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Effectiveness and safety of metoclopramide in treatment of intractable hiccup: a protocol of systematic review and meta-analysis

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ABSTRACT

Introduction Hiccup is a common disease that not only occurred on adults but also on infants, which can severely do harm to patients' physical and psychological health. Metoclopramide has been reported to have effects on intractable hiccup. However, there is a limited evidence that describes the efficacy and safety of metoclopramide in the treatment of intractable hiccup. The aim of this article is to obtain evidence on the effectiveness and safety of metoclopramide in treating patients with intractable hiccup.

Methods and analysis We will search the following databases, including PubMed, Cochrane Library, Embase, Web of Science, CBM, Wan-fang, VIP database, CNKI and MEDLINE from their inception to 11 November 2021. All the randomised controlled trials associated with metoclopramide in treating intractable hiccup will be included. Articles screened, selected and extracted will be performed by two researchers independently. The risk of bias will be assessed by using the Cochrane Collaboration. We will carry out the meta-analysis by using RevMan V.5.4 software.

PROSPERO registration number CRD42021293000.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will strictly follow systematic review and meta-analysis guidelines to minimise bias.
⇒ The quality of the publications included in this review are likely to influence the final results.
⇒ This article will search English and Chinese literature, which will be an updated and more comprehensive review compared with what has been published previously.
⇒ The many aetiologies of hiccup and wide-ranging comorbidities may contribute to highly heterogeneity of the response to metoclopramide.

INTRODUCTION

Hiccup, also known as singultus, originates from Latin. It means the act of holding one's breath while crying.[1] Hiccup is a common physiological phenomenon that almost occurs on everyone.[2] Most patients with acute hiccup are self-limited, and rare patients will persist a few days, a few months or even a few years. Based on their duration, it can be classified into persistent hiccup and intractable hiccup. Hiccup lasting more than 48 hours is called persistent hiccup while lasting more than a month is called intractable hiccup.[3] Intractable hiccup can lead to a significant deterioration in quality of life, with common situation such as insomnia, poor appetite or fatigue. More importantly, intractable hiccup may be a potential signal of some diseases.[4]

Hiccup is caused by spasmodic contraction of the diaphragm and intercostal muscles.[5] It is widely believed that intractable hiccup involves a reflex centre or peripheral reflector, but lack of clear anatomical evidence.[6] Over 100 causes may trigger hiccup, which can be roughly divided into the following categories[7 8]: (1)gastrointestinal diseases: peptic ulcer, stomach spasm, gastro-oesophageal reflux; (2) malignant tumours: lung cancer, stomach cancer, oesophageal cancer, brain tumour; (3) chest diseases: pleurisy, pleural effusion, pneumonia, myocardial infarction; (4) mental stimulation: afraid, excessive anxiety or excitement; (5) drugs: anti-infective drugs (penicillin), corticosteroids (dexamethasone), chemotherapy drugs (cisplatin) and benzodiazepines (diazepam); (6) electrolyte disorder: low sodium, low calcium. Irritation and distention of the stomach are the most common causes of hiccup, such as overeating, eating spicy food and drinking plentiful carbonated drinks.[9]

In the past, chlorpromazine was priority medication in treating hiccup, which was the only drug approved by the US Food and Drug Administration.[10] Due to the adverse effects, it is not recommended as a first-line drug now.[11] At present, many agents have been reported

Box 1 Search strategy in PubMed database

Search items
⇒ Metoclopramide.Mesh.
⇒ Metaclopramide.ti.ab.
⇒ Maxolon.ti.ab.
⇒ Rimetin.ti.ab.
⇒ Metoclopramide Hydrochloride.ti.ab.
⇒ Hydrochloride, Metoclopramide.ti.ab.
⇒ Metoclopramide Monohydrochloride.ti.ab.
⇒ Monohydrochloride, Metoclopramide.ti.ab.
⇒ Metoclopramide Monohydrochloride, Monohydrate.ti.ab.
⇒ Primperan.ti.ab.
⇒ Reglan.ti.ab.
⇒ Cerucal.ti.ab.
⇒ Metoclopramide Dihydrochloride.ti.ab.
⇒ Dihydrochloride, Metoclopramide.ti.ab.
⇒ 1 or 2–14.
⇒ Hiccup.Mesh.
⇒ Hiccups.ti.ab.
⇒ Hiccough.ti.ab.
⇒ Hiccoughs.ti.ab.
⇒ singultus.ti.ab.
⇒ 16 or 17–20.
⇒ Randomized controlled trial. Mesh.
⇒ Controlled clinical trial.ti.ab.
⇒ Randomized.ti.ab.
⇒ Randomly.ti.ab.
⇒ Trial.ti.ab.
⇒ 22 or 23–26.
⇒ 15 and 21 and 27.

to be helpful in treating intractable hiccup, such as metoclopramide, baclofen and gabapentin. Alternate therapies such as acupuncture and hypnosis are also used to treat intractable hiccup. Surgery may be an option in the case of other treatments been failed. Although currently numerous therapies have been proposed, unfortunately the treatment of intractable hiccup still remains challenging.[1 12]

Metoclopramide is used to treat gastrointestinal diseases.[13] It is reported that metoclopramide can be effective on relieving the symptom of intractable hiccup which caused by stroke, cancer, migraine, gastrointestinal diseases and so on.[14 15] This may bring hope to patients with intractable hiccup.[16] Due to a lack of big data studies, it has not reached a consensus. Systematic evaluation and meta-analysis will be conducted to provide evidence for metoclopramide in the treatment of intractable hiccup.

Objective

This study is to assess the efficacy and safety of metoclopramide in treating patients with intractable hiccup.

METHODS

Registration

The protocol in this study was consistent with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[17] The PRISMA-P is shown in online supplemental appendix 1.

Patients and public involved

In this review study, patients and the public will not be directly involved.

Study selection inclusion/exclusion criteria

Types of patients

Patients with hiccup lasting longer than 1 month without self-remission, regardless of age, race, nationality or gender.

Types of studies

All randomised controlled clinical trials published concerning metoclopramide in treating intractable hiccup will be included. Literature studies, animal studies, case reports, dissertations and quasi-randomized control trials (RCTs) will be excluded.

Types of inventions

The experimental group is principally treated with oral or injected metoclopramide, which could be combined with other drugs therapy. The control group is treated with placebo, baclofen, gabapentin or other western medicines.

Types of outcome measures

The primary outcomes include severity of intractable hiccup, frequency of hiccup, increase in hiccup-free periods and effective rate. The secondary outcomes include adverse events, dosage forms of metoclopramide, the therapeutic and toxic dose of metoclopramide.

Search strategy

PubMed, Cochrane Library, Embase, Web of Science, Wan-fang, VIP, CNKI, CBM database and MDELINE will be searched. Randomised controlled studies from their inception to 11 November 2021 will be retrieved. The complete search strategy from PubMed is shown in box 1. And the whole database search strategy provided in online supplemental appendix 2.

Data acquisition

The electronically retrieved articles will be imported into EndNote X9.1 after deleting duplicates. First, two evaluators (LW and TC) will independently screen abstract and title based on the inclusion criteria and exclusion criteria. Then two evaluators will review the full text and determine whether to include the article. The excluding studies will be recorded the reasons. Any disagreement between two evaluators will be resolved by discussion. If a consensus still cannot be reached in the end, it will be decided by a third researcher (BW). The flow diagram of screening the selecting studies is shown in figure 1.

Data extraction and management

Relevant information will be extracted by two evaluators (BZ and CZ) using Excel 2019 software. And we will obtain data from the article including literature source,

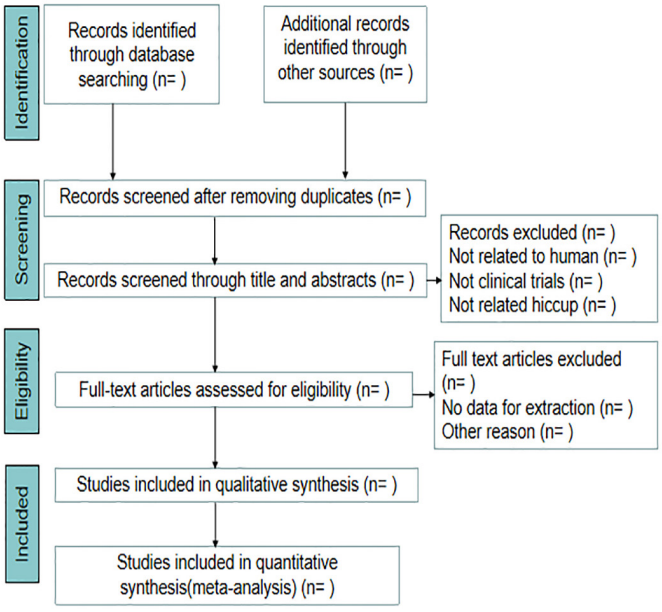

Figure 1 Flow diagram of the study selection process.

year and month of publication, sample size, name of first author, country of origin, intervening measure, participant characteristic, aetiologies of hiccup, severity of intractable hiccup, hiccup-free period, frequency of hiccup, adverse event, dose and dosage form of metoclopramide and duration of follow-up. If the data of the literature are incomplete or not clear, we will contact the corresponding author to obtain further information.

Data synthesis and analysis

We will tabulate the vital information such as methods, results, aetiologies of hiccup and adverse events. When there are more than five studies, RevMan V.5.4 will be used to analyse data. Otherwise, we will implement a systematic narrative synthesis following accepted guidelines. The same interventions and outcomes will be combined to estimate efficacy and safety of metoclopramide in treating patients with intractable hiccup by using a meta-analysis. Dichotomous data will be expressed by OR, RR (risk ratio) or 95% CI while continuous variables will be expressed by SMD and 95% CI. In the absence of heterogeneity, we will pool effect size with 95% CI fixed effects model. If there is significant heterogeneity (I^2>50%), a random effects model will be used.

Subgroup analysis and sensitivity analysis

If there is significant heterogeneity among publication, subgroup analysis about the aetiologies of hiccup will be performed to identify the possible source of heterogeneity. We will reduce sensitivity by reanalysing the data and excluding low-quality research.

Bias assessment

The risk of bias will be assessed by the three investigators (LW, BZ, YG) using the Cochrane Collaboration, which will be classified into three levels of unclear risk, high risk and low risk. The three levels are evaluated by studying allocation concealment, blinding, randomisation, selective outcome reporting, incomplete data and other biases.

Heterogeneity assessment

Heterogeneity comes from clinical heterogeneity, statistical heterogeneity and methodological heterogeneity. When the sample is small, I^2 statistic will be selected for heterogeneity assessment. I^2 is 75%, 50% and 25% representing large, medium and small heterogeneity, respectively. The value of I^2 is greater, the heterogeneity will be greater. It is generally believed that I^2 no more than 50% can be accepted.

Grading the quality of evidence

According to heterogeneity, risk of bias, accuracy, indirectness and publication bias, the level of evidence for the study will be rated as high, medium, low and very low.

Ethics and dissemination

It does not require ethical approval. The final results will be presented at relevant conferences or disseminated in peer-reviewed journals.

Contributors DW designed this protocol and registered in the PROSPERO database. LW and TC will select the articles after reading. BZ and CZ will extract data independently. Any differences should be determined after discussion with the third reviewer BW to ensure that no errors occur during the review process. DW and YG revised the final manuscript. All authors have read and approved the publication of the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	Yes		P1, L1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Yes		P1, L1-2
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Yes		P1, L22
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes		P1, L5-7
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes		P6, L25-28
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		No	
Support					
Sources	5a	Indicate sources of financial or other support for the review	Yes		P6, L29-30
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes		P6, L29-30
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes		P6, L29-30
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes		P3, L9-11
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes		P3, L12-25
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Yes		P3, L12-25
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Yes		P4, L1-4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes		P4
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes		P5, L9-16
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Yes		P5, L1-8
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes		P5, L9-16
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes		P5, L17-23
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes		P3, L26-29
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes		P6, P8-12
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes		P5,L23;P6,L1
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	Yes		P5, L18-22
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Yes		P6, L4-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes		P5, L19-20
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Yes		P6, L8-12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Yes		P6, L19-21

Appendix 2: Search strategy

PubMed/Medline

#1 "Metoclopramide"[Mesh]
#2 ((((((((((((Metaclopramide[Title/Abstract])) OR (Maxolon[Title/Abstract])) OR (Rimetin[Title/Abstract])) OR (Metoclopramide Hydrochloride[Title/Abstract])) OR (Hydrochloride, Metoclopramide[Title/Abstract])) OR (Metoclopramide Monohydrochloride[Title/Abstract])) OR (Monohydrochloride, Metoclopramide[Title/Abstract])) OR (Metoclopramide Monohydrochloride, Monohydrate[Title/Abstract])) OR (Primperan[Title/Abstract])) OR (Reglan[Title/Abstract])) OR (Cerucal[Title/Abstract])) OR (Metoclopramide Dihydrochloride[Title/Abstract])) OR (Dihydrochloride, Metoclopramide[Title/Abstract])
#3 #1OR#2
#4 Hiccup[MeSH Terms]
#5 (((Hiccups[Title/Abstract]) OR (Hiccough[Title/Abstract])) OR (Hiccoughs[Title/Abstract])) OR (singultus[Title/Abstract])
#6 #4OR#5
#7 ((((Randomized controlled trial) OR (Controlled clinical trial)) OR (Randomized)) OR (Randomly)) OR (Trial)
#8 #3AND#6AND#7

Embase

('metoclopramide'/exp OR methoxybenzamide:ab,ti OR metaclopramide:ab,ti OR maxolon:ab,ti OR rimetin:ab,ti OR 'metoclopramide hydrochloride':ab,ti OR 'hydrochloride, metoclopramide':ab,ti OR 'metoclopramide monohydrochloride':ab,ti OR 'monohydrochloride, metoclopramide':ab,ti OR 'metoclopramide monohydrochloride, monohydrate':ab,ti OR primperan:ab,ti OR reglan:ab,ti OR cerucal:ab,ti OR 'metoclopramide dihydrochloride':ab,ti OR 'dihydrochloride, metoclopramide':ab,ti) AND ('hiccup'/exp OR hiccups:ab,ti OR hiccough:ab,ti OR hiccoughs:ab,ti OR singultus:ab,ti) AND ('randomized controlled trial':ab,ti OR 'controlled clinical trial':ab,ti OR randomized:ab,ti OR randomly:ab,ti OR trial:ab,ti)

Cochrane Library

#1 (Metoclopramide) explode all trees OR (methoxybenzamide): ti, ab, kw OR (metoclopramide): ti, ab, kw OR (maxolon): ti, ab, kw OR (Rimetin): ti, ab, kw OR (Metoclopramide Hydrochloride): ti, ab, kw OR (metoclopramide monohydrochloride): ti, ab, kw OR (monohydrochloride, metoclopramide): ti, ab, kw OR (Metoclopramide Monohydrochloride, Monohydrate): ti, ab, kw OR (Primperan): ti, ab, kw OR (Reglan): ti, ab, kw OR (Cerucal): ti, ab, kw OR (Metoclopramide Dihydrochloride): ti, ab, kw OR (Dihydrochloride, Metoclopramide) : ti, ab, kw
#2 (Hiccup) explode all trees OR (Hiccups): ti, ab, kw OR (Hiccoughs): ti, ab, kw OR (singultus): ti, ab, kw
#3 (Randomized controlled trial) explode all trees OR (Controlled clinical trial): ti, ab, kw OR (Randomized): ti, ab, kw OR (Randomly): ti, ab, kw

Web of Science

TS=((Metoclopramide OR methoxybenzamide OR metoclopramide OR maxolon OR Rimetin OR "Metoclopramide Hydrochloride" OR "metoclopramide monohydrochloride" OR

"monohydrochloride, metoclopramide" OR "Metoclopramide Monohydrochloride, Monohydrate" OR Primperan OR Reglan OR Cerucal OR "Metoclopramide Dihydrochloride" OR "Dihydrochloride, Metoclopramide") AND TS=(hiccup OR hiccups OR hiccough OR hiccoughs OR singultus) AND TS=("randomized controlled trial" OR "controlled clinical trial" OR randomized OR randomly OR trial))

Wan-fang data

(主题:(甲氧氯普胺+胃复安+灭吐灵)+题名:(甲氧氯普胺+胃复安+灭吐灵))*(主题:(呃逆+哕+打嗝)+题名:(呃逆+哕+打嗝))*(主题:(随机对照试验+临床对照试验+随机的+随机地+对照+试验)+摘要:(随机对照试验+临床对照试验+随机的+随机地+对照+试验))

VIP data

(M=甲氧氯普胺 OR 胃复安 OR 灭吐灵 OR R=甲氧氯普胺 OR 胃复安 OR 灭吐灵) AND (M=呃逆 OR 哕 OR 打嗝 OR R=呃逆 OR 哕 OR 打嗝) AND (M=随机对照试验 OR 临床对照试验 OR 随机的 OR 随机地 OR 对照 OR 试验 OR R=随机对照试验 OR 临床对照试验 OR 随机的 OR 随机地 OR 对照 OR 试验)

CNKI

(SU=('甲氧氯普胺'+'胃复安'+'灭吐灵') OR TI=('甲氧氯普胺'+'胃复安'+'灭吐灵')) AND (SU=('呃逆'+'哕'+'打嗝') OR TI=('呃逆'+'哕'+'打嗝')) AND (SU=('随机对照试验'+'临床对照试验'+'随机的'+'随机地'+'对照'+'试验') OR AB=('随机对照试验'+'临床对照试验'+'随机的'+'随机地'+'对照'+'试验'))

CBM data

#1 "甲氧氯普胺"(不加权:扩展) OR "甲氧氯普胺"(中文标题:智能) OR "胃复安"(不加权:扩展) OR "胃复安"(中文标题:智能) OR "灭吐灵"(不加权:扩展) OR "灭吐灵"(中文标题:智能)

#2 "呃逆"(不加权:扩展) OR "呃逆"(中文标题:智能) OR "哕"(不加权:扩展) OR "哕"(中文标题:智能) OR "打嗝"(不加权:扩展) OR "打嗝"(中文标题:智能)

#3 "随机对照试验"(不加权:扩展) OR "临床对照试验"(不加权:扩展) OR "随机地"(摘要:智能) OR "随机的"(摘要:智能) OR "对照"(摘要:智能) OR "试验"(摘要:智能)

#4 #1AND#2AND#3

PROSPERO

https://www.crd.york.ac.uk/prospero/#recordDetails ID=CRD42021293000