Metoclopramide versus sumatriptan in the treatment of migraine in the emergency department: a single-center, open-label, cluster-randomized controlled non-inferiority trial

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Study protocol

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Abstract

Background Migraine is a common disease seen in the emergency department (ED). Triptans, which are recommended in therapeutic guidelines for migraine, have some contraindications and possible severe side effects. Metoclopramide, which is commonly used as an antiemetic, also seems to have pain-relieving effects for migraine. In this study, we will investigate whether metoclopramide 10 mg intravenously (IV) is non-inferior to sumatriptan 3 mg subcutaneously (SQ) as migraine treatment in the ED. **Methods** This study is a single-center, open-label, cluster-randomized controlled trial of 80 patients with migraine attacks to investigate the non-inferiority of metoclopramide to sumatriptan. The patients will be cluster-randomized monthly into metoclopramide 10 mg IV and sumatriptan 3 mg SQ arms. The primary outcome will be change in Numerical Rating Scale score for headache at 1 h after baseline. **Discussion** If our hypothesis is confirmed, metoclopramide can be considered as first-line medication for migraine attacks in ED settings.

Background

Migraine is one of the most common diseases among young and middle-aged people and is the third leading cause of disability in people under 50 years of age according to Global Burden of Disease 2015.¹ The annual prevalence of migraine in Japan is 8.4%,² and many migraine patients present to emergency departments (EDs). A variety of parenteral medications are used for acute migraine in the ED, but previous studies have indicated that no medication provides rapid and complete relief of pain and associated symptoms without side effects.³⁴

Although clinical guidelines recommend triptans as first-line therapy for moderate to severe migraine attacks⁵⁶, some ED doctors hesitate to use triptans because of contraindications, such as a history of ischemic disease or uncontrolled hypertension, and possible side effects, such as chest pressure. Metoclopramide, a dopamine antagonist, is frequently used for patients with nausea in ED settings in Japan because its effectiveness, low cost, and few contraindications.

Previous studies have revealed that both metoclopramide and sumatriptan are more effective than placebo for migraine.⁷⁸ One study that compared the effects of metoclopramide and sumatriptan for migraine found no significant difference in pain relief at 2 h after administration.⁹ However, the standard and recommended dose of metoclopramide for treatment for migraine is 10mg, and the dose of both medications used in the past study was higher than the usual dose recommended for Japanese patients.¹⁰

In this study, we will investigate whether intravenous (IV) metoclopramide 10 mg, which is an eighth of the dose used in the previous study, is non-inferior to subcutaneous (SQ) sumatriptan 3 mg, which is half of the dose used in the previous study, for acute migraine attack in the ED setting.

Methods

Objective

The objective of this study is to assess whether metoclopramide 10 mg IV is non-inferior to sumatriptan 3 mg SQ as treatment for acute migraine attack in the ED setting.

Trial design

This is a single-center, prospective, open-label, cluster-randomized controlled, non-inferiority trial that conforms to the Consolidated Standards of Reporting Trials (CONSORT)¹¹. The timing of interventions and data collection is presented in Figure 1. A flowchart of the study is shown in Figure. 2.

Study setting

This trial will be performed in the ED of the Center Hospital of the National Center for Global Health and Medicine in Japan. About 11,000 patients are emergently transported to the ED annually.

Participants

- Patients emergently transported to the ED for headache are eligible to participate if they fulfill the following criteria.
- Eligibility criteria

Inclusion

- Informed consent obtained from the patient
- Age 20–65 years
- Satisfies the criteria for migraine according to the International Classification of Headache Disorders of the International Headache Society, third edition, beta version¹². Time duration can be excluded because of the emergency setting.
- More than moderate headache intensity, having a great deal of difficulty doing daily activities at presentation

Exclusion

- Judged as having a high likelihood of secondary headache
- Temperature $\geq 38.0^{\circ}\text{C}$
- A new objective finding of neurological abnormality
- History of myocardial infarction or suspected ischemic heart disease
- History of cerebrovascular disease or transient ischemic attack

- History of peripheral vascular disorder
- Uncontrolled hypertension or systolic blood pressure > 180 mmHg at presentation
- Severe liver dysfunction
- Suspected gastrointestinal bleeding, perforation, or obstruction
- Suspected pheochromocytoma
- Use of an ergotamine derivative, other kind of triptan, or monoamine oxidase (MAO) inhibitor
- Pregnancy or breastfeeding
- Allergy to any of the investigational medications
- Participation judged to be inappropriate by emergency physicians
- Rationale for exclusion criteria
- 1–3: The cause of headache might be disease other than migraine.
- 4–8: Contraindications to sumatriptan use
- 9–10: Contraindications to metoclopramide use

Interventions

The doctors in charge obtain informed consent from each participant before entry to the study. Informed consent cannot be obtained by proxy. After providing informed consent, participants are allocated to one of the two treatment according to the month (see Randomization and Concealment). Participants in the metoclopramide arm receive metoclopramide 10 mg IV. Participants in the sumatriptan arm receive sumatriptan 3 mg SQ.

- There are no criteria for discontinuing the intervention because participants receive the study drug only once. If improvement of symptoms is unsatisfactory after 30 min, a suppository of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) may be given as rescue medication upon patient request and doctor approval. The peak serum concentration of sumatriptan 3mg SQ is 0.21 h, so patients can receive rescue medication at least 30 min after the study medication, and this will be reported in case report forms (CRFs).

Patients are not allowed to receive ergotamine derivatives, other kinds of triptans, or monoamine oxidase inhibitors during the study period.

Outcomes

- Primary outcome
- Change in headache pain intensity 1 h after baseline, measured with the Numerical Rating Scale for Pain (NRS)¹³.
- Secondary endpoints

- 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
- Concomitant symptoms 1 h after medication administration
- Time duration from study medication administration to leaving the ED
- Receipt of rescue medication during the ED visit
- Adverse events

Sample size

- A previous study indicated an expected NRS pain score reduction of 6 and 5 in the metoclopramide and sumatriptan groups, respectively.¹² Even though the doses of the study medication are not the same, findings from other studies indicate that a high metoclopramide dose is no better than a lower dose for pain relief.¹³ Based on previous data, we set the standard deviation as 3 NRS points. The non-inferiority margin is set as -1.0 NRS points, because findings from a previous study indicated that a 1.3-NRS-point between-group difference is a valid and reproducible minimum clinically significant change in the ED.¹⁵ Thus, a sample size of 37 in each group is calculated to be sufficient with a one-sided α of 0.025 and a power of 0.8.¹⁶ Taking potential dropout rates into account, a sample size of 40 in each group is eventually determined.

Randomization and concealment

Metoclopramide and sumatriptan require different routes of administration, so for patient safety in the busy ED, randomization is performed on a monthly basis and neither physicians nor participants are blinded. The monthly allocation is done with computer-generated random numbers. The principal investigator (PI) generated the random numbers prior to the first enrollment and keeps the list. With cluster randomization by month, participants can receive the study medication soon after enrollment. The doctors in charge fill in the competency checklist to confirm eligibility and allocate the patient to the group for the current month.

Data collection and management

- The time of medication administration is considered Time 0. Pain intensity is assessed with the NRS at Time 0, 30, and 60 min. Patients are then 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 is also assessed with 4 rankings (none, mild, moderate, and severe) at Time 0 and 60 min. Vital signs are monitored after medication administration. The presence of nausea, vomiting, optic hyperesthesia, and auditory hyperesthesia is assessed at Time 0 and 60 min. If rescue medication is used, the

timing and drug used are recorded. At the completion of the visit, patients are asked about adverse symptoms during their ED stay and instructed to call if they have any adverse symptoms. Vital signs are monitored and the duration of ED stay is also recorded after medication administration.

We will use paper CRFs to recode case information with only the study ID number. The PI will enter the data from CRFs into an Excel file, which will be password-protected.

Access to the collected data will be strictly limited to investigators. The collected data will be anonymized and stored in a locked cabinet or a password-protected computer.

Statistical analysis

- All randomized participants who fulfill the eligibility criteria and sign the informed consent form will be included in the intention-to-treat (ITT) set. All participants who take either study medication will be included in the safety analysis set. All analyses of efficacy will be based on the ITT set. Analysis of adverse events will be based on the safety analysis set.
- For the primary outcome, we will report the within-group improvement in NRS pain score between baseline and 1 h. Student's t test will be used to compare mean differences in NRS score and lower one-sided 95% confidence interval (CI), along with a one-sided $p < 0.025$. The missing data will be treated as missing at random, and the multiple imputation procedure will be used for the primary outcome. The
- For secondary analyses, the chi-square test will be used to compare rates, and Student's t tests will be used to compare mean differences.
- For the safety analysis, adverse events will be listed with the relationship to the study medications. The chi-square test will be used to compare the rates of participants who have at least one adverse event between groups in the safety analysis set.
- Statistical analyses will be performed using JMP statistical software, version 14.0.0 (SAS Institute Inc., Cary, NC). A two-sided $p < 0.05$ will be considered significant. No interim analysis will be performed in this study.

Data monitoring

To guarantee the quality of the trial, monitoring staff will audit the trial implementation process and data entry process every 4 months. This periodic audit will be performed to ensure that the protocol and Good Clinical Practice (GCP) guidelines are being followed. The monitoring staff may review source documents to confirm that the data recorded on CRFs are accurate.

Harms

In this study, adverse events may include, but are not limited to, chest symptoms and flushing with sumatriptan, and akathisia, drowsiness, and dystonic reactions with metoclopramide. Patients are closely monitored during the ED stay. If any participant experiences any untoward effects as a direct result of trial participation, compensation will be provided as covered by clinical study insurance.

- Participants are free to withdraw from the study at any time upon request. An investigator may withdraw a participant from the study for the following reasons:
- □ Voluntary withdrawal of consent
- □ Serious adverse events (e.g., shock, loss of consciousness, or ischemic heart diseases)
- □ Disadvantages of the study outweigh the advantages

If serious adverse events occur, the Efficacy and Safety Assessment Committee will meet to evaluate the study's safety and efficacy. The committee will advise the PI of any need for revision of the study protocol or termination of the study.

Discussion

- This study is a non-inferiority study of metoclopramide to sumatriptan for acute migraine attack in the ED setting. Although the efficacy of metoclopramide for migraine has previously been reported, metoclopramide is not yet approved as a treatment for migraine in Japan. However, triptans are recommended for moderate or severe acute migraine attack.
- One randomized clinical trial has compared the efficacy of IV metoclopramide and SQ sumatriptan for acute migraine patients⁹. The dose of IV migraine in the previous study was aggressive (20 mg dosed up to 4 times). There was no significant change in pain intensity as measured on an 11-point pain scale at 2 h, but aggressive IV metoclopramide was superior to sumatriptan 6 mg SQ in terms of the percentage of patients who were pain-free at 2 h (59% vs 35%, $p = 0.04$).
- The doses of metoclopramide and sumatriptan in the previous study were larger than those in this study. But, the standard and recommended dose of IV metoclopramide is 10 mg, which is the same as the dose of this study.¹⁰ The standard dose of SQ sumatriptan in the past studies was 6mg.¹⁷ However, the recommended and approved doses in Japan are metoclopramide 10 mg IV and sumatriptan 3 mg SQ for safety.
- Friedman et al. compared 3 doses of IV metoclopramide (10, 20, and 40 mg) and found that the improvement of NRS score at 1 h was similar across doses (-4.7 vs -4.9 vs -5.3 ; $p = 0.19$).¹⁴
- Finally, we discuss the potential limitations of this study. First, neither participants nor physicians will be blinded to the treatment because each medication requires different routes of administration. NRS score is a subjective index, but it is not affected by overcrowding or the presence of other patients in the ED. Some previous studies set the primary outcome as difference in NRS score at 80 min or 120 min after medication. A pilot retrospective survey of migraine patients at the ED of our hospital indicated that the mean duration of ED visit after medication is 75 min. Thus, we set the primary outcome as the improvement in NRS score at 1 h.

- A second limitation is that randomization will be performed on a monthly basis rather than on a participant basis. The frequency or severity of migraine attacks have no seasonal variation, so this monthly cluster randomization may not lead to bias. A monthly cluster randomization thus enables quick administration of study medications.

A third limitation, which is common to most single-center studies, is that this study will be conducted in a single urban ED in Tokyo, Japan, which cares for mostly Japanese patients. As such, results may not be generalizable to other settings, ethnicities, and socioeconomic groups.

Trial Status

Protocol version:1.3

Study period: Study period: 5 April 2019 to 31 March 2021.

The recruitment will begin on 1 July 2019.

The recruitment will be completed on 30 September 2020, approximately.

Abbreviations

ED: Emergency department; IV: intravenously; SQ: subcutaneously; CONSORT: Consolidated Standards of Reporting Trials; MAO: monoamine oxidase; NSAIDs: non-steroid anti-inflammatory drugs; CRFs: Case report forms; NRS: Numerical Rating Scale; ITT: intention-to-treat; CI: confidence interval; GCP: Good Clinical Practice; PI: principal investigator

Declarations

Ethics approval and consent to participate

The study proposal and study materials were approved by the certified review board of the National Center of Global Health and Medicine (NCGM). This study is registered at the Japan Registry of Clinical Trials (jRCTs031190007). If the protocol is modified, the amendments must be approved by the certified review board and registered to Japan Registry of Clinical Trials. The informed consent will be obtained from all study participants.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YF designed the protocol, wrote the draft of the manuscript, and contributed to the coordination of the study. AK contributed as the senior author and principal investigator (PI) of this study. RS and KK supervised and supported study design and manuscript writing. WM contributed to the data monitoring. TU and FK participated in the design of this study. All authors reviewed and approved the final version of the manuscript.

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Figures

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT			0min	30min	60min	at discharge
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Metoclopramide IV			X			
Sumatriptan SQ			X			
ASSESSMENTS:						
NRS score for pain			X	X	X	
Intensity of pain			X		X	
Concomitant symptoms			X		X	
Rescue use					X	X
Length of ED stay						X
Adverse events						X

Figure 1

Schedule of intervention and assessments ED, emergency department; NRS, Numerical Rating Scale

Figure 2

Flowchart of the study process

Supplementary Files

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- [SPIRITchecklist0526.docx](#)
- [renamed09b12.pdf](#)
- [Ethicalapprovaldocument.pdf](#)