Original Article

Effects of Adding Oral Clonidine to Standard Treatments on Pain Intensity of Patients with Acute Renal Colic: A Randomized Clinical Trial

Abstract

Background: The aim of this study was to compare the effect of adding oral clonidine to standard treatments on pain intensity in patients with acute renal colic. **Materials and Methods:** This is a randomized clinical trial that was performed in 2020 in Isfahan. The study population consisted of 200 patients with renal colic. Pain of the patients was assessed using Visual Analog Scale. Patients were then randomized into 4 groups of 50 patients. Group A received 0.1 mg/kg morphine and clonidine tablets (0.2 mg). Group B received morphine and placebo. Group C received 30 mg ketorolac and clonidine tablets. Group D received 30 mg ketorolac and placebo tablets. Pain of patients was assessed. 0.05 mg/kg morphine was administered and repeated every 40 min if the pain was not reduced. **Results:** Our data showed that there was a significant difference between pains of patient by the time of admission in groups ($P = 0.04$). However, no significant differences were observed between pains of patients in different measuring times ($P > 0.05$). Using general linear model, we showed that the decreases in pain scores of each group were significant ($P < 0.05$) but there were no significant differences in pains of patients in different measuring times ($P > 0.05$). Our data showed that Group A and Group C had lowest frequencies of morphine administrations while Groups B and D had the highest frequencies ($P < 0.001$). **Conclusion:** We showed that administration of clonidine in patients with renal colic resulted in better pain control and lower morphine injections.

Keywords: *Clonidine, ketorolac, morphine, pain, renal colic*

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Introduction

Renal colic is the most common clinical manifestation of kidney stones, which is accompanied by severe and sudden flank pain.[1] The pain is caused by obstruction and increased pressure in the urinary tract when passing stones and may spread to the hypochondrium.[2] Due to the devastating nature of pain and the high prevalence of renal colic in the general population, it is known as a serious health problem. The annual incidence of renal colic is 16 per 10,000 people.[3,4] It should be noted that, over the past few decades, the incidence of kidney stones and renal colic has increased dramatically, most likely due to changes in people's lifestyles.[5]

Based on studies, increased pressure in the renal pelvis leads to the secretion of prostaglandins. Prostaglandins with their vasodilatory effects lead to diuresis and increase intrarenal pressure. The current treatment for renal colic involves the administration of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in combination.[1,6] Opioids have a reasonable price and also high potency. On the other hand, due to patients' dependence and addiction to them and the risk of respiratory depression, they have limited consumption. The use of NSAIDs also has advantages and disadvantages.[7,8] These drugs inhibit prostaglandins and as mentioned above, prostaglandins play an important role in the development of renal colic. Disadvantages of these drugs include increasing the chances of kidney failure and gastrointestinal bleeding. Furthermore, compared to opioids, it takes longer time for their analgesic effects to begin.[9] Ketorolac is the only drug in this category that is advised to be administered intravenously. The bioavailability of this drug is 80% to 100%. The onset of venous injection is <3 min. It is then metabolized in the liver and about 96% of it is excreted in the urine.[10]

Clonidine is an alpha-2 adrenergic receptor agonist that is primarily used to treat hypertension. Other uses for clonidine

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include controlling painful menstrual cycles or hot flashes caused by menopause, preventing migraine attacks, and quickly eliminating the effects of opioid withdrawal syndrome.[11] The most common form of clonidine in Iran is 0.2 mg tablets. This drug is highly absorbed orally. About 50% of the absorbed amount is metabolized in the liver and about 40%–50% is excreted unchanged by the kidneys. The onset of action of clonidine is between 30 and 60 min, with a plasma peak of 3–5 h and a half-life of 12–16 h. One of the side effects of clonidine includes orthostatic hypotension.[12] It is also used as an analgesic and sedation. Studies have shown that systemic clonidine is effective in reducing acute postoperative pain and that systemic clonidine can also be helpful in reducing chronic pain.[13,14] For better control of renal colic, a combination of two drugs can be used instead of one. So far, several studies have been performed to evaluate the effect of opioids alone or in combination with another drug, as well as the effect of systemic clonidine in reducing pain.

According to studies on renal colic and the positive effects of dual drug treatment and due to the proven analgesic effects of clonidine, more analgesic effects can be used with the simultaneous use of morphine and clonidine or ketorolac and clonidine. The aim of this study was to compare the effect of adding oral clonidine to standard treatments on pain intensity in patients with acute renal colic.

Materials and Methods

This is a randomized clinical trial that was performed in 2020 in Kashani and Al Zahra hospitals in Isfahan. The study population consisted of 200 patients with renal colic referring to Kashani and Al Zahra hospitals in 2020. The current study was approved by Research committee of Isfahan University of Medical Sciences, and the ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1397.340, Iranian Registry of Clinical Trials (IRCT) code: IRCT20130108012072N11).

The inclusion criteria were age between 18 and 55 years, blood pressure more than 110/70 mmHg, pain severity more than 47 based on Visual Analog Scale (VAS), and signing the written informed consent to participate in this study. The no-entry criteria were mental retarded patients, pregnancy, lactation, consumption of analgesics <4 h before admission, history of allergic reactions to morphine, ketorolac or clonidine, history of chronic liver or renal diseases, uncontrolled pain and changes in treatment protocols, any side effects related to the drugs, and patient's will to exit the study.

A total number of 200 patients with renal colic entered the study based on inclusion and exclusion criteria. The sample size volume was calculated using Cochran sample size formula.

Required sample size was calculated with using the sample size estimation formula to compare the means with considering the 95% confidence level, 80% test power, standard deviation of mean blood pressure in controlled hypotension which was about 1.5 and the effect size was 0.8 in 100 patients in each group. Furthermore, the data collector and the statistical analyst were also unaware of the dose of fentanyl injected into patients. After analyzing the data, the codes were opened and comparisons are made between groups. Sampling method was convenient.

The names of the patients were entered to the SPSS software and were randomized into two groups. The blinding method was such that the patient and the researcher were unaware of the type of injectable drug to the patients. The drugs were prepared in the same coded syringes by one of the operating room staffs who were not aware about the study and were given to the researcher for injection.

Diagnosis of renal colic was made based on the patient's clinical signs (severe colic pain with diffusion from the flank to the groin with or without nausea and vomiting) and positive hematuria in urine analysis and the presence of stones or hydronephrosis on ultrasound and ruling out other critical causes including acute appendicitis, ovarian, or testis torsion.

Patients were then randomized into 4 groups of 50 patients using random allocation software. Demographic data of all patients were collected at the beginning of the study, and pain of the patients was assessed using VAS. Based on VAS, pain of patients was scored from 0 (least pain) to 100 (most severe pain). Patients with initial VAS >4 entered the study. Patients were treated as following:

Group A received 0.1 mg/kg morphine in 100 ml normal saline (0.9%) within 10 min as intravenous (IV) infusion and clonidine tablets (0.2 mg).

Group B received 0.1 mg/kg morphine in 100 ml normal saline (0.9%) within 10 min as IV infusion and placebo tablets.

Group C received 30 mg ketorolac in 100 ml normal saline (0.9%) within 10 min as IV infusion and clonidine tablets (0.2 mg).

Group D received 30 mg ketorolac in 100 ml normal saline (0.9%) within 10 min as IV infusion and placebo tablets.

Pain of patients was assessed at baseline (pain 0), 20 min after interventions (pain 1), 40 min after interventions (pain 2), 60 min after interventions (pain 3), and 80 min after interventions (pain 4) using VAS, and 40 min after the drug infusions, 0.05 mg/kg morphine was administered and repeated every 40 min if the pain was not reduced.

We collected data regarding pain of patients, frequencies of morphine administration after the interventions and drug

safety and side effects. Safety and side effects of the drugs were assessed every 20 min by monitoring the vital signs of patients and evaluating the possible side effects (nausea and vomiting, dizziness, headache, urinary retention, and hypotension [systolic blood pressure below 90 mmHg]). We should note that all patients, physicians, nurses, clinical assessors, and analyzers received coded syringes and data, and none of these clinical staffs was aware of the injected drugs. At the end of the study, the results were decoded.

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, IL). Quantitative variables were analyzed with mean ± standard deviation, and nonquantitative variables are reported with number and percentage. Basic quantitative variables were compared between groups by independent *t*-test and nonquantitative variables were compared by "Chi-square." Mean score of pain at different times of the study was assessed by repeated measures analysis of variance statistical test.

Results

Here, a total number of 200 patients with renal colic entered the study. The CONSORT flow diagram of patients is shown in Figure 1. Primary analysis of demographic data indicated that the mean age of patients was 38.65 ± 10.39 years. Totally, 139 patients (69.5%) were males and 61 patients (30.5%) were females. There were no significant differences among therapeutic groups regarding age and gender ($P = 0.497$ for age and $P = 0.116$ for gender). Evaluation of history of renal colic in patients also showed no significant differences between groups. Data indicated that 126 patients (63%) had positive history of renal colic. Gender distribution and history of renal colic in patients are summarized in Table 1.

Analysis of patient's initial data regarding age, temperature, systolic and diastolic blood pressures, pulse rate, respiratory rate, and O_2 saturation is also summarized in Table 2. There were no significant differences between groups regarding this information ($P > 0.05$). There were only differences in patient's temperature as indicated in Table 2 ($P = 0.02$).

We also analyzed patient's pain according to VAS score in 5 different measuring times (0–4). These data showed that there was a significant decrease in pain of all groups compared to initial pain (pain 0). There was a difference between pains of patient by the time of admission in groups ($P = 0.04$). However, no significant differences were observed between pains of patients in different measuring times (pain

Table 1: Gender distribution of patients

Variable/group	A	B	C	D	Total	*P*
Male						
Count	29	36	40	34	139	0.116
Percent within group	20.9	25.9	28.8	24.5	100.0	
Female						
Count	21	14	10	16	61	
Percent within group	34.4	23.0	16.4	26.2	100.0	
History of renal colic						
Count	37	31	31	27	126	0.224
Percent within group	29.4	24.6	24.6	21.4	100.0	

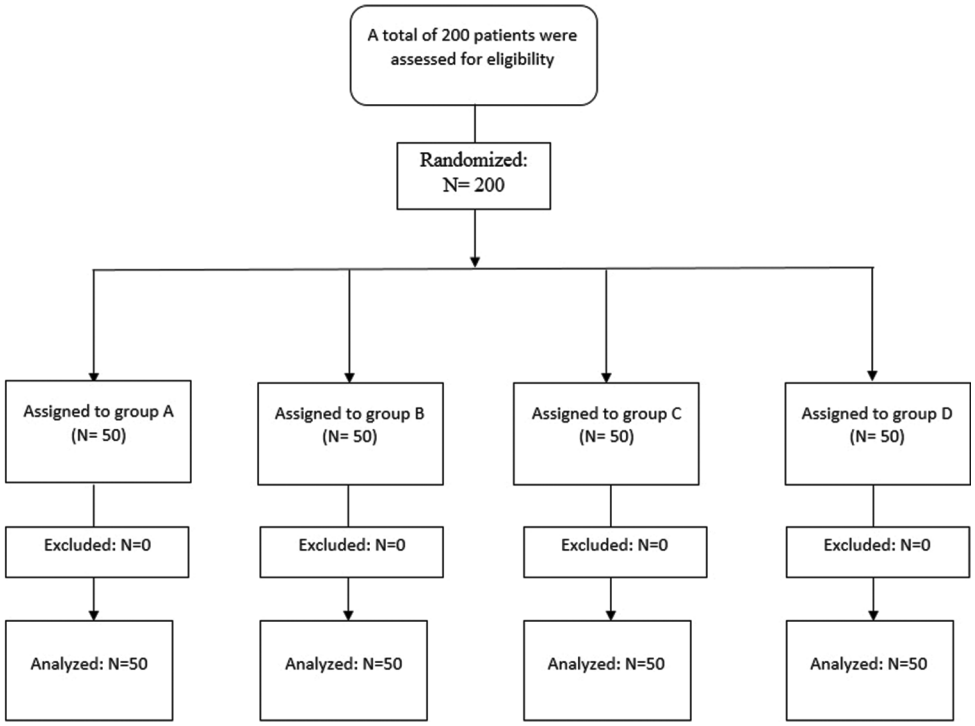

Figure 1: The CONSORT flow diagram of the patients

Table 2: Analysis of initial data regarding age, temperature, systolic and diastolic blood pressures, pulse rate, respiratory rate, and O_2 saturation

Variable	Group	Mean±SD	*P*
Age	A	39.24±9.88	0.49
	B	38.78±11.57	
	C	39.80±9.33	
	D	36.78±10.70	
	Total	38.65±10.39	
Temperature	A	36.90±0.30	0.02
	B	37.00±0.00	
	C	36.92±0.274	
	D	37.00±0.00	
	Total	36.95±0.20	
Systolic blood pressure	A	133.66±11.03	0.64
	B	134.10±11.50	
	C	134.50±8.58	
	D	132.00±10.20	
	Total	133.56±10.35	
Diastolic blood pressure	A	80.90±5.86	0.78
	B	81.30±5.13	
	C	81.50±5.17	
	D	80.50±4.97	
	Total	81.05±5.27	
Pulse rate	A	82.72±5.34	0.24
	B	83.28±4.54	
	C	80.32±11.48	
	D	80.48±12.22	
	Total	81.70±9.11	
Respiratory rate	A	15.38±1.27	0.22
	B	15.20±1.36	
	C	15.12±1.39	
	D	15.56±0.90	
	Total	15.31±1.14	
O_2 saturation	A	95.66±5.76	0.38
	B	96.70±1.86	
	C	96.38±4.68	
	D	96.92±1.04	
	Total	96.41±3.86	

SD: Standard deviation

1–4) ($P > 0.05$) [Figure 2]. As a result, we considered the initial pains of patients as confounder variable. Using general linear model, we showed that the decreases in pain scores of each group were statistically significant ($P < 0.05$), but there were no significant differences in pains of patients in each group in different measuring times (0–4) ($P > 0.05$).

Our data showed significant differences between the groups of patients regarding the frequencies of morphine administration after the interventions ($P < 0.001$). These data showed that Group A and Group C had lowest frequencies of morphine administrations while Groups B and D had the highest frequencies [Table 3].

Analysis and comparison of patient's morphine administration in different measuring times are also

Table 3: Analysis and comparison of patient's pains in different measuring times

Variable	Group	Mean±SD	*P*
Pain-0	A	76.40±9.20	0.04
	B	75.60±11.09	
	C	78.60±8.33	
	D	80.40±8.56	
	Total	77.75±9.48	
Pain-1	A	80.00±0.00	0.39
	B	79.60±2.82	
	C	80.00±0.85	
	D	80.00±0.00	
	Total	79.90±1.41	
Pain-2	A	60.00±0.00	0.39
	B	59.60±2.82	
	C	60.00±0.00	
	D	60.00±0.00	
	Total	59.90±1.41	
Pain-3	A	39.60±2.82	0.39
	B	40.00±0.00	
	C	40.00±0.00	
	D	40.00±0.00	
	Total	39.89±1.41	
Pain-4	A	20.60±3.13	0.14
	B	20.00±0.00	
	C	20.00±0.00	
	D	20.00±0.00	
	Total	20.15±1.57	

SD: Standard deviation

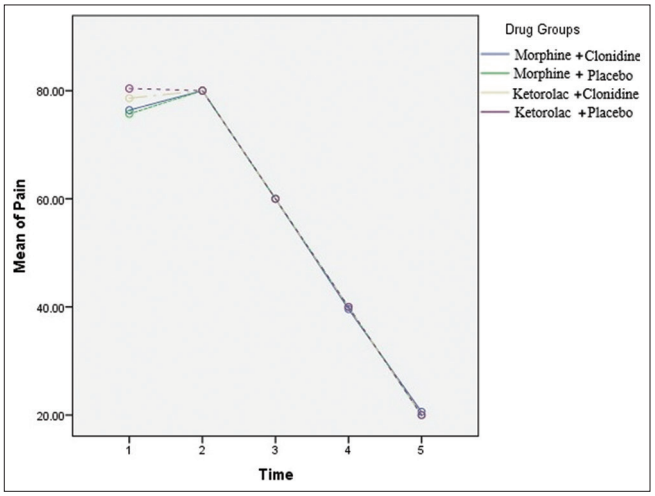

Figure 2: Patient's pain according to Visual Analog Scale score in different measuring times (0–4)

summarized in Table 4. Based on these results, patients in the B and D groups received morphine more frequently than other groups that is an indicator of higher pain in these patients ($P < 0.001$). As mentioned, all patients had similar pain intensity during the study but we showed that the patients in the A and C groups required less morphine. We assume that the

Table 4: Analysis and comparison of patient's morphine administration in different measuring times

Group	Frequent administration of morphine				*P*
	Mean±SD	0, *n* (%)	1, *n* (%)	≥2, *n* (%)	
A	0.20±0.45	41 (82)	8 (16)	1 (2)	<0.001
B	0.96±0.78	16 (32)	20 (40)	14 (28)	
C	0.40±0.69	36 (72)	8 (16)	6 (12)	
D	1.34±0.77	8 (16)	18 (36)	24 (48)	
Total	0.72±0.82	101 (50.5)	54 (27)	45 (22.5)	

SD: Standard deviation

self-reporting nature of VAS was the main reason of these findings.

Assessing the complications of the drugs, we demonstrated that nausea was the most common side effect, detected in 19 patients (9.5%). However, there was no significant difference between the groups ($P = 0.56$).

Discussion

In the present study, we evaluated the beneficial effects of adding clonidine to analgesics in 200 patients with renal colic and demonstrated that the amounts of pain were not significantly different between the therapeutic groups before and after interventions, but we also observed that those patients that received clonidine along with morphine or ketorolac had lower injections of morphine within their admission time. This issue indicates better pain control in these patients.

There have also been some previous studies on the effectiveness of clonidine in pain control in various clinical situations. In a study by Caumo *et al*., 59 patients undergoing hysterectomy were evaluated. They assessed and compared pain control and postoperative morphine injections between patients treated with clonidine and melatonin and reported that clonidine administration resulted in 30% decreased morphine injections in patients.[15] Singh *et al.* also evaluated the effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment cesarean section in 105 participants. They showed that administration of clonidine to hyperbaric bupivacaine led to increased duration of postoperative analgesia and reduced the need for further analgesic injections without any significant complications.[16] The same results were also reported by van Tuijl *et al*.[17] Our results were also in line with the findings of these studies. The key point of the present study was that we assessed the effects of clonidine on pain managements in patients with renal colic that had severe pain but these previous studies had evaluated the analgesic effects of clonidine in patients that received anesthesia.

Another study was performed by Naja *et al*. on 60 patients that were candidates for laparoscopic gastric sleeve. They assessed the effectiveness of clonidine in postoperative pain control and compared the results with dexmedetomidine. They concluded that clonidine and dexmedetomidine yielded similar outcomes with a difference in pain and analgesic consumption at 12 h postoperatively.[18] Effectiveness of clonidine in reducing postoperative pain was also indicated in another study by Huang *et al*.[19] Campbell *et al.* also stated that topical clonidine gel significantly reduces the level of foot pain in painful diabetic neuropathy subjects.[20] On the other hand, both ketorolac and morphine have indicated beneficial effects on reducing pain in patients with renal colic,[21,22] but to the best of our knowledge, this is the first randomized clinical trial that investigates the effects of clonidine on reducing pain in patients with renal colic.

Based on our results, we showed that administration of morphine and ketorolac either with placebo or with clonidine resulted in significant decrease in pains of patients, but the important aspect of the current study was that patients who received clonidine had significantly lower frequencies of morphine injections for pain control after interventions. This emphasizes the effectiveness of clonidine in pain control in renal colic. We suggest that physicians should pay more attention to the beneficial and analgesic effects of clonidine in renal colic.

Conclusion

Taken together, we showed that administration of clonidine in patients with renal colic resulted in better pain control and lower morphine injections. These results were in line with the findings of former studies but so far, no previous study has investigated the effects of clonidine in patients with renal colic. We also suggest that physicians should pay more attention to the beneficial and analgesic effects of clonidine.

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Conflicts of interest

There are no conflicts of interest.

References

1. Farnia MR, Jalali A, Vahidi E, Momeni M, Seyedhosseini J, Saeedi M. Comparison of intranasal ketamine versus IV morphine in reducing pain in patients with renal colic. Am J Emerg Med 2017;35:434-7.
2. Ye Z, Zeng G, Yang H, Tang K, Zhang X, Li H, *et al.* Efficacy and safety of tamsulosin in medical expulsive therapy for distal ureteral stones with renal colic: A multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 2018;73:385-91.
3. Mahamat MA, Diarra A, Kassogué A, Eyongeta D, Valentin V, Allah-Syengar N, *et al*. Renal colic: Epidemiological, clinical etiological and therapeutic aspects at the urology department of the national reference general hospital of n'djamena (Chad). Open J Urol 2020;10:25.
4. Sohgaura A, Bigoniya P. A review on epidemiology and etiology of renal stone. Am J Drug Discov Dev 2017;7:54-62.

5. Aggarwal R, Srivastava A, Jain SK, Sud R, Singh R. Renal stones: A clinical review. EMJ Urol 2017;5:98-103.
6. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, *et al*. Opioids for chronic noncancer pain: A systematic review and meta-analysis. JAMA 2018;320:2448-60.
7. Gu HY, Luo J, Wu JY, Yao QS, Niu YM, Zhang C. Increasing nonsteroidal anti-inflammatory drugs and reducing opioids or paracetamol in the management of acute renal colic: Based on three-stage study design of network meta-analysis of randomized controlled trials. Front Pharmacol 2019;10:96.
8. Shoag JE, Patel N, Posada L, Halpern JA, Stark T, Hu JC, *et al.* Kidney stones and risk of narcotic use. J Urol 2019;202:114-8.
9. Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. Eur Urol 2018;73:583-95.
10. Sotoodehnia M, Farmahini-Farahani M, Safaie A, Rasooli F, Baratloo A. Low-dose intravenous ketamine versus intravenous ketorolac in pain control in patients with acute renal colic in an emergency setting: a double-blind randomized clinical trial. Korean J Pain 2019;32:97.
11. Adegboye MB, Kolawole IK, Bolaji BO. Dose related effects of oral clonidine pre-medication on bupivacaine spinal anaesthesia. Afr Health Sci 2018;18:1283-91.
12. Krieger EM, Drager LF, Giorgi DMA, Pereira AC, Barreto-Filho JA, Nogueira AR, *et al.* Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: The ReHOT randomized study (resistant hypertension optimal treatment). Hypertension 2018;71:681-90.
13. Hsu YP, Chu KC, Bai CH, Huang CJ, Chen C, Hsu CW. Safety and efficacy of clonidine on postoperative vomiting and pain in pediatric ophthalmic surgery: A systematic review and meta-analysis. Pediatr Anesth 2019;29:1011-23.
14. Masud M, Yeasmeen S, Haque AK, Jahan S, Saha NC, Banik D. Role of oral clonidine premedication on intra-operative haemodynamics and PONV in laparoscopic cholecystectomy. Mymensingh Med J 2017;26:913-20.
15. Caumo W, Levandovski R, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: A double-blind, randomized, placebo-controlled study. J Pain 2009;10:100-8.
16. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. Saudi J Anaesth 2013;7:283-90.
17. van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: A randomized controlled trial. Br J Anaesth 2006;97:365-70.
18. Naja ZM, Khatib R, Ziade FM, Moussa G, Naja ZZ, Naja AS, *et al.* Effect of clonidine versus dexmedetomidine on pain control after laparoscopic gastric sleeve: A prospective, randomized, double-blinded study. Saudi J Anaesth 2014;8:S57-62.
19. Huang YS, Lin LC, Huh BK, Sheen MJ, Yeh CC, Wong CS, *et al.* Epidural clonidine for postoperative pain after total knee arthroplasty: A dose-response study. Anesth Analg 2007;104:1230-5, tables of contents.
20. Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, Schmidt WK, *et al*. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain 2012;153:1815-23.
21. Forouzanfar MM, Mohammadi K, Hashemi B, Safari S. Comparison of intravenous ibuprofen with intravenous ketorolac in renal colic pain management; A clinical trial. Anesth Pain Med 2019;9:e86963.
22. Hosseininejad SM, Ahidashti HA, Bozorgi F, Khatir IG, Montazar SH, Jahanian F, *et al*. Efficacy and safety of combination therapy with ketorolac and morphine in patient with acute renal colic; A triple-blind randomized controlled clinical trial. Bull Emerg Trauma 2017;5:165.