



## **Comparison of the Efficacy of Intravenous Ketorolac to that of Intravenous Pethidine in Pain Suppression in Patients with Biliary Colic**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author AMH designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OB and MDS managed the analyses of the study. Author MDS managed the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aim:** The study aimed to compare the effect of intravenous administration of the NSAID (Non-steroidal anti-inflammatory drugs) ketorolac to that of intravenous administration of the opioid pethidine in the suppression of pain in patients with biliary colic.

**Methodology:** The present study is a trial study. Among all the biliary colic patients in Mashhad Referral Hospital Emergency in Iran, 58 patients with inclusion criteria were selected using

convenience sampling. They were randomly divided into two groups of 29 patients. In the first group, 1 mg/kg IV pethidine, and in the second group, 30 mg IV ketorolac was injected. The pain severity was assessed prior to the treatment and 15, 30, and 60 minutes after the onset of the treatment using the Visual Analogue Scale (VAS). The data were analyzed using SPSS 20 and Chi-square tests.

**Findings:** The patients' mean age was  $45 \pm 15$  years old (age ranged from 30 to 60 years old). The results showed no significant relationship between pain suppression and medicine type after 15 minutes ( $P=0.5$ ), 30 minutes ( $P=0.6$ ), and 1 hour ( $P=0.7$ ). It means that pethidine and ketorolac have an equal effect on pain suppression in patients with biliary colic. Also, the more time passes from the injection, the more the medicines suppress pain.

**Conclusion:** the results of this study show that the efficacy of NSAIDs in the suppression of moderate to severe pain; therefore, a plan to use NSAIDs instead of narcotics for this purpose is essential.

*Keywords: Biliary colic; pethidine; ketorolac; pain.*

## 1. INTRODUCTION

Pain is one of the most common problems in the ERs, which interferes with the complete examination and lack of patients' cooperation in proper diagnosis and treatment. Many ERs around the world are facing patients that disrupt the mental environment due to severe pain. Biliary colic also causes severe and sometimes therapeutic resistant pain, requiring multiple narcotic injections [1]. Bile has cholesterol and other ingredients. When the cholesterol concentration increases or the concentration of other ingredients decreases in the bile, cholesterol turns into solid crystals and creates a gallstone's core, which gradually grows and turns into big stones. However, most gallstones are small (the size of a millet), which causes even more problems. Many people get gallstones, and they experience signs and symptoms, which are mistakenly thought to be gastrointestinal problems. Therefore, they do not treat it properly and start getting the wrong medications and treatments. As the patients are unaware of this problem or think that they do not need any surgical treatment, one of the gallstones may get stuck in the gallbladder entry during contractions, leading to more contractions and severe pain. This pain is felt in the upper right quarter of the abdomen above the belly button and sometimes in the back and right shoulder. Severe pain may be accompanied by nausea and vomiting. When the gallbladder contractions stop, the gallstone may fall into the gallbladder, and the pain completely disappears. The attacks are called biliary colic, and they usually take 20 minutes to 1 hour [2].

Morphine and other narcotic agents are the most effective painkillers to relieve pain [3]. However,

due to many side effects of the narcotics such as physical dependence and drug abuse, respiratory center inhibition [4], high cost, and legal problems, it is always preferred to use substitute agents. One of the substitute agents for narcotics are non-steroid anti-inflammatory drugs (NSAIDs). NSAIDs have direct analgesic, anti-inflammatory, and anti-edema effects and indirectly reduce the release of pain factors and chemical intermediates that make analgesic impulses [4,5].

Due to the extended side effects of the narcotics, it is always considered to use NSAIDs instead. The most commonly used painkillers are NSAIDs since they have anti-inflammatory and analgesic effects. This study aims to compare the effect of intravenous pethidine (widely used to control pain) and ketorolac (analgesic and anti-inflammatory medication) in pain suppression of patients with biliary colic.

## 2. METHODOLOGY

### 2.1 Study Design

The present study's goal was to compare the effect of intravenous pethidine and ketorolac in pain suppression of the patients with biliary colic. This is a randomized, parallel, double-blind (patients and assessors), and clinical trial.

### 2.2 Patient Selection Process

This study's statistical population included 58 biliary colic patients in Mashhad Referral Hospital Emergency. They were selected after gaining their or their first-degree relative agreement. Exclusion criteria were a history of addiction or allergy to pethidine or ketorolac, younger than 30

or older than 60 years old. Then the sample was randomly divided into two groups of 29 patients matched in terms of gender. These groups were named group K and group M.

### 2.3 Procedures and Endpoints

First, the advantages and side effects of the two methods were explained to the patients, and if the patients agreed to participate in the study, they were asked to sign an agreement paper. The primary data gathered from the patients included the name, gender, and age. First, the patients were divided into two groups using a random number table. Then, the researcher gave pethidine to one group and ketorolac to the other group. Before this step, a second researcher who did not know in which group the patients are asked the patients (who also did not know which group they are) to determine their pain severity using VAS. Then, 1 mg/kg IV pethidine was given to the pethidine group, and 30 mg IV ketorolac was given to the ketorolac group. Again, the patients' pain severity was assessed 15 minutes, 30 minutes, and 1 hour after the second researcher's medication use using VAS. The amount of pain reduction was recorded, and the results are explained in the next section. In the case of an allergic reaction or VS instability in any of the patients, the research was stopped immediately.

### 2.4 Types of Analysis

The collected data were then entered into SPSS 20 and described using descriptive statistics such as frequency shown in tables and charts. A chi-square test was used for data analysis. The significance level in this study was considered to be 5%.

## 3. RESULTS

Fifty-eight biliary colic patients in Mashhad Referral Hospital Emergency, IRAN, with ages ranged from 30 to 60 were assessed in this study. Nineteen patients (32.8%) were male, and 39 patients (67.2%) were female. Most of the patients were 50 to 60 years old (46.6%), and the least ages ranged from 30 to 40 (19.0%).

Nineteen patients in the pethidine group were female (65.5%), and ten patients in this group were male (34.5%). Twenty patients in the ketorolac group were female (69.0%), and nine were male (31.0%). The statistical analysis results showed no significant difference between

the gender of the patients and the drug type they get ( $P=0.5$ ).

In the pethidine group, six patients (20.7%) were 30 to 40 years old, nine patients (31.0%) were 40 to 50 years old, and 14 patients (48.3%) were 50 to 60 years old. In the ketorolac group, five patients (17.2%) were 30 to 40 years old, 11 patients (37.9%) were 40 to 50 years old, and 13 patients (44.8%) were 50 to 60 years old. There was no significant difference between the patients' age and the drug type they get ( $P=0.5$ ).

The amount of pain reduction for each patient in each group of the study was calculated and compared. It was assessed before administering the medication and after 15 minutes, 30 minutes, and 1 hour after administering the medication.

The pain severity before medication use was assessed using VAS, and the results showed that 26 patients (89.7%) in the pethidine group had severe pain, and three patients (10.3%) had moderate pain. In the ketorolac group, 25 patients (86.2%) had severe pain, and four patients (13.8%) had moderate pain. The statistical analysis results showed no significant difference between the patients' medication type and pain severity before the medication use ( $P=0.5$ ).

After 15 minutes of medication use, two patients (6.9%) in the pethidine group had severe pain, 23 patients (79.3%) had moderate pain, and four patients (13.8%) had mild pain. After 15 minutes of ketorolac administration, four patients (13.8%) had severe pain, 23 patients (79.3%) had moderate pain, and two patients (6.9%) had mild pain. The statistical analysis results showed no significant difference between the patients' medication type and pain severity after 15 minutes of the medication administration ( $P=0.5$ ).

After 30 minutes of medication administration, three patients (10.3%) in the pethidine group had moderate pain, and 26 patients (89.7%) had mild pain. Four patients (13.8%) had moderate pain in the ketorolac group, and 25 patients (86.2%) had mild pain. The statistical analysis results showed no significant difference between the patients' medication type and pain severity after 30 minutes of the medication administration ( $P=0.6$ ).

After 1 hour of medication administration, one patient (3.4%) in the pethidine group had moderate pain, and 28 patients (96.6%) had mild pain. One patient (3.4%) had moderate pain in

the ketorolac group, and 28 patients (96.6%) had mild pain. The statistical analysis results showed no significant difference between the patients' medication type and pain severity after 1 hour of the medication administration ( $P=0.7$ ). These findings indicated that pethidine and ketorolac decrease pain equally in patients with biliary colic. Also, the more time passes from the administration of both of these drugs, the more the decrease in pain (Table 1).

#### 4. DISCUSSION

Gallstones are among the most common disorders of the digestive system that affect 10% of individuals [6,7]. More than 80% of the patients with gallstones have no sign and symptom, and 1-3% have symptomatic manifestations such as acute cholecystitis [8]. The clinical signs and symptoms of acute cholecystitis in patients with localized peritonitis are diagnosed in the right upper quarter of the abdomen [9]. Cystic duct obstruction due to stone leads to gallbladder dilation, inflammation, and wall edema [10]. Acute cholecystitis begins with a biliary colic attack, and its pain continues for several days. Patients with acute cholecystitis in the ERs need IV fluids, antibiotics, and analgesics. Their specific treatment is cholecystectomy. Different analgesics, such as narcotics and NSAIDs, decrease acute cholecystitis pain [3].

The goal of this study is to compare the effect of intravenous pethidine and ketorolac in pain suppression of patients with biliary colic. The results showed that the pain severity decreased significantly after 15, 30, and 60 minutes of the medication administration in both groups. According to the studies, morphine increases the Oddi sphincter pressure; therefore, it is contraindicated in patients with biliary colic [11]. Also, the potential problem of using narcotics in patients with biliary colic or cholecystitis is their interference with a HIDA scan (hepatobiliary iminodiacetic acid), which is a certain method in cholecystitis diagnosis [12]. NSAIDs do not lead into Oddi sphincter contraction and also do not interfere with HIDA scan. These medications inhibit prostaglandins, which prevent acute inflammation of the gallbladder and the related contraction disorders in the primary stages of acute cholecystitis [13]. One NSAID, which is proven to decrease biliary colic pain, is ketorolac [14].

In a study, the effect of 100 mg IM pethidine was compared to 30 mg IM ketorolac in pain

suppression. The results showed their equal consequence, and their IM effect was surprisingly similar to ketorolac's oral administration [15]. In another study performed by Berty et al., it was proved that the use of NSAIDs leads to better pain relief, fewer side effects, and less need for narcotics to control post-surgical pain [16]. This finding is in line with our findings regarding the equal effect of pethidine and ketorolac in pain suppression of the patients.

The results of the study performed by Victor showed that the pain suppression after the administration of pethidine and ketorolac is significant; however, the ability to get back to the routines are better in ketorolac users [17]. Some studies show that ketorolac's pain suppression is more than pethidine, and the side effects of pethidine and the need for life-saving treatment is more than the ketorolac [18]. In another study, pethidine's effect was compared to the Diclofenac suppository in the hernia post-surgical pain suppression in Iran. The results showed no significant difference in the first 24 hours after the surgery (the mean and standard deviation of the pethidine group and Diclofenac group's pain score were  $3.1\pm 0.9$  and  $2.4\pm 0.9$ , respectively) [19]. Holdgate et al. showed that NSAIDs control pain better than morphine, and their side effects and the need for life-saving treatment after their administration is also less [20]. Goman et al. performed a study on the pain control of morphine and ketorolac, and the results showed no significant difference between their effect; however, their simultaneous use decreased the need for life-saving treatment. The side effects of morphine, a combination of morphine and ketorolac, and ketorolac were less, respectively [21]. Turrialba also showed no significance between ketorolac and Tramadol; however, ketorolac's effect after 15 minutes of its administration was significantly higher than Tramadol [22]. Safdar's study also showed better pain control of the combination of ketorolac and morphine or ketorolac than morphine. However, the superiority of the combined medications to ketorolac was not proved [23].

The main advantage of ketorolac to narcotics is its analgesic effects without CNS suppression. Easy administration and quick and prolonged effects made ketorolac an appropriate pain relief option in ERs [24]. Pain control occurs before the brain sensory cortex perceives the pain via different afferent pathways. For instance, the interpretation and modification of painful waves

**Table 1. The statistical analysis results**

Drug type	Pain reduction	Pethidine frequency (percent)	Ketorolac frequency (percent)	Significance level (P-Value)
After 15 minutes	Severe pain	(6.9) 2	(13.8) 4	0.5
	Moderate pain	(79.3) 23	(79.3) 23	
	Mild pain	(13.8) 4	(6.9) 2	
After 30 minutes	Moderate pain	(10.3) 3	(13.8) 4	0.6
	Mild pain	(89.7) 26	(86.2) 25	
After 1 hour	Moderate pain	(3.4) 1	(3.4) 1	0.7
	Mild pain	(96.6) 28	(96.6) 28	

may occur in the membrane of the pain receptors or at any point in the efferent inhibitory descending pathways branching in the brainstem surface [25]. The peripheral sensory modification of pain prevents endogenous mediators' release due to inflammation next to the pain receptors, especially those exposed to injury and inflammation [25]. NSAIDs such as Ibuprofen and Diclofenac Sodium prevent Arachidonic acid's conversion into prostaglandin due to Cyclooxygenase enzyme inhibition [25]. Prostaglandins are the most important pain-producing materials. NSAIDs decrease the production of prostaglandins; therefore, they reduce the feeling of pain in peripheral areas. In other words, these medications destroy pain-producing factors.

On the other hand, narcotics do not omit the pain-producing factors, and the patient still ambiguously feels the pain. NSAIDs do not have any adverse effect on the brain and do not cause drowsiness. Therefore, patients do not need complete bed rest and have a quicker recovery period with fewer post-surgical complications [25].

One of the limitations of this study is the lack of cooperation of some of the patients. The results also cannot be generalized as the study was performed only in one health center.

## 5. CONCLUSIONS

This study shows that NSAIDs' effect in the efficient suppression of moderate to severe pain; therefore, planning to use these medications instead of narcotics seems to be essential.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

The Mashhad Ethical committee approved this study by code IR.MUMS.fm.REC.1395.117.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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