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Metoclopramide for analgesia in renal colic: a narrative systematic review

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Abstract

Metoclopramide, a prokinetic antiemetic with activity at multiple receptor types, may be a useful treatment for renal colic pain. This review investigated whether metoclopramide is an effective analgesic in the management of adults with renal colic.

Eligible studies were randomised, quasi-randomised or case-control trials of metoclopramide for the management renal colic pain. Electronic database searches were performed in November 2022. Screening was performed by two authors independently; disagreement was resolved by discussion or by adjudication by a third author. The Cochrane Collaboration Risk of Bias Tool v2.0 was used to assess bias.

Two studies were included, enrolling 279 patients. Heterogeneity of primary outcome measurement and comparators rendered meta-analysis inappropriate; a narrative review is presented. Both studies showed some evidence of analgesic effect. The largest study had a low risk of bias in all assessed domains, whilst the smaller study was at a high risk of bias.

There is limited evidence that metoclopramide may be an effective analgesic in the management of renal colic, with the highest quality study demonstrating analgesic properties similar to an intravenous non-steroidal anti-inflammatory medication.

Protocol registration Prospero (CRD42022346618).

Keywords Renal colic, Nephrolithiasis, Analgesia, Emergency, Pain, Systematic review

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Background

Renal colic is both common and extremely painful; the lifetime incidence is approximately 12% in males and 6% in females [1], with recurrence rates approaching 50% [2]. Pain occurs due to ureteral obstruction and spasm, followed by peri-ureteral inflammation and oedema [3]. It is often associated with systemic disturbance, including vomiting [4].

The standard analgesic regime for renal colic (usually involving a non-steroidal anti-inflammatory (NSAID) and an opioid) is sometimes ineffective; in some studies less than half of patients achieve complete pain relief and a large proportion of patients require rescue analgesia within four hours [5]. Given previous Patient and Public Involvement (PPI) work has highlighted how agonising the pain of renal colic is and the challenges of its treatment (Tabner A: Patient and Public Involvement Meeting Summary. Internal report to inform the SARC study (Salbutamol for analgesia in renal colic), unpublished), any potentially effective therapies should be explored.

Commonly used treatments (NSAIDS, opioids and alpha blockers) have been well studied and the previous subjects of a Cochrane and other systematic reviews [3, 5, 6] but still provide inadequate analgesia in some cases [3]. They are also associated with side effects: opiates are known to cause nausea, vomiting, drowsiness and respiratory depression; [7] the oral absorption of NSAIDs in this cohort can be poor due to gastroparesis and vomiting; and rectal administration of diclofenac is frequently felt by patients to be unpleasant (Tabner A: Patient and Public Involvement Meeting Summary. Internal report to inform the SARC study (Salbutamol for analgesia in renal colic), unpublished).

The onset of action of the existing analgesic options is slow; [7, 8] NSAIDS require a period of absorption before they are effective and intravenous opioids are controlled drugs, the administration of which is often delayed by practical concerns in their dispensing and prescription.

Metoclopramide is an antiemetic medication with anticholinergic and antidopaminergic properties that was developed in the 1960s; it is also an analogue of procaine, a local anaesthetic. There are multiple mechanisms by which it may act to reduce the pain associated with renal colic; its pharmacology is complex and the response appears to be dose-related.

Antidopaminergic: D1 and D2 receptors are found on the ureter. Stimulation of these has been shown to cause urinary tract hyperactivity, whilst blockade reduces motility [9]. Reduced ureteral activity has been hypothesised to reduce the pain of renal colic [10, 11].

Anticholinergic: Metoclopramide inhibits release of acetylcholine, which is known to be involved in ureteral activity; it may therefore reduce ureteral activity and improve pain as above [12, 13]. However, another case series identified increased ureteral activity and accelerated stone passage with a supramaximal dose of metoclopramide [14], along with an improvement in patients' symptoms.

As an analogue of procaine, metoclopramide has been shown to have local anaesthetic properties when injected subdermally [15] and has been shown to potentiate the effects of local anaesthetic when used for regional anaesthesia [16]. Given approximately 20% of a dose of metoclopramide is secreted, unchanged, through the renal tract [17], there is potential for topical action.

Metoclopramide reduces ureteral motility at high concentrations in vitro [18], and therefore may reduce the pain associated with renal colic [10, 11]. It is worth noting, however, that at lower concentrations metoclopramide has been observed to increase ureteral motility [14, 15], and also to increase bladder activity [18, 19]. There is therefore equipoise within the pre-clinical literature concerning the in-vivo effects of metoclopramide in renal colic and prior reports would appear to be contradictory in terms of physiological effects and mechanism by which symptoms may be ameliorated.

A scoping review has identified one relevant study suggesting that metoclopramide may be as effective as intravenous tenoxicam in managing the pain of renal colic [20].

The objective of this review is to collate and synthesise the evidence concerning metoclopramide as an analgesic in the treatment of renal colic, in comparison to any alternative treatment or treatment regimes, including placebo.

Methods

Study eligibility

Study type

Given the anticipated paucity of data to address the clinical question, both randomised clinical trials and quasi-randomised or case-control clinical trials (with matching for baseline characteristics) evaluating metoclopramide for analgesia in patients with renal colic were included.

Participants

Patients with a diagnosis of renal colic requiring pain relief, as defined by the recruiting studies; there are no standardised diagnostic criteria for this condition and the approach taken varies between authors, with some requiring radiological evidence whilst others accept clinical characteristics.

Intervention

Metoclopramide, administered by any route, and in comparison to any alternative analgesic therapy (including placebo).

Outcome measures

Pain, measured using any recognised measure of pain severity (e.g. visual analogue scale (VAS), numerical rating scale (NRS)) at any time point after intervention administration.

Secondary outcomes

Length of stay in hospital (measured in days), other analgesic requirement (including medication used, time administered, and cumulative dosage); and stone presence, size and position as determined by radiological investigation.

Search strategy

The following databases were searched:

(a) The Cochrane Central Register of Controlled Trials (CENTRAL)
(b) MEDLINE (via OVID) (from January 1960 until the search date)
(c) EMBASE (via OVID) (from January 1960 until the search date)
(d) The WHO International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/)
(e) PROSPERO (from January 1960 until the search date)
(f) Google Scholar – 10 pages after the last relevant result were reviewed
(g) UK Clinical Trials Gateway (UKCTG)
(h) National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio
(i) Clinicaltrials.gov
(j) ISRCTN registry

The search results were limited to those investigating human subjects. No restrictions were applied relating to participant age, ethnicity or clinical setting. Search results were limited to those with a title available in English.

Reference lists from eligible trials identified by electronic searching were hand-searched to identify further relevant trials.

Authors of eligible trials were contacted for any missing data or required supplementary information.

Study selection

Two investigators reviewed the title and abstract of all identified studies independently, disregarding any that were clearly irrelevant to the study question. Any disagreement was resolved by discussion, with the involvement of a third investigator as required. Two investigators independently reviewed the full text of any identified potentially eligible articles to ascertain eligibility; any disagreement was resolved in the same way as during title and abstract review.

Data collection process

Two investigators extracted data independently using a Data Collection Form, and disagreements were resolved by discussion.

Extracted data concerning both study characteristics and the outcome measures of interest were entered directly into a validated MS Excel database.

Where possible, data were extracted concerning study characteristics and outcomes:

- Eligibility criteria
- Study methods
- Participants
- Intervention
- Outcomes
- Results
- Miscellaneous (to include key conclusions and limitations identified by study authors, references to other studies, and detail of any correspondence with study authors)

Risk of bias

Risk of bias was assessed using The Cochrane Collaboration's Risk of Bias Tool v2.0 (RoB2 tool). Two investigators assessed each study independently, with disagreements resolved through discussion.

Conduct and reporting

This systematic review has been conducted in accordance with PRISMA guidelines.

Results

A total of 2 articles were eligible for inclusion in the systematic review; see Fig. 1 for detail of the evidence acquisition process.

The included articles used a different comparator, and it is not clear whether they used the same pain assessment tool; as such, meta-analysis would not have been meaningful and was not performed.

A study by Müller et al [21]. initially appeared to be eligible for inclusion, but was excluded because the outcome presented was pain relief rather than pain; given the small number of studies eligible for inclusion in the review itself, some information is presented here for further context to the study question. Participants marked their assessment of pain relief on a VAS at 10, 20 and 30 minutes after trial medication

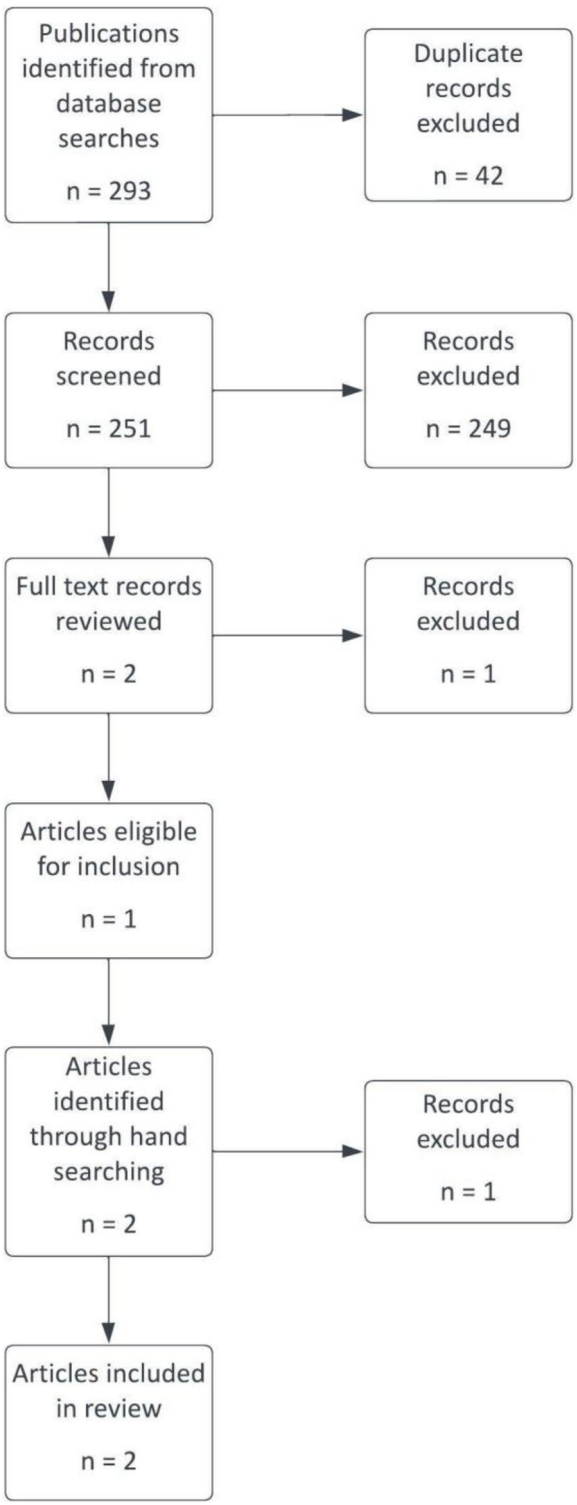

Fig. 1 A PRISMA flow diagram of evidence acquisition in a systematic review of the analgesic properties of metoclopramide for the pain of renal colic

administration. This VAS result was converted to a point value between 1 and 10 for analysis.

The authors compared 20mg intravenous metoclopramide to morphatopin (a subcutaneous injection of 0.5mg atropine and 20mg morphine) for the relief of pain in admitted surgical patients with renal colic confirmed either by intravenous urogram or stone discharge. The study was double blind, but no randomisation methods, power calculation or method of ensuring allocation concealment is described.

Nearly half of recruited participants (21/42) were excluded, predominantly because the diagnosis was not confirmed with further investigations.

The authors present the median pain relief score together with a range for each group at each time point. They describe performing a statistical test demonstrating no difference between groups, and therefore suggest that metoclopramide is as effective as morphatropin in relieving the pain of renal colic.

This study was extremely small (only 21 participants analysed) and presented little in the way of methodological detail with which to assess study quality or risk of bias. There were no sample size calculations, and it is not possible to ascertain whether the study was intended as a superiority or non-inferiority study in its design.

Included studies

Baloglu Kaya et al. (2015) [20]

The authors compared 10mg intravenous metoclopramide as a sole analgesic agent to a combination of metoclopramide and 20mg intravenous tenoxicam, and to tenoxicam alone, for the relief of pain in emergency department patients aged 18-65 with clinically suspected or radiologically proven renal colic. Participants were block randomised with a block size of 1 and a ratio of 1:1:1 by a well-described, simple manual approach to allocation concealment (pulling their group allocation out of a bag.) The study was double blind, with placebo medication used to maintain blinding in the sole agent groups.

Pain was measured on a 100mm Visual Analogue Scale (VAS) at baseline, 10, 20 and 30 minutes after trial medication administration.

They screened 397 patients and randomised 240 participants, with appropriate sample size calculations presented for a superiority study. There were no significant differences in participant baseline characteristics or pain scores.

All groups had a reduction in pain score at all time points compared to baseline, and this reduction increased with time. There was a statistically significant difference between groups at the 20min time point, with

Table 1 Mean reduction in pain scores compared to baseline in each of the three study groups

Time from baseline	Mean reduction in pain score from baseline in millimetres (95% CI)			*p-value*
	Tenoxicam	Tenoxicam and metoclopramide	Metoclopramide	
10 minutes	19 (13 – 24)	21 (16 – 26)	17 (11 – 22)	0.529
20 minutes	28 (21 – 35)	40 (34 – 46)	29 (23 – 36)	0.018
30 minutes	36 (28 – 43)	45 (38 – 52)	37 (30 – 45)	0.163

No data were available for any of the secondary outcome measures, and no response to attempted contact with the corresponding author was received

the greatest pain relief occurring in the combined tenoxicam and metoclopramide group. There was no statistically significant difference between groups at the other time points. Pain relief in the groups can be seen in Table 1.

Limitations

There was no mandated radiological confirmation of diagnosis, and no details were given concerning the number of participants with radiological confirmation; multiple approaches to adjudicating the diagnosis were described, including clinical suspicion, urinalysis, ultrasound and CT.

The authors describe the possibility that participants could have received opiate medication prior to randomisation; this is not quantified or further assessed.

There was a very long interval between data collection and manuscript publication (6 years); the reason for this is not clear.

Risk of bias

There was a low risk of bias in all domains using the RoB2 tool, although it is noted that the allocation concealment is not particularly robust, and that staff performing randomisation processes could have ascertained which groups were represented by the employed code system over time. Furthermore, it is not possible to establish whether one group may have received more opioids than the other prior to randomisation, although there is no evident reason why this may have occurred. Overall the raters felt that there were some concerns about bias in this trial.

Hedenbro and Olsson (1988) [22]

The authors compared 20mg intravenous metoclopramide to -fen, a combination intravenous analgesic containing metylscopolamine nitr. 0.15mg, papaverine hydrochloride 20mg, morphine hydrochloride 6.6mg, noscapine hydrochloride 3mg and codeine chloride 0.4mg. The study was double blind, and medication was presented in unlabelled vials administered in sequence. The method for generation of the sequence is not explicit.

Pain was documented on a 100mm VAS at baseline, 10, 20 and 30 minutes by both the patient and the treating nurse; authors describe a highly significant correlation (p <0.01) between patient and nurse pain assessment but are not explicit about which results are used for the final analysis. No response to contact attempts with the corresponding author was received. Therefore, it is not possible to combine the results from this study with those from Baloglu Kaya et al. (2015) to undertake meta-analysis.

They recruited 40 emergency department patients with clinical suspicion of renal colic, and later excluded 1 in whom this could not be proven radiologically.

Patients were excluded if they required supplementary analgesia; this led to the exclusion of 3 patients in the metoclopramide group and 4 patients in the Spasmofen group. A further patient in the Spasmofen group was excluded due to "inability to cooperate". This left 17 patients in the metoclopramide group and 14 in the Spasmofen group for final analysis.

The pain scores in each group at each time point can be seen in Table 2; the authors describe no significant difference between groups but do not present the results of their statistical analysis.

Limitations

The method for generating the randomisation sequence is not described, and whilst the article suggests that both patient and treating clinician were blinded, it is

Table 2 Pain scores in each of the study groups

Time	Metoclopramide Mean (mm) (SD)	Spasmofen Mean (mm) (SD)
Baseline	78 (23)	73 (23)
10 min	71 (26)	62 (31)
20 min	64 (30)	54 (30)
30 min	55 (36)	51 (34)

No data were available for any of the secondary outcome measures

not possible to assess the rigour of this given the limited description provided.

Using nurse measurement of pain severity is not currently considered good practice, and it is not clear whether the patient or the nurse measurements were used for the final analysis. Furthermore, the authors describe correlation between patient and nurse values, rather than agreement; this calls the utility of the results further into question.

The sample size was small, with a high drop-out rate; it is particularly concerning that patients with a supplemental analgesic requirement were excluded in a study of analgesic efficacy. No sample size calculations are presented, and it is not clear whether the study was intended as a superiority or non-inferiority study.

Risk of bias

The risk of bias in many domains is difficult to assess due to the brevity of the article. Lack of description of allocation sequence generation and of group baseline characteristics gives some concerns in Domain 1 (randomisation process). The high drop-out rate, in part directly attributable to the effectiveness of the study intervention, leads to a high risk of bias in Domain 3 (missing outcome data). The lack of clarity concerning whose measurement of pain constituted the primary outcome leads to some concern in Domain 4 (measurement of the outcome), and similarly gives concern that the chosen metric for the primary analysis may have been decided once the results were known. Overall, the raters felt that the paper was at a high risk of bias, although the direction of this bias was not clear.

Discussion

A systematic review of the literature, including a broad and detailed search strategy, has only identified 2 papers relevant to the clinical question. Authors of both studies describe a potential analgesic role for metoclopramide in the treatment of the pain associated with renal colic; however, both articles have some methodological concerns, and one is at a high risk of bias.

The paper by Baloglu Kaya et al. is the most recent, highest quality and least at risk of bias; it suggests efficacy similar to an intravenous NSAID established in the treatment of pain (including renal colic). The relatively small scale, single centre nature of the study raises concerns about external generalisability. The issues, combined with concerns around lack of information about administration of other analgesics and together with a lack of a standard care pathway that mirrors current practice, means that this study alone is not sufficient to enable change of practice.

The other study identified is small, was conducted over 30 years ago, had a comparator medication no longer in clinical use, has significant methodological concerns, and is at a high risk of bias; its results must be interpreted with extreme caution.

Both included studies describe equivalence in effect between metoclopramide and a comparator group, but it appears that both were designed as superiority studies, rather than as non-inferiority/equivalence studies. The latter study design generally requires a greater number of participants, and a failure to demonstrate superiority in a superiority study is not synonymous with demonstrating equivalence.

There is a lack of evidence comparing metoclopramide to either placebo or what would be considered standard care (i.e. a multimodal parenteral analgesic approach, often including paracetamol, an opioid and a NSAID) in a modern emergency setting; there is also no assessment of the impact of metoclopramide when used in addition to standard care.

None of the included studies assessed any of the secondary outcomes proposed in this review. Stone size and position has been shown to impact the effectiveness of other medications used in renal colic [6], and capture of this data would be important in future studies. Similarly, no studies assessed the potential impact of metoclopramide on time to stone passage; it is notable that Müller et al. identified two patients who passed stones within the study period, although it is not clear to which treatment arm these participants were randomised. Given the potential for ureteral relaxation it is possible that metoclopramide, similarly to tamsulosin, may reduce time taken for stone passage; [6] again, this role may be affected by stone size and position within the urinary tract.

Conclusions

This review has identified some limited evidence to support an analgesic role for metoclopramide in the treatment of pain associated with renal colic, but it is not compelling. It is certainly not sufficient to support the suggestion that metoclopramide should be adopted as standard care, either alone or in conjunction with other therapies, at the current time.

Abbreviations

NSAID	Non-steroidal anti-inflammatory drug
VAS	Visual Analogue Scale
NRS	Numerical Rating Scale
CI	Confidence interval
Mm	Millimetre
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12894-024-01598-2.

Supplementary Material 1.

Supplementary Material 2.

Registration

A full study protocol was written in advance of the review and registered on PROSPERO (CRD42022346618). There were no deviations from the protocol during the conduct of the review.

Authors' contributions

AT, GJ and MR conceived the study. AT, GJ, MR, ST and AF contributed to the study protocol. ST, AT and GJ developed the search strategies. AT, AG, LH, NP and GJ were involved in data collection and analysis. AT and GJ drafted the manuscript, and all authors revised it critically for content. All authors have reviewed the final manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study did not require Research Ethics Committee approval.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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