COMPARISON OF KETOROLAC VERSUS DICLOFENAC AS TREATMENT FOR ACUTE RENAL COLIC: A SYSTEMATIC REVIEW AND A NETWORK META-ANALYSIS (DIRECT AND INDIRECT COMPARISON)

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ABSTRACT

Objective: *The purpose of this study is to compare which analgesic is better between ketorolac and diclofenac.* ***Material & Methods:*** *A systematic search was conducted in Pubmed, Science Direct, Cochrane, EBSCO, Proquest database, and PICO analysis was used in determining the study question. The included article in the analysis was randomized controlled trials.* ***Results:*** *A total of 6 articles were included in the analysis, with no significant differences between ketorolac and diclofenac both in a direct comparison and indirect comparison (OR 2.74 [95%CI 0.72 – 10.43]; p= 0.14 and OR 0.51 [95%CI 0.29 – 0.91]; p= 0.49).* ***Conclusion:*** *Both ketorolac and diclofenac have the same efficacy in treating renal colic.*

Keywords: *Diclofenac, ketorolac, renal coli.*

ABSTRAK

Tujuan: *Tujuan dari penelitian ini adalah untuk membandingkan analgesik mana yang lebih baik antara ketorolak dan diklofenak.* ***Bahan & Cara:*** *Penelusuran sistematis dilakukan pada database Pubmed, Science Direct, Cochrane, EBSCO, Proquest, dan analisis PICO digunakan dalam menentukan pertanyaan studi. Artikel yang disertakan dalam analisis adalah uji coba terkontrol secara acak.* ***Hasil:*** *Sebanyak 6 artikel dimasukkan dalam analisis, tanpa perbedaan yang signifikan antara ketorolak dan diklofenak baik dalam perbandingan langsung maupun tidak langsung (OR 2.74 [95% CI 0.72 – 10.43]; p= 0.14 dan OR 0.51 [95% CI 0.29 – 0.91]; p= 0.49).* ***Simpulan:*** *Baik ketorolak maupun diklofenak memiliki khasiat yang sama dalam mengobati kolik ginjal.*

Kata Kunci: *Diklofenak, ketorolac, kolik ginjal.*

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INTRODUCTION

Currently, acute renal colic is one of the most frequent urologic visits in the Emergency Department (ED). It is usually described as sudden onset of flank pain that sometimes radiate to groin. Upon patients' arrival at ED, early clinical examination, and radiologic investigations are mandatory. Without them, many other life-threatening conditions could be misdiagnosed as renal colic pain.[1-2]

Renal colic is acute pain due to obstruction caused by urinary stones. As most stones will eventually pass without any interventions, early management in emergency should focus on early relief of pain. Non-Steroidal Anti Inflammatory Drugs (NSAIDs), opiates, or combination of both are often used to treat this condition. However, diclofenac is stated in the European Association of Urology (EAU) guideline as first-line treatment.[2-3]

Interestingly, it is ketorolac that currently the most common analgesics used in most EDs. Its low cost and vast availability stood as the main consideration. The usage of which analgesics to relief pain in acute renal colic cases are still controversy. Therefore, we design a Meta-Analysis study to investigate whether ketorolac or diclofenac is a better NSAID for early pain relief in acute renal colic patients.

OBJECTIVE

The purpose of this study is to compare which analgesic is better between ketorolac and diclofenac.

MATERIAL & METHODS

We obtained relevant studies from PubMed, Science Direct, Cochrane, EBSCO, and Proquest. We used "(ketorolac OR diclofenac) AND (pethidine) AND (acute renal colic OR kidney stone OR urolithiasis OR nephrolithiasis)" as keywords. All keywords were searched for their respective MeSH thesaurus. Our search strategy was not limited by date or publication status. Trials included were RCTs, comparing either ketorolac or diclofenac with pethidine, adults sample diagnosed with acute renal colic, and measured pain-free as the outcome. Our PICO and search strategy can be seen in Table 1 and Figure 1.

Table 1. PICO: Study Criteria.

***P**atients*	Patients with acute renal colic pain
***I**nterventions*	Ketorolac OR Diclofenac
***C**omparisons*	Pethidine
***O**utcome*	Pain relief

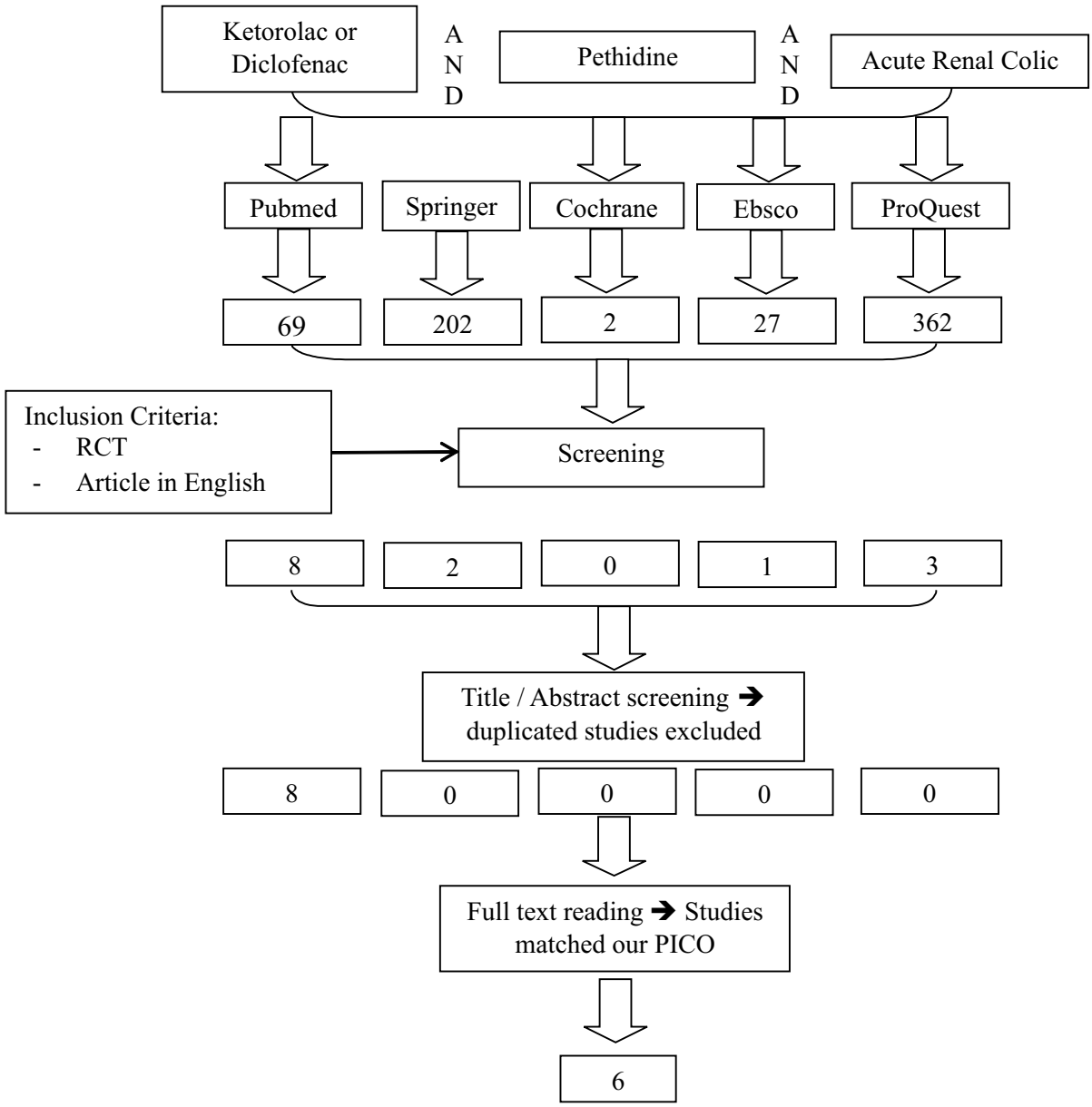


Figure 1. Literature Searching Strategy.

We used several instruments and computer programs for our study. Critical appraisal for each study were done using the Oxford Center of Evidence Based Medicine Worksheet for Therapy. We use SPSS 20 for Windows as our main statistical program for data analysis and Cochrane's Review Manager 5.3 for charts and plots builder. Reference in Vancouver style was made with the help of the Mendeley program.

RESULTS

Our searching found limited studies directly compared to ketorolac and diclofenac. We also faced drawbacks as some studies did not use pain-free as its main output but the Visual Analog Scale (VAS) pain reduction. However, there were several studies comparing NSAIDs with opioids. As seen in Figure 1, we managed to collect a total of 662 studies from 5 search engines using the same keywords. We only include RCTs which were English-written. From that, we focused on 13 studies, with 5 duplicated studies among them. Then we did a full-text reading to screen for studies that matched our PICO.

As a result, we get 6 studies consisting of 1 RCT comparing directly ketorolac and diclofenac, 2 RCTs comparing ketorolac and pethidine, and 3 RCTs comparing diclofenac and pethidine. We include only those with intramuscularly given drugs, on comparable dosage, and outcomes measured at 60 minutes after therapy. The summary of our search results can be seen in Table 2. Based on 6 studies we found earlier, we did a critical appraisal using the Oxford Centre of Evidence-Based Medicine Worksheet (Table 3).

Comparison analysis within the group and subgroups of NSAID and pethidine were done as seen in Table 4. Each of the experimental drugs (ketorolac and diclofenac) were also compared with pethidine (Table 5 and Table 6). Finally, we did a direct and indirect comparison of ketorolac and diclofenac (Table 7 and Table 8).

The opioid used for renal colic treatment in these studies is pethidine. Five studies (752 participants) reported the proportion of patients who failed to achieve complete pain relief at 60 minutes after receiving either NSAID (ketorolac or diclofenac) or pethidine. These five studies were homogenous (P=0.17, I2=37%) with two studies

Table 2. Summary of search results.

Criterias	Studies					
Authors	Oosterlinck	Sandhu	Arnau	Marthak	Hetherington	Cohen
Year	1990	1998	1991	1991	1985	1998
Total Subjects	121	154	451	50	58	57
Intervention (dose) - IM	Ketorolac (30 mg)	Ketorolac (30 mg)	Diclofenac (75mg)	Diclofenac (75 mg)	Diclofenac (75mg)	Ketorolac (30 mg)
Comparison (dose) - IM	Pethidine (100 mg)	Pethidine (100 mg)	Pethidine (100 mg)	Pethidine (100 mg)	Pethidine (100 mg)	Diclofenac (75 mg)
Significance level (OR/RR, CI95, NNT)	0.82 [0.31;2.18]	0.46 [0.23;0.89]	0.81 [0.41;1.58]	0.17 [0.02;1.55]	0.13 [0.03;0.66]	2.74 [0.72;10.43]
Level of evidence	1B	1B	1B	1B	1B	1B

Table 3. Critical appraisal according to the oxford CEBM worksheet for therapy.

Articles	Validity					Relevance		
	Randomization	Intention to treat	Blinding	Treatment equality	Similarity	Domain	Determinant	Outcome
Oosterlinck	+	*	+	+	+	+	-	+
Sandhu	+	+	+	+	+	+	-	+
Arnau	+	*	+	+	+	+	-	+
Marthak	+	-	+	+	+	+	-	+
Hetherington	+	+	+	+	+	+	-	+
Cohen	+	*	+	+	+	+	+	+

* Not mentioned in the article.

(Sandhu et al and Hetherington et al.) found a significant difference (CI of the OR less than 1). Combined analysis of these studies showed a significantly higher rate of complete pain relief in patient with NSAIDs compared with pethidine with OR 0.54 [95% CI 0.36;0.80].

We found only two studies (230 participants) reported the proportion of patients who failed to achieve complete pain relief at 60 minutes after receiving either ketorolac or pethidine. Osterlinck et al in his study on 121 samples, showed that in the comparison between 30 mg ketorolac and 100 mg pethidine, ketorolac was superior than pethidine with OR 0.82 [95% CI 0.31;2.18]. In their report, they measured VAS one-hour post medication as the main outcome. Verbal Rating Scale (VRS) one hour after dosing is also provided by the author.[5] Other studies done by Sandhu et al also showed a similar result. In their study, 30 mg of ketorolac and 100 mg of pethidine were used with VRS as its outcome. We noted the number of patients who did not need any rescue drugs in the first 24 hours. This study reported an OR of 0.46 [95% CI 0.23;0.89].[6]

These two studies were homogenous (P=0.33, I2=0%) with only one study (Sandhu et al.) found a significant difference (CI of the OR less than 1). Combined analysis of these studies showed a significantly higher rate of complete pain relief in patient with ketorolac compared with pethidine with OR 0.55 [95% CI 0.32;0.96]. This result is consistent with previous analysis between NSAIDs and all pethidine.

In the comparison of diclofenac and pethidine, three studies (342 participants) reported the proportion of patients who failed to achieve

Table 4. Comparison of NSAID and Pethidine.

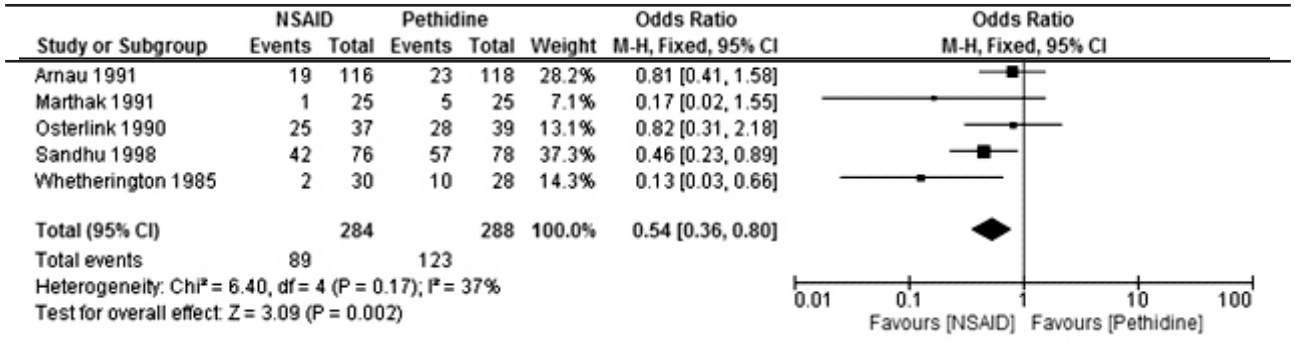


Table 5. Comparison of ketorolac and pethidine.

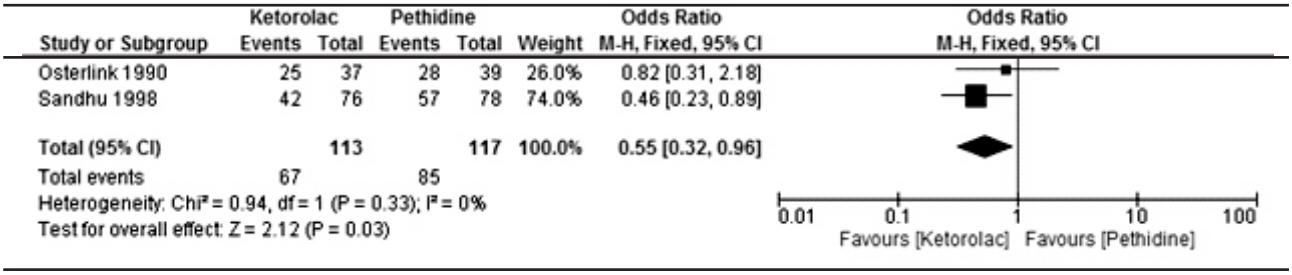


Table 6. Comparison of diclofenac and pethidine.

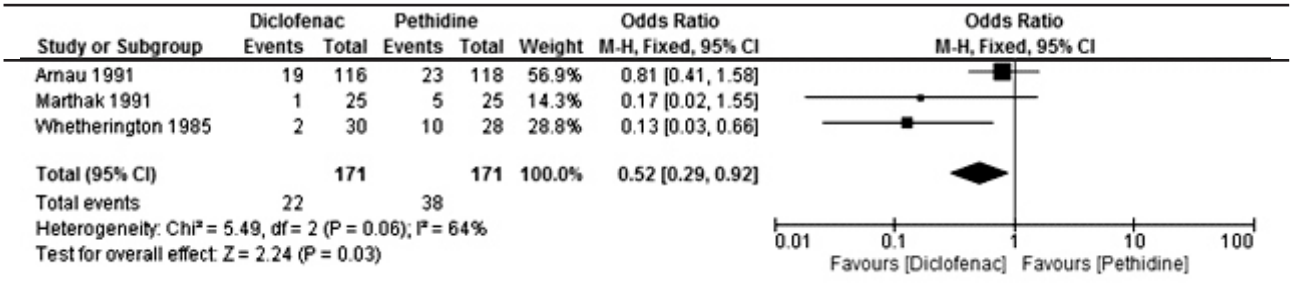


Table 7. Direct comparison of ketorolac and diclofenac.

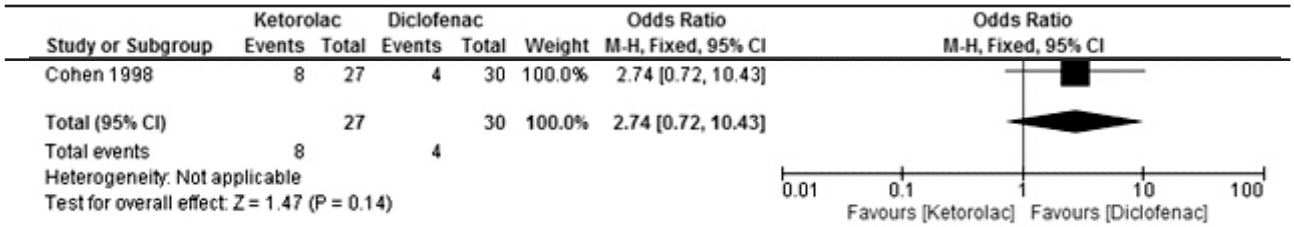
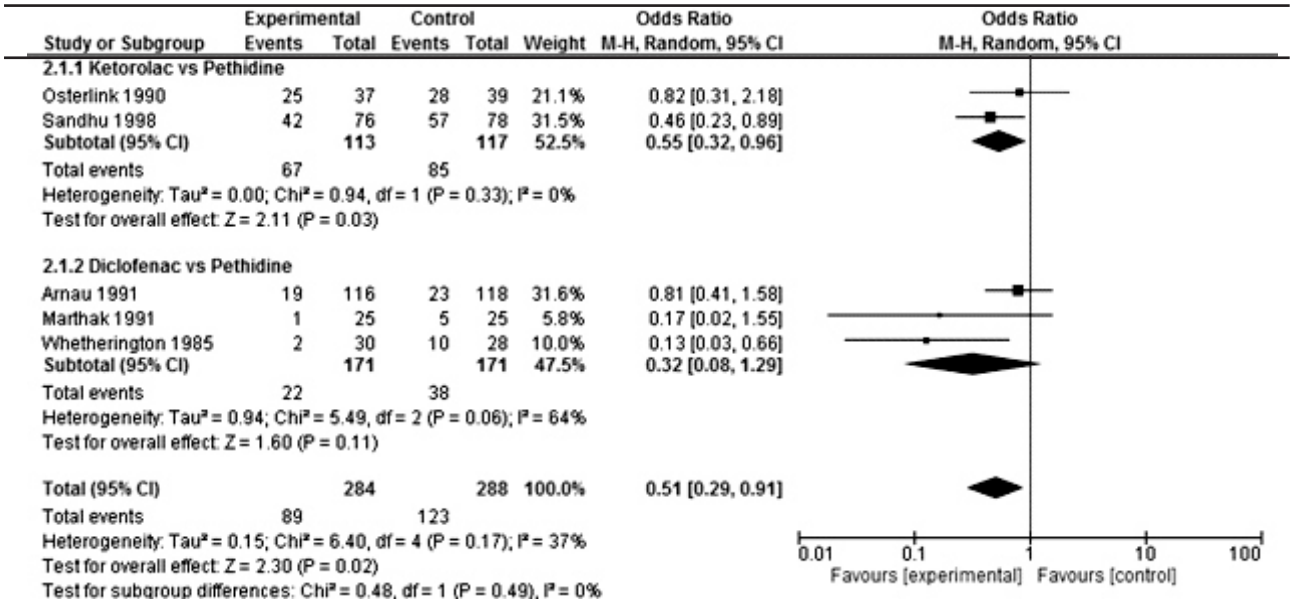


Table 8. Indirect Comparison of ketorolac and diclofenac.



complete pain relief at 60 minutes. Arnau et al. who was incorporated in the Collaborative Group of the Spanish Society of Clinical Pharmacology, showed that out of 116 patients in the diclofenac group and 118 patients pethidine group, there were similar efficacy with OR 0.81 [95% CI 0.41;1.58].[7] On the other hand, Diclofenac showed a better efficacy compare to pethidine ($p<0.05$) with OR 0.17 [95% CI 0.02;1.55] in the study done by Marthak et al. in 1991.[8] Hetherington et al. also showed that diclofenac was superior than pethidine to achieve satisfactory relief of pain with 0.13 as its OR value (0.03; 0.66).[9]

These three studies had moderate heterogenicity (P=0.06, I2=64%) with only one study (Hetherington et al.) found a significant difference (CI of the OR less than 1). Combined analysis of these studies showed a significantly higher rate of complete pain relief in patient with diclofenac compared with pethidine with OR 0.52 [95% CI 0.29;0.92]. This result is still consistent with previous analysis between NSAIDs and all pethidine.

A study by Cohen et al. comparing directly ketorolac and diclofenac. In this study, 27 samples used 30 mg ketorolac and 30 others used diclofenac. The outcome measured in this study was the neediness of using rescue medicine in the first one hour (60 minutes after receiving either ketorolac or diclofenac). This study showed a trend towards a higher rate of complete pain relief in patients treated with diclofenac rather than ketorolac, but this finding was not significant (p= 0.14) with OR 2.74 [95% CI 0.72-10.43].[10]

We used a Bucher Model of indirect comparison using Mantel-Haenszel analysis for subgroups differences.[11] Thus, we can calculate and decided that all studies in both groups are homogenous (p= 0.17, I2= 37%). Therefore, we could use random effect analysis models using RevMan 5.3, as described

by Borrenstein et al., to measure the differences in both subgroups.[12-13] The test reveals that there is no significant difference between ketorolac and diclofenac (p= 0.49).

NSAID has long been reported for its various side effects, primarily gastrointestinal (GI) problems. A study by Conaghan et al. describes that ketorolac has the RR of 14.54 compared to diclofenac with only 3.61 in having a GI adverse effects.[14] Another study by Ong et al also reported a significantly higher relative risk of ketorolac with 24.7 comparing to diclofenac with 2.7.[15] Moreover, an Italian cohort of almost 600 thousand patients by Castellsague et al. stated an adjusted RR of GI adverse event in the ketorolac group is 21.76 compared with diclofenac group of only [3.24.16]

In a specific urologic point of view, ketorolac has a higher risk of acute kidney problems compared with other NSAID. A cohort study in Philadelphia by Feldman et al. documented the event of acute renal failure in patients receiving ketorolac is 3.8 per 1000 courses. This study also stated that the overall incidents of acute renal failure were 1.1% after receiving either ketorolac or opioid as therapy.[17] A more recent study by Ingrasciotta et al. in 2015 reported risks of chronic kidney disease in patients receiving NSAID. Ketorolac group held the highest risk with an adjusted OR of 2.54 compared with diclofenac of only 0.86.[18]

DISCUSSION

The pain in renal colic is due to obstruction in urinary flow resulting in a combination of responses within the urinary system. At first, there will be an increased stimulation for ureteric peristalsis as a natural effort to expel the stone. However, if the stone persists, the surrounding smooth ureteric muscle spasm will occur. Hence, increasing pressure proximally of the stone. This increase in pressure leads to the main mechanism of colic pain: distension of renal capsule and increased prostaglandin synthesis. The distended renal capsule itself will stimulate pain sensation directly. This pain will then be relayed to the central nervous system through renal nerves.[2,4,19]

Furthermore, the release on prostaglandin will initiate a series of the cascade that worsened the condition. First, it causes local inflammation and edema that further increase prostaglandin production. Then more muscle spasm induced causing a further increase in wall tension, which apparently will also increase prostaglandins. Finally, it will affect renal blood flow causing vasodilatation resulting in diuresis and lattermost, cycling back for an increased intrarenal pressure. The mechanism of colic pain is described in Figure 2. [2,4,19]

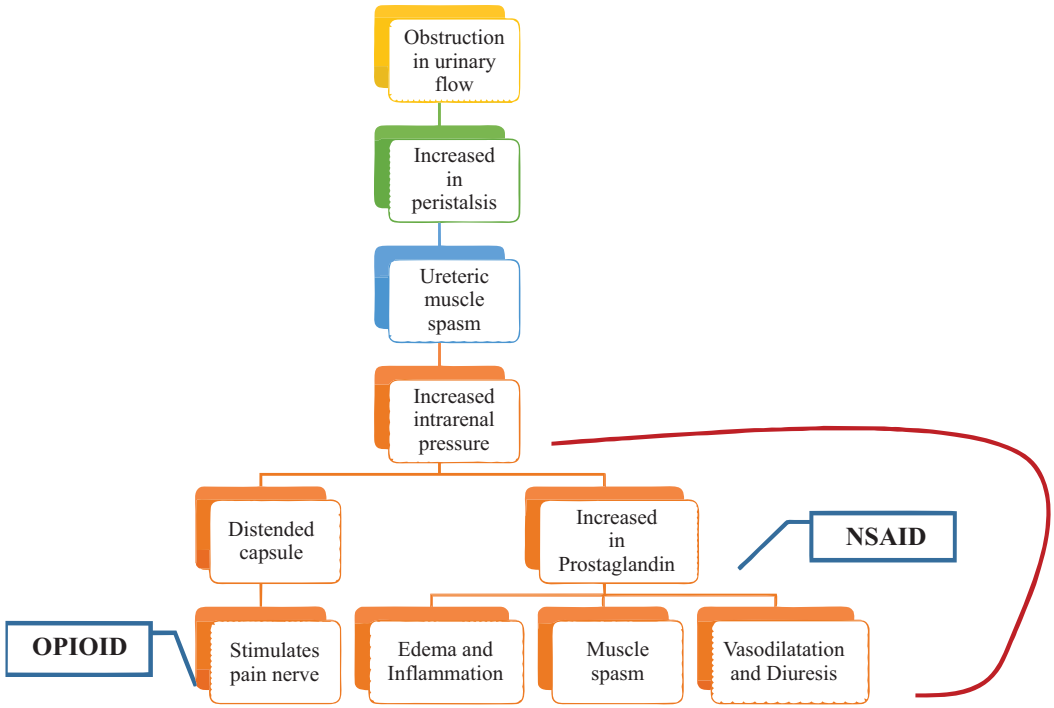


Figure 2. Pathophysiology and target therapy of colic pain.

Our findings in this study suggest that NSAID have a better pain relief rate than opioid. As seen in Table 4, we analyzed five studies comparing NSAID (either ketorolac or diclofenac) with opioid (pethidine). The combined analyses significantly favoring NSAID over pethidine for the difference in pain relief. Moreover, further analyses comparing ketorolac or diclofenac with pethidine separately, also resulting in significant favor of both ketorolac and diclofenac over pethidine (seen in Table 5 and Table 6). This result could be well explained by the mechanism of actions of both NSAID and opioid.

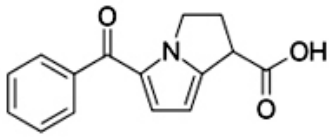
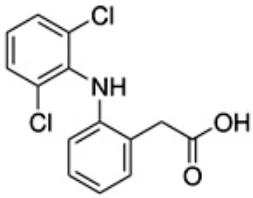
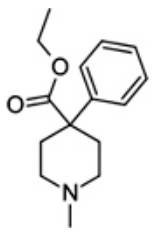
Both NSAID and opioid provide pain relief for acute renal colic patients in their distinct pathways (as seen in Figure 2). The usage of the narcotic agent, such as pethidine, has long been known to effectively reduced pain. It exerts its analgesic effect by acting agonist at the μ opioid receptor at the central nervous system, thereby reducing pain sensation. However, no data is supporting the ability of opioid to reduce muscle spasm. They also have minimum effect on the core problems in colic pain; the synthesis of prostaglandins.[2,19,20]

Meanwhile, NSAID groups acted primarily on the reduction of prostaglandin production. They work by inhibiting cyclooxygenase (COX) enzymes activity at the cellular level. The usage of NSAID could reduce locale edema and inflammation, thus preventing further narrowing of the passage. It can also directly reduce muscle spasm at the stone level, allowing it to pass through. Finally, NSAID able to cut through the worsening cycle of colic pain by reducing glomerular filtration rate (GFR), which in turn decreasing intrarenal pressure and stopping the stimulation of stretch receptors.[4,19,20]

In our study, we found no significant difference between ketorolac and diclofenac. A direct comparison by Cohen et al reported comparable effectivity between both drugs.[10] Based on the other five studies, we performed an indirect analysis that gave similar results. Even though ketorolac was regarded as the most potent pain reliever among NSAIDs for various other pain conditions, in accordance with our results, we might assume that, in managing acute renal colic pain, there is no difference between ketorolac and diclofenac.

However, it is well noted that ketorolac has a much higher risk of adverse events as stated before. These differences in side effects (GI and kidney problems) might be explained by further particularizing on both drugs' pharmacokinetics and pharmacodynamics (Table 9). Problems in the GI system is caused by the abundance of COX-1 receptor in the GI mucosal lining. Therefore,

Table 9. Pharmacokinetics and pharmacodynamics.

Drugs	Structure	Receptors	Metabolism	Halftime (hours)	Excretion
Ketorolac		Cox-1 Cox-2	Hepatic	3.5 - 9	Urine (>90%)
Diclofenac		Cox-1 Cox-2	Hepatic	1.5 - 2	Biliary (40%) Urine (60%)
Pethidine		μ-opioid	Hepatic	2.5 - 4	Urine (>90%)

compared to COX-2 selective NSAID, the nonselective class of NSAID (including ketorolac and diclofenac) has a significantly higher risk of GI side effects.[2,4,14-16]

On the other hand, the receptors that exist in the urinary system are also COX-1, making GI issues unavoidable. We could minimize it, however as studies reported a much lower incidence of GI problems in diclofenac compared to ketorolac. Even though both drugs are classified as non-selective, it seems that diclofenac provides a safer option. [2,4,14-16]

Yet a more important topic arises, as ketorolac is also associated with serious kidney problems. Studies reported that ketorolac has a higher risk of inducing AKI or CKD after its treatment, especially for those with previously diagnosed kidney disease. This might be affected due to ketorolac is mainly excreted through the kidney (90%), compared with diclofenac that is excreted through the liver and kidney (40% liver, 60% kidney). A complete review can be seen in Table 9.[17-18]

CONCLUSION

As conclusion, for patients with acute renal colic in the emergency department, we recommend an expedient usage of analgesics. Based on current studies, both ketorolac and diclofenac are found superior than pethidine, while both providing comparable pain relief with diclofenac regarded as a safer option. Consideration left is the applicability issue, of which is yet to be decided as further prospective data is needed in Indonesian clinical settings for its assurance in efficacy and safety.

DISCLAIMER

All authors contributed to the critical review of this manuscript, with the first author taking responsibility for the paper as a whole. No funding is granted by any pharmaceuticals or institutions.

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