# Comparison of Ketorolac versus Diclofenac as Treatment for Acute Renal Colic: A Systematic Review and A Network Meta-Analysis

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ABSTRACT

Acute renal colic is one of the most frequent urologic visits in Emergency Department (ED), and early management 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. Diclofenac is stated in European Association of Urology (EAU) guideline as first line treatment. Interestingly, it is ketorolac that currently the most common analgesics used in most EDs. A meta-analysis study was designed to investigate whether ketorolac or diclofenac is a better NSAID for early pain relief in acute renal colic patients. Relevant studies were obtained from PubMed, Science Direct, Cochrane, EBSCO, and Proquest. Based on current studies, both ketorolac and diclofenac are found superior than pethidine, while both providing a comparable pain relief with diclofenac regarded as a safer option. Further prospective data is needed in Indonesian clinical settings for its assurance in efficacy and safety

**Keywords:** Acute renal colic, diclofenac, ketorolac, pain

ABSTRAK

Kolik ginjal akut adalah salah satu kunjungan urologi yang paling sering di departemen darurat (*Emergency Department*/ED), dan manajemen dini fokus untuk mengatasi rasa nyeri. Obat antiinflamasi nonsteroid (NSAID), opiat, atau kombinasi keduanya sering digunakan untuk mengatasi kondisi ini. Diklofenak disebutkan dalam pedoman *European Association of Urology* (EAU) sebagai pengobatan lini pertama. Menariknya, ketorolak adalah analgesik paling umum yang digunakan pada kebanyakan ED. Sebuah studi meta-analisis dirancang untuk mengetahui apakah ketorolak atau diklofenak adalah NSAID yang lebih baik untuk menghilangkan nyeri pada pasien kolik ginjal akut. Studi yang relevan diperoleh dari PubMed, Science Direct, Cochrane, EBSCO, dan Proquest. Berdasarkan penelitian-penelitian tersebut, ketorolak dan diklofenak ditemukan lebih unggul daripada pethidin, sementara keduanya menghilangkan rasa sakit yang sebanding, dengan diklofenak yang dianggap sebagai pilihan yang lebih aman. Data prospektif lebih lanjut diperlukan untuk penggunaan klinis di Indonesia untuk memastikan efektivitas dan keamanannya. **Eko Arianto, Arry Rodjani, Irfan Wahyudi. Perbandingan Ketorolak versus Diklofenak sebagai Pengobatan Kolik Ginjal Akut: Tinjauan Sistematik dan Meta-Analisis.**

**Kata kunci:** Diklofenak, ketorolak, kolik ginjal akut, nyeri

## INTRODUCTION

Acute renal colic is one of the most frequent urologic visits in Emergency Department (ED).[1,2] It is usually described as sudden onset of flank pain that sometimes radiate to groin. Upon patients' arrival at ED, early clinical examination and radiology investigations is mandatory because 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. Diclofenac is stated in 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.[4] A meta-analysis study was designed to investigate whether ketorolac or diclofenac is a better NSAID for early pain relief in acute renal colic patients.

## METHODS

Relevant studies were obtained 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 outcome. Our PICO and search strategy can be seen in table

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1 and diagram 1.

Table 1. *PICO*: Study criteria

| | |
|---|---|
| *Patients* | Patients with acurate renal colic pain |
| *Interventions* | Ketorolac OR Diclofenac |
| *Comparisons* | Pethidine |
| *Outcome* | Pain relief |

Several instruments and computer programs were used for our study. Critical appraisal for each study was done using Oxford Center of Evidence Based Medicine Worksheet for Therapy. SPSS 20 for Windows was 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 by the help of Mendeley program.

## RESULTS

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

As a result, 6 studies consisting of 1 RCT comparing directly ketorolac and diclofenac, 2 RCTs comparing ketorolac and pethidine, and 3 RCTs comparing diclofenac and pethidine were found. We include only those with intramuscularly given drugs, on comparable dosage, and outcomes measured at 60 minutes after therapy. The summary of search results can be seen in table 2. Based on those 6 studies, a critical appraisal was done using Oxford Centre of Evidence-Based Medicine Worksheet (Table 3). Comparison analysis within group and subgroups of NSAID and pethidine were done as seen in table 4. Each experimental drugs (ketorolac and diclofenac) were also compared with pethidine (table 5 and table 6). Finally, a direct and indirect comparison of ketorolac and diclofenac was done (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 recieving either NSAID (ketorolac or diclofenac) or pethidine. These five studies were homogenous (P=0,17; $I^2$=37%) with two studies (Sandhu, *et al*, and Hetherington, *et al*) found significant difference (CI of the OR less than 1). Combined analysis of these studies showed a significant 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 recieving either ketorolac or pethidine. Osterlinck, *et al*, in his study on 121 samples, showed that in 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 also provided by the author.[5] Other study 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; $I^2$=0%) with only one study (Sandhu, *et al*) found significant difference (CI of the OR less than 1). Combined analysis of these studies showed a significant 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 comparison of diclofenac and pethidine, three studies (342 participants) reported the proportion of patients who failed to achieve complete pain relief at 60 minutes. Arnau, *et al*, in the Collaborative Group of the Spanish Society of Clinical Pharmacology, showed that out of 116 patients in diclofenac group

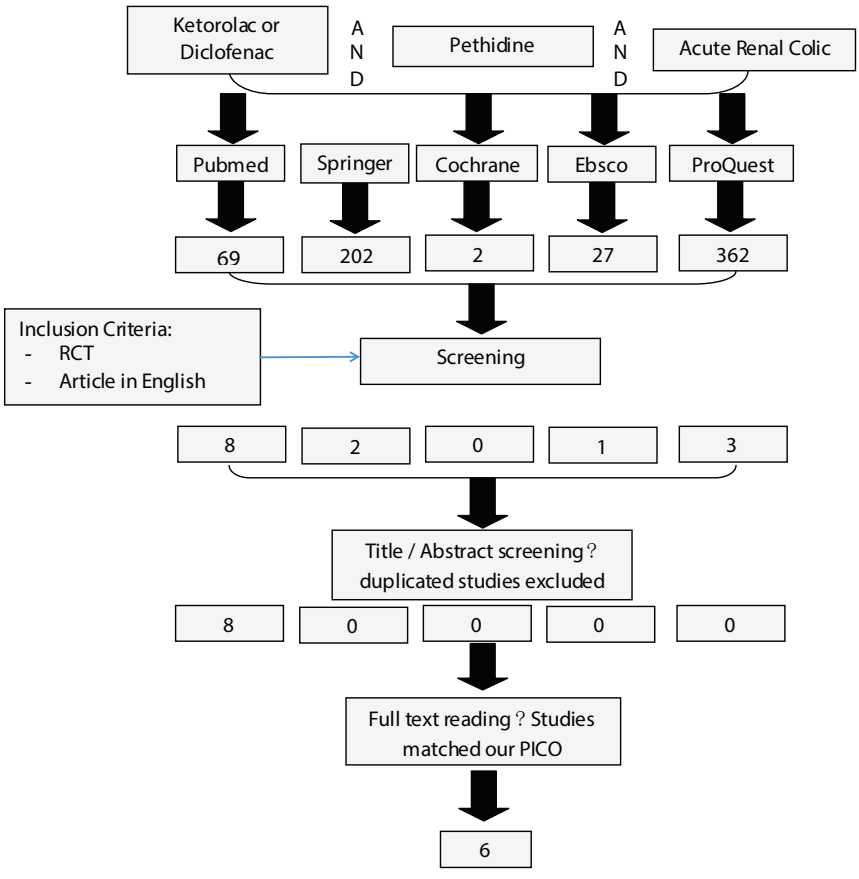



Diagram 1. Literature searching strategy

Table 2. Summary of search results

| CRITERIA | 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 (75 mg) | Diclofenac (75 mg) | Diclofenac (75 mg) | 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 [0.003;0.66] | 2.74 [0.72;10.43] |
| Level of evidence | 1B | 1B | 1B | 1B | 1B | 1B |

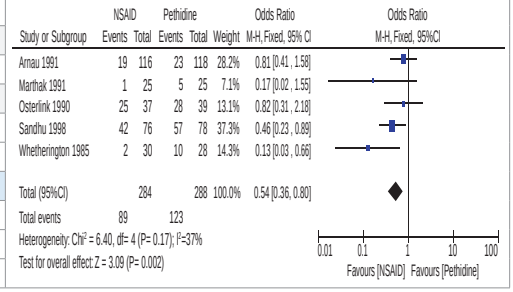
Table 3. Critical appraisal according to Oxford CEBM worksheet for therapy

| 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

Table 4. Comparison of NSAID and Pethidine

| | NSAID | | PETHIDINE | | | ODDS RATIO |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI |
| Arnau 1991 | 19 | 116 | 23 | 118 | 28.2% | 0.81 [0.41, 1.58] |
| Marthak 1991 | 1 | 25 | 5 | 25 | 7.1% | 0.17 [0.02, 1.55] |
| Osterlink 1990 | 25 | 37 | 28 | 39 | 13.1% | 0.82 [0.31, 2.18] |
| Sandhu 1998 | 42 | 76 | 57 | 78 | 37.3% | 0.46 [0.23, 0.89] |
| Whetherington 1985 | 2 | 30 | 10 | 28 | 14.3% | 0.13 [0.003, 0.66] |
| | | | | | | |
| **Total (95% CI)** | | **284** | | **288** | **100.0%** | **0.54 [0.36, 0.80]** |
| Total events | 89 | | 123 | | | |
| Heterogeneity: $Chi^2 = 6.40$, df = 4 (P = 0.17); $I^2 = 37\%$ | | | | | | |
| Test for overall effect: Z = 3.09 (P = 0.002) | | | | | | |




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 compared to pethidine (p<0.05) with OR 0.17 [95% CI 0.02;1.55] in study done by Marthak, *et al*, in 1991.[8] Hetherington, *et al*, also showed that diclofenac was superior to pethidine to achieve satisfactory relief of pain with OR 0.13 (0.03; 0.66).[9]

These three studies had moderate heterogenicity (P=0,06; $I^2$=64%) with only one study (Hetherington, *et al*) found significant difference (CI of the OR less than 1). Combined analysis of these studies showed a significant higher rate of complete pain relief in patient with diclofenac compared to 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*, compared 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 need of rescue medicine in the first one hour (60 minutes after recieving either ketorolac or diclofenac). This study showed a trend towards a higher rate of complete pain relief in patients treated with diclofenac, 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 are able to calculate and decided that all studies in both groups are homogenous (p = 0.17; $I^2$ = 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 = 0.48).

### Adverse Effects Consideration

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 ketorolac group is 21.76 compared with diclofenac group of only 3.24.[16]



**Table 5.** Comparison of ketorolac and pethidine

| | KETOROLAC | | PETHIDINE | | | ODDS RATIO |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI |
| Osterlink 1990 | 25 | 37 | 28 | 39 | 26.0% | 0.82 [0.31, 2.18] |
| Sandhu 1998 | 42 | 76 | 57 | 78 | 74.0% | 0.46 [0.23, 0.89] |
| | | | | | | |
| **Total (95% CI)** | | **113** | | **117** | **100.0%** | **0.55 [0.32, 0.96]** |
| Total events | 67 | | 85 | | | |
| Heterogeneity: Chi² = 0.94, df = 1 (P = 0.33); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.12 (P = 0.03) | | | | | | |

| ODDS RATIO |
|---|
| M-H, Fixed, 95% CI |

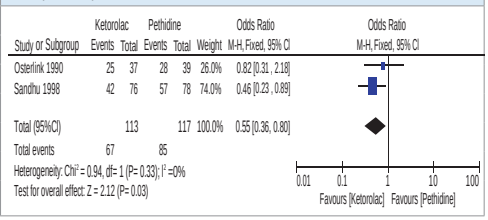



**Table 6.** Comparison of diclofenac and pethidine

| STUDY OR SUBGROUP | EXPERIMENTAL | | CONTROL | | | ODDS RATIO |
|---|---|---|---|---|---|---|
| | EVENTS | TOTAL | EVENTS | TOTAL | WEIGHT | M-H, FIXED, 95% CI |
| Arnau 1991 | 19 | 116 | 23 | 118 | 56.9% | 0.81 [0.41, 1.58] |
| Marthak 1991 | 1 | 25 | 5 | 25 | 14.3% | 0.17 [0.02, 1.55] |
| Whetherington 1985 | 2 | 30 | 10 | 28 | 28.8% | 0.13 [0.03, 0.66] |
| | | | | | | |
| **Total (95% CI)** | | **171** | | **171** | **100.0%** | **0.52 [0.29, 0.92]** |
| Total events | 22 | | 38 | | | |
| Heterogeneity: Chi² = 5.49, df = 2 (P = 0.06); I² = 64% | | | | | | |
| Test for overall effect: Z = 2.24 (P = 0.03) | | | | | | |

| ODDS RATIO |
|---|
| M-H, FIXED, 95% CI |

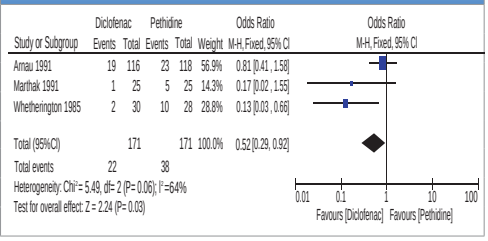



**Table 7.** Direct comparison of ketorolac and diclofenac

| STUDY OR SUBGROUP | EXPERIMENTAL | | CONTROL | | | ODDS RATIO |
|---|---|---|---|---|---|---|
| | EVENTS | TOTAL | EVENTS | TOTAL | WEIGHT | M-H, FIXED, 95% CI |
| Cohen 1998 | 8 | 27 | 4 | 30 | 100.0% | 2.74 [0.72, 10.43] |
| | | | | | | |
| **Total (95% CI)** | | **27** | | **30** | **100.0%** | **2.74 [0.72, 10.43]** |
| Total events | 8 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.47 (P = 0.14) | | | | | | |

| ODDS RATIO |
|---|
| M-H, FIXED, 95% CI |

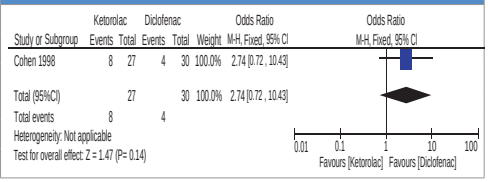
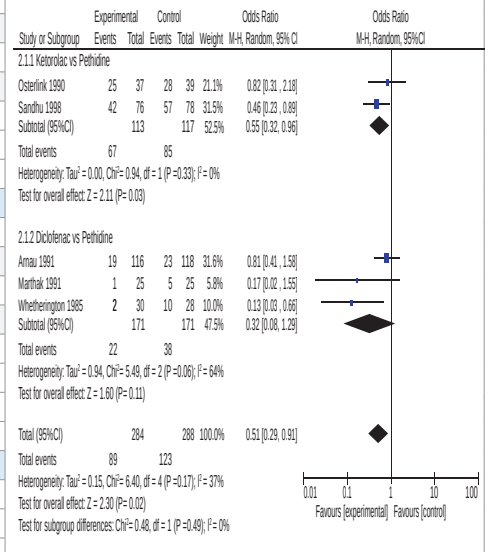



**Table 8.** Indirect comparison of ketorolac and diclofenac

| STUDY OR SUBGROUP | EXPERIMENTAL | | CONTROL | | | ODDS RATIO |
|---|---|---|---|---|---|---|
| | EVENTS | TOTAL | EVENTS | TOTAL | WEIGHT | M-H, FIXED, 95% CI |
| **2.1.1 Ketorolac vs Pethidine** | | | | | | |
| Osterlink 1990 | 25 | 37 | 28 | 39 | 21.1% | 0.82 [0.31, 2.18] |
| Sandhu 1998 | 42 | 76 | 57 | 78 | 31.5% | 0.46 [0.23, 0.89] |
| **Subtotal (95% CI)** | | **113** | | **117** | **52.5%** | **0.55 [0.32, 0.96]** |
| Total events | 67 | | 85 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.11 (P = 0.03) | | | | | | |
| | | | | | | |
| **2.1.2 Diclofenac vs Pethidine** | | | | | | |
| Arnau 1991 | 19 | 116 | 23 | 118 | 31.6% | 0.81 [0.41, 1.58] |
| Marthak 1991 | 1 | 25 | 5 | 25 | 5.8% | 0.17 [0.02, 1.55] |
| Whetherington 1985 | 2 | 30 | 10 | 28 | 10.0% | 0.13 [0.03, 0.66] |
| **Subtotal (95% CI)** | | **171** | | **171** | **47.5%** | **0.32 [0.08, 1.29]** |
| Total events | 22 | | 38 | | | |
| Heterogeneity: Tau² = 0.94; Chi² = 5.49, df = 2 (P = 0.06); I² = 64% | | | | | | |
| Test for overall effect: Z = 1.60 (P = 0.11) | | | | | | |
| | | | | | | |
| **Total (95% CI)** | | **284** | | **288** | **100.0%** | **0.51 [0.29, 0.91]** |
| Total events | 89 | | 123 | | | |
| Heterogeneity: Tau² = 0.15; Chi² = 6.40, df = 4 (P = 0.17); I² = 37% | | | | | | |
| Test for overall effect: Z = 2.30 (P = 0.02) | | | | | | |
| Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49); I² = 0% | | | | | | |

| ODDS RATIO |
|---|
| M-H, FIXED, 95% CI |



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 was 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 adjusted OR of 2.54 compared with diclofenac of only 0.86.[18]

## DISCUSSION AND ANALYSIS

### Pathophysiology of Colic Pain

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 natural effort to expel the stone. However, if the stone persist, 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 in prostaglandin synthesis. Distended renal capsule itself will stimulate pain sensation directly. This pain will then be relayed to central nerves system through renal nerves.[2,4,19]

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

### Therapeutic Strategy

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 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 own distinct

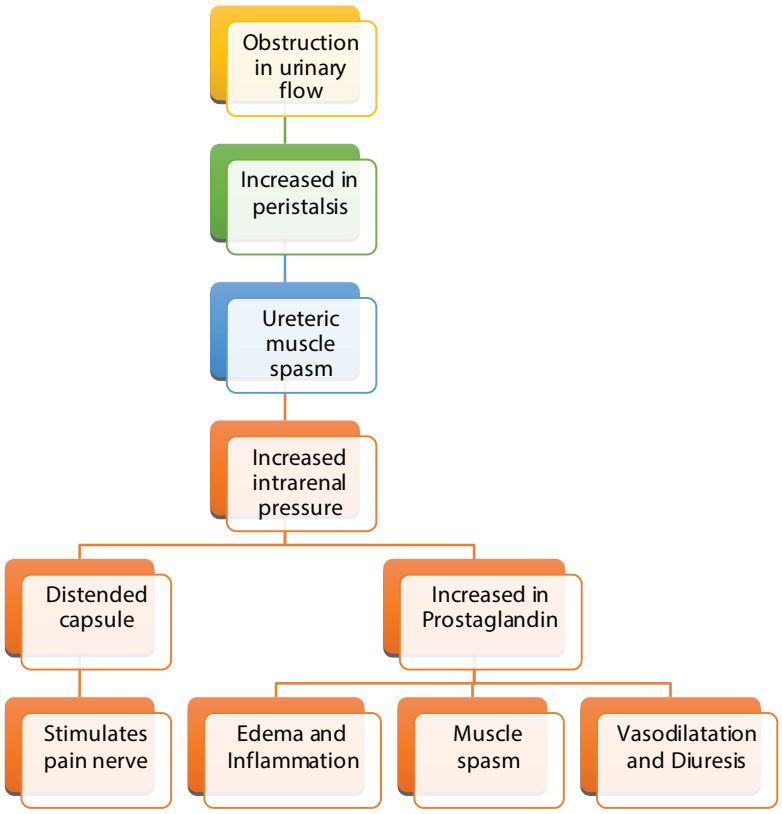
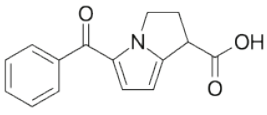
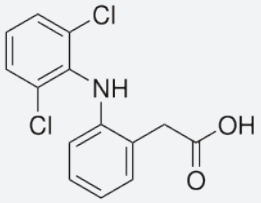
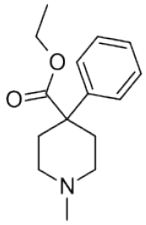



**Diagram 2.** Pathophysiology and target therapy of colic pain.[2,4,19]

**Table 9.** Pharmacokinetics and pharmacodynamics

| DRUGS | STRUCTURE | RECEPTORS | METABOLISM | HALFTIME (HOURS) | EXCRETION |
|---|---|---|---|---|---|
| Ketorolac |  | Cox-1<br>Cox-2 | Hepatic | 3.5 – 9 | Urine (>90%) |
| Diclofenac |  | Cox-1<br>Cox-2 | Hepatic | 1.5 – 2 | Biliary (40%)<br>Urine (60%) |
| Pethidine |  | M-opioid | Hepatic | 2.5 – 4 | Urine (>90%) |



pathways (as seen in diagram 2). The usage of 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 nerves system, thereby reducing pain sensation. However, there is no data 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 prostaglandins 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]

### Direct and Indirect Comparison

In our study, we found no significant difference between ketorolac and diclofenac. Direct comparison by Cohen et al reported comparable effectivity between both drugs.[10] Based on the other five studies, we performed an indirect analysis which gave similar results. Even though ketorolac was regarded as the most potent pain reliever among NSAIDs for various other pain condition, 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 effect (GI and kidney problems) might be explained with further particularizing on both drugs' pharmacokinetics and pharmacodynamics (Table 9). Problems in GI system are caused by the abundance of COX-1 receptor in GI mucosal lining. Therefore, 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 exist in 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 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 kidney (90%), compared with diclofenac that is excreted through liver and kidney (40% liver, 60% kidney). A complete review can be seen in table 9.[17,18]

## CONCLUSION

For patients with acute renal colic in 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 a comparable pain relief with diclofenac regarded as a safer option. Consideration left is 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

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