Original Contribution

Comparison of the analgesic effects of haloperidol with or without morphine in patients with acute renal colic: A randomized double-blind clinical trial study

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A R T I C L E   I N F O

A B S T R A C T

Background: Given the increasing number of patients with acute renal colic, the present study examined the analgesic effects of haloperidol with or without morphine in order to find an effective method with fewer side effects for pain reduction in these patients.
Method: In the present randomized double-blind clinical trial study, patients with a pain severity score of above 3 were randomly divided into 2 equal groups: Group A received intravenous morphine and haloperidol, and Group B received intravenous morphine with normal saline. Pain severity was recorded at Times 0, 20, 40, and 60 min following the injections based on a visual pain analog scale (VPAS) from 0 to 10.
Results: A total of 140 patients were included in this study. A comparison of the recorded pain severity scores did not show a significant difference between the 2 study groups ($P = 0.38$). The mean heart rate, the mean systolic and diastolic blood pressures, and the mean incidence rate of nausea and vomiting were not significantly different between Group A and Group B. The frequency of extrapyramidal side effects was 4.3% in the haloperidol group, which was not significantly different from that of the other group. The frequency of extra analgesic requirement was not significantly different between the 2 groups ($P = 0.05$).
Conclusion: In our patients with acute renal colic, haloperidol failed to reduce pain and the incidence of nausea or vomiting, while it caused extrapyramidal side effects. Therefore, the prescription of this medication for acute pains, especially in renal colic, is not recommended.

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1. Introduction

Kidney stones are a relatively common condition in patients visiting the emergency department with acute abdominal and flank pains [1]. In general, between 5% and 15% of the world's population suffer from this disease, with approximately half of these individuals experiencing relapse [2]. The pain caused by kidney stones is the result of the passage of the stones from the ureter. Most patients describe the pain as the worst illness and the most sudden, painful, and refractory pain [3].

The major aim in colic treatment is reducing the prescription of repeated doses of analgesics [4-6]. In general, 2 categories of medications—namely injectable nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics (in case of no response to the treatment)—are employed, each with numerous contraindications and side effects [7,8]. Narcotics such as morphine sulfate are highly effective in treating renal colic and can lessen pain faster than NSAIDs, but they have more side effects. Little evidence is available for the use of anticholinergics or steroids for treating renal colic [9].

Currently, acetaminophen—available in the form of pills, suppositories, and injection—is used as an analgesic with fewer side effects than narcotics and NSAIDs at therapeutic doses [10]. The ability of narcotics to alleviate pain swiftly has contributed to a rapid rise in the application of this category of medications. On the other hand, the side effects of these medications—including physical and psychological dependence, hypotension, tachycardia, bradycardia, and respiratory depression—create more risks for emergency patients [11].

Haloperidol is a derivative of butyrophenone used in cases of delirium, aggression, hyperactivity, psychological disorders, nausea, and vomiting. The mechanism of the action of haloperidol has yet to be fully elucidated; nonetheless, one of its most important activities is blocking dopamine receptors. In the autonomic nervous system, haloperidol has mild anticholinergic activities by bonding to narcotic receptors [12].

Another approach is to seek adjuvant medications in order to decrease doses and, thus, side effects. This approach may be the beginning of the process of replacing these medications with narcotics. Various medications have been employed as adjuvant medications to morphine for alleviating severe pains, of which ketamine, antidepressants, and neuroleptics have had promising results [13].

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The aim of the present study was to answer the question of whether haloperidol could be an appropriate alternative to routine medications for quick pain relief in patients with renal colic.

2. Methods

This study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) [14].

2.1. Study design

The present randomized double-blind clinical trial study was registered in the Iranian Registry of Clinical Trials. The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University.

2.2. Selection of participants

After providing informed consent for study participation, patients with acute renal colic visiting the emergency department of Imam Khomeini Hospital between 2016 and 2017 were included.

2.3. Inclusion criteria

The inclusion criteria comprised age between 18 and 55 years, a history of urinary tract stones, severe flank pain, dysuria, and macroscopic and microscopic hematuria.

Urinalysis was performed using a combination of dipsticks and microscopic analyses. In the patients who experienced renal colic pain for the first time, an imaging method appropriate for the patients' condition and availability was used in order to confirm the diagnosis. Viewing a stone in abdominal and pelvic computed tomography (CT) scan without contrast or, if CT scan was not available, ultrasonography results in the form of a report of the presence of stone or sonographic evidence of stone by the sonologist was used to confirm renal colic.

2.4. Exclusion criteria

The exclusion criteria consisted of decreased levels of consciousness, a history of chronic cardio-renal problems, chronic hepatic disease, chronic respiratory disease, allergy or contraindication for haloperidol and morphine, having received an analgesic 6 h before arriving at the emergency department, a history of seizures, metabolic disease, pregnancy, addiction, systolic pressure of <90 mmHg, abdominal tenderness in the form of peritoneal inflammation, suspicious aneurysm or aortic dissection, body temperature of >38 °C, inability to speak, a history of kidney transplantation, a history of gastrointestinal bleeding, and active gastrointestinal bleeding.

2.5. Interventions

After renal colic was diagnosed for the patients and it was ensured that they did not have any of the exclusion criteria, they were hospitalized in the emergency department. In terms of pain, the patients were assigned scores of 0 (no pain); 1, 2, and 3 (mild pain); 4 and 5 (moderate pain); 6 and 7 (considerable pain); and 8, 9, and 10 (severe pain). Based on a visual pain analog scale (VPAS), the patients with a pain severity score of above 3 were divided into 2 groups of 70 through block randomization: Group A received intravenous (IV) morphine (Darou Pakhsh, Tehran, Iran) and haloperidol (Caspian Tamin, Rasht, Iran) and Group B received IV morphine and normal saline.

Next, the researcher or a trained nurse randomly allocated the patients to each group and started pharmacotherapy. During cardiac monitoring and pulse oximetry (minimum 15 min) as well as the recording of vital signs, the therapeutic regimen for each group was administered to the patients after disinfection and cannulation on the non-dominant hand while the researcher/nurse was unaware of the type of the prescribed regimen. The duration of the haloperidol or placebo infusion (dose of 5 mg, diluted in 100 cc of a normal saline solution) was 10 min, while the duration of the diluted morphine injection (dose of 5 mg) was 5 min.

2.6. Discharge criteria

At Times 0, 20, 40, and 60 min after the injections, the patients were asked to report pain on a scale of 0 to 10 based on the VPAS, and the data were recorded. Moreover, possible side effects such as respiratory problems, hypotension, nausea, vomiting, itching, lightheadedness, headache, drowsiness, dizziness, and extrapyramidal side effects were recorded. Biperiden was available to treat the possible severe extrapyramidal side effects of haloperidol.

At Time 20 of pain evaluation, the presence of a variation of 2 based on the VPAS in pain alleviation degree was regarded as considerable. If the pain continued with the initial severity, or if the pain was over 5 at Time 40, or if the patient refused to continue the study for any reasons, fentanyl at a dose of 1 μg·kg body weight was intravenously injected to alleviate the pain. Additionally, if the pain at Time 60 was <2 based on the VPAS, the patient was discharged from the emergency department with no further measures. However, if any degree of pain existed at Time 60, fentanyl at a dose of 1 μg·kg body weight was used. Finally, the patient was hospitalized and urologic consultation was sought in case of no pain alleviation.

2.7. Statistical methods

The data were analyzed using descriptive statistical methods, including frequency distribution tables and figures, so as to describe the variables of the study. The comparison of the scores of pain severity between the groups was performed by entering the data into the SPSS software, version 22, and analyzing them with the independent samples t-test and the Mann–Whitney U test. The χ^2 test (confidence interval: 95%) was employed to analyze and compare the incidence of the side effects and to compare the frequency percentage of sex between the groups.

3. Results

Of the 140 patients studied (Fig. 1), 100 (71.4%) were male and 40 (28.6%) were female. The mean age of the subjects was 38.62 ± 9.61 years. There were no statistically significant differences between Group A and Group in terms of sex and age ($P = 0.05$) (Table 1), the pain scores recorded based on the VPAS before the intervention and at the different study time points ($P = 0.05$) (Table 1), the pain severity score recorded after 1 h ($P = 0.38$) (Fig. 2), the mean heart rate prior to and during the intervention ($P = 0.05$) (Table 1 and Fig. 3), the mean systolic and diastolic blood pressures prior to and during the intervention ($P = 0.05$) (Table 1 and Fig. 4a and b), the incidence of nausea ($P = 0.398$), and the incidence of vomiting ($P = 0.612$). In addition, the frequency of the extrapyramidal side effects was 4.3% in the haloperidol group, but the difference between the haloperidol group and the placebo group did not constitute statistical significance ($P = 0.08$). Furthermore, the frequency of extra analgesic requirement was not significantly different between the two groups ($P = 0.785$) (Table 2).

4. Discussion

The results of examining and comparing the analgesic effects of haloperidol with or without morphine prescription in our patients with acute renal colic visiting the emergency department showed no significant differences in terms of pain intensity; vital signs such as systolic and diastolic blood pressures and heart rate; the incidence of nausea and vomiting; and extra medication requirement between the groups. Although the incidence rate of the extrapyramidal side effects was
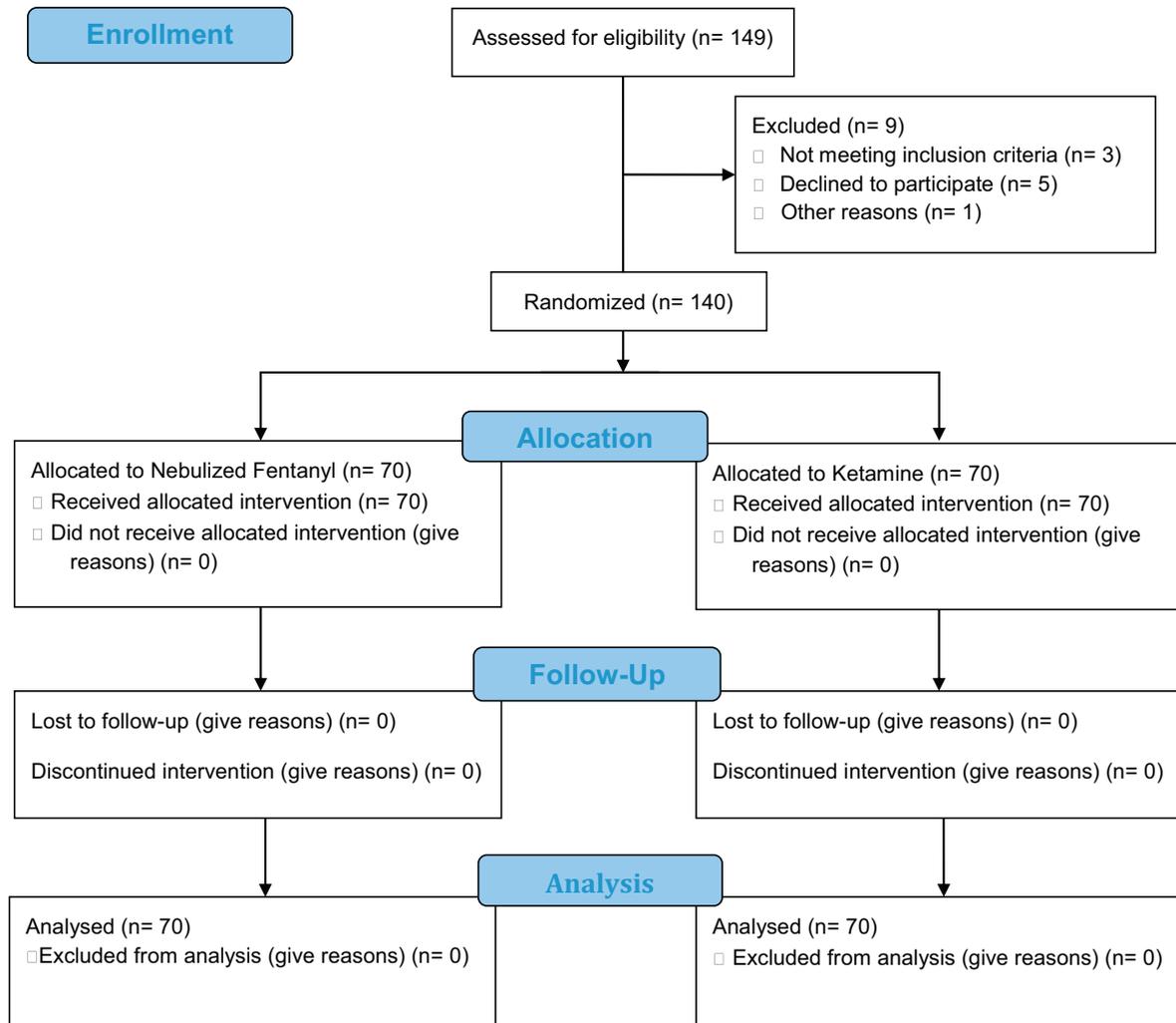
Fig. 1. Study flow diagram.

4.3% in the haloperidol group, this difference was not statistically signif-
icant. Bartolini et al. found that haloperidol induced analgesia in their
study mice insofar as 1 mg·kg of haloperidol increased the pain thresh-
old and significantly reduced the pain intensity at a dose of 0.5 mg·kg in
the animals [15]. Their results are in contrast with those of the present
study, and the discrepancy may be due to the difference in the type of
the population examined. We examined humans, while Bartolini and
colleagues investigated an animal population. On the other hand, we
prescribed haloperidol along with morphine, which may have affected
our study results. Furthermore, the patients in our study had acute
pain, while haloperidol may exert more effects on chronic pains.

In a study by Cavenar et al., haloperidol was prescribed to psychotic
patients complaining of chronic pains and the results indicated that

haloperidol was able to reduce both psychotic symptoms and pain.
The authors also reported that the pain intensity was alleviated by hal-
operidol in 4 patients with carcinoma [16]. Their results are not in line
with those of the current study, and the disagreement may be due to
the difference in the populations studied: We examined healthy sub-
jects with no underlying psychopathy, while Cavenar and coworkers
evaluated psychotic patients. Moreover, pain was acute in the present
study but chronic in their study.

A double-blind placebo-controlled randomized study by
Honkaniemi et al. showed that IV haloperidol was highly effective in
treating migraine pains. Forty patients (36 women and 4 men) at a
mean age of 26 years and 67 h of headache before admittance on aver-
age were studied. One group received 5 mg of IV haloperidol in 500 cc of
a normal saline solution and the other group received 500 cc of a normal
saline solution alone over 20 to 30 s in a random manner. The intensity
of pain was evaluated before the infusion and at 1 to 3 h after the infu-
sion using the VPAS. If the patient did not feel pain reduction 1 to 3 h
after the infusion and had received a placebo, haloperidol infusion was
performed. Before the infusion, the VPAS scores were 7.7 and 7.2 in
the haloperidol and placebo groups, respectively. Following the infu-
sion, the VPAS scores were 2.2 and 6.3 in the haloperidol and placebo
groups, correspondingly ($P < 0.0001$). Eighty percent of the patients re-
ceiving haloperidol showed considerable improvement, while only 3
(15%) patients responded to the placebo ($P < 0.0001$). The most com-
mon side effects of haloperidol were sedation and akathisia (80%). Six-
teen percent of the patients had unbearable side effects and reported

Table 1
Patient's characteristics.

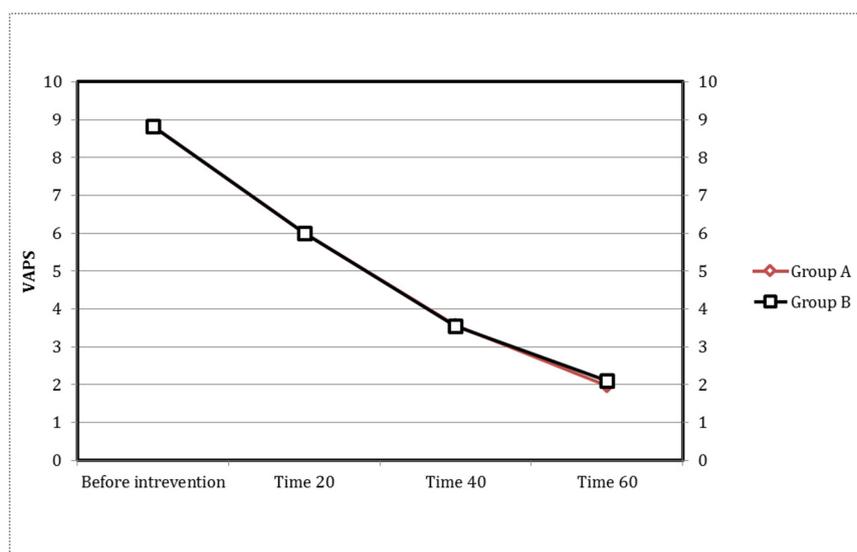| Group variable	Haloperidol (n = 70)	Morphine (n = 70)	P-value
Age, years	10.33 ± 37.5	8.76 ± 39.74	0.168
Sex, n (%)			
Male	49 (70%)	51 (72.9%)	0.708
Female	21 (30%)	19 (27.1%)	
Visual analog scale for pain (VPAS)	8.82 ± 0.85	8.88 ± 0.73	0.671
Heart Rate, bpm	90.38 ± 5.87	90.88 ± 6.01	0.675
Systolic blood pressure, mmHg	118 ± 7.21	117.2 ± 6.55	0.563
Diastolic blood pressure, mmHg	79.6 ± 10.63	79.7 ± 10.71	0.963

Fig. 2. Pain score changes during the study.

that they did not wish to be treated with haloperidol in the future in case of migraine attacks. Three (7%) patients returned to the emergency department due to relapse. The authors concluded that IV haloperidol was highly effective in alleviating migraine pains and that it might be an effective medication for patients for whom other treatments have failed. They also reported that relapse is rare, but side effects are common, limiting the use of this medication in some patients [17]. Their results do not chime in with the results of the present study, and the difference is probably due to the dissimilarities in the type of studies and methods. We did not administer haloperidol alone in our study population and instead used it along with morphine. Therefore, haloperidol might not have been able to show its analgesic effects in the presence of morphine, a strong narcotic and analgesic. On the other hand, our patients had renal colic, whereas Honkaniemi and colleagues evaluated patients with migraine, which is a chronic pain.

Colcloug et al. demonstrated that epidural haloperidol and morphine injection augmented the analgesic effect of morphine alone in major surgeries [18]. These results are discordant with the results of the current study, probably due to the difference in the population, the sample size, and the medication dosage.

Kocher et al. reported that psychotropic medications such as haloperidol were effective in treating chronic and highly resistant pains

resulting from neurotic issues. They evaluated 103 patients, 82% of whom showed considerable improvement [19]. Their results demonstrated that haloperidol affected chronic pains and not acute ones.

In a study by Amin Ebne Shahidi, the effect of intraoperative IV haloperidol was examined on pain improvement and control in general anesthesia. Ninety-eight patients undergoing elective general, obstetric, and orthopedic surgeries were selected and randomly administered 2 mg of IV haloperidol or sterile water after anesthesia induction. All the patients received morphine pumps for postoperative pain control. The quality of recovery was evaluated 20 min after transfer to the recovery room and 6 h after surgery. The quality of recovery was not significantly different between the study groups. Haloperidol significantly reduced nausea, but the VPAS showed that the pain intensity was higher in the haloperidol group than the placebo group (4.7 ± 2.4 vs 3.8 ± 2.5; $P = 0.05$). The authors concluded that a small dose of IV haloperidol affected postoperative nausea and vomiting, but it failed to exert a significant effect on the general quality of recovery [20]. Their results are almost consistent with the findings of the current study; nevertheless, we observed no difference in the incidence of nausea and vomiting between our study groups.

In a study by Shir and Shenkman, the effect of haloperidol was examined on neuropathic pains with a nerve damage origin often resistant to
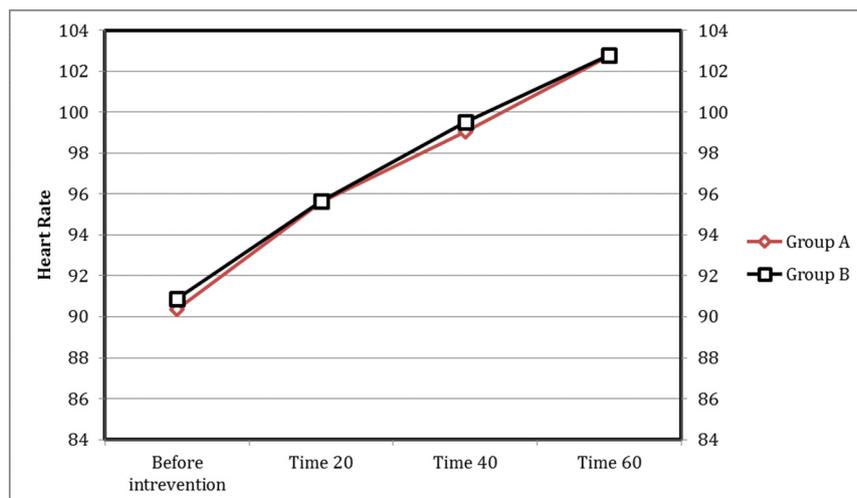

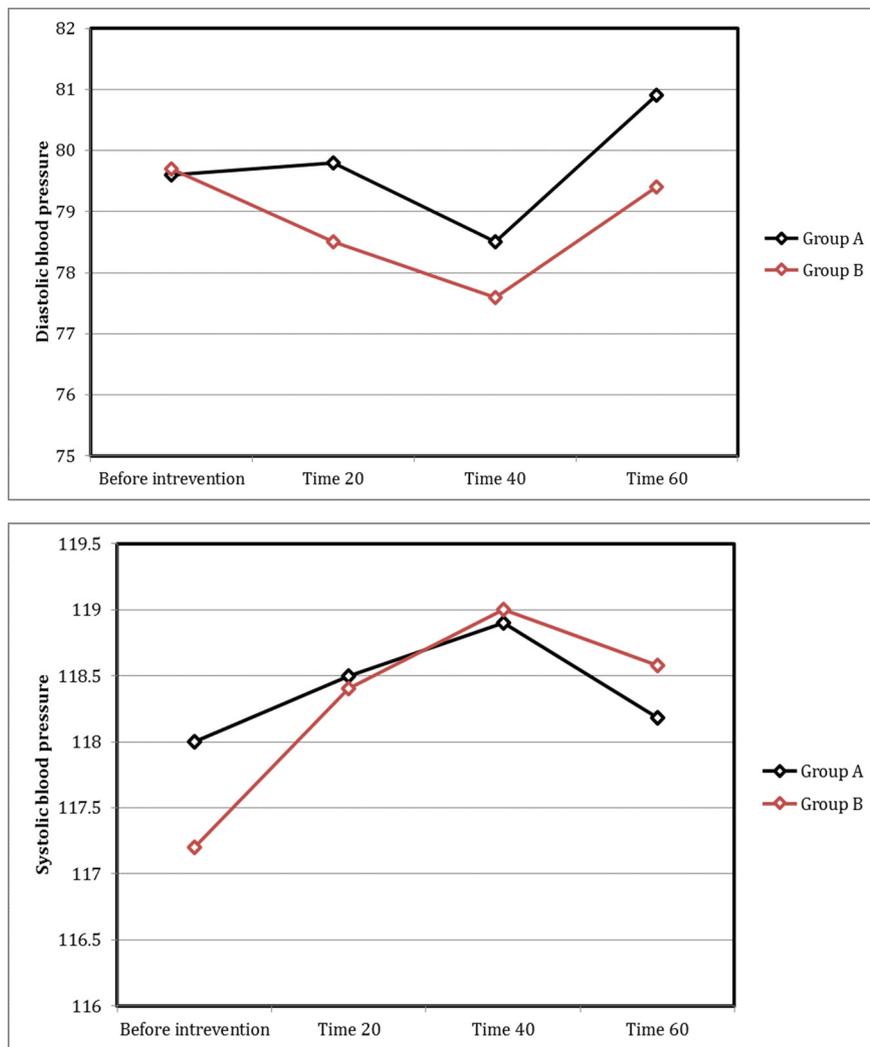**Fig. 3.** Heart rate changes during the study.

Fig. 4. a. Mean systolic and b. diastolic blood pressures changes during the study.

oral, injectable, and spinal opioids. In this study, a 56-year-old man suffering from intractable pain in his left knee after L2–3 vertebral decompression following collapse due to metastatic disease received 12 mg of IV morphine and 10 mg of IV diazepam simultaneously, which did not reduce the pain, while 2 mg of IV haloperidol completely treated the pain without causing hypotension or deep sedation [21]. This result is in contrast to the findings of the current study.

In a study by Judkins et al. [20], the effect of haloperidol as a supplementary analgesic was investigated in the treatment of postoperative pains. Thirty-four patients aged between 18 and 70 years admitted for elective major upper-abdominal surgery were examined. In this double-blind study, the patients received 10 mg of oral diazepam together with 10 mg of haloperidol (12 patients), 5 mg of haloperidol (11 patients), and a placebo (11 patients) before general anesthesia. Twenty-four hours following the surgery, the VPAS showed no statistical difference between the groups for pain. However, a considerable difference was observed between the haloperidol-receiving group and the placebo group in terms of nausea ($P = 0.78$) [22].

Given the sensitivity of the treatment of acute renal colic and the limitations of the present study such as its small sample size, we would recommend further prospective investigations drawing upon more comprehensive data and more efficient statistical methods.

Table 2
The frequency of extra analgesic requirement between the two groups

Adverse effect	Haloperidol (n = 70)	Morphine (n = 70)	P-value
Nausea, n (%)	34 (48.6%)	39 (55.7%)	0.398
Vomiting, n (%)	36 (51.4%)	33 (47.1%)	0.612
Extrapyramidal, n (%)	3 (4.3%)	0	0.08
Extra analgesic, n (%)	7 (10%)	8 (11.4%)	0.785

5. Conclusion

The results of the present study showed that haloperidol had no effect in terms of alleviating pain in patients with acute renal colic and diminishing the incidence of nausea or vomiting. The administration of haloperidol, however, caused extrapyramidal side effects in the study subjects. Therefore, the prescription of this medication for acute pains, especially in renal colic, is not recommended.

Regular assessments of positive signs and symptoms, physical examinations, and paraclinical tests are necessary for the timely identification of patients suffering from renal colic with a view to providing them with appropriate counseling and treatment services using morphine and not haloperidol.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethic code

(IR.AJUMS.REC.1394.173).

Contribute

K.M: conceived the original idea, designed the scenarios and collected the data.

A.D: carried out the analysis of data, approved the final version that was submitted, revised it.

M.S.: drafted the manuscript.

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