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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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Abstract: 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 article, we will introduce a study in progress, which investigates whether metoclopramide 10 mg intravenously (IV) is non-inferior to sumatriptan 3 mg subcutaneously (SQ) as migraine treatment in the ED. 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. In discussion, if our hypothesis is confirmed, metoclopramide can be considered as first-line medication for migraine attacks in ED settings.

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

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 the emergency department (ED). The pathophysiology of migraine has not been definitively elucidated, and there are two theories of the origin of the pain: the peripheral origin theory from cerebral vascular and trigeminal nerve endings, and the central origin theory from brainstem. It has been shown that sensitization to non-nociceptive stimuli occurs in both peripheral and central regions, and it has been shown that nitric oxide, histamine, serotonin, glutamate, dopamine, and calcitonin gene-related peptide (CGRP) are involved in this pathology (*3,4*).

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 (*5,6*). The clinical guidelines recommend triptans as first-line therapy for moderate to severe migraine attacks (*7,8*). Triptans are serotonin receptor: 5-HT1B/1D receptor agonists, which act on vascular smooth muscle for promotion of vasoconstriction and act on the trigeminal nerve for pain relief. However, 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.

Meanwhile, 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. It was reported that the frequency of alleles of the dopamine D2 receptor gene was increased in patients with a diagnosis of migraine. Dopamine antagonists act on postsynaptic cells especially in the limbic system and basal ganglia, and have sympathetic inhibition, anti-serotonin, anticholinergic, and antihistamine effects, so are expected to be effective against migraine mechanistically (*9*). Previous studies which compared metoclopramide to other agents for migraine therapy are shown in Table 1.

Previous studies have revealed that both metoclopramide and sumatriptan are more effective than placebo for migraine (*10,11*). One study that compared the effects of metoclopramide and sumatriptan for migraine found no significant difference in pain relief at 2 h after administration (*12*). However, the standard and recommended dose of metoclopramide for treatment for migraine is 10 mg, and the dose of both medications used in the past study was higher than the usual dose recommended for Japanese patients.

Table 1. Studies comparing Metoclopramide to other agents for migraine therapy

Study first author (Year)	Treatment	Control	%Pain Relief
Coppola (1995)	MTC 10 mg IV	PCB IV	48 *vs*. 29
Tek (1990)	MTC 10 mg IV	PCB IV	67 *vs*. 19
Cete (2004)	MTC 10 mg IV	PCB IV	52 *vs*. 35
Ellis (1993)	MTC 10 mg IV	PCB IV	88 *vs*. 31
Cicek (2004)	MTC 10 mg IV	PCB IV	85 *vs*.56
Friedman (2008)	MTC 20 mg IV	PCZ 10 mg IV	78 *vs*. 87
Haugh (1992)	MTC 10 mg IV	DHE 1 mg IV	38 *vs*. 38
Benjamin (2014)	MTC 10 mg IV	VPT 1 g IV	63 *vs*. 40
Benjamin (2014)	MTC 10 mg IV	KET 30 mg IV	63 *vs*. 54
Friedman (2005)	MTC 20 mg IV up to 4 times	STP 6 mg SQ	73 *vs*. 47

DHE, dihydroergotamine; IV, intravenously; KET, ketorolac; MTC, metoclopramide; PCB, placebo; PCZ, prochlorperazine; SQ, subcutaneously; STP, sumatriptan; VPT, valproate.

Table 2. Eligible criteria

Inclusion Criteria
1. Informed consent obtained from the patient.
2. Age 20-65 years.
3. Satisfies the criteria for migraine according to the International Classification of Headache Disorders of the International Headache Society, third beta edition. Time duration can be excluded because of the emergency setting (*14*).
4. More than moderate headache intensity, having a great deal of difficulty doing daily activities at presentation.

Exclusion Criteria
1. Judged as having a high likelihood of secondary headache
2. Temperature ≥ 38.0℃
3. A new objective finding of neurological abnormality
4. History of myocardial infarction or suspected ischemic heart disease
5. History of cerebrovascular disease or transient ischemic attack
6. History of peripheral vascular disorder
7. Uncontrolled hypertension or systolic blood pressure > 180 mmHg at presentation
8. Severe liver dysfunction
9. Suspected gastrointestinal bleeding, perforation, or obstruction
10. Suspected pheochromocytoma
11. Use of an ergotamine derivative, other kind of triptan, or monoamine oxidase (MAO) inhibitor
12. Pregnancy or breastfeeding
13. Allergy to any of the investigational medications
14. Participation judged to be inappropriate by emergency physicians

The recommended and approved doses in Japan are metoclopramide 10 mg intravenously (IV) and sumatriptan 3 mg subcutaneously (SQ) for safety. So, in this study we will investigate whether IV metoclopramide 10 mg, which is an eighth of the dose used in the previous study, is non-inferior to SQ sumatriptan 3 mg, which is half of the dose used in the previous study, for acute migraine attack in the ED setting. Metoclopramide is less expensive and has fewer side effects, and is more widely and easily used in the ED, so it is considered to be a possible standard care for migraine in the ED if metoclopramide is shown to be noninferior to sumatriptan. Therefore, we are conducting a study 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.

Study design, setting, and patients: This is a single-center, prospective, open-label, cluster-randomized controlled, non-inferiority trial (Trial registration: jRCT registration number: jRCTs031190007; Registered on 5 April 2019). The cluster is the month, and the study period will be 36 months, so there will be 36 clusters. This trial is 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. Patients emergently transported to the ED for headache are eligible to participate if they fulfill the eligibility criteria in Table 2.

Interventions: After providing informed consent, participants are allocated to one of the two treatments according to the month. Participants in the metoclopramide arm receive metoclopramide 10 mg IV. Participants in the sumatriptan arm receive sumatriptan 3 mg SQ.

Outcomes: Primary outcome is change in headache pain intensity 1 h after baseline, measured with the Numerical Rating Scale for Pain (NRS) (*13*). Secondary endpoints are 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, and adverse events are also secondary outcomes.

Sample size: A previous study indicated an expected NRS pain score reduction of 6 and 5 in the metoclopramide and sumatriptan groups, respectively (*14*). Even though the doses of the study medication were not the same, findings from other studies indicated that a high metoclopramide dose was no better than a lower dose for pain relief (*15*). 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 was a valid and reproducible minimum clinically significant change in the ED (*16*). 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 (*17*). 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. With cluster randomization by month, participants can receive the study medication quickly after enrollment.

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. 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 $p < 0.025$. Statistical analyses will be performed using JMP statistical software, version 14.0.0 (SAS Institute Inc., Cary, NC).

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.

Metoclopramide is less expensive and has fewer side effects, and is more widely and easily used in the ED than sumatriptan. So, if our hypothesis that metoclopramide is not inferior to sumatriptan for pain relief of migraine attack in the ED is confirmed, metoclopramide can be considered as first-line medication for migraine attacks in ED settings.

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.

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