Progrès en urologie (2017) **27**, 654—665

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Article of the month

LITERATURE REVIEW

Pharmacologic interventions to treat renal colic pain in acute stone episodes: Systematic review and meta-analysis

Interventions pharmacologiques pour traiter la douleur colique rénale dans les épisodes aigus de la pierre : revue systématique et méta-analyse

H.A. García-Perdomo[a,b], **F. Echeverría-García**[a], **H. López**[d], **N. Fernández**[e], **R. Manzano-Nunez**[c,*]

[a] *Universidad del Valle, calle 13 #100-00, Cali, Colombia*
[b] *Universidad Libre-Cali, Diagonal 37A No. 3-29, Cali, Colombia*
[c] *Fundación Valle del Lili, Cra 98# 18-49, Cali, Colombia*
[d] *Universidad del Rosario, Calle 12C No. 6-25, Bogotá, Colombia*
[e] *Universidad Javeriana, Carrera 7 No. 40-62, Bogotá, Colombia*

Received 11 November 2016; accepted 25 May 2017
Available online 23 June 2017

KEYWORDS
Renal colic;
Pain;
Pain management;
Urology

Summary
Objective. — To assess effectiveness of pharmacologic interventions to relieve pain in patients suffering an acute stone episode.
Methods. — Relevant trials that included patients with acute renal colic and radiological findings of urinary stones were identified in four databases. The main outcome was pain relief evaluated by Visual Analogue Scale score (VAS).
Results. — In overall, diclofenac was superior to other NSAIDs for pain relief (MD of −12.57 [95% CI: −19.26, −5.88]). Paracetamol was superior to morphine for pain reduction at 30 minutes (MD of −3.92 [95% CI: −6.41, −1.43]) and also to placebo at 15 minutes (MD of −24.77 [95% CI: −33.19, −16.35]) and at 30 minutes (MD of −16 [95% CI:−29, −2.96]) after drug administration. Finally, diclofenac was superior to paracetamol for pain reduction at 60 (MD of 6.60 [95% CI: 4.37, 8.83]) and 90 minutes (MD of 3.4 [95% CI: 2.01, 4.79]).

* Corresponding author. Cra 98 #18-49, 760001 Fundacion Valle del Lili, Cali, Colombia.
E-mail address: ramiro.manzano@correounivalle.edu.co (R. Manzano-Nunez).

http://dx.doi.org/10.1016/j.purol.2017.05.011

Conclusions. — Diclofenac was superior to other NSAIDs and paracetamol for diminishing pain in patients suffering an acute stone episode. Paracetamol was superior to morphine and placebo for short pain relief. Future trials should address the role of paracetamol in the management of pain in patients suffering an acute stone episode.

MOTS CLÉS
Coliques rénales ;
Douleur ;
Gestion de la douleur ;
Urologie

Résumé
Objectif. — Évaluer l'efficacité des interventions pharmacologiques pour soulager la douleur chez les patients souffrant d'un épisode de pierre aiguë.
Méthodes. — Les essais pertinents qui comprenaient des patients atteints de colique rénale aiguë et des résultats radiologiques de calculs urinaires ont été identifiés dans quatre bases de données. Le principal résultat était le soulagement de la douleur évalué par le score d'échelle visuelle analogique (EVA).
Résultats. — Dans l'ensemble, le diclofénac était supérieur aux autres AINS pour le soulagement de la douleur [MD de −12,57 (IC : 95 % −19,26, −5,88)]. Le paracétamol était supérieur à la morphine pour la réduction de la douleur à 30 minutes (MD de −3,92 [IC : 95 % −6,41, −1,43]) et également au placebo à 15 minutes (MD de −24,77 [IC : 95 % −33,19, −16,35]) et à 30 minutes (MD de −16 [IC : 95 % −29, −2,96]) après l'administration du médicament. Enfin, le diclofénac était supérieur au paracétamol pour la réduction de la douleur à 60 (MD 6,60 [IC : 95 % 4,37, 8,83]) et 90 minutes (MD de 3,4 [IC : 95 % 2,01, 4,79]).
Conclusions. — Le diclofénac était supérieur aux autres AINS et au paracétamol pour la diminution de la douleur chez les patients souffrant d'un épisode de pierre aiguë. Le paracétamol était supérieur à la morphine et au placebo pour le soulagement de la douleur courte. Les essais futurs devraient aborder le rôle du paracétamol dans la prise en charge de la douleur chez les patients souffrant d'un épisode de pierre aiguë.

Introduction

Renal colic is the most common type of abdominal pain at the emergency room [1]. It affects about 1.2 million people each year in United States and accounts about 1% of all hospital admissions [1,2]. According to validated instruments, recurrent renal colic produces a negative impact in quality of life and is associated with anxiety and depression [3—5]. Therefore, rapid and effective analgesia is crucial in renal colic management at the emergency room. International Guidelines recommend Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and opioids as standard of care [6—8]. However, opioids are associated with a worse adverse events profile.

The most commonly used medications for pain relief in renal colic are NSAIDs [9,10]. Recent European Association of Urology guidelines [8] on urolithiasis recommend NSAIDs, such as metimazole, as a safe and effective alternative for pain relief in patients with an acute stone episode instead of opioids. A 2008 French guideline [11] proposes the use of ketoprofen as the first option for pain relief in patients with an acute stone episode. This guideline also recommends the use of opioids in the cases where ketoprofen has failed.

Although NSAIDs and opioids are used worldwide, several clinical trials have evaluated the effectiveness of diclofenac, paracetamol, desketoprofen, meperidine and combination of interventions for pain relief in acute stone episodes [12] and thus, strong recommendations on the appropriate intervention for pain relief in patients suffering an acute stone episode are lacking. That's why the objective of this systematic review was to assess the effectiveness of different pharmacologic interventions to relieve renal colic pain in patients suffering an acute stone episode.

Methods

This study was conducted according to the recommendations of the Cochrane Collaboration and following PRISMA Statement. The PROSPERO registration number is CRD42016036718.

Inclusion and exclusion criteria

Randomized controlled trials assessing adult patients older than 18 years old, admitted to the emergency room with a diagnosis of renal colic and comparing the effectiveness of medications for pain relief. Patients must also have radiological findings suggestive of the presence of kidney and/or ureteral stones (plain abdominal imaging, renal ultrasonography, low dose computed tomography,

intravenous pyelogram or excretory urogram CT). We evaluated the effectiveness of different interventions for pain relief in patients suffering an acute stone episode. Evaluated interventions were: non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, opioids, hyoscine-butylbromide and dipyrone. Exclusion criteria were trials where participants received analgesia prior to enrolment in study and those with no description of renal colic management and evaluation. We did not find any article that included hyoscine-butyilbromide and accomplished the inclusion criteria.

Outcome

The primary outcome was: Pain relief assessed by Visual Analogue Score (0—100 mm/0—10 cm). We did not include studies where pain was measured with a different scale since this could introduce a high degree of heterogeneity.

Search Methods

We searched MEDLINE (OVID), EMBASE, CENTRAL and LILACS from inception to March 2016. The search strategy for each database is described in supplementary data Appendix A. We also hand-searched references from relevant narrative reviews, and previous systematic-reviews for more trials. Other sources were thesis databases, Opengrey and Google scholar. Authors were contacted to complement data by e-mail and phone calls. No language restrictions were used.

Data collection

Two reviewers (HG, RM) independently reviewed each reference by title and abstract. Then, scanned full-texts of relevant studies, applied pre-specified inclusion and exclusion criteria and extracted the data. Disagreements were resolved by consensus and where disagreement could not be solved, a third reviewer dissolved conflict.

The following information was independently extracted from each article by two trained reviewers (RM) and (HG) using a standardized form: study design, geographic location, authors names, title, objectives, inclusion and exclusion criteria, number of patients included, losses to follow up, setting, definition of interventions, definitions of outcomes, outcomes measures (reported VAS), adverse events, need for rescue medication and funding.

Risk of bias

The assessment of the risk of bias for each study was made using the Cochrane Collaboration tool for assessing the risk of bias [13], which covers: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other biases. Two independent researchers (HG, RM) made a judgment about the possible risk of bias from extracted information, rated as ''high risk'', ''low risk'' or ''unclear risk''. We computed graphic representation of potential bias using RevMan 5.3.

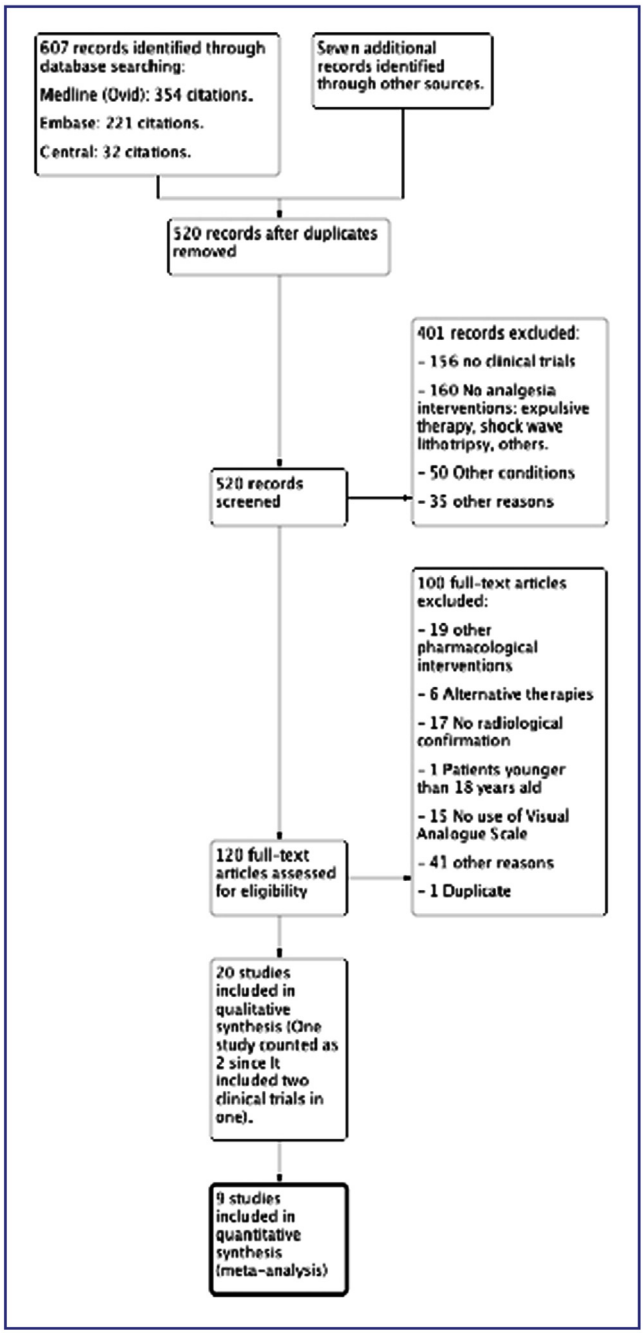

Figure 1. Flowchart.

Data analysis/Synthesis of results

The statistical analysis was performed using Review Manager 5.3 (RevMan® 5.3). For continuous outcomes we extracted end-value means with Standard Deviations (SD). In studies that reported median with interquartile ranges, we converted the reported values to means according to recommended [14,15]. Mean Differences (MD) were pooled using a random effect model. The results are reported in

Table 1 Characteristics of included studies.

Study	Outcome	Intervention	N patients	Mean age	Baseline VAS	VAS 15 min	VAS 30 min
Serinken Mustafa et al., 2012 Turkey/SC [16]	VAS	Paracetamol IV	38	29.1 ± 8.2	80.1 ± 13.3	46.3 ± 24.3	16.5 ± 19.9
		Morphine IV	35	31.3 ± 9.0	82.7 ± 10.4	43.3 ± 26.7	26.1 ± 21.9
Altay B 2007 Turkey/SC [17]	VAS	IM injection of distilled water + 20 mg sublingual piroxicam	31		[a]	[a]	[a]
		IM injection with 40 mg piroxicam + 2 sublingual tablets of placebo	41		[a]	[a]	[a]
Sidney Glina et al., 2011 Brasil/MC [18]	VAS	Parecoxib 40 mg IV	156	38.6 ± 10.3	[a]	[a]	[a]
		Ketoprofen 100 mg IV	141	40.1 ± 12.1	[a]	[a]	[a]
F. Bektas et al., 2009. Turkey/SC [19]	VAS	Paracetamol IV	46	35 ± 10	73 (55–87)[b]	21.5 (9–38)[b]	19 (5–42)[b]
		Morphine IV	49	39 ± 11	78 (64–98)[b]	40 (20–68)[b]	23 (4–59)[b]
		Placebo	51	36 ± 10	73 (53–87)[b]	57 (29–57)[b]	33 (15–66)[b]
E. Cohen 1998. Israel/SC [20]	VAS	Ketorolac	27	44.0 ± 12.8	74.1 ± 21.2	[a]	[a]
		Diclofenac	30	42.4 ± 13.0	79.7 ± 18.8	[a]	[a]
A. Supervía. 1998. Spain/SC [21]	VAS	IM distilled water + two sublingual tablets of piroxicam 20 mg	40	36.5 ± 14.1	79.8 (14.7)	[a]	24.9 ± 36.1
		IM diclofenac 75 mg + 2 sublingual tablets of placebo	40	41.5 ± 15.2	76.0 (14.2)		15.5 ± 25.7
W.H. Cordell 1996. USA/MC[22]	VAS	IV ketorolac 60 mg and placebo.	36	38,8 ± 1.7	80.3 ± 3.5	34.8 ± 4.5	24.7 ± 4.6
		IV meperidine 50 mg and placebo	35	42.0 ± 1.9	77.4 ± 3.6	55.0 ± 4.3	56.6 ± 5.2
		IV ketorolac 60mg + IV meperidine 50 mg	35	36.1 ± 1.7	73.3 ± 3.3	25.8 ± 4.5	23.5 ± 4.7
D.P.S. Sandhu et al., 1994. UK/SC [23]	VAS	Ketorolac 30 mg	76	45.2 ± 14.6	[a]	[a]	[a]
		Pethidine 100 mg	78	42.1 ± 14.6			
G Stankov 1994. Germany/MC [24]	VAS	Dypirone 2.5 g	36	46.4 + 16.2 (range, 18 −83 years)	82.3 ± 12.4	[a]	[a]
		Tramadol 100 mg	35		80.6 ± 10		
		Butylscopolamine 20 mg	33		84.2 ± 11.2		
M. Walden et al., 1993. Findland-Sweden/MC [25]	VAS	Ketoprofen 100 mg	41	[a]	[a]	[a]	[a]
		Diclofenac 50 mg	45				

Table 1 (*Continued*)

Study	Outcome	Intervention	N patients	Mean age	Baseline VAS	VAS 15 min	VAS 30 min
Marthak (a) 1991. India/MC [26]	VAS	Diclofenac	75	32.3	[a]	[a]	[a]
		Dypirone/spasmolytics	78	32.8			
Marthak (b)		Diclofenac	25	36.4			
		Pethidine	25	34			
W. Oosterlinck 1990. Belgium-UK/MC [27]	VAS	Ketorolac 10 mg	45	40	80 ± 20	[a]	[a]
		Ketorolac 90 mg	37	41	82 ± 11		
		Pethidine 100 mg	39	39	80 ± 13		
P. Sommer 1989. Denmark/SC [28]	VAS	Diclofenac	29	57 (20—83)[b]	[a]	[a]	[a]
		Ketogan (Morphine derivate) + Spasmolytic agent	27	54 (21—69)[b]			
Finlay 1982. Scotland/SC [29]	VAS	Buprenofphine 0.3 mg	13	40.5 ± 15.4	[a]	[a]	[a]
		Pethidine 100 mg	13	42.6 ± 13.7			
Fraga A 2003. Portugal/MC [30]	VAS	Etofenamate 1 g	59	47.4 ± 17	80.1 ± 17.7	[a]	40.7 ± 27.8
		Diclofenac 75 mg	60	45 ± 14.7	78.5 ± 16.5		33.2 ± 25.3
Sánchez-Carpena 2003. Spain/MC [31]	VAS	Dexketoprofen 25 mg	112	42.1 ± 12.4	71.4 ± 16	[a]	[a]
		Dexketoprofen 50 mg	112	41.7 ± 13.4	72 ± 16.6		
		Dypirone 2 g	108	39.7 ± 13.0	70.4 ± 16.4		
Jin Choi 2011. Korea/SC [32]	VAS	Hydromorphone	26	52.2 ± 8.7	8.2 ± 1.7	4.0 ± 2.8	[a]
		Pethidine	26	48.4 ± 11.4	8.4 ± 1.6	5.7 ± 2.4	
R. Azizkanhi 2011. Iran [33]	VAS	Morphine IV	62	39.73 ± 11.62	[a]	[a]	[a]
		Paracetamol IV	62	38.40 ± 11.60			
Pathan 2016 - Qatar [34]	VAS	Paracetamol 1 g IV	548	34.4 (28.6—41.5)	8 (7—10)	[a]	3 (2—5)
		Diclofenac 75 mg IM	547	35.1 (29.2—42.6)	8 (7—10)		3 (2—5)
		Morphine 0.1 mg/kg IV	549	34.7)28.8—41.7)	8 (7—10)		4 (2—5)

Table 1 (*Continued*)

Study	VAS 60 min	VAS 120 min	VAS 360 min	Losses to follow-up	Adverse effects	Radiological assessment
S. Mustafa et al., 2012 Turkey/SC [16]	a	a	a	2	2	US, CT
	a	a	a	5	5	
Altay B 2007 Turkey/SC [17]	a	a	a	0	a	US, CT
	a	a	a	0	a	
S. Glina et al., 2011 Brasil/MC [18]	a	a	a	10	10	Rx, CT, US, MRI
	a	a	a	14	12	
Firat Bektas et al., 2009. Turkey/SC [19]	a	a	a	19	26	CT, US, Rx, stone recovery
	a		a		41	
	a	a	a		17	
E. Cohen 1998. Israel/SC [20]	24.0 ± 27.8 21.7 ± 25.7	23.6 ± 33.4 16.7 ± 22.0	22.4 ± 33.1 12.3 ± 20.6	No data	No data	US
A. Supervía, 1998. Spain/SC [21]	a	a	a	No data	0 1	Rx, US
W.H. Cordell 1996. USA/MC [22]	a	a	a	48	409	Urography, US, stone recovery
D.P.S. Sandhu et al., 1994. UK/SC [23]	a	a	a	a	a	Urography, X-ray, US, stone recovery
G. Stankov 1994. Germany/MC [24]	a	a	a	a	5 13 11	Urography, X-ray, US.
M. Walden et al., 1993. Findland-Sweden/MC [25]	a	a	a	a	a	Urography, Stone recovery

Table 1 (*Continued*)

Study	VAS 60 min	VAS 120 min	VAS 360 min	Losses to follow-up	Adverse effects	Radiological assessment
Marthak (a) 1991. India/MC [26]	[a]	[a]	[a]	[a]	5	[a]
Marthak (b)					11 1 36	
W. Oosterlinck 1990. Belgium-UK/MC [27]	54 ± 26	[a]	[a]	18	[a]	Radiological evidence/No specified
	65 ± 18 57 ± 26					
P. Sommer 1989. Denmark/SC [28]	[a]	[a]	[a]	7	ND	Intravenous Urography
				7		
Finlay 1982. Scotland/SC [29]	[a]	[a]	[a]	6	ND	X-Ray
A. Fraga 2003. Portugal/MC [30]	23.1 ± 26.5	[a]	[a]	0	2	Urography, X- Ray, US, stone recovery
	18.3 ± 24.9			0	3	
Sánchez-Carpena 2003. Spain/MC [31]	[a]	[a]	60.5 ± 23.2	ND	34	X-Ray
			60.6 ± 23.3		30	
			58.6 ± 22.7		39	
Jin Choi 2011. Korea/SC [32]	[a]	[a]	[a]	ND	8	US
					8	
R. Azizkanhi 2011. Iran [33]	[a]	[a]	[a]	ND	22	US
					0	
Pathan 2016 - Qatar [34]	1 (0—3)	[a]	[a]	113	7	CT, US
	0 (0—2)			110	7	
	1 (0—4)			111	19	

General charactetistics of included studies. SC: single center; MC: multicenter; IV: intravenous; IM: intramuscular.
[a] No information.
[b] Median and IQ range.

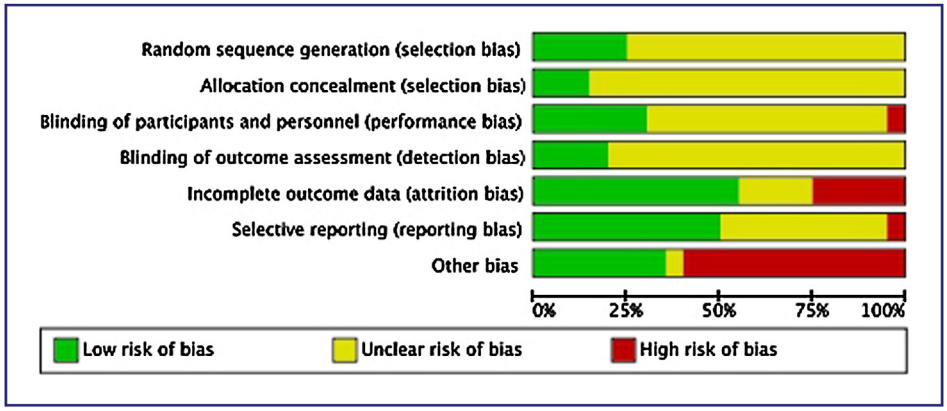

Figure 2. Risk of bias across studies.

forest plots of the estimated effects of the included studies with a 95% confidence interval (95% CI). Heterogeneity was evaluated using the I^2 test. For the interpretation, it was determined that the values of 25%, 50%, and 75% in the I^2 test corresponded to low, medium, and high levels of heterogeneity, respectively.

Results

Main results from individual studies are summarized in Table 1. The search yielded 614 publications of which 120 were potentially relevant. After applying inclusion and exclusion criteria, 20 studies were included in the systematic review [16—34] (all published in peer-review journals) and 9 were included in quantitative synthesis (Meta-Analysis) [16,19—22,27,30,31,34] (Fig. 1).

Included studies randomized 3852 patients. The main comparisons were between Paracetamol and morphine (3 trials); Diclofenac and NSAIDs (3 trials); NSAIDs and Meperidine (2 trials); Desketoprofen and Dipyrone (1 trial—Two different doses) and Morphine and other interventions (2 trials).

The follow up was stated in all trials. All studies were done in the emergency department. Diagnosis of renal colic was based on clinical data and performed by a blinded physician in all trials. There was a combination of several radiological tools in most of the trials. Presence of stones was confirmed by computed tomography in 4 trials [16—19,34]; and/or abdominal radiography in 8 trials [18,19,21,23,24,29—31]; and/or ultrasonography in 13 trials [16—24,30,32—34] and/or intravenous urography in seven trials [19,22—25,28,30]; and/or a voiding calculus in seven trials [19,21—23,25,26,30]; and/or magnetic resonance in one trial [18]. Radiological confirmation was stated in two trials but no details of the method used and no data about individual results were mentioned. Adverse effects were measured in 12 trials [16,18—22,24—26,30,32,34]. In all trials the primary outcome was pain relief measured by Visual-Analogue-Scale.

Risk of bias

Risk of bias is detailed in Figs. 2 and 3. Low risk sequence generation and allocation concealment were reported in 5/20 (25%) and 3/20 (15%) trials, respectively. Twelve studies had a small sample size. Seventeen studies were double-blinded [16—25,27—29,31—34], three were single-blinded [26,30]. Results were analyzed by intention-to-treat analysis in six trials [16—18,20,30,35]. Sponsorship was stated in four trials [17,19,23,30] and two of these trials were sponsored by pharmaceutical industry [17,23]. Informed consent and ethical committee approval were described in all trials.

Outcomes

The primary outcome measured in all trials was pain reduction. Pain reduction was pooled from 9 trials.

In overall, diclofenac was superior to other NSAIDs for pain relief in patients suffering an acute stone episode (MD of −12.57 [95% CI: −19.26, −5.88]) (Fig. 4). Furthermore, diclofenac was superior to other NSAIDs for short pain relief (30 minutes after drug administration) (MD −14.95 [95% CI: −22.76, −7.14]) but this effect was not sustained at 60 minutes after drug administration (MD −9.77 [95% CI: −21.9, 2.36]). No significant differences between diclofenac and other NSAIDs were found with respect to adverse events (RD 0.02 [95% CI: −0.03, 0.07]).

We pooled results from different studies comparing paracetamol with other pharmacologic interventions. Paracetamol and morphine were compared in three studies [16,19,34]. No significant differences were found between paracetamol and morphine for pain relief in patients suffering an acute stone episode (MD of −3.72 [95% CI: −10.55, 3.11]) (Fig. 5). Furthermore, no significant differences were found between paracetamol and morphine for short pain relief (VAS evaluated 15 minutes after drug administration) (MD of −8.39 [95% CI: −30.70, 13.93]) [16,19]. However, paracetamol was superior to morphine for pain relief after 30 minutes (MD of −3.92 [95% CI: −6.41, −1.43]). No significant differences between paracetamol and morphine were found with respect to adverse events (RD −0.11 [95% CI: −0.27, 0.05]).

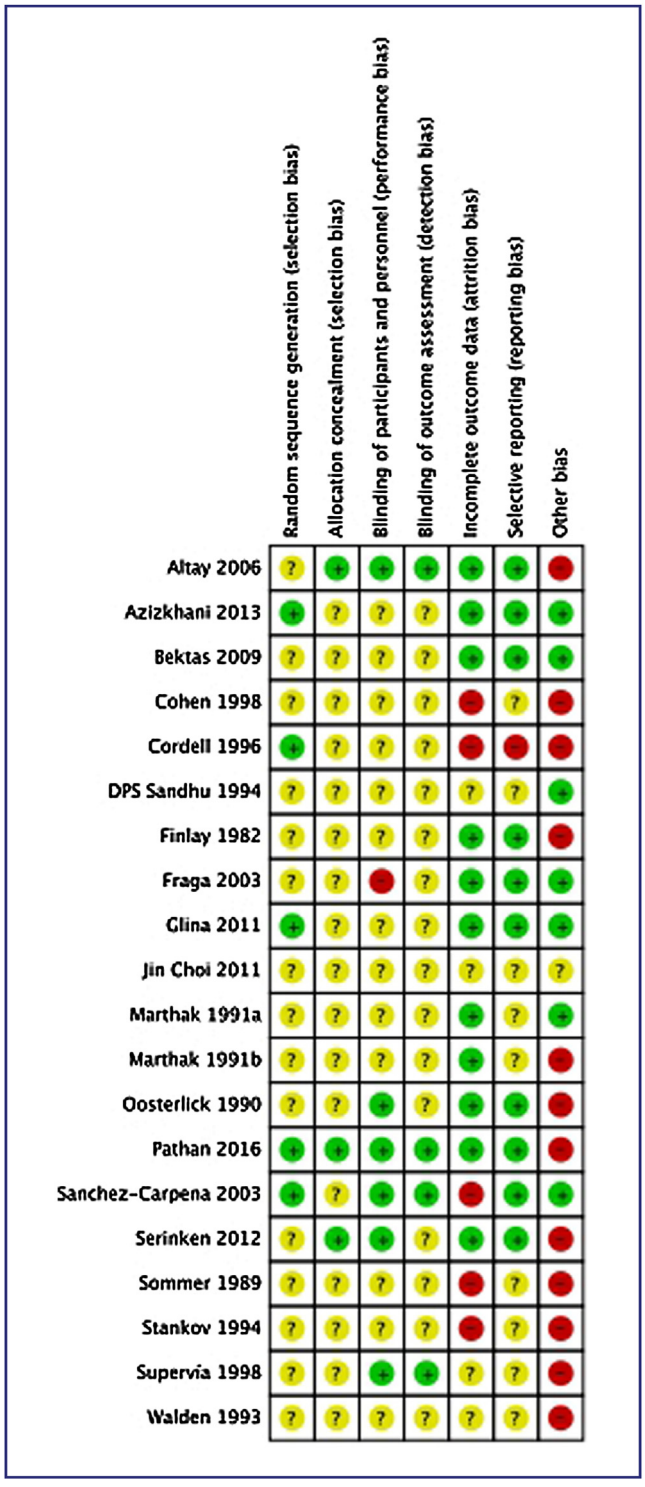

Figure 3. Risk of bias within studies.

Regarding paracetamol and placebo we found one study [19] that provided information on values of pain reduction at 15 and 30 minutes after drug administration. Paracetamol was superior to placebo at 15 (MD −24.77 [95% CI: −33.19, −16.35]) and at 30 minutes after drug administration (MD −16 [95% CI: −29, −2.96]).

Pathan et al., 2016 [34] compared paracetamol and diclofenac for pain relief in patients suffering an acute stone episode. Diclofenac was superior to paracetamol at 60 minutes after drug administration (MD 6.60 [95% CI: 4.37, 8.83]). Furthermore, this effect was sustained at 90 minutes after drug administration (MD 3.4 [95% CI: 2.01, 4.79]). We found two studies that compared NSAIDs and Meperidine [22,27]. In these studies no significant results were found between the two treatments (MD −5.57 [95% CI: −24.81, 13.67]).

We included the study by Marthak et al. [26]. This study described two clinical trials inside the article, however we could not include it in the meta-analysis because the way they measured VAS was contrary to the usual. Finally, one study [31] compared desketoprofen and metimazole using two different doses of desketoprofen with no significant results (MD 1.96 [95%CI: −2.80, 6.71]). When measuring adverse effects no significant differences were found between desketoprofen and metimazole (RD −0.08 [95% CI: −0.16, 0.01]).

Discussion

The cornerstone of ureteral colic management is analgesia. Current international guidelines recommend analgesia with parenteral narcotics or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [6–8].

In summary we found that diclofenac was superior to other NSAIDs and paracetamol for improving pain in patients suffering an acute stone episode. On the other hand, paracetamol was superior to placebo for short pain relief and it was superior to morphine at 30 minutes assessment. We did not find any differences for desketoprofen vs metimazole and also between NSAIDs and metimazole in terms of pain relief in patients suffering an acute stone episode.

NSAIDs have the property of cause prostaglandin inhibition and the ability to decrease ureteral smooth muscle tone. Therefore, they have a theoretical superiority for pain reduction. In 2004, a systematic review conducted by Holdgate et al. found that both NSAIDs and opioids were able to achieve pain relief, but when compared to opioids, NSAIDs were associated with fewer side effects, particularly vomiting. The study concluded that given the favorable general profile of NSAIDs, those were the preferred analgesic for renal colic [36]. However, our pooled analysis did not show that NSAIDs were superior to other drugs.

Consistent with previous findings, our results showed that diclofenac was significantly superior to decrease pain when compared to other drugs and also was effective to achieve short-term pain relief. The superiority of diclofenac in comparison to other NSAIDs could be explained by other mechanisms of action that goes beyond the inhibition of prostaglandin synthesis via blockade of COX-1 and COX-2. Diclofenac could cause the inhibition of the thromboxane-prostanoid receptor, affecting arachidonic acid release and particularly lipoxygenase enzymes, thus reducing formation of leukotrienes, which have a demonstrated proinflamatory effect. Diclofenac could also activate the nitric oxide-cGMP antinociceptive pathway, inhibit substrate P and peroxisome proliferator activated receptor gamma (PPARgamma). These additional mechanisms of action may support the high potency of diclofenac [37]. Despite of diclofenac and other NSAIDs effectiveness, we must remark that they use

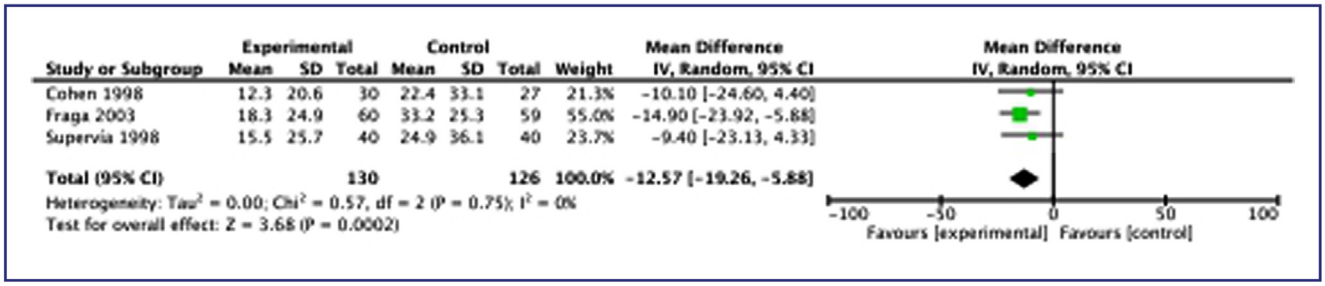

Figure 4. Diclofenac vs any other NSAID.

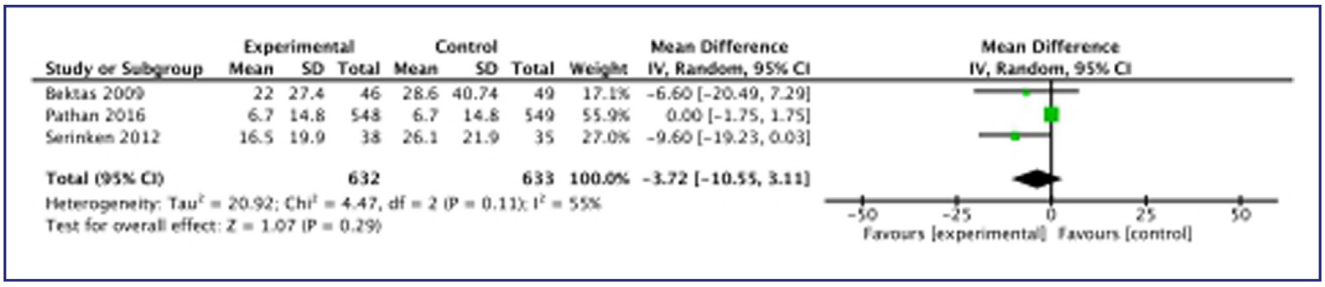

Figure 5. Paracetamol vs morphine.

should be individualized in patients with preexisting renal disease, active bleeding or risk of bleeding and in the elderly patient with multiple comorbidities [38]. Therefore beyond potential benefits of diclofenac and other NSAIDs, their potential harms must be acknowledged. NSAIDs with higher risk of harms comprise about one-third of the market shares in several countries with no differences between low and high-income countries [39] and serious adverse events of NSAIDs are well understood from studies that have documented hazards, specially serious gastrointestinal [40] and cardiovascular complications [41]. In particular, NSAIDs that have consistently higher cardiovascular risk are rofecoxib, etoricoxib, and diclofenac [41]. However, we did not find any differences regarding adverse effects for diclofenac and other comparisons. Although diclofenac was superior to other drugs for decrease pain, this drug is not authorized for the treatment of renal colic pain in France.

We found that parecetamol was superior to placebo and to morphine for short pain relief. This finding is really important if we take into account that paracetamol is not associated with the increased incidence of nausea, vomiting, and respiratory depression that can occur with opioids, or the platelet dysfunction, gastritis, and renal toxicity that are sometimes associated with NSAIDs [42].

We acknowledge our weaknesses by describing degree of clinical diversity, methodological diversity and statistical diversity [43,44]. First, let us take a look at clinical diversity. Since our objective was to assess effectiveness of different pharmacologic interventions to relieve renal colic pain, this could have led to the inclusion of a broader selection of studies. Secondly, some degree of misclassification could have affected validity from individual studies because of the use of several and diverse radiological methods to objectively diagnose the presence of ureteral stones. With respect to methodological diversity it is best described in Risk of bias figures (Figs. 3 and 4). In addition, high degree of statistical heterogeneity was found, as it can be seen at the forest plots (Fig. 5). To deal with this, and aware of the degree of clinical diversity, we conducted meta-analysis using a random effects model and performed a sub-group analysis by type of intervention and the time of assessment.

Finally, future studies should address the role of paracetamol in the management of pain in patients suffering an acute stone episode.

Conclusions

This systematic review and meta-analysis shows that diclofenac is superior to other NSAIDs and paracetamol for diminishing renal colic pain in patients suffering an acute stone episode. Additionally paracetamol was superior to morphine and placebo for short pain relief. Finally, physicians should be aware of potential risk of NSAIDs, particularly those related to cardiovascular and gastrointestinal risks. Future studies should address the role of paracetamol in the management of pain in patients suffering an acute stone episode.

Author's contributions

Herney Andrés García Perdomo: study conception and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision.

Ramiro Manzano Nunez: study conception and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision.

Fernando Echeverría García: analysis and interpretation of data; drafting of manuscript; critical revision.

Hugo López: analysis and interpretation of data; drafting of manuscript; critical revision.

Nicolas Fernández: analysis and interpretation of data; drafting of manuscript; critical revision.

Authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

Authors participated in drafting the article or revising it critically for important intellectual content.

Authors gave final approval of the version to be submitted and any revised version.

Acknowledgments

None.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.purol.2017.05.011.

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