REVIEW

Alternative Medical Interventions Versus Conventional Treatment of Renal Colic: An Updated Systematic Review and Network Meta-Analysis

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Purpose: To systematically review the recent alternative medical interventions on renal colic pain and compare their efficiency with conventional treatments.

Materials and Methods: This was a systematic review and network meta-analysis (NMA) study, based on the PRISMA guidelines on online databases of PubMed, Scopus, and web of science. We quarried these databases with relevant keywords for clinical trial studies that aimed at reducing renal colic pain in patients refereeing to the ED from after January 2011 to February 2022. Randomized clinical trials that used the Visual Analogue Scale (VAS) for assessment of renal colic pain before and after medical interventions in adult patients were included in this study. NMA was conducted based on the continuous values of the mean difference of the pain after 30 and 60 minutes of the medication administration.

Results: Twenty-four studies that were meeting the inclusion criteria were included in our review with 2724 adult participants who were mostly male. Study arms included conventional medications (NSAID, Opioid, paracetamol), ketamine, MgSo4, desmopressin, and lidocaine. Based on the qualitative synthesis, ten studies (41.7%) did not find significant differences between conventional and alternative treatments. Also, there is no agreement on some more recent medications like using ketamine or desmopressin while MgSO4 and lidocaine use are supported by most studies. NMA revealed that desmopressin is significantly having worse pain reduction properties. NMA did not show any difference between ketamine, lidocaine, and MgSo4, versus the conventional treatment.

Conclusion: To conclude, lidocaine and MgSo4 might be good alternative treatments for renal colic when conventional treatments are contraindicated or pain is not responding to those. Ketamine might be indicated in patient-based circumstances. Desmopressin may be agreeably avoided in further research or clinics.

Keywords: urolithiasis; emergency department; renal colic

INTRODUCTION

Renal colic is a severe pain caused by transient kidney stones through the urinary tract and urinary system that 12% in males and 6% in women can experience in a lifetime[(1)] and is a common reason for emergency room visits worldwide[(2)]. Management of renal colic pain is mainly a conservative approach that focused on treating the symptoms like pain and nausea and vomiting[(3)]. In case of pain, renal colic pain is caused by a rise in prostaglandin production, which causes arterial vasodilation, vascular permeability, and ureteric edema and contractions. Renal colic is characterized by referral and migratory pain, which is peculiar to renal colic due to the stone's gradual transit down the ureter[(4)]. Several major systematic reviews and meta-analyses studies have supported various medications to help achieve a longer duration of pain relief, a lower requirement for further analgesia, and fewer adverse effects[(5)]. Systematic review studies have compared many

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Table 1. Characteristics of included studies

ID	Country	Setting	Design	intervention	IV therapy	age	Sex (male)	end points	clinical response	conclusion	Jaded score
Motov et al., 2019 (12)	USA	multicenter	prospective, interventional, blinded	a- IV lidocaine (1.5 mg/k), n = 50 b- ketorolac 30 mg, n = 50 c- a+b, n = 50	100 ml IV normal saline	a- 39.34 b- 42.34 c- 43.92	a-54% b- 56% b- 56% c- 56%	60 min Pain relief rate; Adverse event	NA	no difference	5
Soleimanpour et al., 2012 (13)	Iran	single-center	prospective randomized double-blind clinical trial	a- 0.1 mg/kg Morphine IV slowly, n = 120 b- IV lidocaine (1.5 mg/k), n = 120	NA	a- 35.23 ± 12.37 b- 37.71 ± 11.08	a-75% b- 71%	VAS till 30 min values	NA	b was better	3
Sadrabad et al., 2021 (14)	Iran	single-center	double-blind randomized clinical trial	a- 0.1 mg/kg IV morphine sulfate (maximum of 5 mgs), n=40 b- 50 mg/kg (maximum 2 grams) MgSo4, N=40	a- 10 cc distilled water + 20-minute infusion of 100 cc normal saline. B- 100 cc normal saline for 20 minutes	a- 34.65(8.47) b-34.97 (9.71)	a- 27 (67.5) b- 30 (75)	10, 20 min VAS	3 scores reduction of VAS	no difference	4
Kumar et al., 2011 (15)	India	single-center	nonblind randomized clinical trial	a- desmopressin 40 gm IN, n=24 b- diclofenac 75 mg IM, n=24 c- both, n=24	None	NA in detail, matched groups	NA in detail, matcched groups	second analagesic; VAS at 10, 30 min and 1 h	NA	all patients in group a received secondary analagesic; 2 in group b, and 3 in group c	3
Ghafouri et al., 2020 (16)	Iran	single-center	nonblind randomized clinical trial	a- 40 mcg of IN desmopressin spray, n=120 b- IV paracetamol (15 mg/kg), n=120	NA	matched	a- 99 (82.5) b- 88 (73.3)	second analgesic (Morphine use after 15 min); VAS at 0, 15, 30 min and 1 h	30 mm decrease	no difference	5
Drapkin et al., 2018 (17)	USA	single-center double-blind	randomized,	a- IV lidocaine (1.5 mg/k),n = 50 b- ketorolac 30 mg, n = 50 c- a+b, n = 50	None	NA	NA	VAS at 0, 15, 30 min and 1 h	NA	c is better	-
Forouzan et al., 2019 (18)	Iran	single-center placebo-controlled, double-blinded	randomized,	a- intravenous ketamine (0.3 mg/kg) b- intravenous morphine (0.1 mg/kg) total 135 participants	None	matched	NA	VAS at 30, 45, and 60 min & adverse event	NA	no difference	-
Sotoodehnia et al., 2019 (19)	Iran	single-center double-blind	randomized	a- intravenous ketamine (0.6 mg/kg), n=62 b- intravenous ketorolac 30 mg, n=64	NA	matched	a- 71% b- 81.2%	VAS till 120 min & adverse event	NA	no difference	4
Grill et al., 2019 (20)	USA	single-center	randomized non blind	a- ketorolac 30 mg, n=26 b- intravenous ketamine (0.3 mg/kg) plus ketorolac, n=8	Ketamine in 50 cc NS	a- 37.25 b- 41.69	a- 75.0% b- 30.8%	120 min 11-point VAS, results of MD were multiplied by 1.1	NA	b was better	4
Pouraghaei et al., 2021 (21)	Iran	single-center	randomized double blind	a- 1 mg/kg intranasal (IN) ketamine, n=95 b- - intravenous morphine (0.1 mg/kg) , n=89	None	a- 39.39±3.7 b- 41.27±5.2	matched	VAS at 20, 40 and 60 minutes	NA	no difference	5
Metry et al., 2021(22)	Egypt	single-center	prospective, open-label, randomized, double-blindedn=60	a- IV pethidine 50 mg, b- lornoxicam 8 mg+ 0.15 mg.kg−1 ketamine, n=60	None	a- 39.8±11.3 b- 37.8±12.8	a- n=40 b- n=38	VAS till 30 min	NA	b was better	4
Dolatabadi et al., 2017 (23)	Iran	single-center	double-blind randomized clinical trial,	a- 40 µg of intranasal desmopressin spray, n=20 b- 30 mg of IV ketorolac, n=20	None.	a- 31.0 ± 6.5 b- 34.1 ± 7.1	a- 13 (65) b- 16 (80)	VAS at 10, 30, and 60 min	3 cm change	b is better. Avoid a	4
Ahmed et al., 2019 (24)	Egypt	multi center	randomized, double-blind, double-dummy comparative	a- IV magnesium sulfate 50%, n=48 b- ketorolac 30 mg IV, n=48	100ml intravenous normal saline	a- 31.96±8.29 b- 31.94±8.08	a- 60.4% b- 56.3%	VAS at 15, 30, 45, and 60 minutes	NA	a was better	3
Verki et al. 2019 (25)	Iran	multicenter	randomized, double-blind,	a- 50 mg/kg magnesium sulfate 50% +, ketorolac 30 mg IV, n=44 b- ketorolac 30 mg IV, n= 43	100ml intravenous normal saline	a- 39.43±12.089 b- 37.19±10.032	matched	VAS till 30 min	NA	no difference	4
Motamed and Verki, 2017 (26)	Iran	single center	Randomized Clinical Trial, double blind	a- fentanyl (1.5 µg/kg), n=45 b- lidocaine (1.5 mg/kg), n=45	IV infusion during 2 minutes	a- 39.08 ± 6.64 b- 34.08 ± 9.49	a- 39 (86.7) b- 42 (93.3)	VAS at 30 min; rescue	NA	no difference	4
Jokar et al., 2017(27)	Iran	single center	randomized double-blind	a- 0.1 mg/Kg of IV morphine sulfate, 30 mg of IV ketorolac, and 100 ml IV normal saline, n=50 b- 15 mg/Kg of IV magnesium sulfate 50% , n=50	a- 100 ml IV normal saline b- 100 ml normal saline within 15 minutes	a- 35.16±8.97 b- 33.64±8.61	a- 29 (58%) b- 30 (60%)	30 and 60 min VAS; morphine dose	NA	b was better	4
Shirazi et al., 2015 (28)	Iran	single center	prospective, single blind randomized clinical	a- tramadol 50 mg IM ly, n=40 b- desmopressin 40 µg intranasally, n=40 c- indomethacin 100mg rectally , n=40	None	a- 39.1±8.9 b- 38.8±7.6 c- 36.7±9.2	a- 23 (57.5%) b- 25 (62.5%) c- 22 (55%)	30 min VAS; Complete relief ; Rescue	NA	a was best	4

ID	Country	Setting	Design	intervention	IV therapy	age	Sex (male)	end points	clinical response	conclusion	Jaded score
Majidi and Derakhshani, 2020(29)	Iran	single center	double blind randomized	a- IV 2cc of 50% Mg sulfate, n=45 b- IV morphine (0.1 mg/kg dose), n=45	normal saline 100 ml injected during 15 minutes	a- 39.1 ± 13.2 b- 35.6 ± 10.8	a- 27 (60.0) b- 32 (71.1)	180 min VAS	3 scores reduction of VAS	no difference	4
Shirvani et al., 2015 (30)	Iran	single center	single blind randomized, clinical trial	a- 0.1 mg/kg IM 60 µg of morphine + sublingual desmopressin b- morphine + placebo total 81 cases	NA	matched	matched	30 min VAS	NA	no difference	4
Firouzian et al., 2016 (31)	Iran	single center	double-blind, randomized controlled trial	a- morphine (0.1 mg/kg) + lidocaine (1.5 mg/kg), n= 47 b- morphine (0.1 mg/kg) + normal saline 0.9% [placebo], n=42	NA	a- 37.91 ± 10.76 b- 37.95 ± 12.6	a- 36 b- 35	VAS till 120 min for both pain and naussea	NA	a was better	4
Farnia et al., 2017 (32)	Iran	single center	prospective, randomized, double-blind	a- A 0.1 mg/kg diluted IV morphine + IN placebo, n=20 b- 1 mg/kg IN ketamine + IV placebo. n=20	NA	a-34.75 ± 11.71 b- 39.25 ± 10.75	a- 17 (85.0%) b- 12 (60.0%)	30 min VAS	NA	a was better	5
Abbasi et al., 2018 (33)	Iran	single center	double blind randomized clinical trial	a- Morphine 0.1 mg/kg IV and placebo, n=53 b- morphine 0.1 mg/kg IV and ketamine 0.15 mg/kg IV, n=53	NA	matched	matched	120 min VAS	NA	b was better	4
Jalili et al., 2019(34)	Iran	single center	prospective, double-blinded, , randomized placebo-controlled clinical trial	a- indomethacin suppository (100 mg) + desmopressin intranasal spray (4 puffs with 10 microgram per puff), n=62 b- indomethacin suppository (100 mg) + palcebo intranasal spray , n=62	NA	a- 34.67 ± 10.03 b- 34.31 ± 10.73	a- 70.15% b- 69.35%	60 minVAS	NA	a was better	4
Mozafari et al., 2020 (35)	Iran	single center	double-blind clinical trial	a- 1 mg/kg of intranasal drops of ketamine + IV palcebo, n=65 b- 50 µg/(kg/bw) IV fentanyl + intranasal palcebo, n=65	NA	matched	matched	30 min VAS; Rescue medication;	NA	b was better	4

NA, not addresed.

types of medications and some review studies have only focused on a special medication[6]. A review of 36 RCTs, published in 2016, showed that many available medical choices among the medications belonging to the NSAIDs, opioids, and paracetamol are having comparable efficiency in relieving acute renal colic pain; while the adverse events might be different[7]. One more systematic review study on 183 studies till 2020 revealed that as a common choice, opioid medications were linked to lower or equivalent efficacy to NSAIDs for several acute pain situations, but also a higher risk of short-term side effects[8]. Multiple drugs are proven to be effective for renal colic pain in individuals accused of carrying kidney stones; nevertheless, much research on novel treatment options or novel combinations of previous medications is being released that are not reviewed in recent years. As mentioned, the pain induced by urolithiasis is one of the most annoying pain experiences that an individual can sense and is responsible for a high rate of emergency department (ED) visits worldwide. Multiple conventional medications (Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids) are known to be efficient for renal colic pain in patients suspected of kidney stones, but yet some patients might still not respond to conventional methods that necessitate alternative methods. So, we aimed at conducting an updated systematic review study of the alternative methods from 2011 to 2022.

MATERIALS AND METHODS

This was a systematic review study on renal colic pain treatment in the emergency department that was conducted based on the PRISMA guidelines.

Study questions were structured based on a PICO model. (P)opulation of interest was acute renal colic patients. Suspected or definitive cases were considered for the study. Based on the ICD-10 definitions [2022 ICD-10-CM Diagnosis Code N23], renal colic was defined as "A condition characterized by intermittent and severe flank pain due to kidney stone (renal calculus) moving through the ureter or other urinary channel obstruction is the most common cause of acute discomfort in the lower back extending to the groin, scrotum, or labia. Nausea, vomiting, fever, restlessness, dull discomfort, frequent urine, and hematuria are all common symptoms."

(I)ntervention was pain relief interventions (medical or non-medical). Based on the preliminary search of the literature, high-quality pooled studies were available comparing NSAIDs, Opioids, Paracetamol, and Desmopressin. Network Meta-analysis was available on different routes of NSAIDs and paracetamol administration[9]. There was a lack of pooled data in comparison of newer interventions with previously interventions that have stood the test of time. So, we aimed at categorizing interventions into 4 categories of (i) Conventional monotherapy [including monotherapy with NSAIDs,

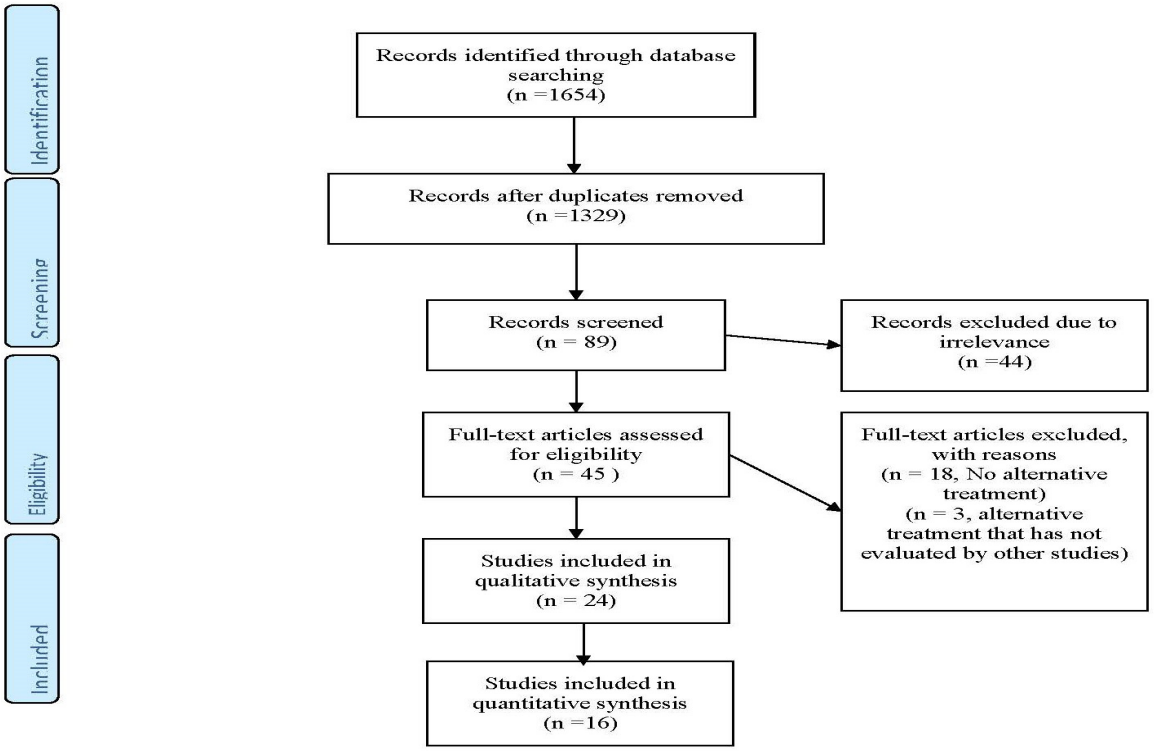

Figure 1. PRISMA flowchart

Opioids, and Paracetamol] or combined with each other; (ii) Alternative treatments; (iii) combination of the conventional and alternative methods. Nonpharmacological methods were not included in the study.
(C)omparisons were tried to be conducted between these three types of interventions being compared pairwise and versus the conventional treatment. The route of the medication administration was waived to observe the prerequisites of NMA.
(O)utccome of interest was the analgesic effects of interventions and the need for rescue treatment.
Based on the preliminary review, some studies of filed are not reporting rescue treatment rates that we only considered 30- and 60-min pain.

Search strategy

Searches were performed from 1 January 2011 to 2022 in online databases of Scopus, PubMed, and Web of science. Two independent researchers ran the search

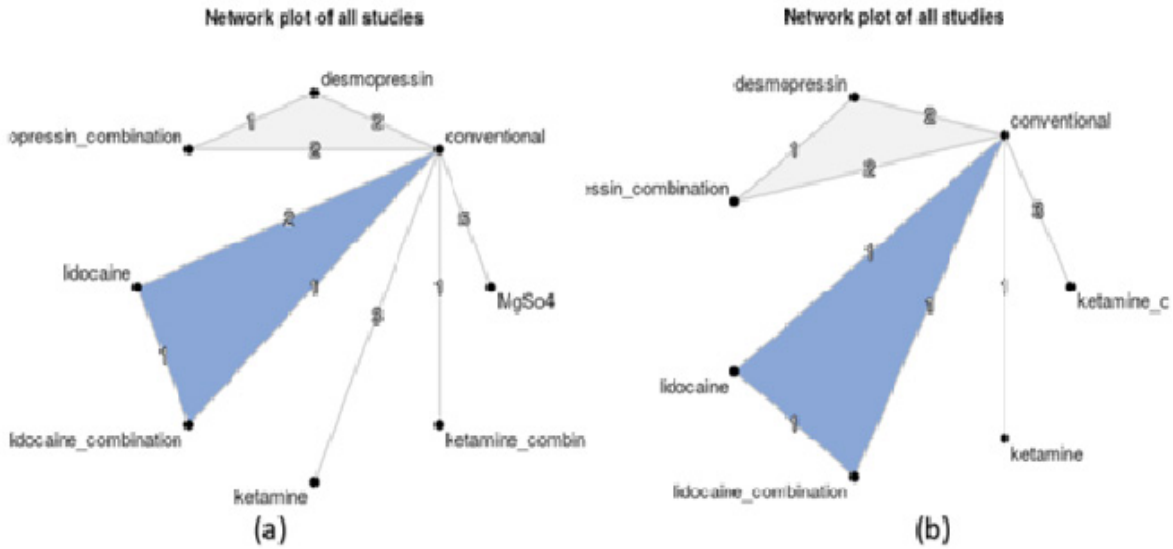

Figure 2. Network plot of included studies. (a) 30 min pairwise analysis network. (b) 60 min pairwise analysis network. Each node representing a single intervention and connecting lines between nodes showing where one or more trials have compared the two therapies head-to-head.

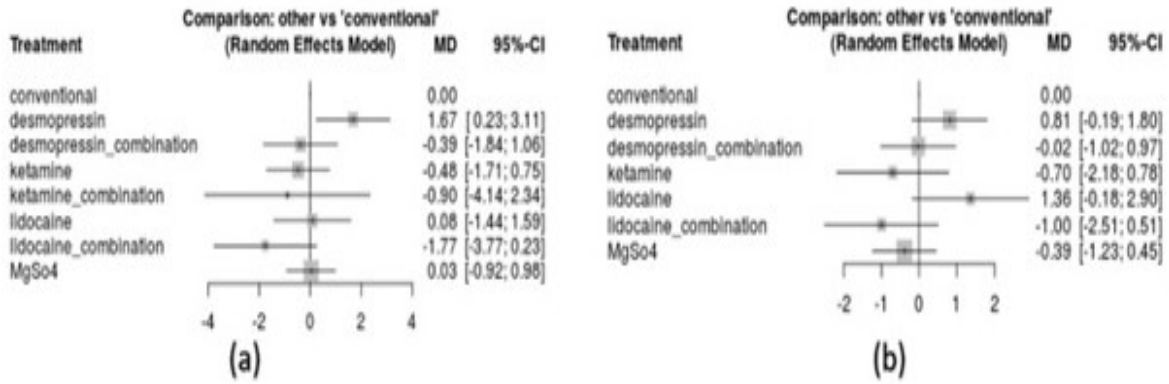

Figure 3. Forrest plot of NMA in 30 min (a) and 60 min (b) pain reduction mean differences.

strategy of the combination of the MeSH keywords. The detailed search strategy was "(Renal colic OR Urolithiasis OR Acute Nephrolithiasis OR Nephrolithiasis OR renal colic pain OR Urolithiasis pain OR ureteric colic) AND (randomized controlled trials OR Trial OR randomized trial OR Blinded trial OR RCT) AND (Pain OR VAS OR Visual Analogue Scale OR analgesia OR analgesic) AND emergency department". Searches were conducted by two independent researchers. The reference list of the selected articles for full-text review was also hand-quarried for relevant studies.

Study selection, data extraction, and quality assessment

Studies were limited to randomized clinical trials, in the English language, published after January 2011. The study setting was also limited to the Emergency department. Pre-print studies and gray literature did not include in the study. Any studies on subjects with trauma to the flank or any other concurrent significant trauma were not included. The age of study subjects had to be higher than 16 years old and lower than 65 years; subjects did not have any previous renal failure. Any disagreement between independent researchers was judged by a third researcher. Inclusion criteria were also containing a non-conventional treatment arm of the study in RCT.

The quality of studies was assessed by Jadad Score to prevent any bias[10]. A checklist containing study id, country, Setting, design, minimum vas for inclusion, intervention, amount of iv therapy, age, sex, endpoints, conclusion, and clinical response definition was provided along with the amount of the mean difference between the 30 and 60 min VAS pain score.

Network meta-analysis

We used MetaInsight based on the "netmeta" R package to perform the meta-analysis[11]. Mean differences were calculated based on the baseline VAS pain score and 30 and 60 min scores. Lower values (more negative) of mean difference were considered desirable outcomes. The random effects model was used to pool the mean differences in each arm of intervention. Network plots were used as a graphic illustration of the network of evidence to indicate pairwise interventions, as well as if there is a linked network of evidence, which is a prerequisite for NMA. A Forest plot was used to show the pooled effect estimate. Consistencies were checked for each comparison by "netmeta", where a P value of lower than 0.05 shows inconsistency and not achieving the perquisites of the NMA.

RESULTS

Following the literature review, our primary search came into 1654 records. After removing duplicated cases and selecting studies for abstract review based on the title, 89 potentially relevant studies were included for full-text review. Seven studies were not retrieved due to having retrospective design, two were case reports, 3 studies were review studies and 7 studies had not used VAS for scoring the pain. The remaining excluded studies were out of date. Finally, 24 studies that were meeting the inclusion criteria were selected among those studies. Continuous data was not extractable from 7 studies and one was due to a lack of reporting bassline pain, so 16 studies were entered the NMA (**Figure 1**). In this systematic review, we included 24 studies with 2724 adult participants. There were 18 studies conducted in Iran, 3 in the USA, one in India, and 2 in Egypt (**Table 1**). IV therapy volume was also recorded. Studies with IV infusion medications were using the maximum volume of 500 ml of normal saline. In most studies, the male participants were more than female ones. Study timelines of pain reassessment after administration of the medication was ranging from a minimum of 30 minutes to 120 minutes. Some studies had also evaluated the need for rescue medication if the main intervention was not able to relieve the pain. Most studies had used continuous amounts of the pain based on the VAS scores for statistical decisions; while some had defined clinical response. Fifty percent pain reduction or 3 scores (30 mm) reduction in pain was considered for most studies.

Qualitative synthesis

Ten studies (41.7%) did not find significant differences between conventional and alternative treatments. Desmopressin was showing fewer analgesic effects than conventional. Only one study mentioned its combination with NSAID to be more effective than NSAID; while MgSO4 and lidocaine use are supported by most studies.

NMA results

In our NMA analysis, 1759 participants were included in 30 min VAS mean difference analyses and 1038 in 60 min analysis. The number of the pairwise compari-

sons is shown in Figure 2, a for 30 min pain scores, and figure 2,b for 60 min. There were a total number of 8 interventions [Dessmopressin, Lidocaine, Ketamine, MgSo4, and combinations of lidocaine, ketamine, and desmopressin with conventional medicine] in 30 min NMA and 7 in 60 min. 16 studies included the 30 min analysis and 9 in 60 min analysis. As shown in Figure 2. We did not achieve the perquisites of head-to-head comparison in most comparisons and only desmopressin and lidocaine-based studies had such performances. Consistency results are shown in supplementary tables 1&2. While there was a satisfactory number of studies that we compared different interventions individually with conventional medicines.

The forest plot of the results of the studies based on the study arms is presented in **Figure 3**.

Using the random-effects model, arms are compared versus conventional treatment. Mean differences of VAS after 30 min were not significantly higher or lower than conventional treatment in any of the evaluated arms ($P > 0.05$) except for the desmopressin that showed significantly lower pain decrease than conventional treatment (MD=1.67, 95%CI: 0.23-3.11). Mean differences of VAS after 60 min were not significantly higher or lower than conventional treatment in any of the evaluated arms ($P > 0.05$). Individual study's mean differences are shown in supplementary **Figures 1&2**.

DISCUSSION

Our network meta-analysis was carried out to determine the most effective medications that can be used as an alternative treatment for renal colic pain. While many previous meta-analyses and systematic reviews are conducted in the field, those are comparing different methods of the conventional medication prescription as well as different types of the NSAIDs or opioids and their different routes of administration. Leng et al. compared the efficacy of these conventional medications (NSAIDs versus Opioids) and found no significant differences based on the meta-analysis[36]. Another systematic review suggests that some particular NSAIDs might act better for acute renal colic pain reliving[37]. Systematic review and meta-analysis by Pathan et al. also showed the same results of the equivalent efficacy of NSAIDs, Opioids, and paracetamol[7].

While in some circumstances, due to pre-existing medical conditions, administration of conventional medications might get contraindicated, as well as in kidney disease and liver failure patients. So, there is a need for alternative treatments as well as for patients whose pain does not relieve by conventional medications. Our review showed that there are multiple pharmacological choices as the alternative. We included Desmopressin, Lidocaine, Ketamine, MgSo4, and combinations of lidocaine, ketamine, and desmopressin with conventional medicine as the alternative treatment; while other potential interventions exist that we did not include due to not achieving saturation of the number of required studies for the meta-analysis as well as the Aminophylline and Hyoscine[38,39].

Our review showed that there were no significant differences between conventional and alternative therapies in twelve trials (41.7%). Furthermore, there is no consensus on the use of certain more modern drugs, such as ketamine or desmopressin. but MgSO4 and lidocaine are supported by the majority of research. Desmopressin has many inferior pain-relieving abilities, according to NMA. Ketamine, lidocaine, and MgSo4 had no superior effect compared to the standard therapy based on our NMA.

In the case of desmopressin, we suggest that this medication might not have a good pain-reducing capacity and should be avoided in further research and clinical management as better choices are available. In the study of Jalili et al., pain relief with NSAIDs (e.g. indomethacin) in renal colic did not improve appreciably when administered in conjunction with intranasal desmopressin (34). Kumar et al. imply that desmopressin is not efficient analgesia in renal colic, since it only has a minor analgesic effect after 30 minutes. More effective and fast-acting analgesics in the form of NSAIDs or opioids are more appropriate than desmopressin alone because of the agonizing character of renal colic[15]. In one more study, Desmopressin has been found to be less effective than ketorolac[23]. But, the addition of sublingual desmopressin to morphine had no benefit[30]. On the other hand. Ghafouri et al. findings revealed that both IV paracetamol and intranasal desmopressin were effective in the ED for the treatment of renal colic pain, while desmopressin had a faster beginning of the action, while finally had no difference[16].

Our study showed that MgSO4 and lidocaine use are supported by most studies. In Motamed and Verki's study, the mean pain severity did not change substantially between IV fentanyl and IV lidocaine at various intervals after injection, but, the treatment failure rate in the IV lidocaine group was considerably greater 15 minutes after administration[26]. Lidocaine may be prescribed as an effective, safe, and economical adjuvant to morphine for shortening the time it takes to get pain and nausea relief.

Our search was limited to English language papers that might make biased as some important studies might not get included in the review. Also, there are some major limitations in combining all studies of NSAIDs, Opioids, and paracetamol into one category; while pooled evidence in literature is showing no significant difference between these medications. We also merged all routes of the administration of medication as there were not enough studies to individually analyze routes of medication administration.

CONCLUSIONS

Our review showed that there were no significant differences between conventional and alternative therapies in twelve trials (41.7%). Furthermore, there is no consensus on the use of certain more modern drugs, such as ketamine or desmopressin. but MgSO4 and lidocaine are supported by the majority of research. Desmopressin has many inferior pain-relieving abilities, according to NMA. Ketamine, lidocaine, and MgSo4 had no superior effect compared to the standard therapy based on our NMA. Because several studies support the use of various drugs to treat renal colic pain, physicians can choose medications based on their patient's condition and response to therapy.

CONFLICT ON INTEREST

None declared by the authors.

SUMMARY

lidocaine and MgSo4 can be used for kidney pain of not responding to ordinary medications.
Ketamine might be useful in some circumstances.
Desmopressin is better to be avoided

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