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Pain relief effect of metoclopramide *vs*. sumatriptan for acute migraine attack: A single-center, open-label, cluster-randomized controlled non-inferiority trial

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Abstract: Triptans are recommended as a treatment for moderate to severe migraines; however, barriers to administration include contraindications or possible side effects. In contrast, metoclopramide, which is frequently used as an antiemetic in the emergency department setting, has shown efficacy in alleviating migraine pain. This study investigated the non-inferiority of intravenously (IV) administered metoclopramide 10 mg compared with subcutaneously (SQ) administered sumatriptan 3 mg for alleviating migraine pain. In this single-center, open-label, cluster-randomized controlled trial, patients presenting to the emergency department with migraine attacks were allocated to either the IV metoclopramide 10 mg group or the SQ sumatriptan 3 mg group. The primary outcome was change in numerical rating scale (NRS) score for headache at 1 h after baseline. The non-inferiority margin was set as −1.0 NRS points. Thirty-six patients were enrolled over a period of 3 years, starting from July 2019. Reduction in NRS at 1 h was 4.1 (95% confidence interval [CI]: 2.8, 5.4) in the metoclopramide group and 5.2 (95% CI: 4.2, 6.1) in the sumatriptan group, with a mean difference of −1.1 (95% CI: −2.7, 0.4), indicating that metoclopramide was not non-inferior to sumatriptan. Four patients required rescue medication: 3 (18%) in the metoclopramide group and 1 (7%) in the sumatriptan group ($p = 0.34$). There were no serious adverse events in either group. One hour after metoclopramide administration, migraine pain was reduced compared with baseline, but metoclopramide did not demonstrate non-inferiority for alleviating acute migraine pain compared with sumatriptan.

***Keywords*:** emergency department, pain management, primary headache

Introduction

Migraine is one of the most common diseases among young and middle-aged people and is the world's second leading cause of disability, according to the Global Burden of Disease 2019 (*1*). The annual prevalence of migraine in Japan is 8.4% (*2*), and the number of patients who are transported to emergency departments (EDs) for migraine attacks is high. Previous studies have reported the analgesic effects of various medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, triptans, antiemetics (*e.g*., metoclopramide, prochlorperazine), antipsychotics (*e.g*., chlorpromazine, haloperidol), and ergotamine (*3,4*). However, consistent results have not been obtained in comparative studies of these drugs (*3,4*).

Although clinical guidelines recommend triptans as first-line therapy for moderate to severe migraine attacks (*5*), some doctors hesitate to use triptans in the ED setting because of contraindications, including history of ischemic disease and uncontrolled hypertension, or possible side effects such as chest pressure. Additionally, in Japan, the injectable formulation of sumatriptan has been discontinued, making it urgent to find an effective injectable treatment for migraines that can be used in emergency departments.

Metoclopramide, a dopamine antagonist, is frequently used for patients with nausea in ED settings in Japan because of its effectiveness, low cost, and few contraindications. Metoclopramide has long been used for nausea associated with migraine headaches, and past studies have shown that it can improve pain in migraine headaches. It was also reported that metoclopramide is effective as a single agent in the treatment of migraine headaches due to its dopamine antagonist effect (*6*). A meta-analysis of studies comparing metoclopramide with placebo showed that metoclopramide was more likely to provide a significant reduction in migraine pain (odds ratio 2.84, 95% confidence interval 1.05 to 7.68) (*7*). Previous studies have compared the efficacy of metoclopramide and sumatriptan. Friedman *et al*. found no significant difference between intravenous (IV) metoclopramide (up to 80 mg) and subcutaneous (SQ) sumatriptan (6 mg) in terms of pain improvement after 2

h (*8*). Talabi *et al*. compared intravenous metoclopramide (20 mg) and sumatriptan (6 mg) for the treatment of migraine and found that metoclopramide was superior in reducing pain at 1 h post-administration (*9*). However, it should be noted that the dosages of the medications used in those previous studies were higher than the dosages commonly used in Japan (*i.e.*, metoclopramide 10 mg, sumatriptan 3 mg).

In the present study, our objective was to assess whether IV metoclopramide 10 mg is non-inferior to SQ sumatriptan 3 mg for alleviating acute migraine pain in the ED setting.

Study design

This single-center, prospective, open-label, cluster-randomized controlled, non-inferiority trial was conducted over a 3-year period from July 1, 2019 to June 30, 2022 in the ED of the Center Hospital of the National Center for Global Health and Medicine in Japan, where about 11,000 patients are emergently transported each year. The study was approved by the certified review board of the National Center of Global Health and Medicine (NCGM) (Approved number: NCGM-C-003164-03) and conducted in accordance with the Declaration of Helsinki. The trial registration number is jRCTs031190007.

Patients

Patients emergently transported to the ED for headache were eligible for participation if they satisfied the criteria for migraine according to the International Classification of Headache Disorders of the International Headache Society, third edition (*10*), had moderate to severe headache intensity, were between the ages of 20 and 65 years, and provided written informed consent. Exclusion criteria are listed in the protocol paper (*11*).

Interventions

After providing informed consent, participants were allocated to one of the two treatment groups according to the month (see *randomization and data collection* below). Participants in the metoclopramide group received IV metoclopramide 10 mg and those in the sumatriptan group received SQ sumatriptan 3 mg.

Outcomes

The primary outcome was change in headache pain intensity at 1 h after baseline, evaluated according to NRS score. Secondary endpoints were change in NRS score 30 min after medication administration, headache relief 1 h after medication administration (defined as the patient's description of headache from severe or moderate to either mild or none), and adverse events.

Randomization and data collection

Metoclopramide and sumatriptan have different routes of administration, so for patient safety in the busy ED, randomization was performed on a monthly basis and neither physicians nor participants were blinded. The monthly allocation was carried out using computer-generated random numbers. The time of medication administration was considered Time 0, and pain intensity was assessed using NRS at Time 0 and again at 30 min and 1 h. Patients were asked to rate their pain on a scale between 0 and 10, with 0 representing no pain and 10 representing the worst pain imaginable. Pain intensity was also assessed according to four rankings (none, mild, moderate, and severe) at Time 0 and 1 h.

Sample size and statistical analysis

A previous study indicated an expected reduction in NRS pain score of 6 and 5 for participants in the metoclopramide and sumatriptan groups, respectively (*8*). Based on previous data, we set the standard deviation as ±3 NRS points. The non-inferiority cutoff was set as −1.0 NRS points, based on findings from a previous study that a between-group difference of 1.3 NRS points is a valid and reproducible minimum clinically significant change in the ED setting (*12*). Thus, a sample size of 37 per group was calculated to be sufficient, with a one-sided α of 0.025 and a power of 0.8. Taking potential dropout rates into account, the sample size for each group was set at 40. All randomized participants who satisfied the inclusion criteria and signed the informed consent form were included in the intention-to-treat (ITT) set. For the primary outcome, we reported the within-group improvement in NRS pain score between baseline and 1 h. Student's t-test was used to compare mean differences in NRS score and the lower one-sided 95% confidence interval (CI). A two-sided p value of < 0.05 was considered to indicate significance.

Key research findings

Patient background

Participant enrollment began in July 2019 and continued for 36 months. During the study period, a total of 1,025 patients with acute headache were screened, and migraine was diagnosed in 104 patients. A total of 36 patients satisfied the eligibility criteria and consented to participate in this study; 19 and 17 were randomized to the metoclopramide group and the sumatriptan group, respectively. In the metoclopramide group, 1 participant was discharged before the 1-h follow-up, and thus the data from only 18 participants were included for the analysis of the primary outcome. The target number of patients was 80, but due to the COVID-19 epidemic, we

Table 1. Baseline characteristics, headache severity at baseline

Characteristics	Metoclopramide (*n* = 19)	Sumatriptan (*n* = 17)	*p* value
Median age, y [IQR]	28 [24, 40]	29 [24, 41]	0.95
Female sex, *n* (%)	22 (58%)	12 (71%)	0.43
Median attack duration, h [IQR]	7 [3, 24]	5 [2, 10.5]	0.22
Self-medicated prior to ED visit, *n* (%)	10 (53%)	10 (58%)	0.71
Baseline NRS score, mean (SD)	5.9 (2.7)	6.9 (1.7)	0.18

ED, emergency department; NRS, numerical rating scale for pain, ranging from 0 (no pain) to 10 (worst pain imaginable); IQR, interquartile range; represents 25th, 75th percentile; SD, standard deviation.

determined that it would be difficult to reach the target, even if the study period were extended.

Table 1 shows the baseline characteristics, the headache severity at baseline. There were no differences between the two groups in terms of age or sex. More than half of the patients in both groups self-medicated prior to visiting the ED. The baseline NRS score (standard deviation) was 5.9 (± 2.7) in the metoclopramide group, and 6.9 (± 1.7) in sumatriptan group ($p = 0.18$).

Improvement in NRS after 30 min and 1 hour post-medication

The mean NRS score at 30 min was 3.3 (± 2.9) in the metoclopramide group and 3.6 (± 1.9) in the sumatriptan group, while the scores at 1 h were 1.9 (± 2.8) and 1.8 (± 1.8), respectively (Figure 1). The mean differences in reduction of NRS score from baseline to 1 h were −4.1 (± 2.6) in the metoclopramide group and −5.2 (± 1.8) in the sumatriptan group.

NRS scores were significantly reduced 1 h after administration of the treatment medications in both groups. However, metoclopramide was not statistically non-inferior to sumatriptan, given that the 95% confidence interval (CI) lower boundary of the absolute difference in mean NRS reduction was smaller than the inferiority margin of −1.0 (absolute difference −1.1; one-sided 95% CI −2.7). On the other hand, the proportion of patients whose pain disappeared one hour after medication was 50% in the metoclopramide group, compared to 35% in the sumatriptan group (Supplemental Table S1, *https://www.ghmopen.com/site/supplementaldata.html?ID=92*).

Comparison with previous studies

Compared with previous studies, the mean baseline NRS score prior to medication administration was lower in the present study. In the sample-size calculation based on a previous study, the mean baseline NRS score was over 8, and the reduction in NRS score for the metoclopramide group at 1 h was assumed to be 6 points (*8*). However, in the present study, the mean baseline NRS score was 6.4, which was lower than that in the previous study. The difference in baseline NRS scores between the previous study and the present study may

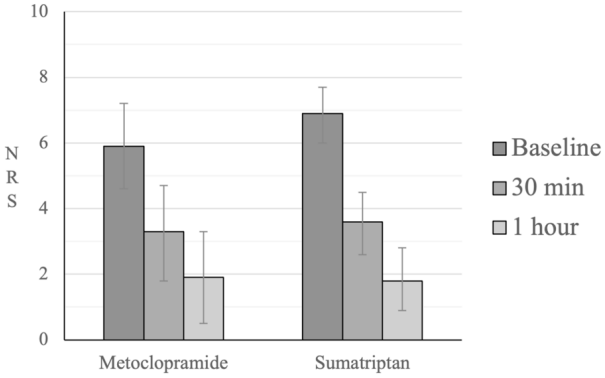

Figure 1. Numerical rating scale (NRS) scores for headache. The graph represents NRS before medication, 30 minutes after medication, and 1 hour after medication. Bars represent the 95% confidence intervals. Both groups showed a temporal decrease in NRS scores after medication, with no significant differences observed between the groups at each time point.

have implications for the interpretation of the results. In a study by Talabi *et al*., metoclopramide demonstrated a greater decrease in visual analog scale scores compared with sumatriptan, but there were differences between the two groups in terms of patient age and baseline pain scales (*9*). Additionally, both groups received a higher dose than we used in our study. Meanwhile, in studies investigating the optimal dosage of metoclopramide for migraine treatment, no significant increase in pain improvement effect was observed with doses of 20 mg or 40 mg compared with 10 mg (*13*). In a previous study comparing subcutaneous injections of 3 mg and 6 mg sumatriptan for the treatment of migraine attacks, there was no significant difference between the two groups in terms of the proportion of subjects who were pain-free 1 h after administration or in reduction in pain intensity (*14*).

Adverse events

There were no serious adverse events in either group. No side effects were reported in the metoclopramide group but 1 patient (5.6%) in the sumatriptan group complained of nausea after administration, but the nausea resolved spontaneously.

In this study, there were no serious adverse events or chest symptoms, which might be a concern with sumatriptan, in either group. In addition, other side

effects were minimal, with only one participant in the sumatriptan group experiencing worsened nausea. The limited occurrence of side effects can be attributed to several factors, including the relatively small sample size, lower dosage compared with previous studies, and the short duration of observation. It has been previously reported that side effects called "triptan sensations", which include paresthesia and chest symptoms, are dose related (*15*).

Limitations

There are several limitations to this study. First, because of the COVID-19 epidemic, the study was terminated before the target sample size was reached; therefore, the sample size was small and the statistical power was insufficient. Despite randomization, there was a difference of more than 1.0 in the baseline mean NRS scores between the two groups. Second, blinding was impractical due to differences in administration methods. Third, this study was conducted at a single center, which may limit the generalizability of the findings. Finally, we did not evaluate the persistence of the pain-improving effect.

In conclusion, 1 h after metoclopramide administration, migraine pain was reduced compared with baseline, but metoclopramide did not demonstrate non-inferiority or inferiority for pain relief of acute migraine pain compared with sumatriptan, and thus the results are inconclusive.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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