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Antiemetic effect of ondansetron versus metoclopramide in nauseous isolated head trauma patients: a double-blind randomized clinical trial

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Abstract: **Objective:** As nausea is one of the most common annoying symptoms in isolated head trauma (IHT) and needs timely management to prevent further adverse outcomes, this study was performed to compare ondansetron and metoclopramide as therapeutic agents in nauseous IHT.

Methods: This study was a double-blind clinical trial. Participants were patients visiting the ED with the chief complaint of nauseous IHT event. Group A received 10mg/2ml of metoclopramide and group B 4mg/2ml of ondansetron through slow intravenous (IV) injection. The primary outcome was the severity of nausea 20 minutes after the intervention based on the visual analogue scale (VAS) score.

Results: A total of 130 patients participated in the study (65 in each group). The mean age was 30.5±20.5 years, and 73.1% of the participants were male. The decrease in the mean nausea severity scores was statistically significant in both group A (78.3±9.7 before vs. 29.8±16.8 mm after the intervention; $P < 0.001$) and group B (78.5±11.1 vs. 27.8±13.9 mm; $P < 0.001$). There was no significant difference between the mean nausea severity scores of groups A and B before the intervention ($P = 0.93$) or after it ($P = 0.65$). The decrease in the severity score of nausea was 48.5 mm in group A and 50.6 mm in group B, with no significant difference between the two groups ($P = 0.63$).

Conclusion: Both Ondansetron and metoclopramide significantly reduced the severity of nausea in patients with mild IHT visiting ED but no treatment arm was superior. Both drugs showed good safety profiles.

Keywords: Clinical Trial; Head Trauma; Metoclopramide; Nausea; Ondansetron

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1. Introduction

Isolated head trauma (IHT) is one of the most important and common types of traumas seen in patients visiting the emergency department (ED) (1, 2). Head injury occurs in 22.1 per 1000 persons in a year (3) and accounts for one-third of deaths caused by trauma and 16000 deaths daily. It is a leading cause of disability worldwide (2). Developing countries like Iran experience a high incidence of IHT due to the high prevalence of accidents as its most common mechanism (2, 4, 5). A range of symptoms and signs are observed in patients with IHT including headache, nausea, vertigo, and loss of consciousness. Nausea in IHT is one of the most common annoying symptoms and needs timely management to prevent further adverse outcomes such as aspiration or rise of intracranial pressure (1, 6). The incidence of nauseous IHT has been reported between 25% to 28% in different studies and has become one of the important challenges in the ED (3, 7). Ondansetron, a serotonin receptor antagonist, and metoclopramide, a dopamine receptor antagonist, are widely used in the ED for the management of this condition. Differences in the onset of actions, effective dosages, and side effects make it difficult to choose the best antiemetic drug in patients with various causes of nausea and different clinical conditions (1, 8-12). Past studies mostly compared the antiemetic effects of ondansetron and metoclopramide in preventing or treating nausea related to chemotherapy and gastroenteritis and post-operative nausea (1, 8, 13-18). Because of the limited number of studies, there is no consensus among physicians regarding the best antiemetic drug for patients with IHT. Therefore, this study was performed to compare ondansetron and metoclopramide as therapeutic agents for the management of patients with nauseous IHT.

2. Methods

2.1. Trial design

This study was a double-blind clinical trial conducted at Imam Hossein Hospital affiliated with Shahid Beheshti University of Medical Sciences, in Tehran, Iran, between September 2016 and February 2017. The executive protocol of the study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.SM.REC.1394.209) and registered in the Iranian Registry of Clinical Trials (IRCT2017010231731N1). The study was conducted in accordance with the Declaration of Helsinki (seventh revision 2013). Written informed consent was obtained from all patients before they participated in the study. Performing this study did not impose additional costs on the participants.

2.2. Participants

Participants in the study were patients visiting the ED with the chief complaint of nauseous IHT event. The included patients were aged ≥ 15 years, had a score of at least 13 on the Glasgow coma scale (GCS) (19), and had been assigned to the triage level 3 or below on admission (20). The exclusion criteria were as follows: GCS score less than 13, triage level of 1 or 2, breastfeeding, pregnancy, alcohol use, current chemotherapy or radiotherapy, hemodynamic instability, neurological deficits, restless legs syndrome, known allergy to metoclopramide or ondansetron, use of illicit drugs or antiemetic medication within eight hours before the intervention, and receiving IV fluids during the admission. Those who could not complete the study were also excluded.

All patients visiting the ED with IHT underwent primary assessment, including evaluation of the airway status and head and neck condition and measurement of vital signs and level of consciousness based on GCS. A checklist, including items regarding age, gender, weight, mechanism of trauma (assault, motor vehicle collision, and fall), and accompanying symptoms (vertigo, headache, and blurred vision), was filled in for the participants.

2.3. Interventions

Group A received 10mg/2ml of metoclopramide and group B received 4m/2ml of ondansetron, through slow IV injection (1, 21). Ondansetron and metoclopramide were manufactured by Tehran Chemistry Company, Iran. A pharmacologist blinded to the study process provided the drugs, filled the syringes, and put number codes on them. The number code did not reveal which drug the syringe contained. The prepared drugs were kept in a fridge in the ED. A resident of emergency medicine was in charge of patient assessment and drug administration. The nausea severity score of the patient was determined before and 20 minutes after the intervention. If the nausea severity score did not show a significant decrease (at least 20 mm) after 20 minutes, 4mg ondansetron was administered as the rescue dose. The main researcher was the only person who knew about treatment arms and the content of syringes used in drug administration. All other people involved in the study, including patients, nurses, and other researchers, were blinded to the assessments unless extrapyramidal side effects, such as flushing, dystonia, and drowsiness, occurred (1).

2.4. Primary assessment

The visual analogue scale (VAS) is a standard self-report psychometric scale. The patient marks the severity of nausea along a straight-line scale from zero to 100 mm. Scores of zero and 100 refer to the lowest and highest severity of nausea, respectively. Scores of less than 50mm, 50mm to 70mm, 70mm and higher than 70 mm denote mild, moderate, and severe degrees of nausea, respectively (22).

2.5. Outcomes

The primary outcome was the severity of nausea, 20 minutes after the intervention, based on VAS. The requirement for a rescue dose and reported drug side effects, such as extrapyramidal side effects, were the secondary outcomes.

2.6. Sample size

Using the formula below, the sample size was calculated as at least 65 subjects in each arm of the study, with α=0.05, a power of 80%, a mean difference of 5, and a standard deviation (SD) of 14 in the nausea severity score of ondansetron and metoclopramide groups. The sampling of eligible participants was done by convenience method.

$$n = \frac{2S^2(Z_{1-\alpha/2} + Z_{1-\beta})^2}{d^2}$$

2.7. Randomization and blinding

Permuted block randomization was performed to balance the number of subjects assigned to each group, and patients were randomly assigned to blocks. Using a computer-generated table, the project supervisor randomly allocated letters A or B to the patients and assigned them to respective groups to receive the coded drugs.

2.8. Statistical analysis

SPSS Version 21.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The normality of distribution was assessed using the Shapiro-Wilks test and graphical approach. The quantitative variables were described using mean ± SD and qualitative variables using frequency and percentage. The independent sample t-test was used to assess the difference between the means of the two groups and the paired sample t-test to assess the difference between the means before and after the intervention in each group. The difference in qualitative variables was assessed based on the Chi-square and Fisher's exact tests (for normal variables) or Mann Whitney U test (for non-normal variables). A $P < 0.05$ was considered as statistically significant.

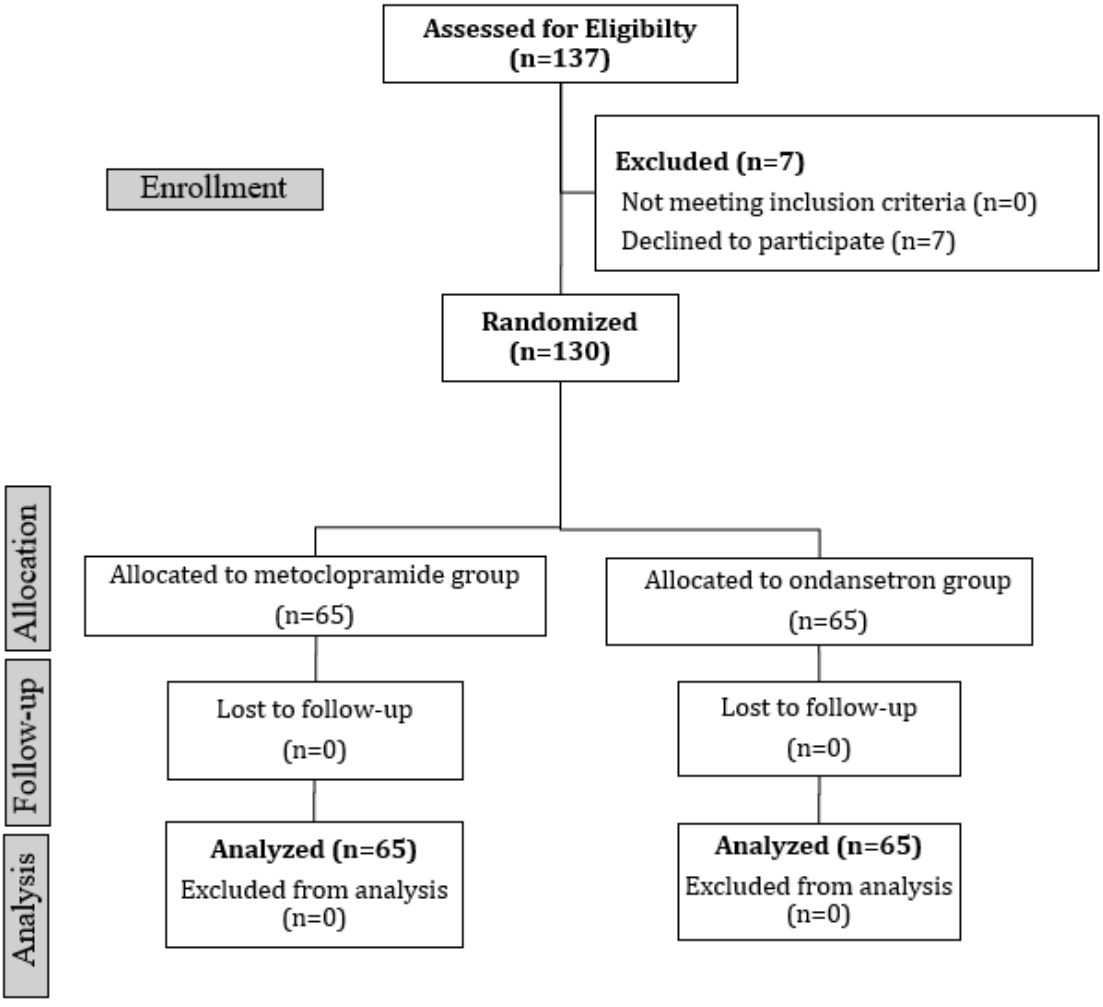

Figure 1 CONSORT flow diagram of the trial

3. Results

A total of 130 patients participated in the study (65 in each group). Figure 1 shows the CONSORT flowchart for the study patients. The mean age of the subjects was 30.5±20.5 years and 73.1% of them were male. The frequencies of accompanying symptoms, including vertigo, headache, and blurred vision, were 51(39.2%), 81(62.3%), and 17(13.1%), respectively. The frequencies of IHT mechanisms, including assault, motor-vehicle-collision, and falls, were 42(32.3%), 61(46.9%), and 27(20.8%), respectively. Before the intervention, the nausea severity scores of the patients were in the range of 60 mm to 100 mm, with 70 mm being the most frequent score reported by the patients (34.6%). However, 10 mm was the most frequent score in the secondary VAS assessment after the intervention (34.6%) (Figure 2).

The mean nausea severity scores for all patients before and after the intervention were 78.4±10.4 mm and 28.8±15.3 mm, respectively, and their difference was statistically significant ($P < 0.001$).

The mean nausea severity scores of group A before and after the intervention were 78.3±9.7 mm and 29.8±16.8 mm, respectively, and the decrease in the score was statistically significant ($P < 0.001$).

The mean nausea severity scores of group B before and after the intervention were 78.5±11.1 mm and 27.8±13.9 mm, respectively, and the decrease in the score was statistically significant ($P < 0.001$).

The mean severity scores of groups A and B before the intervention were not significantly different (P=0.93). Likewise, there was no significant difference between the mean nausea severity scores of the two groups after the intervention ($P = 0.65$) (Figure 3). Furthermore, the decrease in the severity scores of groups A and B were 48.5 mm and 50.6 mm, respectively, with no significant difference between the two groups in this regard ($P = 0.63$).

In both treatment arms, the requirement for a rescue dose was less frequent than non-requirement. Furthermore, there was no significant difference between treatment arms in terms of requirement and non-requirement for a rescue dose (P= 0.641) (Table 1). Finally, none of the participants reported any side effects.

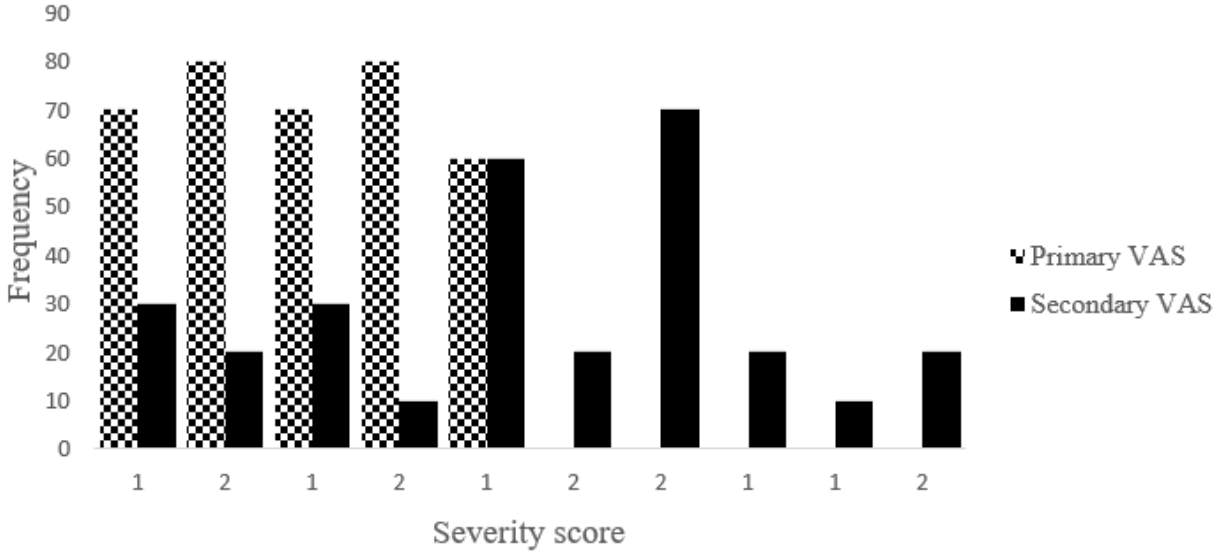

Figure 2 Distribution of the severity score of nausea and vomiting among treatment groups based on primary and secondary VAS scores

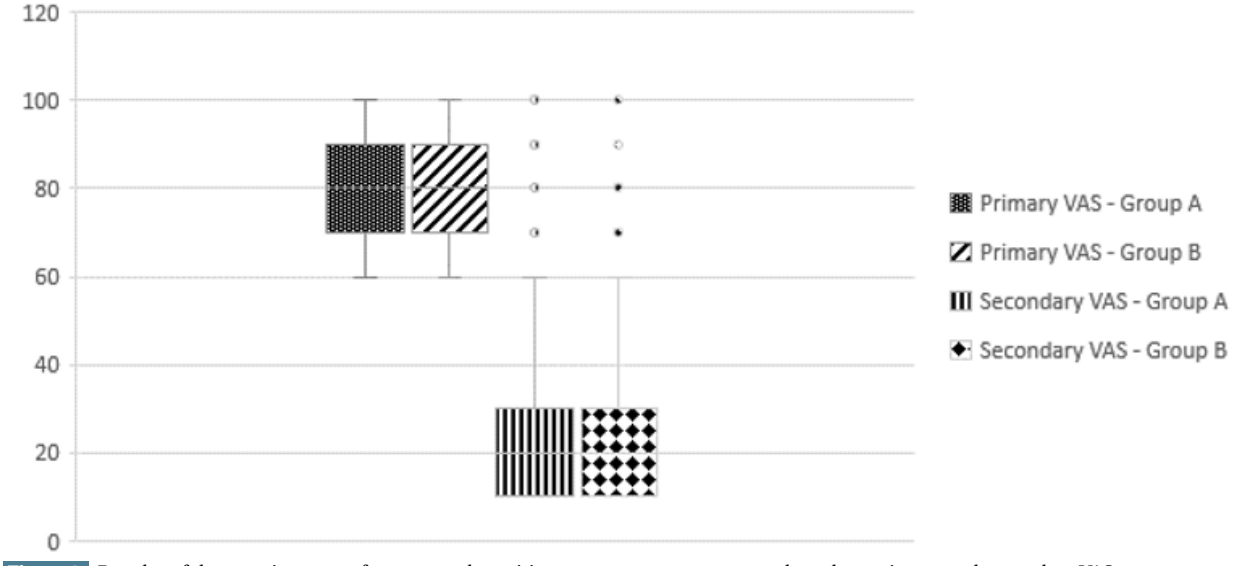

Figure 3 Boxplot of the severity score of nausea and vomiting among treatment groups based on primary and secondary VAS score

Table 1 The number of patients in each treatment arm according to the requirement for a rescue dose

Treatment arm	Not required	Required	P-value*
	Number (%)		
A: Metoclopramide	53 (81.5)	12 (18.5)	0.641
B: Ondansetron	55 (85.6)	10 (15.4)	

*The p-value refers to the difference between treatment arms in terms of requirement and non-requirement for a rescue dose

4. Discussion

Treating nausea is one of the most important challenges in the management of IHT patients visiting the ED. In this study, the antiemetic effect of ondansetron was compared to metoclopramide in patients with mild IHT. Most patients had nausea of moderate severity before the intervention, and both ondansetron and metoclopramide showed a significant effect in reducing its severity. There was no significant difference between the two treatment arms in terms of the drug effectiveness in reducing nausea severity and the frequency of requirement for a rescue dose.

Consistent with the results of the present study, Zamani et al. compared ondansetron and metoclopramide in 120 patients with mild IHT in Iran and reported that the severity of nau-

sea was significantly reduced by both drugs and the efficacy of the drugs showed no significant difference (1).

Various studies have compared the antiemetic effect of ondansetron and metoclopramide in patients with other mechanisms and causes of nausea. One study compared the effects of dexamethasone, in combination with metoclopramide or ondansetron, on preventing nausea after laparoscopic surgery and showed no significant difference between the two treatment arms (16). Abas et al. compared the efficacy of ondansetron and metoclopramide in the treatment of hyperemesis gravidarum, and the results showed no significant difference between the two drugs (9).

In contrast to our findings, some studies have shown significant differences in the antiemetic effects of ondansetron and metoclopramide. Dalhat et al. compared the preventive effect of ondansetron and metoclopramide against nausea in 66 patients after laparoscopic surgery. They reported that ondansetron was superior to metoclopramide in preventing post-operative nausea (8). In the study of Dalhat, et al., the dosage of ondansetron and metoclopramide was similar to that in the present study. The difference in the results of that study and the present study can be related to the fact that different groups were investigated in the two studies and Dalhat et al. studied the preventive, rather than therapeutic effects, of the drugs.

Moreover, several studies have questioned the antiemetic effect of ondansetron and metoclopramide as they did not find a significant difference between either ondansetron or metoclopramide and placebo in terms of antiemetic effects. These studies reported that supportive treatment and hydration of patients were as effective as antiemetic medication (17, 23, 24). In two studies reviewed by Patanwala et al., metoclopramide was not more effective than placebo (21). Pitts et al. conducted a study of 270 patients visiting the ED with nausea from any cause. They administered ondansetron in a dose similar to our study and metoclopramide in a dose twice that used in the present study and placebo intravenously to different groups of patients and measured the severity of nausea based on the VAS 35 minutes later. The results showed no significant difference between the three groups in treating nausea, and the metoclopramide group had the lowest frequency of the requirement for a rescue dose (25). The difference in results might be related to the severity of nausea before the intervention in our study, the number of participants, cause of nausea, age groups, and dosage of drugs.

In the present study, ondansetron and metoclopramide had no side effects and no significant difference in terms of the frequency of requirement for a rescue dose. These findings are in line with the results of some earlier studies (26, 27); however, Zamani et al. stated that both drugs had several side effects and caused drowsiness and anxiety and also that the required rescue dose was significantly more frequent among those receiving metoclopramide (1). Khatereh et al. showed that the required rescue dose was more frequent in metoclopramide (20%) compared to ondansetron (0%) (15). Abas reported that the frequency of headache, diarrhea, palpitation, and sleep issues showed no significant difference in those treated with ondansetron and metoclopramide but dry mouth mostly occurred in the metoclopramide arm (9). The difference between the results of these studies and the present study might be related to differences in the study population, dosage and way of administration of the drugs, time of side effects evaluation, mechanism and cause of nausea, and supportive treatments provided.

5. Limitations

Conducting a single-center study and using the convenience method for sampling increased the risk of selection bias. Given the mental and physical stressful conditions of patients at the time of the first measurements of nausea severity, the high scores might be influenced by bias. On the other hand, the significant reduction of nausea severity in the second measurement might be related not only to antiemetic medication but also to changes in patients' conditions. Therefore, it is highly recommended to assess the placebo effect and patients' distress before and after the intervention.

6. Conclusion

Both ondansetron and metoclopramide significantly reduced the severity of nausea in patients with mild IHT visiting the ED; however, neither of the treatment arms was superior to the other. Both drugs demonstrated good safety profiles.

7. Declarations

7.1. Acknowledgment

None.

7.2. Authors' contribution

The conception and design of the work and also data acquisition by HA, HP, and MS; Analysis and interpretation of data by EA and SB; Drafting the work by HP, EA, and SB; Revising it critically for important intellectual content by HA and MS; All the authors approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

7.3. Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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