ARTICLE

COMPARISON OF KETOROLAC, APOTEL AND THEIR COMBINATIONS FOR PAIN CONTROL IN ACUTE CHOLECYSTITIS

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ABSTRACT

Background: *Pain is a common problem between patients and delays returning to daily life. So the aim of this study is to compare ketorolac, apotel and their combination in management of acute cholecystitis pain.* ***Methods:*** *In this clinical trial study, 90 patients with acute cholecystitis candidate for cholecystectomy surgery selected for study based on inclusion and exclusion criteria and were randomly divided into three equal groups. The first group received ketorolac 30 mg, while the second group received apotel 2 gr, and the third group received a combination of both medications. Patients' pain was evaluated with visual analog scale in 5 steps.* ***Results:*** *The results of this study showed that simultaneous administration of ketorolac 30 mg and apotel 2 gr is more analgesic than any of them alone.* ***Conclusions:*** *Ketorolac and paracetamol are two analgesics used commonly in clinic. The present study demonstrated that simultaneous administration of these medications in a same time will significantly manage the pre-operative pain of cholecystitis.*

KEY WORDS
Cholecystitis, Ketorolac, Pain, Paracetamol

INTRODUCTION

Gallstones are common problem of the digestive system that afflict 10% of the people in the world. As many as 80% of the people with gallstones show no signs. One to three present of the patients with marked gallstones with its symptoms such as acute Cholecystitis [1]. Acute Cholecystitis is diagnosed based upon clinical symptoms and signs in patients with peritonitis localized in the upper, right-hand quadrant of the abdomen. Obstruction of the Cystic duct as a result of stone will cause in distension of the gallbladder, inflammation and edema of gallbladder wall [1, 2, 3]. Acute Cholecystitis begins with a biliary colic attack, but the pain doesn't subside and it may last for several days. Patients referred to hospital with acute cholecystitis require reception of intravenous liquids, anti-biotic and analgesia and the final treatment for them is Cholecystectomy. To prevent the pain caused by the acute inflammation of gallbladder, analgesics are used such as non-steroid narcotics and anti-inflammatories. As various many studies indicate, morphine results in high sphincter Oddi pressure, thus it should never be prescribed in patients with Biliary colic [1, 4, 5]. The potential problem of using narcotics in patients suffering fromwith Biliary colic or Cholecystitis is its interference with HIDA scan which is the definitive method used to diagnose acute Cholecystitis [2]. Non-steroid anti-inflammatory medicines don't result in contraction of Oddi sphincter and show no interference with HIDA scan. By harnessing Prostaglandins, non-steroid anti-inflammatories prevent the progress of acute gallbladder inflammation and the resulting contraction complications in the initial phases of acute cholecystitis. One of these non-steroid, anti-inflammatory medicines that its effect on reducing the biliary colic pain has been approved is Ketorolac. The main advantage of using Ketorolac is its analgesic effect without reducing the performance of the central nervous system which is typical of narcotics. Ease of prescription, immediate commencement of the effect and its durability make Ketorolac a good choice to reduce pain in the emergency ward of a hospital [3, 5, 6]. Apotel (acetaminophen) also reduces production of prostaglandins. The analgesic properties of apotel can be justified by harnessing nitric oxide synthase enzyme and the analgesic mechanism which depends on supra-spinal serotonin [4, 5, 7, 8]. Finally, the present research aims to compare the effect of ketorolac and apotel and their mixture on controlling acute pre-operation cholecystitis pain.

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MATERIALS AND METHODS

For this double-blind, randomized clinical trial. All patients referring to Vali Asr and Amir Al-Momenin hospitals of Arak, Iran with the possible symptoms of acute cholecystitis (fever, pain in the upper, right-hand quadrant of the abdomen, leukocytosis, etc.) who had undergone sonography, were selected for the research based on the exclusion and inclusion criteria after taking their written informed consent. All patients underwent standard, anti-biotic (Ceftriaxone and Metronidazole) and hydration treatment. The pain scale of the patients was measured using VAS criteria which is essentially a 10 cm ruler expanding from 0 to 10. In this ruler, zero indicates no pain, while 10 indicates intolerable pain. The patients were asked to mark their pain on this ruler and the distance between the mark made by the patient and point zero shows patient's pain. Then patients were divided into 3 groups based on the block model. The patients in first group who had received 30 mg ketorolac solved in 100 cc normal saline for 30 minutes. Patients in the second group received 2 mg apotel solved in 100 cc normal saline for 30 minutes (mixed group) received 30 mg ketorolac and apotel 2 g solved in 100 cc normal saline. The pain scale of the patients was measured 0.5, 1, 2, and 6 hours before operation based upon visual analog scale (VAS). To measure the inflammation factor in 0 and 6 time, LFT was also measured. To observe the rule of double-blindness, the medicines were given by an assistant and the pain level was measured by plan executor who had no information concerning the groups. Those patients who had VAS level of 10 one hour after

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prescription of medicine or placebo were excluded and underwent routine treatment using Pethidine. Then, necessary tests were used to analyze the tests in SPSS software version 20. The medicines used were produced by Exir Iran Co. (ketorolac) and Uni Farma Co. (Apotel). The data was entered in SPSS, and Chi square and one-sided variance analysis tests were utilized to compare the data of each group. The P-value level below 0.05 was considered to be significant. The sample size was calculated using the following formula. Considering the type of research, randomized clinical trial method was used for sampling. The patients with acute cholecystitis were selected and divided into three groups using the following formula:

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)}$$

Inclusion criteria: patients diagnosed with acute cholecystitis, aging 18 to -65- years -old.
Exclusion criteria: patient's declined to take participate in the research, aging younger than 18 and older than 65 years old

- Pregnancy or breast feeding, clinical symptoms indicating sepsis or other inflammatory diseases
- Lack of cooperation on the side of patient to determine level of pain, no toleration of pain, sensitivity to non-steroid anti-inflammatories and acetaminophen, renal or liver failure, history of digestive system bleeding
- Coagulation disorders, symptoms indicating neuropathy, patients with gangrenous cholecystitis
- Patients diagnosed with generalized Peritonitis

RESULTS

As many as 90 patients with acute cholecystitis were studied in this clinical trial. There were 15 male and 15 female patients in ketorolac group 14 female and 16 male in apotel group and 13 female and 17 male in the group that received both the apotel and ketorolac. The chi square test showed no significant difference between the three groups in terms of gender (P = 0.875). The following average ages were observed: 38.23 ± 8.13 years in ketorolac group, 34 ± 5.98 years in apotel group and 36.06 ± 7.73 in the mixed group. One way ANOVA results showed no statistically significant difference between the three groups in terms of their age (P = 0.089). Patients' pain levels were measured 0.5, 1, 2, and 6 hours immediately following diagnosis and before the operation based on VAS. The following values for VAS before receiving medicines in each group: 7.33 ± 1.15 in ketorolac group, 7.1 ± 66.26 in apotel group, and 7.43 ± 1.07 in the mixed group. One way ANOVA results found no statistically significant difference between groups in terms of pain levels before receiving the medicines (P = 0.528). The average pain score 30 minutes after receiving the medicine in groups receiving ketorolac, apotel, and both medicines was 2.76±0.43, 3±0.83, and 2.73±0.44 respectively. One way ANOVA results found no statistically significant difference between groups in terms of pain levels 30 minutes after receiving the medicines (P = 0.177). The average pain score 1 hour after receiving the medicine in groups receiving ketorolac, apotel, and both medicines was 3.23±0.62, 3.0±13.34, and 2.96±0.41 respectively. One way ANOVA results found no statistically significant difference between groups in terms of pain levels 1 hour after receiving the medicines (P = 0.097). The average pain score 2 hours after receiving the medicine in groups receiving ketorolac, apotel, and both medicines was 4.83±0.59, 4.0±46.62, and 4.33±0.99 respectively. One way ANOVA results found a statistically significant difference between groups in terms of pain levels 2 hours after receiving the medicines (P = 0.035). The average pain score 6 hours after receiving the medicine in groups receiving ketorolac, apotel, and both medicines was 6.83±0.87, 6.6±1.13, and 5.4±0.89 respectively. One way ANOVA results found a statistically significant difference between groups in terms of pain levels 6 hours after receiving the medicines (P = 0.0001) [Fig. 1]. Liver enzymes of the patients were measured at the beginning and 6 hours after receiving the medicine and no significant difference was observed in their levels (P = 0.45).

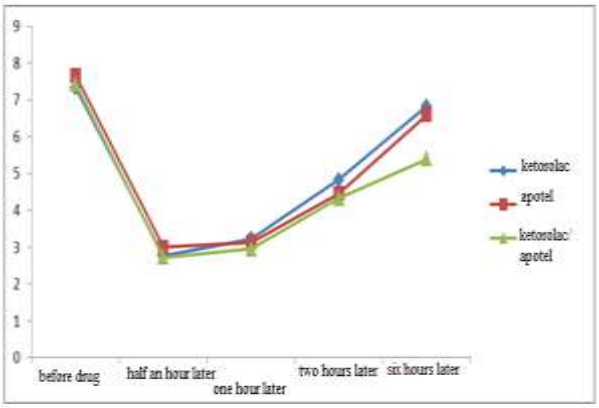

Fig. 1: Average pain scores before and after receiving the drug.

DISCUSSION

As the results of the present research, the simultaneous prescription of ketorolac (30 mg) and apotel (2 g) has a much stronger analgesic effect than prescribe them individually for cholecystitis pain. Pethidine is regularly used now to reduce the pain in patients with acute cholecystitis. Considering the current sanctions and shortage of this medicine observed in hospitals, it is necessary to find alternative medicines for these patients. According to the results of this research, a mixture of ketorolac and Paracetamol can be a good choice to reduce the pain in patients with acute cholecystitis. In a review research conducted by Hilsted et al., it was shown that mixing Paracetamol and non-steroid anti-inflammatory medicines was very useful to reduce acute pains. As many as eight clinical trials on this issue have been published over the recent years [9,10]. Four of these researches have confirmed that mixing one NSAID with paracetamol has a much better analgesic influence in compare of using the, individually. In their researches, Romanstad et al. added that Propacetamol to ketorolac and measured their analgesic effects by tolerating painful pressure [11]. It showed that 30 mg ketorolac resulted in high levels of pain toleration which were not more than the basic levels of pain toleration. However, addition of two gr Propacetamol (equal to 1 gr apotel) to 30 mg ketorolac could significantly enhance pain toleration [11]. This result supports the hypothesis of mixing Paracetamol with an NSAID to reduce acute pains which is confirm the results of present study. Pain is an unpleasant feeling and an emotional experience accompanied by real or possible damages caused to tissues or it is justified by such damages [3, 5, 12]. Multimodal analgesia includes mixing different sets of painkillers to amplify the effect and complications of medicines. Mixing paracetamol and non-steroid anti-inflammatory drugs (NSAIDs) is largely used in clinics [13, 14]. The hypothetical cause of this issue is the site and different performance of these two medicines (central nervous system vs. peripheral nervous system, serotoninergic system vs. synthesis of prostaglandins) [13, 15, 16]. It has been shown that the inhibitory effect of paracetamol on synthesis of prostaglandins can be observed in peripheral tissues as well. As a result, apotel can have significant peripheral effects only if it is prescribed along with an NSAID besides its central effects [10, 15, 17, 18]. Various materials such as modified biliary fats, prostanoids and cytokines can act as mediators of damage during cholecystitis [1, 12]. Prostaglandins can play a major role as mediators of acute inflammatory procedures through various effects such as hyperemia, edema, and contractile dysfunction [15, 16]. In this research, we used ketorolac which is an inhibitor of prostaglandin synthesis to reduce inflammation. Using NSAIDs to reduce acute cholecystitis pain in various researches has resulted in positive effects. Parkman et al studied the effects of Indomethacin and placebo on inflammation and contraction of gallbladder. In this research, the researchers realized that inflammation and contractile dysfunction of gallbladder had vanished after common bile duct ligation within 6 and 24 hours after operation [15]. In another research, Olsen et al compared the effects of ketorolac and butorphanol in treating the biliary colic pain. The results of our research point to this fact that both drugs help reduce the pain in the patients with biliary colic, thus they may be used in the emergency service unit of hospitals [3]. The results of our research also confirmed the analgesic effect of ketorolac in acute cholecystitis. Patients reported no severe complication in our research. However, in the research conducted by Olsen, 26% of the patients who had received ketorolac were exhibiting symptoms of nausea and vomiting [3]. This research was conducted on patients with biliary colic, while the current research studied the pain levels of patients with acute cholecystitis before cholecystectomy.

CONCLUSION

Ketorolac and apotel are two analgesic medicines used separately to reduce pain in different patients. According to the results of this research, simultaneous application and use of these medicines in a same time can effectively reduce the pain caused by acute cholecystitis in the period before and after operation.

CONFLICT OF INTEREST
The authors declare no competing interests in relation to the work.

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There is no financial disclosure.

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