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# Safety of metoclopramide in traumatic brain injury patients. A systematic review of literature

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## ABSTRACT

**Background:** One in every three related-injury deaths in United State are linked directly to traumatic brain injury (TBI), for which it is considered as a leading cause of death. Traumatic brain injury took place 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 traumatic brain injury patients.

**Methods:** A literature review was conducted in 6 databases, we determine 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. 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 reported in (24.7%), while dystonia was the least common and developed only in 5.3%.

**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. Alternative options with lower CNS side effects may be better tried.

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

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## BACKGROUND

One in every three related-injury deaths in the US are linked directly to TBI, for which it is considered as a leading cause of death (1). As for paediatric cases the prevalence across countries varies from 47 and 280 per 100,000 children, more than 80% of which are minor head injuries with GCS of 14-15(2). Traumatic brain injury took place due to

severe head assault to a hard object, which then can be classified into mild, moderate, and sever 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 (4). 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 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, in order to enhance upper gastrointestinal motility without affecting its secretion (3). Metoclopramide administration through PO takes about 1-2 hours for maximum plasma concentration while it takes only 15min 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; Traumatic Head Injury, Head Injury, Brain Injury, Subdural Injury, Epidural Injury, Metoclopramide, Safety of Metoclopramide, and Metoclopramide side effect. Furthermore, the inclusion criteria were; all English literature and articles about TBI that used metoclopramide and reported drug side effects while we excluded any articles that are non-completed, 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; article type and author's name, number of patients, the average age, gender, the 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.

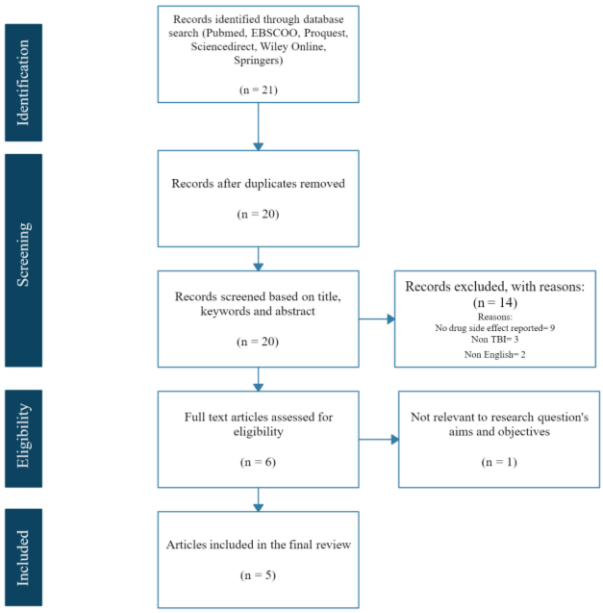


**Figure 1.** PRISMA flow diagram show Methodology characteristic of included study

Figure 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. 5 pertinent literature were studied thoroughly for data extraction.

### Data Analysis

Data were collected in an EXCEL sheet, formula builder was used to calculating simple mathematic, including the total number of patients, the number of females and males, and the percentage of each, 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 5 articles, as shown in Table 1. Two studies were randomized controlled, one was

prospective, and two case reports. There were variations in the drug side effects reported in each study. Two studies used Diphenhydramine 25mg and Cisapride as a combination thereby, while the remained used metoclopramide alone. All the studies used 10 mg IV metoclopramide except one study used 20 mg IV. Headache was the most common reported side effect by 2 studies. There was some missing data especially on the mechanism of injury.

Our sample size was 93 patients with an average of age 38.5 years. 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 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 trial 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 (4-69). Male was relatively higher than female in our sample size as 51.6% of our sample size were male compared to 48.4% female. Comparing done to identify the incidence and management of moderate to a severe head injury which 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.

In our review, 77.4% received 10 mg metoclopramide intravenously, and 22.5% received 20 mg intravenously. 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 in order to decrease the risk of neurological and other adverse effect (7). Metoclopramide is a prokinetic agent that have been widely used in critically ill patient to improve gastric motility and the symptoms of head concussion, nausea, and vomiting (8). However, the concerns of 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 inpatient with TBI (10). In TBI patient with an enteral feeding problem, the use of erythromycin instead of metoclopramide in some situation has been studied which show there is a significant decrease in high gastric aspirate volume with the use of erythromycin compared to metoclopramide (11).

In the current systemic review, the most common symptom was the headache as it is presented in 45.2% of the sample size [10,12]. In contrast to a survey study done by *Hale.T* which showed that among 32 participants in the study, 1-7% 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 to others (13). 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%)(10)(12). 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 (14). Dystonia was represented in 5 patients (5.3%). The incidence of dystonia in the previous systemic review was in an approximately 0.2–6% of patients who received metoclopramide (14). These side effects may explain by the ability of metoclopramide to cross the blood-brain barrier easily (15).

The early signs of an increased 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 - 20mmHg to 36mmHg following a 10mg intravenous metoclopramide and the same dose in the following day reports another increases to 34 mmHg (16). Such side effects raise a question of the safety of the metoclopramide in patients with TBI. 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 follows up was also noticed. In addition, 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. Alternative options with lower CNS side effects may be better tried.

**Table 1.** Summary of Metoclopramide and TBI studies

| Article type | Author<br>Year of publication | No. of patients | Age | Gender | | Dose of metoclopramide | Combination | Side effect | Mechanism of injury | GCS | Duration of Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Controlled, randomize, double blind clinical trial | Majid Zamani et al.<br>2015 | 60 | 36.1 | M<br>F | 33<br>27 | 10 mg, IV | NA | - Headache 30/60(30%)<br>- Drowsiness 26/60(43.3%)<br>- Fatigue 23/60(38.3%)<br>- Anxiety 37/60(61.7%)<br>- Dystonia 5/60 (8.3%) | NA | 14-15 | NA |
| Prospective, randomize, controlled, double-blind | Tarik Zafer Nursal<br>2007 | 10 | 43 | M<br>F | 8<br>2 | 10 mg, IV | NA | 5/10 develop complication * | TBI not defined | 11-6 | 5 days |
| Prospective | Benjamin W<br>2018 | 21 | 45 | M<br>F | 5<br>16 | 20 mg, IV | Diphenhydramine 25mg | headache 12/19 (63%) | - Trip/fall 9<br>- Impacted stationary object 4.<br>- Projectile 4<br>- Assault 3<br>- RTA 1 | NA | 5 days |
| Case report | Simon Deehan<br>2002 | 1 | 22 | M | 1 | 10 mg, IV | NA | - Increase ICP<br>- Raised MAP | RTA | 3 | 4 days |
| Case report | Thomas Altmayer,<br>1996 | 1 | 22 | M | 1 | 10mg, IV | Cisapride | None | RTA | 9 | 69 days |

GCS: Glasco coma scale
RTA: road traffic accident
*Not defined but none of which were extrapyramidal symptoms

**Table 2.** Summary of Metoclopramide and TBI studies finings

| | | |
|---|---|---|
| **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<br>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) |

## Abbreviation

TBI: Traumatic brain injury
ICP: Intracranial pressure
CNS: Central nervous system
GCS: Glasgow Coma Scale
ER: Emergency Room
RTA: Road Traffic Accident
MAP: Mean Arterial Pressure

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