


Sublingual Buprenorphine Efficacy in Renal Colic Pain Relief: A Randomized Placebo-Controlled Clinical Trial

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ABSTRACT

Introduction: This study was designed to compare the analgesic efficacy of sublingual (SL) buprenorphine and intravenous (IV) ketorolac for renal colic pain relief.

Methods: The present study was carried out as a double-blind, double-dummy randomized clinical trial in patients diagnosed with acute renal colic attending the emergency department. The study subjects were 63 patients with confirmed renal stones. The subjects were randomly divided into two groups. One group, which included 32 patients, received SL buprenorphine tablets (2 mg) with an IV placebo, and another group, including 31 patients, received ketorolac tromethamine (30 mg) with a SL placebo. After medication, the pain of subjects was measured by a standard visual pain analogous scale (VPAS)

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in minutes 0, 20, 40, and 60 of study. Also, probable adverse effects were recorded.

Results: In 28.1% of patients in the buprenorphine group, the mean pain score decreased from 9.2 to 5.9, 2.8, and 1.5 after 20, 40, and 60 min, respectively, as determined by VPAS. Also, in 38.7% of patients in the ketorolac group, the mean pain score decreased from 9.1 to 5.5, 3.0, and 1.6 after 20, 40, and 60 min, respectively, as determined by VPAS. The two groups did not significantly differ for pain reduction at 20, 40, and 60 min (P value = 0.16, 0.34, and 0.3, respectively). No adverse effects were seen in the ketorolac group, but vomiting (18.8%), nausea (18.8%), and dizziness (21.9%) were detected in the buprenorphine group.

Conclusions: We found no difference between SL buprenorphine and intravenous ketorolac in renal colic pain relief but more adverse effects in the buprenorphine group.

Trial Registration Iranian Registry of Clinical trials identifier, IRCT2015041421773N1.

Keywords: Ketorolac; Pain relief; Renal colic; Sublingual buprenorphine; VPAS

INTRODUCTION

Pain is the most common reason that patients visit an emergency department (ED) [1]. Renal colic is known with severe pain and frequently encountered in EDs, with 5–15% prevalence in

the population [2]. Kidney stones cause pain by obstructing the uterus, and may lead to hydronephrosis [2]. The patient's pain relief places the responsibility on emergency physicians to find safe and effective methods of treatment [1]. Often, pain relief in renal colic patients is a challenge in ED, but the cornerstone of treatment includes narcotics and NSAIDs.

New effective analgesics have been studied for the treatment of pain. Buprenorphine is a partial opioid receptor agonist with opioid receptor antagonist properties. It has a high affinity and low-to-moderate intrinsic activity at the opioid receptor [3]. Buprenorphine is effective for the treatment of moderate to severe pain [4]. It also demonstrates the potential of sublingual opioids for the release of the baseline pain. It is a lipophilic molecule with poor oral bioavailability (approximately 10%) and undergoes first-pass metabolism, but it has good sublingual bioavailability (approximately 50%), with large intersubject variability [3]. Following its sublingual administration, there is no considerable rise in its plasma concentrations for 20 min; the time to maximum concentration is variable, ranging from 40 min to 6 h [4]. Potency is high and serum concentrations are linearly related to dose (from 1 to 32 mg) [3].

Intravenous (IV) administration of either NSAIDs or opioids is the common route for pain relief in renal colic. Sometimes, this route is accompanied by adverse effects, and takes more time than the oral or sublingual route. It may be not suitable in overcrowded emergency wards. Furthermore, there are a few investigations about pain management by buprenorphine, especially for renal colic [5]. Therefore, this study was designed to compare the effectiveness of sublingual buprenorphine versus intravenous ketorolac tromethamine for pain relief in renal colic.

METHODS

A clinical trial, double-blind, double-dummy, randomized study was carried out in patients diagnosed with renal colic. The symptoms for inclusion criteria were colic flank pain

associated with costo-vertebral angle tenderness and urinary tract irritation symptoms that suggest clinical diagnosis of renal colic based on history and physical examination and pain score greater than 3, as determined by visual pain analogous scale (VPAS), attending emergency departments of Golestan general Hospital at Ahvaz, southwest of Iran, with 73,000 annual visits from August 2015 to April 2016.

Exclusion Criteria

Age < 18 years and age > 55 years, any pain killer during the previous 6 h, addiction (self-report or medical record), history of allergic reaction to opioids or NSAIDs, systolic blood pressure < 90 mmHg, abdominal tenderness and rebound, body temperature > 38 °C, history or documents suggesting ischemic heart disease, liver disorder, respiratory disease, renal failure, gastrointestinal bleeding, active peptic ulcer, seizure, metabolic disorder, pregnancy, clinical concern for abdominal aortic aneurysm or dissection, inability to speak, and any intervention beyond the study protocol because of intolerable pain or patient disagreement.

Study Design

The subjects were randomly divided into two groups. After applying inclusion and exclusion criteria, one group received either 2 mg sublingual buprenorphine tablet [Mehr darou Pharmaceutical Company, Razi distribution company; Tehran, Iran; 2 mg, Sublingual Tab] with 1 cc intravenous sterile water as placebo simultaneously, and another group received 30 mg ketorolac tromethamine [Caspian Tamin Pharmaceutical Company; Rasht, Iran; 30 mg/cc, Ampule] with a sublingual tab similar to buprenorphine (made by the college pharmacy laboratory simultaneously; Ahvaz Jundishapur University of Medical Sciences) as placebo. Before intervention, and at 20, 40, and 60 min after administration, pain scores were measured and recorded by a fixed emergency medicine attending consultant based on a standard 10-gauge VPAS [0 = no pain, 10 = the worst pain].

At 40 min after administration, any patient with a pain score > 5 or any patient with a pain score > 2 in minute of 60 min, received 1 $\mu\text{g}/\text{kg}$ of intravenous fentanyl [Caspian Tamin Pharmaceutical Company; Rasht, Iran; Ampule, 0.5 mg/10 ml] as rescue treatment.

During 1 h of intervention, if we needed to use any medicine apart from the study protocol, we excluded that patient from the study. After 60 min, if renal colic pain continued or recurred, we used additional or other medications and hospitalized the patient in the urology department in order to make more evaluations based on their situation.

Both groups were monitored for adequate pain control and probable adverse effects, including respiratory depression (a respiratory rate below 12 breaths/min), hypotension (a drop of more than 20% in systolic blood pressure), nausea, vomiting, pruritus, headache, lightheadedness, and drowsiness, during study.

Also, just before, and 60 min after medication, vital signs and O_2 saturation were recorded in each patient. Both groups were followed for presumptive complications until 24 h after medication. Baseline demographic characteristics of all patients were gathered, including gender, age, weight, past medical history, and family history. Additional interventions were recorded.

Acute renal colic because of renal stones was confirmed by clinical manifestations associated with urine analysis and ultrasonography or CT scanning. If renal stones were not confirmed, patients were excluded.

All authors confirmed that the study received the approval of an institutional review board at Ahvaz Jundishapur University of Medical Sciences (ethical number of AJUMS.REC.1393.433). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Analysis

According to the study by Jalili et al. [6], the mean \pm SD of pain scores at 60 min is 2.2 ± 0.7 . In addition, according to 0.6 difference in pain score, $\alpha = 0.05$ and power of 80%, the sample size in each group was 30 patients.

The independent Student's *t* test was used to compare the baseline demographic characteristics and the effect of intervention on pain scores between the study groups at each time point. Adverse effects were compared using Chi-square tests, and the value of $p < 0.05$ was regarded as statistically significant. Statistical analysis was achieved using dependent Student's *t* test, which aimed to compare variation of vital signs before and after medication. Finally, data were analyzed using the Statistical Package for Social Science (SPSS) version 17.

RESULTS

Of 95 patients, 32 of them were excluded (Fig. 1). Of the 63 patients, 32 and 31 patients were assigned into buprenorphine and ketorolac groups, respectively. There were no significant differences in baseline characteristics between the two groups statistically (Table 1).

The comparison of pain scores over time in the two groups is shown in Table 2 and Fig. 2. The mean pain score in nine (28.1%) of patients in the buprenorphine group (no need for rescue treatment) decreased from 9.2 to 5.9, 2.8 and 1.5 within 20, 40, and 60 min, respectively, as determined by VPAS. Also, in 12 (38.7%) patients in the ketorolac group (no need for rescue treatment), the mean pain score decreased from 9.1 to 5.5, 3.0 and 1.6 after 20, 40, and 60 min, respectively, as determined by VPAS (Table 3).

There was no pain relief (less than a score of 5) at 40 min in 23 patients (71.9%) in the buprenorphine group and 19 patients (61.3%) in the ketorolac group; therefore fentanyl was used as rescue pain killer. The two regimens did not significantly differ for pain reduction ($P > 0.05$). No adverse effects were seen in the ketorolac group, but vomiting (18.8%), nausea

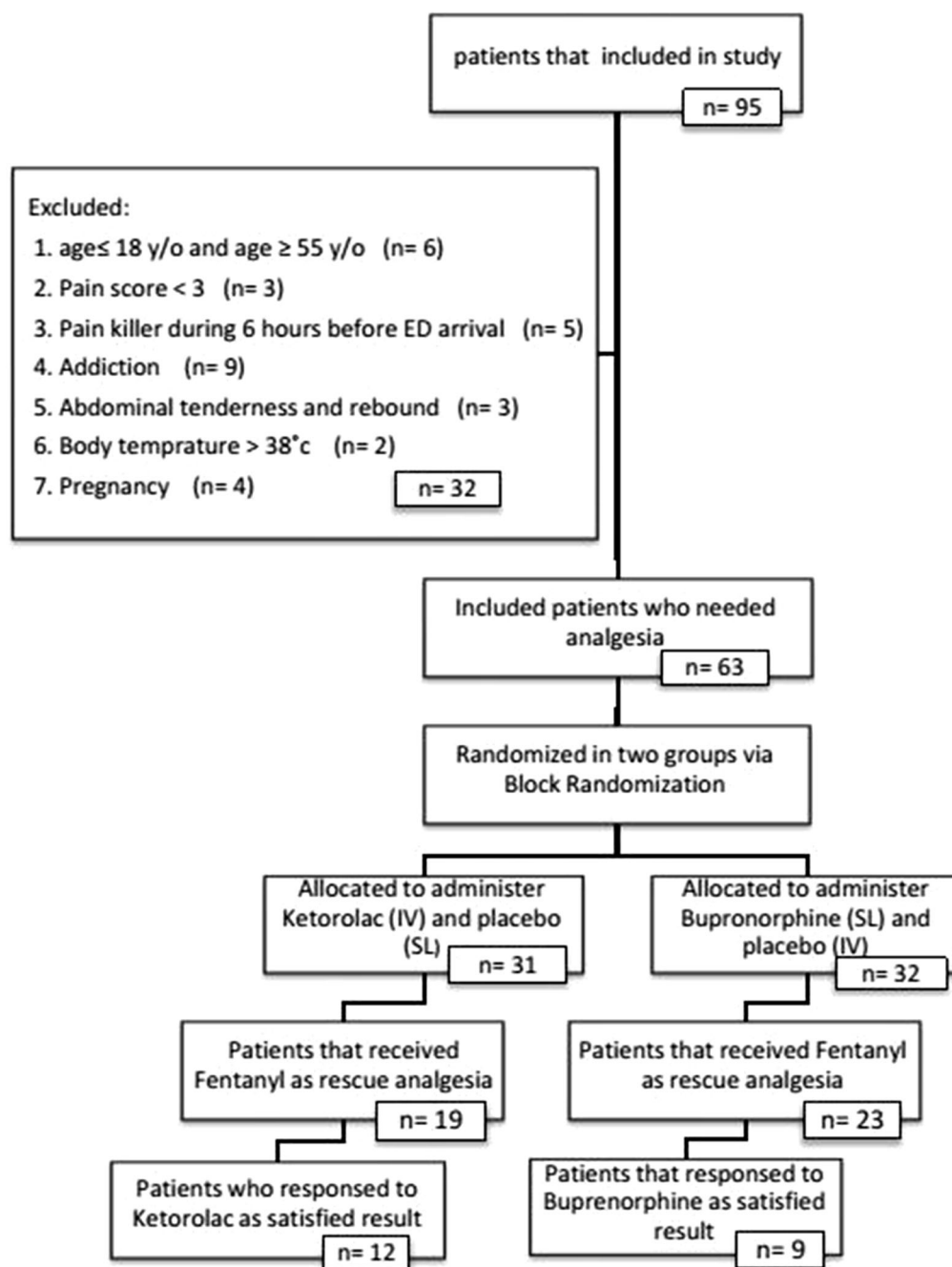


Fig. 1 Flowchart of the study

(18.8%), and dizziness (21.9%) were seen in patients of buprenorphine group (Table 4).

The vital signs of each group were not statistically different (Table 5).

DISCUSSION

Buprenorphine has been approved as an analgesic for various types of pain. Jakobs et al. showed that buprenorphine leads to

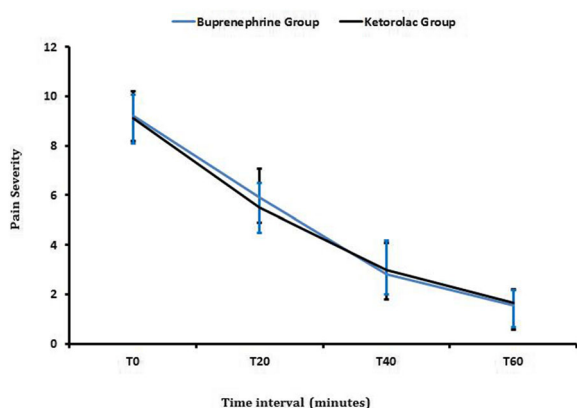
Table 1 Baseline demographic characteristics of study patients

Variables	Buprenorphine (<i>n</i> = 32)	Ketorolac (<i>n</i> = 31)	All patients	<i>P</i> value
Male	78.4%	87.1%	82.75%	0.52
Mean age (year) ^a	39.18 ± 1.63	35.58 ± 2.04	37.38 ± 1.83	0.17
Mean weight (kg) ^a	72.43 ± 1.43	74.64 ± 1.52	73.53 ± 1.47	0.4
Past medical history	75%	67.7%	71.35%	0.58
Family history	78.1%	80.6%	79.35%	1.000

^a Values are mean (± SD)

Table 2 Comparison of pain severity (mean ± SD) in two groups at different time points

Time points		<i>T</i> ₀	<i>T</i> ₂₀	<i>T</i> ₄₀	<i>T</i> ₆₀
Groups	Buprenorphine group	9.2 ± 0.97	5.9 ± 1	2.8 ± 1.16	1.55 ± 0.52
	Ketorolac group	9.1 ± 0.99	5.5 ± 1.16	3 ± 1.28	1.66 ± 0.65
<i>P</i> value		0.28	0.16	0.34	0.3

**Fig. 2** Trend of pain score changes in buprenorphine and ketorolac groups (*P* > 0.05, not significant)

significantly reduced pain scores in comparison to procaine in pancreatitis [7]. It is also used for treating various behavioral and psychiatric disorders [8], but there are few studies regarding pain management of acute renal colic by buprenorphine. In addition, some studies have indicated that ketorolac [8–10] is an effective analgesic for acute renal colic pain relief.

In our study, we found that 2 mg of sublingual buprenorphine was as effective as 30 mg intramuscular ketorolac for renal colic pain

relief. Two agents showed a similar decreased trend. However, our results did not show any significant differences among the two groups over time.

Our results are also comparable with the results of Jalili et al. [6], who studied the effectiveness of 0.4 mg sublingual buprenorphine and 5 mg intravenous morphine in patients with acute extremity fractures. The pain scores were compared, and no significant difference was seen between the two groups. Also, they did not find any adverse effects in the buprenorphine group. Payandemehr et al. [5] evaluated the efficacy of 2 mg sublingual buprenorphine with 1 mg/kg intravenous morphine sulfate for pain management of acute renal colic. They have shown that 86.5% of patients in the buprenorphine group did not require rescue analgesia and sublingual buprenorphine can be used as an effective analgesic with minor side effects for acute pain relief in patients with renal colic, and its effectiveness is comparable to that of IV morphine. They reported that dizziness was the only prominent side effect in the buprenorphine group compared to the morphine group. Although in the present study, in the buprenorphine group, 28.1% of patients did not need rescue analgesia, and some adverse

Table 3 Comparison of pain severity between responders of two groups

	Group	T_0	T_{20}	T_{40}	T_{60}
Responder (no need for rescue treatment)	Buprenorphine ($n = 9$)	9.2	5.9	2.8	1.5
	Ketorolac ($n = 12$)	9.1	5.5	3	1.6

Table 4 Frequency of adverse effects of two analgesia regimens in renal colic patients

Adverse effects	Vomiting (%)	Nausea (%)	Dizziness (%)
Buprenorphine group	18	18	21.9
Ketorolac group	0	0	0

effects including nausea (18%), vomiting (18%), and dizziness (21.9%) were observed. The dose, drug form, and administration route of buprenorphine were similar in both studies, but there was no consistency between percentage pain relief and side effects of buprenorphine in the two trials; thus, the reason for this difference is unknown based on the current study.

There is wide inter-patient variability in the sublingual absorption of buprenorphine, but within subjects the variability is low. Both maximum serum concentration (C_{max}) and area under the curve (AUC) of buprenorphine have positive linear relationships with dose of buprenorphine, although the increase is not directly dose-proportional. Maybe this characteristic of buprenorphine can explain the difference of pain relief in various studies.

Common side effects following buprenorphine administration may include sedation, nausea, vomiting, dizziness, headache, and respiratory depression. However, as a mu-opioid partial agonist with a demonstrated ceiling on respiratory depression, buprenorphine may have a better safety profile compared to a full mu agonist [4]. Buprenorphine side effects may be because of the other components inside the buprenorphine tablets (lactose monohydrate, mannitol, povidone, anhydrous citric acid, sodium citrate, butylated hydroxyanisole, corn starch, pregelatinized starch, and magnesium stearate) or higher dose of buprenorphine.

There is a potential limitation of buprenorphine in the setting of severe pain: its purported analgesic ceiling. Preclinical studies of buprenorphine indicated that it exhibits an analgesic ceiling or even a bell-shaped dose-response curve, where in doses exceeding the maximal analgesic dose were associated with decreased analgesic efficacy. More recent work has found such dose-response curves in some pain models but not in others [3]. The limitation of this study was its small sample size. So, to find any real difference in efficacy between two drugs.

Table 5 Vital signs of study patients in both groups before and after medication

Vital signs	Buprenorphine group			Ketorolac group		
	T_0	T_{40}	<i>P</i> value	T_0	T_{40}	<i>P</i> value
Systolic pressure	133.9 ± 2.8	131.2 ± 2.4	0.35	127.7 ± 2.9	125.2 ± 2	0.29
Diastolic pressure	82.8 ± 1.43	81.9 ± 1.3	0.52	83.06 ± 1.7	80.9 ± 1.2	0.11
RR	16 ± 0.46	16.8 ± 0.41	0.09	16.9 ± 0.40	16.8 ± 0.47	0.93
HR	81.7 ± 1.6	83.3 ± 1.2	0.1	83.8 ± 1.7	82.9 ± 1.5	0.52
O ₂ Sat %	98.3 ± 0.3	99.1 ± 0.23	0.001	98.2 ± 0.3	98.8 ± 0.3	0.05

RR respiratory rate, HR heart rate

*Values are mean (± SD)

LIMITATIONS

The limitation of current study is that we would like to compare pain scores over time between responders (subjects who did not require fentanyl) of buprenorphine group (28.1%) and ketorolac group (38.7%). We could not conduct this analysis due to a small number of responders in each group (nine and 12 patients in buprenorphine and ketorolac groups, respectively).

CONCLUSIONS

The results of this study indicate that although ketorolac was more effective than buprenorphine (ketorolac 38.7% versus buprenorphine 28.1%), there was no significant difference between two analgesic regimens in acute renal colic pain management. Buprenorphine has not been as extensively studied in certain populations (e.g., in individuals suffering from pain of malignant origin) as other opioid analgesics, and additional research is needed to better define the role of buprenorphine in various patient subpopulations.

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Compliance with Ethics Guidelines. All authors confirm that this study received the approval of an institutional review board at Ahvaz Jundishapur University of Medical Sciences (ethical number of AJUMS.-REC.1393.433). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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