75565_Auto_Edited.docx

Pain reduction and adverse effects of intravenous metoclopramide for acute migraine attack: a systematic review and meta-analysis of randomized-controlled trial

Nat Ungrungseesopon, Wachira Wongtanasarasin

Abstract

BACKGROUND

Metoclopramide may be used to treat people suffering from acute migraine. However, no comprehensive investigation on this issue has been recorded. This review will provide more solid evidence for the use of metoclopramide in treating acute migraine.

AIM

To compare the efficacy of intravenous metoclopramide with other therapies in migraine attack treatment in an Emergency Department (ED).

METHODS

We included randomized controlled trials of participants older than 18 with acute migraine headaches and at least one arm that received intravenous (IV) metoclopramide at the ED. A literature search of PubMed, Web of Science, and Cochrane Collaboration on 31 December 2021 retrieved other drugs or placebo-controlled studies without language limitation. The risk of bias will be assessed using the Cochrane risk of bias tool. The primary endpoint was pain reduction at the sixtieth minute or closest to one hour after treatment, as measured by the pain scale. Secondary endpoints included adverse effects or reactions resulting from metoclopramide or comparisons.

RESULTS

Fourteen trials with a total of 1,661 individuals were eligible for review. The risk of bias ranged from low to intermediate. IV metoclopramide administration was not associated with higher pain reduction at one hour (SMD -0.03, 95%CI: -0.33-0.28, P = 0.87). However, metoclopramide was associated with better pain reduction than placebo (SMD 1.04, 95%CI: 0.50-1.58, P = 0.0002). In addition, side effects were not significant different between IV metoclopramide with other drugs or placebo (OR: 0.76, 95%CI: 0.48-1.19, P = 0.09 and OR: 0.92, 95%CI: 0.31-2.74, P = 0.54, respectively).

CONCLUSION

Metoclopramide is more effective than a placebo in treating migraine in the ED. Despite the observed tendency of decreased side effects, its effectiveness compared to other regimens is poorly understood. More research on this area is needed to identify migraine in acute care settings effectively.

INTRODUCTION

Migraine, a chronic neurological disease, is one of the most common causes that lead patients to seek medical attention[1]. Apart from regular follow-up at the outpatient department, many patients with migraine suffer from acute migraine attacks requiring an emergency department (ED) visit. Approximately 1.2 million annual ED visits for an acute migraine headaches in the United States[2]. At the same time, persons who suffer from this illness frequently encounter several other accompanying symptoms, such as nausea, vomiting, and sensitivity to light, sound, touch, or scent[3,4]. Unfortunately, its pathogenesis remains complicated and little understood. As a result, if such a problem cannot be effectively treated, it significantly impacts the health-related quality of life of individuals suffering from acute migraine[5,6].

According to the American Headache Society recommendations, several acute migraine treatments include triptans, ergotamine, non-steroidal anti-inflammatory drugs (NSAIDs), combination analgesic, and anti-emetics[7]. Metoclopramide, an anti-emetic drug acting as a dopamine/serotonin antagonist, was initially used in migraine patients who experienced nauseating symptoms[8]. Later, it was shown to be effective in pain control of acute migraine attacks [9,10]. In the recent recommendation, metoclopramide was considered the "probably effective drug," even though several studies showed the efficacy of metoclopramide monotherapy. It has been investigated that the efficacy of metoclopramide was neither inferior to sumatriptan nor opioid[11,12].

Moreover, apart from the efficacy aspect, metoclopramide showed superiority in other aspects, such as lower adverse severe effects and lower addiction rates which are considered an essential issue in the ED as patients with migraine tend to revisit. It is undeniable that metoclopramide might not be the first choice for clinicians to use in acute migraine as its efficacy might not be outstanding compared to other drugs. As prior mentioned, the severe side effect of metoclopramide, which are extrapyramidal symptoms, such as tardive dyskinesia and akathisia, though rarely reported in short term use and less worrisome than the triptans and opioids, should also be concerned as it might be an irreversible and sufferable experience for the patient[11].

To comprehend the big picture of using metoclopramide in acute care for migraine, this study aims to compare metoclopramide use with other therapy in migraine attack treatment in an acute care setting. Our study hypothesizes that metoclopramide monotherapy should effectively treat acute migraine attacks in an ED.

MATERIALS AND METHODS
Protocol
We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement guidelines[13]. We

prospectively registered our protocol with the International prospective register of systematic reviews (ID: CRD42022322609).

Search Strategy and Inclusion Criteria

We (N.U. and W.W.) independently searched three standard databases, PubMed, Web of Science, and Cochrane Collaboration, from their inception until 31 December 2021, without language restriction. The search words "metoclopramide," "Meclopran," "Plasil," "Reglan," "methoxyprocainamide," "migraine," and "headache" were the Medical Subject Headings used, in combination and with different spellings and endings. We also searched websites, organizations, relevant reviews, grey literature, and references to identify additional eligible studies. Additionally, we searched for any unpublished trials registered on the "clinicaltrials.gov" Internet site.

The selection criteria were as follows: (1) Randomized Controlled-Trials (RCTs) including adults more than 18 years of age with acute migraine headaches, regardless of their types (i.e., with or without aura); (2) at least one arm having received an intravenous (IV) metoclopramide during ED stay; (3) comparing of at least one agent or placebo; (4) reporting of average pain scale before the administration of each agent; and (5) reporting of at least one of the following, pain scale at 60th or other minutes, any adverse effects, and rescue medications needed at the ED. We excluded pre-clinical studies, review articles, and studies without a control group (e.g., case reports, case series). Two authors (N.U. and W.W.) independently screened the search results to identify eligible studies. Full-text articles of the retrieved studies were retrieved and independently assessed by two authors against the pre-specified criteria (Figure 1). Any discrepancies were discussed with a third party and concluded by consensus.

Outcomes of Interests

The primary endpoint was pain reduction at the 60th minute or closest to one hour after treatment administration, as measured by the Visual Analog Scale (VAS) or others.

Secondary endpoints included adverse effects or reactions resulting from metoclopramide or interventions. Adverse effects in this study were defined by any of the following symptoms: upper gastrointestinal complaints (dyspepsia, heartburn, and bloating), allergic reaction, dizziness, drowsiness, nasal congestion, dry mouth, dystonic reaction, akathisia, and significant blood pressure drop.

Data Extraction and Assessment of the Risk of Bias

We separately extracted the data from the included articles using a prepared data extraction form. Specifically, we extracted basic characteristics (first author, publication year, study location and setting, number and age of participants), treatment details and interventions in the study groups, and the outcomes of interest. We sought to contact the associated author by email for incomplete or missing data or clarification. Two authors (N.U. and W.W.) independently assessed the risk of study bias using the latest version of the Cochrane Collaboration tool for assessing the trial risk of bias[14]. Any disagreements will be handled through discussion with the assistance of a third independent expert.

Data Synthesis and Statistical Analysis

The data was imported into pre-formatted record forms. We calculated individuals and pooled estimates as standard mean differences (SMDs) for continuous endpoints, with 95% confidence intervals (CIs). We calculated individuals and pooled estimates using odds ratios (ORs) with CIs for dichotomous endpoints. We estimated heterogeneity among the included studies using the I2 statistic (the percentage of total variation across studies due to heterogeneity). We applied a fixed-effect model if the heterogeneity was minor ($I^2 \leq 50\%$). However, if there was evidence of strong heterogeneity ($I^2 > 50\%$), a random-effect model was employed instead. Visual assessment of funnel plots and Egger's test were used to assess publication bias caused by small-study effects. For statistical analyses, we applied RevMan version 5.3 (Nordic Cochrane Center, Cochrane

Collaboration, 2014, Copenhagen, Denmark)[15]. All tests were two-tailed, and P-values <0.05 were considered statistically significant.

RESULTS

Study Selection

Figure 1 demonstrates how the 820 retrieved articles were screened for inclusion in the review and analysis. After excluding duplicated studies, 533 remained. Of those, 470 were excluded following title and abstract screening according to the inclusion and exclusion criteria. The remaining sixty-three articles were retrieved and reviewed for full-text copies before including 12 studies in the data analysis. In addition, three articles were also searched by citation searching, and two articles met the pre-specified criteria. Finally, 14 articles[10,16–28] with 1661 participants were included in the meta-analysis.

Characteristics of included studies

Data extraction and meta-analysis were performed on fourteen papers published between 1990 and 2020. The research was carried out in the United States of America (n = 7), Turkey (n = 3), and Iran (n = 4). The mean ages were around 34-40 years. Most studies applied 10 mg of IV metoclopramide, while three administered 20 mg of metoclopramide as interventions. Five trials investigated the efficacy of IV metoclopramide against placebo. Most studies compared more than one arm of comparison. All trials reported pain intensity at 0th and other minutes after drugs administration, as VAS or other appropriate methods. Table 1 summarizes the baseline demographics and clinical characteristics of included studies. Deviation from the intended interventions and randomization contributed to a high proportion of concerns risk of bias. Five out of fourteen had an overall low risk of bias. The risk of bias assessment by Cochrane risk of bias assessment was illustrated in Figures 2 and 3.

Primary outcome

Pain reduction at 60th minute: All fourteen studies reported average pain reduction at 60th minutes or at the time closest to one hour. The overall effect size showed no statistical significance of the efficacy between IV metoclopramide and other drugs (SMD -0.03, 95%CI: -0.33-0.28, P = 0.87). However, IV metoclopramide demonstrated a significant pain reduction comparing with placebo (SMD 1.04, 95%CI: 0.50-1.58, P = 0.0002). Subgroup analyses found that IV metoclopramide had a significant advantage in pain reduction comparing with subcutaneous sumatriptan (SMD 0.73, 95%CI: 0.11-1.35, P = 0.03), IV valproate (SMD 0.27, 95%CI: 0.01-0.54, P = 0.04), and oral ibuprofen (SMD 1.41, 95%CI: 0.41-2.41, P = 0.006). Heterogeneity was observed among the subgroups comparing IV metoclopramide and other drugs (I^2 = 81.5%, P < 0.0001; Figure 4). Figures 4 and 5 demonstrate the forest plot comparing pain reduction at 60th minute between IV metoclopramide and other drugs and placebo, respectively.

Secondary outcome

Adverse effects: Eight studies measured adverse effects across IV metoclopramide and comparisons. The pooled effect size was homogenous both comparing with others (I^2 = 13.3%, P = 0.33; Figure 6) and with placebo (I^2 = 0%, P = 0.89; Figure 7). Adverse effects were not different across IV metoclopramide and other comparisons (OR: 0.76, 95%CI: 0.48-1.19, P = 0.09) or placebo (OR: 0.92, 95%CI: 0.31-2.74, P = 0.54). Subgroup analyses yielded similar results for all comparisons (Figure 6).

Publication bias

There was no substantial publication bias in the funnel plot for the meta-analysis of the average pain reduction between IV metoclopramide and comparisons (Figure 8). The regression-based Egger's test was performed using random-effect model with restricted maximum-likelihood method and found that p-value was 0.0814.

DISCUSSION

This meta-analysis investigated the clinical efficacy of IV metoclopramide for treating acute migraine attacks in the ED. This study's findings illustrate that administration of IV metoclopramide was an effective treatment for a migraine headache in adults, compared with placebo. However, the benefit of metoclopramide was not superior when compared with other drugs. Our systematic review also demonstrated that IV metoclopramide tended to have fewer side effects than other interventions. The overall study risk of bias ranged from low to some concerns.

Acute migraine is a common neurovascular disorder. It is described as a moderate to severe, predominantly unilateral, and recurrent headache that lasts for several hours to a few days[3,29]. Metoclopramide is initially used to treat acute migraine for decades[11]. A few studies over the years have highlighted that metoclopramide has substantial therapeutic effectiveness in treating acute migraine episodes[26,30]. The reasons behind the use of metoclopramide could be that it antagonizes the dopamine D2 receptor, which is proposed to be one of the pathogeneses of pain in migraine[11]. A meta-analysis of pooled data illustrated that metoclopramide significantly reduced headache pain, and those patients were less likely to rescue medicines than the placebo groups[3]. However, the authors chose various inclusion and exclusion criteria for this study, which may contain data on non-migraine headaches, confounding any conclusions to be derived[3]. Furthermore, metoclopramide also had an anti-emetic effect that ameliorates migraine patients' symptoms[11]. Therefore, metoclopramide could be a first-line treatment for acute migraine episodes. Our findings are consistent with prior research that metoclopramide was more effective than placebo in pain reduction[9]. In addition, metoclopramide had a higher benefit than some drugs in our analysis (subcutaneous sumatriptan, intravenous valproate, oral ibuprofen). These findings fit with the pattern described previously by Colman[9]. However, that study selected both ED and headache clinic settings, which differed from ours. Besides, Colman and teams analyzed the pain using a complete relief of headache or significant reduction in headache pain. As a result, discrepancies were likely to occur across that definition. Our

study provides the difference aiming to close this gap. We compare all studies based on the pre-, and post-intervention mean pain intensity in each study which is more feasible to apply and compare.

However, the side effects of metoclopramide might be serious and irreversible, for example, tardive dyskinesia. It is characterized by the uncontrollable movement of the tongue, face, and extremities. Nonetheless, our findings found that the adverse effects resulting from metoclopramide were not different across the other drugs. Results obtained by Orr and colleagues[31] are consistent with our findings. Moreover, compared to other suggested therapies, metoclopramide's adverse effect profile is less concerning than triptans, which are commonly utilized in ED situations [32,33].

Limitation

This review contains some limitations. Firstly, all included studies were conducted in only three countries, including Iran, United States, and Turkey, which possibly resulted in the generalizability bias. Secondly, most trials did not report exclusion criteria in sufficient detail; therefore, the definitions for migraine might be varied among studies. In addition, several studies did not report the confirmation of migraine diagnosis, duration of headache, and prior therapies. As a result, we probably combined studies with varying patient characteristics, making it difficult to determine if our findings are generalizable to other contexts. Finally, this meta-analysis included studies done at different dates (between 1990 and 2020), resulting in the observed heterogeneity.

CONCLUSION

To conclude, metoclopramide was proven to benefit treating migraine in the acute care setting, such as in the ED, compared to placebo. Despite the demonstrated trend of a lower adverse effect, its efficacy compared to other regimens is little comprehended. More studies on this topic should be further conducted to improve migraine treatment in acute care settings effectively.

ARTICLE HIGHLIGHTS

Research background

Metoclopramide may be used to treat people suffering from acute migraine. However, no comprehensive investigation on this issue has been recorded. This review will provide more solid evidence for the use of metoclopramide in treating acute migraine.

Research motivation

Metoclopramide was considered the "probably effective drug," even though several studies showed the efficacy of metoclopramide monotherapy. It has been investigated that the efficacy of metoclopramide was neither inferior to sumatriptan nor opioid. Moreover, apart from the efficacy aspect, metoclopramide showed superiority in other aspects, such as lower adverse severe effects and lower addiction rates.

Research objectives

The objectives of this review were to investigate the efficacy of intravenous metoclopramide with other therapies in migraine attack treatment in an Emergency Department (ED).

Research methods

We conducted a systematic review and meta-analysis of randomized-controlled trials.

Research results

The administration of IV metoclopramide was an effective treatment for a migraine headache in adults, compared with placebo. However, the benefit of metoclopramide was not superior when compared with other drugs.

Research conclusions

Metoclopramide is more effective than a placebo in treating migraine in the ED. Although its effectiveness was not observed on other medications, clinicians may select metoclopramide as one of the first line in treating acute migraine.

Research perspectives

Despite the observed tendency of decreased side effects, its effectiveness compared to other regimens is poorly understood. More research on this area is needed to identify migraine in acute care settings effectively.

75565_Auto_Edited.docx

ORIGINALITY REPORT

4%

SIMILARITY INDEX

PRIMARY SOURCES

1	www.wjgnet.com Internet	36 words —	1%
2	onlinelibrary.wiley.com Internet	18 words —	1%
3	Bu-Chun Zhang, Qiang Wu, Cheng Wang, Dong-Ye Li, Zhi-Rong Wang. "A meta-analysis of the risk of total cardiovascular events of isosmolar iodixanol compared with low-osmolar contrast media", Journal of Cardiology, 2014 Crossref	16 words —	1%
4	bmccancer.biomedcentral.com Internet	16 words —	1%
5	www.science.gov Internet	14 words —	< 1%
6	bmcpsychiatry.biomedcentral.com Internet	12 words —	< 1%
7	www.ncbi.nlm.nih.gov Internet	12 words —	< 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS