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Efficacy and Safety of Combination Therapy with Ketorolac and Morphine in Patient with Acute Renal Colic; A Triple-Blind Randomized Controlled Clinical Trial

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ABSTRACT

Objective: To compare the efficacy of combination therapy with ketorolac and morphine with monotherapy with each in patients with acute renal colic.
Methods: This triple-blind, randomized clinical trial was conducted during a 6-month period from March to September 2014 in Northern Iran. We included 300 patients with clinical diagnosis of acute renal colic and pain score greater than 4 on 10 cm visual analogue scale (VAS) score. Patients were randomly assigned to three study groups to receive 0.1 mg/kg morphine in combination with 30 mg ketorolac (n=100), or only 0.1 mg/kg morphine (n=100) or only 30mg ketorolac (n=100). All the patients were evaluated at 0, 20 minute,40 minute later. Our outcomes were pain reduction and need for additive morphine in 20 and 40 minutes. We also recorded and compared the adverse effects between the study groups.
Results: There was no significant difference between the study groups. The pain intensity was comparable between three study groups after 20-min of intervention. However, we found that the pain intensity was significantly lower in balanced analgesia group when compared to morphine (3.01±0.98 *vs.* 3.66±1.02; p=0.012) or ketorolac alone (3.01±0.98 *vs.* 3.68±0.88; p=0.018). However, those receiving the balanced analgesia, required significantly less rescue analgesia when compared to morphine (16% *vs.* 20%; p=0.041) or ketorolac (16% *vs.* 24%; p=0.012) alone.
Conclusion: Balanced analgesia with morphine and ketorolac is more effective compared to morphine or ketorolac alone determine by lower pain scores after 40-min of injection and lower need for rescue analgesia.

Keywords: Renal colic; Morphine; Ketorolac; Pain; Efficacy; Safety.

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Introduction

Nephrolithiasis and renal colic are among the common causes of referrals to the emergency departments. It has been reported that about 5-12% of individuals in developed countries experience the renal colic at least once during the life-time and recurs in about 50% of the cases [1-3]. Despite the dramatic presentation, the majority of stones pass spontaneously without requiring intervention [4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the primary choice of analgesics in the treatment of renal colic, as they have a direct action on the ureter by inhibiting prostaglandin synthesis. Intravenous administration of NSAIDs achieves more rapid relief than oral or intramuscular dosing. Narcotics are good analgesics but do not affect the cause of pain [5]. Both NSAIDs and opioids provide pain relief in acute renal colic [6-10]. Currently it has been demonstrated that intravenous rout of analgesic administration is the best one for pain relief [11-13]. Opioids are non-expensive, effective, and titratable, but are associated with severe side effects such as nausea, vomiting, sedation, dizziness, respiratory depression, and hypotension [14]. Ketorolac tromethamine is the only NSAID labeled for intramuscular and intravenous administration for acute pain and morphine is the best choice of opioids in renal colic [8]. Although rare, gastrointestinal bleeding and acute renal failure have been associated with ketorolac [6, 11]. However, recent reviews indicate that in short-term use and in typical doses, ketorolac poses little risk of renal failure [15] and does not increase the risk of surgical bleeding [16].

In review of other randomized controlled trials, some researchers achieved greater reduction in pain scores in nonsteroidal anti-inflammatory drugs and had fewer adverse effects when compared to opioids for renal colic [11]. These trials had limitations in dosage, route or the choice of opioid (meperidine) [10, 11]. In addition, the concept of "balanced analgesia," ie, combining different groups of drugs to achieve sufficient analgesia through additive or synergistic effect with concomitant reduction in adverse effects, has been proposed in previous studies but was not found to be significant [6, 8, 17].

The limitations of the previous studies include the lack of ketorolac comparison with selective opioid (morphine), non-injection drug loading dose based on weight, the preferred method is the intravenous injection of both drugs, not applying a combination of the two drugs, use of miscellaneous drugs such as sedatives that causes reduced pain score and lack of evaluating of NSAIDS synergistic relationship with opioids in order to reduce the opium dose [11]. Thus, we designed this triple-blinded randomized controlled trial to compare the efficacy of balanced analgesia with intravenous ketorolac and morphine with each drug alone in patients with acute renal colic.

Materials and Methods

Study Population

This randomized, controlled, triple-blinded, clinical trial was conducted in the adult emergency department (ED) of Emam Khomeini hospital, a tertiary general hospital affiliated with Mazandaran University of Medical Sciences, in Northern Iran, during a 6-month period from March to September 2014. We included adult patients (18-55 years of age), with clinical diagnosis of acute renal colic (sudden sharp colic flank pain with or without radiation to genitalia or groin and with or without urinary symptoms) who had pain score of 5 or more measured by 10-cm visual analogue scale (VAS). We excluded those who had history of kidney or renal dysfunction and severe dehydration, pregnancy, breastfeeding, single kidney or kidney transplantation, history of peptic ulcers and gastrointestinal bleeding, receiving analgesics within 6 hours before presentation, history of bleeding diathesis, history of cardiovascular disease and the use of angiotensin-converting-enzyme inhibitor (ACE inhibitor) or angiotensin receptor blockers (ARB), anticoagulant medication or coagulation disorders, history of drug dependence or current use of methadone or chronic consumption of tobacco and alcohol and peritonitis or presence of any peritoneal sign. The study protocol was approved by the institutional review board (IRB) and the medical ethics committee of the Mazandaran University of Medical Sciences and all the patients provided their informed written consents before inclusion in the study. The study protocol was also registered with the Iranian Registry for Clinical Trials (IRCT201706032445N6; www.irct.ir).

Randomization and Intervention

All the patients were randomly assigned into three study groups using a computer based random digit generator utilizing the patients' admission codes. All the patients received an admission code based on their referral order and the number was used for randomization. Those assigned to the first study group received 30mg intravenous injection of ketorolac (Keterolac-Combaxona, 30mg/mL, Combino Pharmaceutical, Spain) in combination with 0.1mg/kg intravenous morphine (Morphien Sulfate,10mg/mL, Daru Pakhsh, Iran). Those assigned to the second group received 0.1mg/kg intravenous morphine (Morphien Sulfate,10mg/mL, Daru Pakhsh, Iran) and same amount of intravenous normal saline as placebo. The patients who were assigned to the third group received 30mg intravenous injection of ketorolac (Keterolac-Combaxona, 30mg/mL, Combino Pharmaceutical, Spain) in combination with placebo. All the injections were given during a 1-min period through a cubital venous line. The drugs were prepared in same syringes which were opaque. All the drugs were prepared in laboratory of pharmacology school. Nor those injecting the drugs,

neither the patients nor those measuring the outcome were aware of the study groups. Only statisticians knew the study groups. The drugs were administered by a nurse being blinded toward the study group.

Study Protocol

All the patients were evaluated on presentation by an emergency medicine physician regarding the history and clinical examination. The positive findings were recorded in a data gathering form. Urinanalysis and kidney, ureter and bladder (KUB) sonography was performed in all the patients in order to rule out hematuria and hydronephrosis. All the patients received the intervention as described above. Rescue analgesia, defined as 0.05 mg/kg of intravenous morphine, was administered for persistent pain (pain score more than 4 in VAS after 20 and 40 minutes of intervention). Ondansetrone was used to treat nausea and vomiting.

Outcome Measures

The pain intensity was measured on a 10-cm VAS before intervention and at 20 and 40-min after the intervention. We also recorded the amount of administered rescue analgesia. Adverse effects including nausea, vomiting, hypotension, respiratory depression, dizziness, hives and itching, were also recorded in each study group. The outcome was measured by a nurse who was blinded toward the study groups.

Statistical Analysis

In order to have 80% power to detect 5% difference between three study groups regarding the primary endpoint (pain intensity measured by VAS) by considering the α equal to 0.05 we assumed to include 95 patients in each study group. In order to compensate for non-evaluable patients, we included 100 patients in each study group. All the statistical analysis was performed using statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 18.0. data are presented as mean±SD and proportions as appropriate. All the parametric variables with normal distribution were compared using one-way analysis of variance (ANOVA) utilizing Tukey's test as post HOC. Parametric variables without normal distribution were compared using Kruskal-Wallis test. Proportions were compared using Chi-square test. A 2-sided *p*-value of less than 0.05 was considered statistically significant.

Results

We screened a total number of 483 patients for inclusion in the study from whom, 300 were eligible and were randomly assigned to three study group (each group containing 100 patients). All the patients finished the study and none were lost to follow up and thus the final number of patients was 300 (Figure 1). The baseline characteristics of the patients is summarized in Table 1. There was no significant difference between the study groups regarding the baseline characteristics.

The pain intensity decreased significantly in all the three study groups after 20- and 40-min of intervention (Figure 2). The pain intensity was comparable between three study groups after 20-min of intervention. However, we found that the

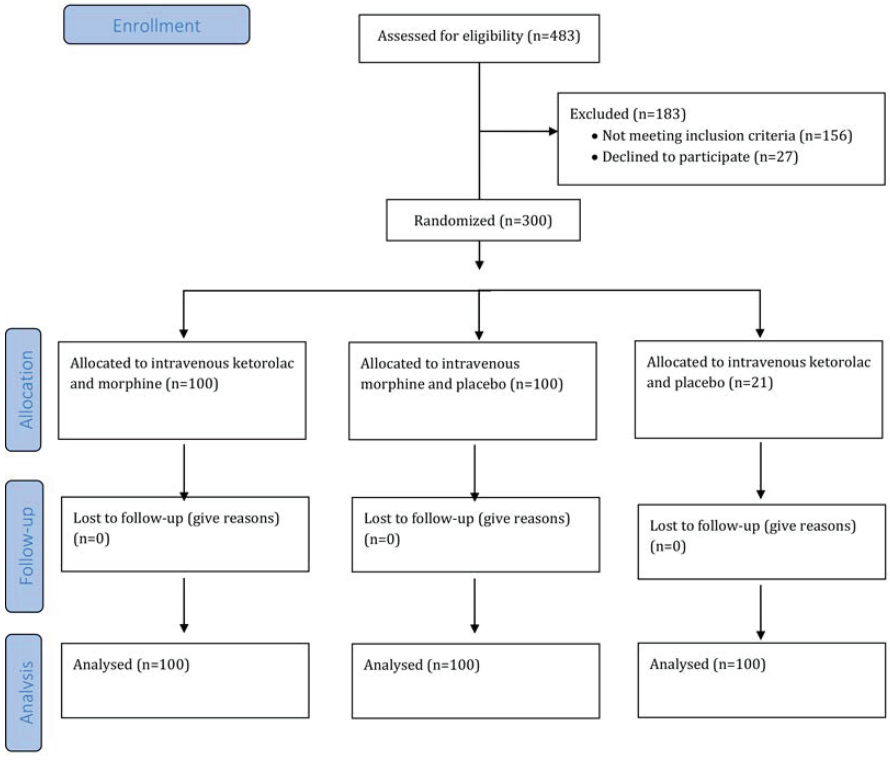

Fig. 1. CONSORT flow diagram of the study.

Table 1. The baseline characteristics of 300 patients with renal colic being assigned to three study groups.

Variables	Balanced analgesia (n=100)	Morphine (n=100)	Ketorolac (n=100)	*p*-value
Age (years)	30.28±10.3	28.81±9.8	29.66±9.7	0.126
Gender				
Men (%)	67 (67%)	72 (72%)	69 (69%)	0.211
Women (%)	33 (33%)	28 (28%)	31 (31%)	
Hematuria (%)	71 (71%)	56 (56%)	80 (80%)	0.096
Nephrolithiasis (%)	54 (54%)	31 (31%)	39 (39%)	0.064
Hydronephrosis (%)	83 (83%)	80 (80%)	86 (86%)	0.358

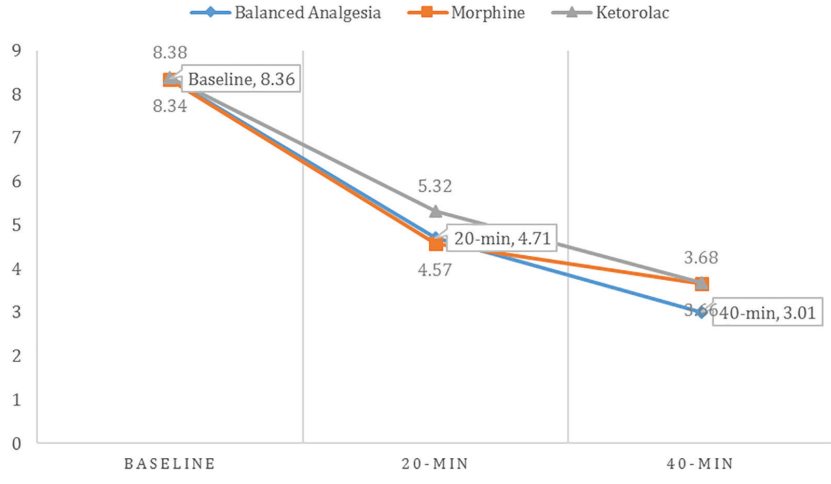

Fig. 2. The changes in the pain intensity measured by visual analogue scale in three study groups.

pain intensity was significantly lower in balanced analgesia group when compared to morphine (3.01±0.98 *vs.* 3.66±1.02; p=0.012) or ketorolac alone (3.01±0.98 *vs.* 3.68±0.88; p=0.018). The pain scores were comparable between morphine and ketorolac alone after 40-min (3.66±1.02 *vs.* 3.68±0.88; p=0.166). The side effects of the administered drugs are summarized in Table 2. As demonstrated, there was no significant difference between the three study groups regarding the incidence of nausea (p=0.388), vomiting (p=0.415), urticarial (p=0.767) and vertigo (p=0.122). The number of administered antiemetic (p=0.388) and rescue analgesia in 20-min (p=0.609) was also comparable between the three study groups. However, those receiving the balanced analgesia, required significantly less rescue analgesia when compared to morphine (16% *vs.* 20%; p=0.041) or ketorolac (16% *vs.* 24%; p=0.012) alone.

Discussion

The use of appropriate, effective and safe analgesia for patients with renal colic presenting to the emergency rooms is still a matter of debate. In the current study we tried to determine the efficacy and safety of balanced analgesia with an intravenous NSAID and opioid. We found that the balanced analgesia is associated with better pain control determined by lower pain scores after 40-min of injection compared to monotherapy by each agent. The results of the current study is in accordance with previously reported results indicating that balanced analgesia is superior to monotherapy in patients with acute renal colic [6, 8, 11].

Ureteral obstruction stimulates the release of prostaglandin E2 in the renal medulla. Prostaglandin E2 causes ureteral contractility, increases renal blood flow, and increases pressure in the renal pelvis, thus

Table 2. The adverse effects of the different analgesics in 300 patients with renal colic.

Variables	Balanced analgesia (n=100)	Morphine (n=100)	Ketorolac (n=100)	*p*-value
Nausea (%)	2 (2.0%)	4 (4.0%)	4 (4.0%)	0.388
Vomiting (%)	2 (2.0%)	4 (4.0%)	2 (2.0%)	0.415
Urticaria (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0.767
Vertigo (%)	3 (3.0%)	6 (6.0%)	1 (1.0%)	0.122
Antiemetic at 40-min (%)	2 (2.0%)	4 (4.0%)	4 (4.0%)	0.388
Rescue Analgesic at 20-min (%)	10 (10.0%)	12 (12.0%)	11 (11.0%)	0.609
Rescue Analgesic at 40-min (%)	16 (16.0%)	20 (20.0%)	24 (24.0%)	0.043

exacerbating pain [18]. NSAIDs interrupt this vicious cycle by inhibiting prostaglandin synthesis, resulting in reduced ureteral pressures, decreased contractility and inflammation, and, thereby, less pain [19, 20]. Although the analgesic effect of parenteral ketorolac in several pain states, including postsurgical pain has been investigated in randomized double-blind comparative trials, few studies have evaluated its use in renal colic [6, 8, 11, 20]. The rationale for balanced analgesia is to achieve sufficient analgesia through additive or synergistic effects between different analgesics with concomitant reduction of side effects as a result of lower doses of analgesics and differences in side-effect profile [21]. Our study compared intravenous ketorolac with intravenous morphine for the treatment of acute renal colic using a randomized, controlled, triple-blinded design. We found that combining 30 mg ketorolac and 10 mg morphine provided more effective pain relief, reduced the need for rescue analgesia. Patients who received combination therapy were significantly less likely to require rescue analgesia compared with each drugs alone.

We assume that most of the side effects caused by the nature of the disease, not opium injection. Nausea and vomiting before receiving the drug has confirmed this. On the other hand, we recommend that if a single agent must be chosen, intravenous morphine should be considered over intravenous ketorolac for patients with moderate or severe renal colic pain because although there is no significant difference in pain score and side effect and additive morphine between two groups, but morphine has a clear advantage over ketorolac because it does not have a limit for administration. Additional ketorolac has the risk of dangerous side effects like GI bleeding.

Our study results are similar to the findings of previous trial performed by Safdar *et al*., [8] in pain score and need for additional opium injection. They found the combination drugs have better pain relief, less nausea and vomiting and fewer requirements for additive morphine in 20, 40 minutes compared to each drug alone. They also found the morphine group have more side effect than ketorolac. There were no significant differences between the groups regarding the changes in blood pressure, pulse rate, respiratory rate, or oxygen saturation. The proportion of patients experiencing any adverse event was greater in the morphine group than either of the other groups. The combination group required less rescue analgesic compared to the ketorolac group [8]. These are in concordance with our findings. Sandhu *et al*., [22] compared 30 mg intramuscular ketorolac with 100 mg of intramuscular meperidine in a double-blinded study of 76 patients. They found that ketorolac was associate with better pain relief, fewer adverse effects, and fewer requirements for rescue analgesia compared with the meperidine.

Unlike the findings published in the above trials, ours showed no difference in pain relief or use of rescue morphine between morphine and ketorolac when used alone. In our protocol, we controlled for factors that we identified as possible confounders in the previous trials. Second, we chose to compare ketorolac with morphine, a standard opioid for severe pain. Morphine is about 10 to 15 times more potent than meperidine. In addition, it has a less troublesome adverse effect profile than meperidine [23]. Although one may argue that both medications can be titrated to achieve the desired analgesic effect, more meperidine is required compared with morphine to obtain a given analgesic endpoint. The higher dose causes more adverse effects for the same analgesic effect achieved by morphine. Also, meperidine is more lipid soluble, leading to rapid concentration in the central nervous system and therefore has more abuse potential. For these reasons, morphine is a preferred opioid for treating severe pain in most emergency departments.

We note some limitations to our study. First, the number of patients included in the current study was limited. However, the study had an 80% power to detect 5% difference between the primary endpoints. We recommend further multicenter clinical trials to shed light on the issue. The other limitation was that we only recorded the pain intensity based on the VAS scale. Some other variables such as hemodynamic changes are important factors that could also be addressed and compared between the study groups.

In conclusion, balanced analgesia with morphine and ketorolac is more effective compared to morphine or ketorolac alone determine by lower pain scores after 40-min of injection and lower need for rescue analgesia. Further studies are required to complete the results of the current study.

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Conflicts of Interest: None declared.

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