Safety of Metoclopramide in Traumatic Brain Injury Patients

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Abstract

Introduction Traumatic brain injuries (TBIs) occur due to severe head assault to a hard object, with headache and vomiting being amongst the most common presenting symptoms. Metoclopramide is an old antiemetic agent that has been used widely for nausea and vomiting in TBI patients.

Aim A systematic review of the literature to investigate the safety of metoclopramide in treating TBI patients.

Methods A literature review was conducted in six databases, where we determined the pertinence of a study to the inclusion criteria by assessing the title, keywords, and abstracts. Five studies were found to be relevant. Data were extracted using multiple variables that were formulated incongruent with the study aim and then further analyzed.

Results The collective sample size was 93 patients with an average of age 38.5 years. As much as 51.6% were male and 48.6% were females. Most patients received 10 mg metoclopramide IV with a percentage of 77.4%, while only 22.5% received 20 mg IV metoclopramide. Seventy-one patients received metoclopramide alone and 22 received combination therapy. Headache was the most common reported side effect (46.2%), followed by anxiety and drowsiness with (39.7%) and (27.9%), respectively. Fatigue was reported in 24.7%, while dystonia was the least common and developed in only 5.3% of patients.

Conclusion Metoclopramide is a common medication used to treat TBI patients in the emergency department. However, the review demonstrated that the central nervous system (CNS) side effect is excepted. Treatments with lower CNS side effects may be better options.

Keywords
- traumatic head injury
- metoclopramide
- safety
- side effect
- headache
- vomiting

Introduction

One in every three related-injury deaths in the US are linked directly to traumatic brain injuries (TBIs), for which it is considered as a leading cause of death.[1] As for pediatric cases, the prevalence across countries varies from 47 and 280 per 100,000 children, more than 80% of which are minor head injuries with Glasgow coma scale (GCS) score of 14 to 15.[2] TBIs occur due to severe head assault to a hard object, which then can be classified into mild, moderate, and severe using GCS.[3] Moreover, the main causes of TBI are road traffic accidents (RTA), falling, physical violence, exercise-related head injuries, among others.[1,3] Patients with TBI usually present to the emergency room (ER) with headache, nausea, and vomiting. Other common presentations are dizziness, blurred vision, loss of consciousness, amnesia, and disturbance in concentration.[1,2,4] As for headache, 1 in every 4 patients reported persistent headache syndrome.[4] TBI patients were treated with antiemetic agents for their symptoms. Metoclopramide (4-amino-5-chloro-2-methoxy-N- (2 dimethylamino methyl

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benzamide) is an old antiemetic agent that has been used widely for nausea and vomiting as well as other gastrointestinal disorders.[2] It is an antidopaminergic agent, centrally and peripherally acting, to enhance upper gastrointestinal motility without affecting its secretion.[3] Metoclopramide administration through PO takes approximately 1 to 2 hours for maximum plasma concentration, while it takes only 15 minutes on an IV root.[2,3] It is metabolized by the hepatic cytochrome P450 CYP2D6 enzyme.[2] The drug has multiple side effects such as dystonia, restlessness or anxiety, fatigue, drowsiness, confusion, insomnia, and flushing.[2,3] Our main aim is to study the safety of metoclopramide in treating TBI cases by reviewing the literature.

Methodology

Literature Search and Formulating Selection Criteria

This study is a literature review, with the main aim being to study the safety of metoclopramide in treating TBI cases. We searched Pubmed, EBSCO, Proquest, ScienceDirect, Wiley Online, and Springer for pertinent studies. Moreover, we determined the pertinence of a study to the inclusion criteria by assessing the title, keywords, and abstracts. The keywords we used were as follows: traumatic head injury, head injury, brain injury, subdural injury, epidural injury, metoclopramide, safety of metoclopramide, and metoclopramide side effect. Furthermore, the inclusion criteria were as follows: all English literature and articles about TBI that used metoclopramide and reported drug side effects, while we excluded any articles that are noncompleted, repeated, or did not meet any of the aforementioned criteria.

Data Extraction

Data were extracted using multiple variables that were formulated incongruent with the study aim. The variables are as follows: article type and author's name, number of patients, average age, gender, dose of metoclopramide, drug combination, drug side effects, mechanism of injury, GCS, and duration of follow-up. All of which were gathered in a table and were set for analysis. ►**Fig. 1** represents flow chart depicting the study selection process. Of 21 relevant studies, one of them was found to be a repetition, 14 were not eligible and one was irrelevant to the research aim. Five pertinent literature were studied thoroughly for data extraction.

Data Analysis

Data were collected in an MS Excel sheet, formula builder was used to calculating simple mathematic, including total number of patients, number of females and males, percentage of each, and total number of side effects reported. SPSS has been used to calculate the mean of age and the days of follow-up using a bar of weight cases.

Result

Our study included five articles, as shown in ►**Table 1**. Two studies were randomized controlled, one was prospective, and there were two case reports. There were variations in the drug side effects reported in each study. Two studies used Diphenhydramine 25 mg and Cisapride as a combination, while the remaining used metoclopramide alone. All the studies used 10 mg IV metoclopramide, except one study, which used 20 mg IV. Headache was the most common reported side effect by two studies. There was some missing data, especially on the mechanism of injury.

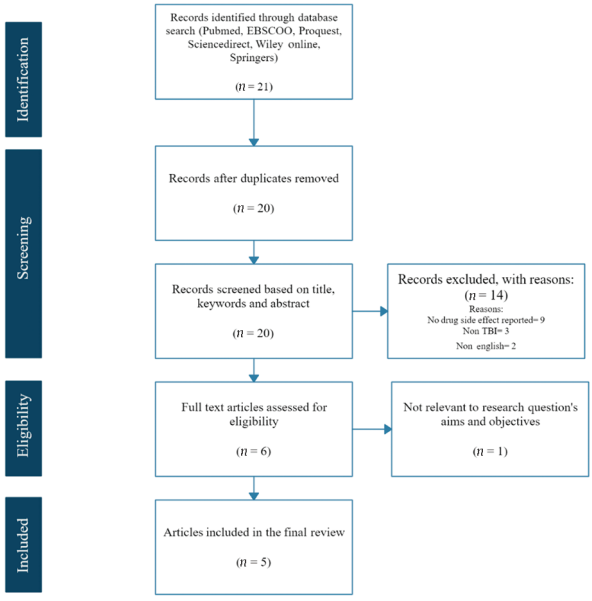

Fig. 1 PRISMA flow diagram of the included articles

Our sample size was 93 patients with an average of age 38.5 years. As much as 51.6% were male and 48.6% were female (►**Table 2**). Most patients received 10 mg metoclopramide IV with a percentage of 77.4%, while only 22.5% received 20 mg IV metoclopramide. Seventy-one patients received metoclopramide alone and 22 received combination therapy. Headache was the most common reported side effect (46.2%), followed by anxiety and drowsiness with (39.7%) and (27.9%), respectively. Fatigue was reported in 24.7%, while dystonia was the least common and developed only in 5.3%.

Discussion

This is the first systemic review study of metoclopramide side effects on patients with TBI. There is a lack of clinical trials which study the side effect of metoclopramide in patients with TBI. Our study identified 93 patients who received metoclopramide after TBI. The average age of patients was 6.9 years.[4-6] Males were relatively higher than females in our sample size, as 51.6% of our sample size were males compared with 48.4% of females. Comparison done to identify the incidence and management of moderate to a severe head injury showed that male to female ratio is 2:1.[5] This might be due to the type of our research, as it is a systemic review and most of our data were collected from prospective and clinical trial research. A previous study on the identification of the efficacy of metoclopramide in TBI showed that the leading causes of TBI were RTA, followed by fall.[6] In comparison to our study, fall and trip were the highest.

Table 1 Summary of metoclopramide and TBI studies

Article type	Author	Number of patients	Average of age	Gender		Dose of metoclopramide	Combination	Side effect	Mechanism of injury	GCS	Duration of follow-up
Controlled, randomized, double blind clinical trial	Majid Zamani et al[10]	60	36.1	M	33	10 mg, IV	NA	- Headache 30/60 (30%) - Drowsiness 26/60 (43.3%) - Fatigue 23/60 (38.3%) - Anxiety 37/60 (61.7%) - Dystonia 5/60 (8.3%)	NA	14–15	NA
				F	27						
Prospective, randomized, controlled, double-blind	Tarik Zafer Nursal 2007[8]	10	43	M	8	10 mg, IV	NA	5/10 develop complications[a]	TBI not defined	11–6	5 days
				F	2						
Prospective	Benjamin W 2018[4]	21	45	M	5	20 mg, IV	Diphenhydramine 25 mg	Headache 12/19 (63%)	- Trip/fall 9 - Impacted stationary object 4. - Projectile 4 - Assault 3 - RTA 1	NA	5 days
				F	16						
Case report	Deehan and Dobb[15]	1	22	M	1	10 mg, IV	NA	- Increase ICP - Raised MAP	RTA	3	4 days
Case report	Altmayer[16]	1	22	M	1	10mg, IV	Cisapride	None	RTA	9	69 days

Abbreviations: GCS, Glasgow coma scale; ICP, intracranial pressure; MAP, mean arterial pressure; M:F: male:female; NA, not applicable; RTA, road traffic accident.
[a]Not defined but none of which were extrapyramidal symptoms

Table 2 Summery of metoclopramide and TBI study findings

Number of patients		93
Average of age		38.5
Gender	Male	48 (51.6%)
	Female	45 (48.4%)
Treatment	Metoclopramide only	71 (76.3%)
	Metoclopramide and Diphenhydramine	21 (22.5%)
	Metoclopramide and Cisapride	1 (1.1%)
Dose of metoclopramide	10 mg, IV	72 (77.4%)
	20 mg, IV	21 (22.5%)
Side effect	Headache	42 (45.2%)
	drowsiness	26 (27.9%)
	Fatigue	23 (24.7%)
	Anxiety	37 (29.0%)
	Dystonia	5 (5.3%)
	Increase ICP Increase MAP	1 (1.1%)
Mechanism of injury	Not defined	70 (75.2%)
	RTA	3 (3.2%)
	Trip/fall	9 (9.7%)
	Impacted stationary object, assault	7 (7.5%)
	Projectile	4 (4.3%)
	Undefined complication	5 (5.3%)
Average of the follow-up		6.9 (4–69)

Abbreviations: ICP, intracranial pressure; Map, mean arterial pressure; RTA, road traffic accident.

In our review, 77.4% received 10 mg metoclopramide IV, and 22.5% received 20 mg IV. This dose was supported by the recommendation of the European Medicines Agency that the maximum daily dose of Metoclopramide is between 10 mg to 30 mg to decrease the risk of neurological and other adverse effects.[7] Metoclopramide is a prokinetic agent that has been widely used in critically ill patients to improve gastric motility and the symptoms of head concussion, nausea, and vomiting.[8] However, the concerns regarding metoclopramide's safety have been raised.[9] One of the studies included in our review showed that the effectiveness of metoclopramide and ondansetron was similar. However, because of the incidence of the complications in patients treated with metoclopramide were higher than ondansetron, they concluded with the suggestion to use ondansetron instead of metoclopramide in patients with TBI.[10] In TBI patient with an enteral feeding problem, the use of erythromycin instead of metoclopramide in some situations has been studied, which show there is a significant decrease in high-gastric aspirate volume with the use of erythromycin compared with metoclopramide.[11]

In the current systemic review, the most common symptom was headache, as it is presented in 45.2% of the sample size.[4,10] In contrast to a survey study done by Hale et al, which showed that among 32 participants in the study, 1 to 7% of participants complained of some central side effects ranging from dizziness and headache. We can see that patients with TBI are more susceptible to develop a headache and other neurological side effects, including extrapyramidal side effects, from metoclopramide compared with others.[12] In our review, the incidence of anxiety and drowsiness were 37 patients (29.0%) and 26 patients (27.9%), respectively. Fatigue was only represented in 23 patients (24.7%).[4,10] While another systemic review study done to study the use of metoclopramide in diabetic gastroparesis showed that fatigue, drowsiness and lethargy were presented in 10% of patients.[13] Dystonia was represented in five patients (5.3%). The incidence of dystonia in the previous systemic review was an approximately 0.2 to 6% of patients who received metoclopramide.[13] These side effects may explain by the ability of metoclopramide to cross the blood–brain barrier easily.[14]

The early signs of an increased intracranial pressure (ICP) are headache, vomiting or nausea, ocular palsies, and altered level of consciousness. Side effects of metoclopramide overlap with raised ICP symptoms, since it is subtle it is difficult to recognize a rise in ICP unless you investigate it. In our literature review, a case report identifies an increased in ICP from baseline of 15 to 20 mm Hg to 36 mm Hg following a 10 mg intravenous metoclopramide, and the same dose in the following day reports another increase to 34 mm Hg.[15] Such side effects raise questions concerning the safety of the metoclopramide in patients with TBI. It is inconsistent with our results that found an increased susceptibility for neurological side effects after metoclopramide administration in TBI patients. A controlled randomized clinical trial is recommended to exploit the relationship between raised ICP and metoclopramide.

Limitations

The limitation of the study includes the lack of high-evidence studies as there were only two randomized controlled trials and one prospective study. Publication bias was not done because of the same reason. In addition, the lack of long-term follow-ups were also noticed. Moreover, in 75.2% of cases, the mechanism of injury was not mentioned.

Conclusion

Metoclopramide is a common medication used to treat TBI patients in the emergency department. However, the review demonstrated that the CNS side effects are excepted. Treatments with lower CNS side effects may be better options.

Conflict of Interest
None declared.

Reference

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