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Review Article:

# Is Nefopam Effective in Treating Acute Renal Colic? A narrative review

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**Abstract**

**Background**: Acute renal colic is a severe and sudden form of loin pain that usually radiates from the flank towards the groin. Acute renal colic is one of the common causes of emergency department admission worldwide. Nefopam has a unique analgesic effect, that differs pharmacologically from nonsteroidal anti-inflammatory drugs, opioids, or paracetamol and has a potential role in multimodal analgesia. Furthermore, studies have found that nefopam has opioid-sparing effects postoperatively following urological surgery, making it a suitable option for urologists and emergency physicians. **Aim**: This review aims to survey the literature regarding the efficacy of nefopam in treating acute renal colic. **Conclusion**: This review revealed that the efficacy of nefopam in treating acute renal colic has not been established in any clinical trial, nor has it been included in any international guidelines. Nonsteroidal anti-inflammatory drugs and intravenous paracetamol are first-line agents in the management of acute renal colic.



## 1. Introduction

### 1.1 History of nefopam

In the 1960s, a new drug was developed under the name of fenazocine, since it is a derivative of benzoxazocine [1]. The new drug was marketed as a centrally-acting muscle relaxant [2] with antispasmodic and antidepressant effects [3]. Then, in 1976, the name of fenazocine changed to nefopam, and the studies found it to have central analgesic rather than muscle relaxant effects (**Figure 1**) [2].

### 1.2 Pharmacological properties of nefopam

Nefopam is a racemate of dextronefopam and levonefopam [4]. Nefopam is structurally similar to diphenhydramine and orphenadrine and inherited some antimuscarinic properties [5]. Nefopam has a unique mechanism of action that differs from nonsteroidal anti-inflammatory drugs and opioids. It exhibits its analgesic effect by inhibiting the presynaptic reuptake of catecholaminergic (dopamine, and norepinephrine) and serotonergic neurons centrally [4]. It also acts on alpha2 - adrenergic receptors and alters the $Ca^{+2}$ and $Na^{+}$ channels of the glutamatergic pathway, thus decreasing the stimulation of N-methyl-D-aspartate (NMDA) receptor and decreasing the release of glutamate, and producing hyperalgesia [6]. Nefopam has a unique analgesic effect that is far away different pharmacologically from NSAIDs, opioids, or paracetamol. Therefore, it lacks anti-inflammatory, antiplatelet aggregation effects and does not cause respiratory depression [7].

Studies have found that nefopam has opioid-sparing effects postoperatively, and the dose of opioids can be reduced by one-third, in abdominal, cardiovascular, gynecological, maxillofacial, and orthopedic surgeries [8-16]. Sunshine and Laska (1975) and Tigerstedt et al., (1977) studies suggested that everyone milligram of nefopam is equivalent to 0.3 – 0.6 mg of morphine and 2.5 mg of meperidine, respectively [17, 18]. Kerr and Fletcher (2010)

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study found that one mg of nefopam is equivalent to 10 mg of aspirin [19]. Goucke et al., (1990) study also found that the intramuscularly administered dose of 20mg of nefopam is equivalent to 75mg of diclofenac [20].

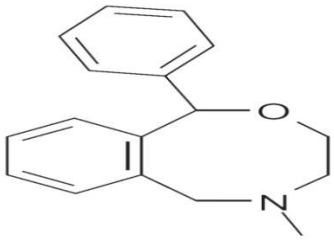

**Figure 1**. Nefopam structure [2]

### 1.3 Multimodal analgesia

Multimodal analgesia is the practice of using two or more analgesics of different pharmacological classes having distinct mechanisms of action to produce synergistic effect and/or lowering the doses of used agents or minimizing the incidence of side effects [21]. The use of multimodal analgesia is recommended by the World Health Organization, American College of Rheumatology, American Pain Society, and American Society of Anesthesiologists [21 – 24].

Paracetamol is usually combined with nefopam for the management of moderate postoperative pain due to their different mechanisms of action [25]. Studies found that a combination of paracetamol plus nefopam is more effective than paracetamol plus tramadol in the management of postoperative elective laparoscopic cholecystectomy [26], and decreases the required dose of morphine postoperatively in abdominal surgery [27], in which morphine dose is decreased by one-third during the first day after surgery [28]. Similarly, the combined administration of nefopam with fentanyl would induce superior analgesia and reduce the fentanyl dose postoperative renal transplantation [29]. On the other hand, studies have shown that nefopam had equal analgesic potency to ketamine and diclofenac [28, 30], and acts synergistically with ketoprofen in managing moderate to severe pain postoperatively [31].

### 1.4 Pharmacokinetic/pharmacodynamic properties of nefopam

Nefopam can be administered orally, intramuscularly (IM), and intravenously (IV). The oral dose is 30-90 mg thrice daily (max dose 200 mg/day). While the IM and IV dose is 20mg which can be repeated 4-6 daily (max dose 120 mg/day) [32]. Oral nefopam undergoes extensive hepatic metabolism via the cytochrome P450 system. In which the oral bioavailability is 40% and the half-life is 3-5 hours [33]. The majority (87%) of the dose of nefopam is eliminated renally, therefore, the dose of nefopam should be adjusted in patients with poor renal function or in those on dialysis [34]. In elderly patients (regardless the renal function), the dose of nefopam administered intravenously, should be given over 30 - 45 minutes to minimize the risk of infusion-related adverse effects [35].

### 1.5 Adverse effects and contraindications of nefopam

Despite its good tolerability, the most common side effects associated with nefopam are nausea and vomiting, and sweating which occurs in about 10 – 30% of the patients [21]. Nefopam is also associated with antimuscarinic side effects including dry mouth, dizziness, and cutaneous reactions. Infusion-related side effects (with rapid administration) are injection site pain, tachycardia, and convulsions. Rarely, nefopam can cause severe neurological side effects like confusion, disorientation, sedation, restlessness, delirium and hallucinations, and anaphylactic reactions [9, 25].

Revol et al., (2021) study suggested that the abuse and dependence of nefopam are similar to that of psychostimulant agents, in which between 2006 and 2017, more than 30 cases of nefopam dependence were recorded [36].

Nefopam overdosage and / or intoxication can cause tachycardia, convulsions, agitation, hallucinations, oliguria, dilated pupils, hyporeflexia and hyperreflexia. In this situation, and in the absence of a nefopam antidote, supportive treatment is recommended with the administration of activated charcoal within one hour of intoxication. To manage the above-mentioned symptoms, beta blockers and benzodiazepines are recommended [19].

Nefopam is contraindicated in patients with limited coronary reserve, convulsive disorders, glaucoma or benign prostatic hyperplasia, and those with end-stage kidney disease [36].

### 1.6 Indications of nefopam

Oral nefopam is indicated for relieving postoperative, dental, musculoskeletal, traumatic, and cancer pain of moderate intensity acutely and or chronically [37, 38]. Parenteral nefopam is indicated for acute postoperative pain [37 -39]. Schulz et al., (2022) survey results showed that French physicians commonly prescribe nefopam for managing acute and chronic pain [40].

Studies also found that perioperative nefopam is effective in reducing postoperative pain, the chance of developing chronic pain, and the dose of opioid analgesic if chronic pain was experienced [13]. Van Elstraete and Sitbon (2013) and Ostwal (2019) studies have shown that nefopam is also effective in the modulation of non-surgical neuropathic pain and in treating chronic neuropathic pain [25, 41]. The meta-analysis conducted by Lv et al. (2015) found that the randomized controlled trials studied showed nefopam to be associated with a reduction in the risk of perioperative shivering following anesthesia [42].

### 1.7 Acute renal colic

Acute renal colic is a severe and sudden form of loin pain that usually radiates from the flank towards the groin [43]. The lifetime incidence of acute renal colic varies considerably between different countries from 2 - 20%, with the highest incidence in the Middle East area [44, 45]. The majority of cases of acute renal colic are caused by partial or complete occlusion of the urinary flow by renal calculus. This occlusion increases the pressure on the walls of the urinary tract and the renal pelvis. The increased pressure would stimulate the local synthesis of prostaglandin E2 (PGE2) and prostacyclin I2 with subsequent preglomerular

vasodilation and increases renal blood flow and diuresis. However, this would lead to a further increase in ureteral pressure. PGE2 has a direct effect on the ureter smooth muscles and causes a spasm of these muscles [46, 47]. Acute renal colic can also result from ureteral occlusions by nonrenal lesions, e.g., cancers (of the prostate, pelvis, or cervix), intestinal, gynecological, retroperitoneal, and vascular lesions [48].

The pain of acute renal colic is a complex interplay of different causes, including spasm of ureteral muscle, increased tone of proximal peristalsis due to activation of intrinsic ureteral pacemakers, localized inflammatory changes induced by the stone, renal swelling accompanied with capsular stretching, edema, and irritation. These processes stimulate submucosal stretch receptors in the ureter, renal pelvis, and capsule, which are the primary cause of pain [49]. The intensity and the severity of the pain are correlated with the level and the site of occlusion of the tracts, rather than the size of the calculi [50, 51]. In more than 50% of the cases, the onset of acute renal colic is associated with nausea and vomiting. This can be explained by the shared innervation pathway of the renal and the gastrointestinal tracts through afferents of the vagus nerve and celiac axis. These symptoms can be more aggravated by the administration of relieving agents that already have gastrointestinal side effects like opioids and NSAIDs [52].

### 1.8 Management of acute renal colic

Acute renal colic is one of the common causes of emergency department admission worldwide due to the associated excruciating pain [53]. Although the majority of patients can be treated as outpatients by general practitioners or senior resident physicians, about one-third of patients with acute renal colic would require hospital admission and treatment by specialists [54].

The management of acute renal colic has changed during the last 30 years in which scopolamine is rarely used in the management of acute pain nowadays. Schriger (2014) study found that the choice of an analgesic agent is based on the patient's and physician's preferences, the safety profile, efficacy, cost, and insurance coverage [55].

According to the National Institute for Health and Care Excellence (NICE) (in 2015) and the European Association of Urology (EAU) (in 2018), guidelines recommended NSAIDs and paracetamol as first-line treatment of acute renal colic and opioids as second-line agents [56, 57]. The NICE guideline also recommended the use of parenteral ondansetron or metoclopramide to manage renal colic-associated nausea and vomiting. Many studies and systematic reviews have found that NSAIDs are superior or at least not inferior to paracetamol, nefopam, and opioids since NSAIDs have the advantages of better compliance due to their long duration of action with high analgesic effect (pain relief) even when used as monotherapy and fewer side effects in comparison with other agents [56 - 60]. NSAIDs' mechanism of action involves the inhibition of prostaglandin synthesis, thus decreasing ureteral spasm [61]. They are contraindicated in patients with chronic kidney disease, peptic and duodenal ulcers, chronic obstructive airway disease, and asthma [56].

In contrast, the American Urological Association (AUA) guideline recommended the use of opioids as a first line in the management of acute renal colic [62]. In comparison with NSAIDs, opioids tend to be less expensive, have dose titratability, higher potency, and physicians' familiarity. However, they are associated with nausea, vomiting, liability for abuse, and psychological dependence [63].

Intravenous paracetamol is a commonly used analgesic in emergency departments due to its efficacy, safety, and cost [64]. It is recommended for the management of acute renal colic in NICE, EAU, and AUA guidelines when first-line agents are contraindicated [56, 57, 62]. Furthermore, the role of IV paracetamol in renal colic is more evident in pregnant women, renal failure, and patients with peptic ulcers [65, 66]. The analgesic effect of IV paracetamol is thought to be mediated through the inhibition of the synthesis of prostaglandin via blocking the oxidation of cyclooxygenase enzyme in the central nervous system [67].

Paracetamol is the most commonly used analgesic around the world due to its good tolerability, safety profile, cost, and availability as an over-the-counter analgesic. However, in high doses, (7.5 grams in single administration) it causes liver toxicity [67].

In acute renal colic management, studies have shown that IV paracetamol is equal to or superior to opioids [68 – 71]. Furthermore, some studies found that it produces a comparable level of analgesia to NSAIDs in patients with renal colic, but IV paracetamol requires more rescue analgesia than NSAIDs [72 – 74].

### 1.9 Nefopam in the management of acute renal colic

In some cases of acute renal colic, when the first-line agents are contraindicated, not included in the institution formulary, or when a combination of analgesics is required, an analgesic with a different mechanism of action can be used and/or added. Since nefopam was found to have postoperative morphine-sparing effects following urological surgery, it is thought to be a suitable option for urologists and emergency physicians [75]. The analgesic effect of nefopam after shock wave lithotripsy and ureteroscopic litholapaxy has been confirmed in many studies [76 - 78].

In France, intramuscular nefopam is indicated in patients with acute renal colic admitted to emergency departments [79]. Evans et al., (2008) study was one of the very few meta-analyses that suggested that nefopam has a comparable effect to NSAIDs in treating acute renal colic but is associated with tachycardia and sweating [28].

The analgesic effect of nefopam in acute renal colic was only studied in one randomized clinical trial conducted by Moustafa et al., (2013) [80]. In which 30 patients who were admitted to the emergency department of the University Hospital in Clermont-Ferrand, France, between 2008 and 2009, with acute renal colic, and were randomized into two equal groups and given nefopam and placebo respectively. The pain of admitted patients was assessed at their admission via a visual analog scale and 10 minutes after the administration of 100 mg of IV ketoprofen, those patients who did not respond to IV ketoprofen were allocated randomly to receive either IV nefopam or placebo and the pain reassessed after 10 minutes at the end of the infusion. The results of the above-mentioned study showed that there was no statistically significant difference between nefopam and placebo in pain reduction scores. In which nefopam reduced pain from 60 mm to 37.3 mm, while, placebo reduced pain from 58.33 mm to 31.67 mm. Furthermore, two-thirds of nefopam-administered patients and about half of placebo-administered patients required morphine to

control their pain. The limitation of this trial is that it was conducted on a small number of patients and therefore the statistical power of the study was questionable.

## 2. Conclusions

The distinct mechanism of action of nefopam, along with its favourable safety and efficacy profile, as well as its opioid-sparing effect, indicates that nefopam may have a potential role in ambulatory units and postoperative settings. However, despite its potential use in multimodal analgesia, there is currently no clinical trial evidence to establish the efficacy of nefopam in treating acute renal colic. Furthermore, it has not been included in any international guidelines. Nonsteroidal anti-inflammatory drugs and intravenous paracetamol are the recommended first-line agents for managing acute renal colic.

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**هل عقار النيفوبام فعال في علاج المغص الكلوي الحاد؟ مقال مراجعة**

**الخلاصة:**

**المقدمة:** المغص الكلوي الحاد هو شكل حاد ومفاجئ من ألم الخاصرة والذي ينتشر عادة من الخاصرة نحو الفخذ. المغص الكلوي الحاد هو أحد الأسباب الشائعة لدخول قسم الطوارئ في جميع أنحاء العالم. النيفوبام له تأثير مسكن فريد يختلف دوائيًا عن العقاقير غير الستيرويدية المضادة للالتهابات أو المواد الأفيونية أو الباراسيتامول وله دور محتمل في التسكين متعدد الوسائط. علاوة على ذلك ، فقد وجدت الدراسات أن النيفوبام له آثار تعويض المواد الأفيونية بعد الجراحة البولية ، ويعتقد أنه خيار مناسب لأطباء المسالك البولية وأطباء الطوارئ. **الهدف**: ان الهدف من هذا المقال هو مراجعة الدراسات المتعلقة بفاعلية النيفوبام في علاج المغص الكلوي الحاد. **الاستنتاج:** كشفت هذه المراجعة أن فعالية النيفوبام في علاج المغص الكلوي الحاد لم تثبت في أي تجربة سريرية ، ولم يتم تضمينها في أي من البروتوكولات الدولية لعلاج المغص الكلوي الحاد. وان العقاقير غير الستيرويدية المضادة للالتهابات والباراسيتامول الوريدي هي ادوية الخط الأول في علاج المغص الكلوي الحاد.