit primary healthcare providers in medical settings an average of 31 times from birth to age 21 for general wellness; and encounter ancillary medical caregivers, including medical assistants, nursing staff, laboratory, and physical and mental health therapists. Furthermore, up to 20% of the people report feeling "white coat syndrome" when coming into contact with medical doctors.<sup>1</sup> Typically, anticipating and engaging in healthcare settings with medical professionals for children produce feelings of being afraid or anxious. Due to limited cognitive development, children use behavior rather than words to

communicate their emotions. Common behavioral expressions of anxiety include aggression, lack of cooperation, and regression. These behavioral expressions impede provider execution of medical protocols, requiring more time in the treatment process.<sup>2,3</sup> Approximately more than 15% of children will experience some condition of relative trauma throughout life. Developmentally speaking about medical care can lead to heightened anxiety.<sup>4,5</sup> For example, detailed examinations and diagnostic procedures are essential for ophthalmologists to treat pediatric patients with eye diseases appropriately.

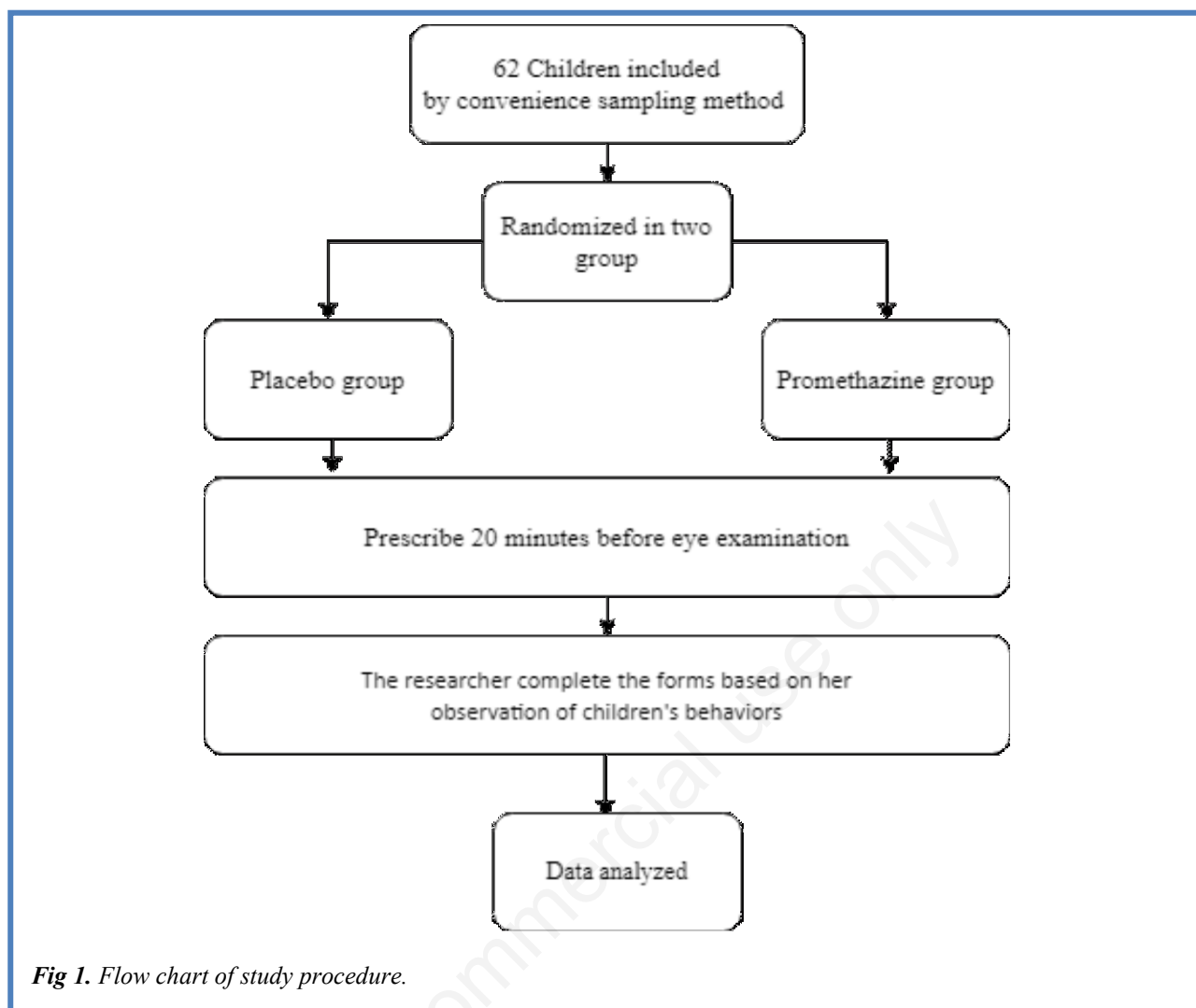


Fig 1. Flow chart of study procedure.

However, careful ophthalmic examinations are a considerable challenge for successful eyes test performance in a suitable position due to children's noncooperation. Maintaining a fixed eye position, with a vertical alignment of the head, on the scanner during ophthalmic examinations is required for obtaining accurate data and may require moderate to deep sedation in children.<sup>6</sup> Behavior management for young pediatric patients may be challenging. In this respect, the use of pharmacologic methods, including conscious sedation or general anesthesia, is advised to avoid unsafe, substandard treatments.<sup>7,8</sup> Since general anesthesia desires a minimum hospital setup and an experienced operator, conscious sedation is proposed as a proven cheaper and more convenient method. Thus, sedative agents need to be administered to complete examinations, i.e., it is essential to sedate uncooperative children.<sup>9,10</sup> The clinical outcome of sedative approaches depends on the patient's response to sedative medication. Therefore, appropriate drug regimens and routes, proper patient selection, and close monitoring seem to enhance the efficacy of sedation

and, therefore, clinical procedures.<sup>11</sup> Promethazine hydrochloride is an old, affordable, and readily available oral antihistamine drug with hypnotic and sedative effects that can be used as a sedative. It also shows anticholinergic properties because it can block postsynaptic dopaminergic receptors.<sup>12,13</sup> It is worth noting that promethazine hydrochloride has been used successfully for clinical procedures.<sup>14-17</sup>

Considering the importance of ocular examinations in children and behavioral avoidance caused by age, this study aims to evaluate the effect of promethazine hydrochloride on reducing children's agitation before performing physical procedures to provide a suitable solution for physicians other than the use of solid sedatives with high side effects.

#### Materials and Methods

This study was designed as a randomized controlled trial by two groups. The Ethics Committee of Zahedan University of Medical Science approved the study protocol (IR.ZAUMS.REC.1398.430). The study procedure was also registered in the Iranian Registry of Clinical Trials. Sample size (considering  $\alpha = 0.01$ ,  $B =$

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**Table 1.** Mean and Standard Deviation of variables in the two study groups.

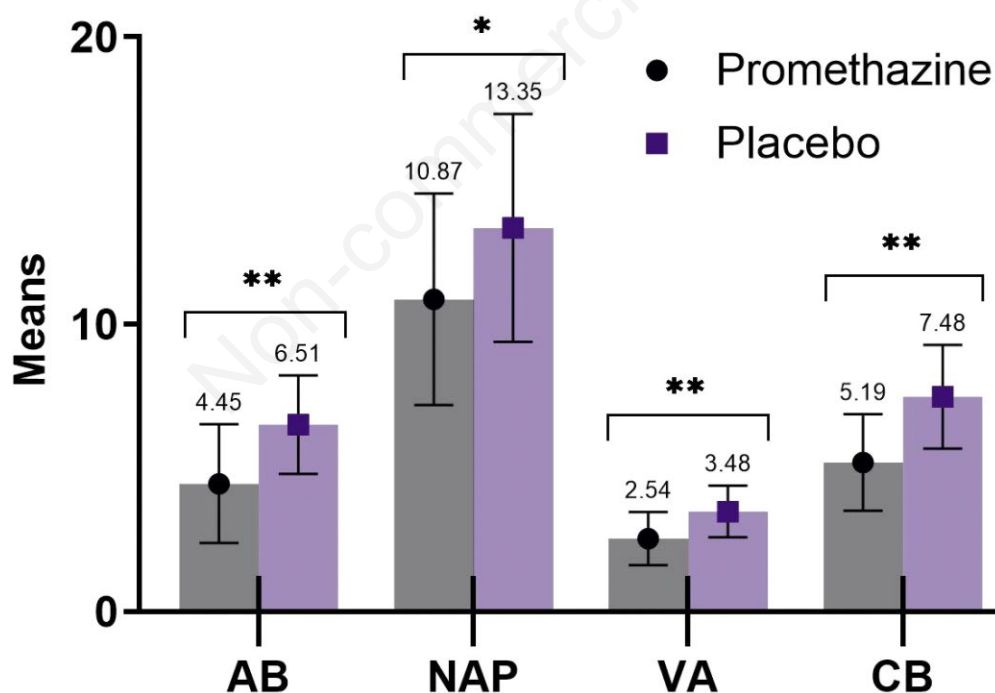
Variables	Case (Promethazine hydrochloride)	Control (Placebo)
Physical/aggressive behaviors	4.45 ± 2.07	4.51 ± 1.71
Physical/nonaggressive behaviors	10.87 ± 3.68	13.35 ± 3.97
Verbal/aggressive behaviors	2.54 ± 0.92	3.48 ± 0.92
Hiding behaviors	5.19 ± 1.68	7.48 ± 1.80

0.05, and  $k = 1$ ) included 31 participants for case and control groups; 2 to 7-year-old children were chosen for this study using convenience sampling method. The informed consent was taken from all children's parents. The exclusion criteria were as follows: history of seizure disorders, liver problems, coagulopathy, drug allergy, and having childhood squint/amblyopia problems.

In the present study, 62 children were randomized into two groups. One group received promethazine hydrochloride (the case group) and the second group received placebo (the control group) (0.05 mg/kg) 20 minutes before ocular examination. The researcher observed the children's behaviors and completed the researcher-made questionnaire (Figure 1). The researchers completed the forms based on their

observation of children's behaviors; all information has been kept confidential.

The questionnaires included demographic information (including age and gender), a researcher-made questionnaire modeled on the Cohen-Mansfield Agitation Inventory (CMAI),<sup>16</sup> which consisted of 4 subscales of physical/aggressive behaviors (2 questions), physical/nonaggressive behaviors (4 questions), verbal/aggressive behaviors (1 question), and hiding behaviors (2 questions) (see Appendix 1). The content validity index (CVI) and the content validity ratio (CVR) were employed to assess the content validity, and Cronbach's alpha coefficient was calculated to evaluate the internal reliability. Values of more than 70% would be acceptable for all three components. We reported the Cronbach's alpha



**Fig 2.** Results of independent *t* test between groups. \* $p < 0.05$ ; \*\* $p < 0.01$ .

AB: Physical/aggressive behaviors; NAP: Physical/nonaggressive behaviors; VA: Verbal /aggressive behaviors; CB: Hiding behavior.

coefficient for the subscales of physical/aggressive behaviors, physical / nonaggressive behaviors, verbal / aggressive behaviors, and hiding behaviors to be 0.85, 0.80, 0.88, and 0.76, respectively.

The collected data were entered into SPSS v22 software, and the statistical significance level was set at  $p < 0.05$ . Descriptive statistics were used to describe the sample mean and standard deviation. After examining the normality of the data, the independent t-test was performed to compare the means of the quantitative variables. Also, the relationship between the nominal variables were studied using the chi-square test.

### Results and Discussion

A total of 62 children (31 in each group) participated in this study—two groups matched by age and gender. The average age of each group was  $4.48 \pm 1.71$ , and 18 participants (58.1%) of each group were boys. Table 1 shows the means of physical/aggressive behaviors, physical/nonaggressive behaviors, verbal/aggressive behaviors, and hiding behaviors. Based on the independent t-test, there was a significant difference between the two groups in physical/aggressive behaviors ( $p < 0.001$ ), physical/nonaggressive behaviors ( $p = 0.013$ ), verbal/aggressive behaviors ( $p < 0.001$ ), and hiding behaviors ( $p < 0.001$ ) (see Figure. 2).

This study was conducted to assess the applicability of promethazine hydrochloride in controlling agitation during the ophthalmic examinations. The results revealed that the use of promethazine hydrochloride before the pediatric examination effectively reduced the agitation rate in children, and it made it even easier for the physician to examine the patient. Promethazine is used as an antihistamine, sedative, and antiemetic. The body releases histamine during different kinds of allergic responses. When histamine binds to its receptors at the cell surface, it produces changes that lead to itching and sneezing. Antihistamines (like promethazine hydrochloride) compete with histamine for one of the receptors on the cell's surface. Promethazine hydrochloride blocks the action of acetylcholine, which may explain its benefit in reducing the nausea of motion sickness. It is used as a sedative because it causes drowsiness as a side effect.<sup>17</sup>

In our study, participants experienced varying degrees of stress and anxiety during the examination, which affected their psychological and physiological levels. In general, fear and anxiety also exacerbate muscle contraction. If this condition persists, lactic acid builds up in the muscles, causing muscle hypoxia, general fatigue, and increased pain. It is a common antiemetic that has been used as a safe and effective drug with a low rate of side effects and failure.<sup>18</sup> Since promethazine hydrochloride has parasympathetic blocking effects in the body, this drug blocks the muscarinic effects of acetylcholine on parasympathetic nerve fibers. Therefore, it seems that the administration of this drug reduces muscle contraction.<sup>19,20</sup>

The ophthalmic examinations for the uncooperative pediatric can be conducted under either sedation or general anesthesia. Because the cost of anesthesia is higher, many pediatric ophthalmic examinations are carried out outside the operating room with sedation.<sup>21</sup> In a study by Mathai et al. of 2011,<sup>15</sup> comparing the effects of oral midazolam and promethazine on pediatric sedation, the results showed that both drugs could be easily used in pediatric sedation before each procedure, with no significant advantage between the two medicines. The results of our study are consistent with those research.<sup>15</sup> Pao et al. conducted a study on restlessness and illness in children and adults, showing that antihistamines were often used to relieve restlessness in children but should not be used for persistent restlessness; they can have many side effects due to their anticholinergic properties. Diphenhydramine, hydroxyzine, and promethazine hydrochloride may be used for sedation in adolescents and children. The results of this study also agreed with our research.<sup>22</sup> Ansari et al. studied the effects of oral midazolam and oral promethazine as a dental sedative pro-drug. They concluded that promethazine hydrochloride seemed to be the most suitable treatment strategy due to its availability and effectiveness in sedation in children, which is consistent with our results.<sup>23</sup> However, additional studies with higher sample sizes are needed to confirm the conclusions.

Overall, promethazine is a promising drug to use for medical examination. Despite the studies on this drug in dental settings, the evidence to use it in ophthalmology hospitals is limited. So, future studies should try to replicate the results of this study in a larger sample size and under more controlled conditions. Although our cumulative results showed the superiority of promethazine hydrochloride over placebo, future studies need to compare the effect of promethazine alone and in combination with other medications.

In conclusion, the current study showed that the use of promethazine hydrochloride facilitates examination in children with ocular trauma.

Therefore, promethazine hydrochloride was suggested to reduce pediatric agitation at the discretion of the specialist physician. Further investigations on promethazine hydrochloride (alone or in combination with other drugs) may be beneficial for developing an efficient approach to using this classical compound as a new drug in children's agitation.

### List of acronyms

- AB - physical/aggressive behaviors
- CB - hiding behavior
- CMAI - Cohen-Mansfield agitation inventory
- CVI - content validity index
- CVR - content validity ratio
- NAP - Physical/nonaggressive behaviors
- VA - Verbal /aggressive behaviors

### Contributions of Authors

All authors have read and approved the final edited typescript.

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### Conflict of Interest

The authors declare no financial, personal, or other conflicts of interest.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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