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Comparison of efficacy nebulized fentanyl with intravenous ketorolac for renal colic in patients over 12 years old

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ABSTRACT

Objectives: Acute renal colic is one of the common causes of referral to the hospitals. The aim of this study is to compare the efficacy of nebulized fentanyl with that of intravenous ketorolac in renal colic patients.

Materials & methods: This double-blinded clinical study included 186 patients with acute renal colic who were referred to the emergency department of Besat Hospital, Iran. Patient selection. After selecting patients, according to study inclusion and exclusion criteria, they were divided into 2 groups of 93 using random block allocation method. The patients in the groups were treated with either nebulized fentanyl or intravenous ketorolac. The severity of pain was measured using the Numeric Pain Rating Scale (NPRS) of pain. The severity of pain at different times and demographic data were recorded.

Results: One hundred and thirty four males and 52 females with a mean age of 42.95 ± 13.13 years were included in the study. The two groups were matched in terms of age, sex, and the severity of the pain before the treatment. Fifteen minutes following the treatment, the severity of pain was decreased in the ketorolac group but did not change in the nebulized fentanyl group. Thirty minutes after the administration of the drug, the severity of pain in the nebulized fentanyl group decreased. At any time, the severity of pain in the ketorolac group was lower than that of the nebulized fentanyl group.

Conclusion: Intravenous ketorolac had better analgesic effects in renal colic patients compared with nebulized fentanyl. Further studies that include complications and combinational therapy are required.

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1. Introduction

Urinary tract stones are a common urological problem where renal colic is the most common clinical manifestation of urinary stones [1]. Renal colic often presents with severe unilateral flank pain and accounts for a significant number of hospitalizations and referrals to the emergency department [2]. It is estimated to affect 1.2 million people each year in the world [3]. Acute renal colic is caused by increased pressure within the upper urinary system or dilated kidney and pelvic capsule above the obstruction site [4].

Following the preliminary diagnosis, since most urinary stones are removed by expectant treatment, pain relief is one of the most important therapeutic priorities in the acute phase [5]. Opioid and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapeutic agents for the management of renal colic [6,7].

The analgesic effects of NSAIDs equivalent to that of opioids are usually seen 20–30 min following the administration [8,9]. The antinociceptive effects of NSAIDs are as the result of the inhibition of the production and release of prostaglandins which reduce vasodilatation, increase the permeability, impose diuretic effects on the kidneys [10] and decrease the pressure in pelvis and the urinary collecting system [11]. They also reduce swelling and inflammation and contractile activity of the ureter muscles [12]. The gastric and renal effects of non-steroidal anti-inflammatory drugs have limited their use. Nonetheless, IV administration has minimized these side-effects [13].

Along with analgesic effects of opioids, their side effects on central nervous system are well-known [14]. They can cause ureteral spasm and prevent the possible progression of stone excretion. The dose of the opioids requires repeated administration, and they can also cause severe nausea, vomiting, constipation, drowsiness at higher doses, respiratory weakness, and hypotension. Fentanyl is a synthetic opioid analgesic that has rapid action of mechanism due to its high solubility in fats [15]. Fentanyl can be administered intramuscularly, intravenously, neuro-axially (epidural and intrathecal), transdermally and trans-

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mucosally. Studies have shown that nebulized fentanyl is effective in controlling pain in cases of acute emergencies [16]. Therefore, based on the aforementioned discussion, the present study was aimed to compare the efficacy of nebulized fentanyl with intravenous ketorolac for renal colic in patients over 12 years of the age at the Emergency Department of Besat Hospital.

2. Methods

This double-blind clinical study was conducted in the emergency department of Besat hospital, Hamadan-Iran. All patients suspected of having renal colic and with acute pain (flank pain radiating inferiorly and anteriorly), nausea and vomiting along with a history of urinary stone aged over 12 years were included in the study. Written consent was obtained from the patients or their parents/guardian and the procedure of the study was briefed to them. Patients presented with abdominal pain, hypersensitivity to opioid and NSAIDs, inaccurate diagnosis of renal colic, receiving other analgesics, sedative, antidepressants, pregnancy, lactation, asthma, renal failure, bleeding disorders, age <12 years and those unwilling to participate in the study were excluded. Each included patient was then randomly assigned to receive ketorolac (block A) or fentanyl (block B). The physician was unaware of the type of the block given to each patient. The method of administration was as follows:

Nebulized fentanyl: Patients received 50 µg/1 mL fentanyl in 5 mL normal saline at a dose of 3 µg/kg (0.06 mL/kg) given in nebulized form in 15 min and 0.03 mL/kg normal saline intravenously over 2 min.

An ultrasonic nebulizer (Hikoneb Home-Type) having vapor capacity of 5 ml and a reservoir of 400 ml was used for nebulizing fentanyl.

Ketorolac group: Patients received 0.9 mg/kg ketorolac by slow intravenous injection. Patients in this group received nebulized 6 ml of normal saline for 15 min. This study was double-blind because all patients and examiner were not aware of the type of intervention. Pain was measured according to the Numeric Pain Rating Scale (NPRS) before the commencement of the treatment, at the time of drug administration, and at 15, 30, 45, 60, 75, 90, 105 and 120 min after the administration of the drug. The intensity of the pain, measured by a scale consisting of a horizontal line numbered from 0 to 10, with 0 indicating no pain and 10 indicating severe pain was the primary outcome measured [25]. The demographic information of the patients was also recorded in the form.

After data collection, data was computerized and analyzed with SPSSv21 software. The frequency and percentage were used to describe qualitative data and mean and standard deviation were used to describe quantitative data. Chi-square was used for the comparison of categorical variables between the two groups whereas, paired *t*-test was used for the comparison of normally distributed variables. The independent *t*-test was used for the comparison of the mean of the two groups. $P < 0.05$ was considered as the level of significance in all statistical tests. This study was approved by the Research Ethics Board of Hamedan University of Medical Sciences.

3. Results

Of 186 patients presenting with acute renal colic, 134 males (72%) and 52 females (28%) were included with the mean age 42.95 ± 13.13 years. The mean age in nebulized fentanyl was 42.33 ± 13.92 years and in intravenous ketorolac group was 45.56 ± 12.33 years. There were 70 males and 23 females in ketorolac group and 69 males and 29 female in fentanyl group. The mean age, gender and the intensity of the pain before the intervention was similar in the two groups (p -value<0.05).

The intensity of the pain is shown in Table 1. At all times after the treatment, pain intensity was significantly higher in the ketorolac group compared to nebulization fentanyl group ($p < 0.001$). Paired *t*-test results showed that pain severity decreased significantly in

Table 1
Comparison of pain intensity between treatment groups at different times.

Time	Severity of pain Standard deviation \pm mean	
	Ketorolac	Nebulized fentanyl
Before treatment	7.44 \pm 1.49	7.24 \pm 1.74
15 min	5.70 \pm 1.75	7.09 \pm 1.80
30 min	3.95 \pm 1.32	6.46 \pm 1.55
45 min	3.73 \pm 1.37	4.88 \pm 1.75
60 min	3.18 \pm 1.35	4.80 \pm 1.91
75 min	2.93 \pm 1.22	4.37 \pm 1.68
90 min	2.22 \pm 1.28	4.03 \pm 1.69
105 min	1.26 \pm 1.10	3.30 \pm 1.61
120 min	0.65 \pm 0.91	2.83 \pm 1.49

ketorolac group at 15 min. But in the fentanyl group, the reduction was not significant (p -value \geq 0.05). According to the pain intensity averages, pain intensity in the ketorolac group at 60 min after the administration of the drug reduced to 57% and within the first 120 min, 91.26% reduction in the pain was seen. Also, pain intensity in the fentanyl group decreased by 70.33% at 1 h post-injection and 91.60% following 120 min of the drug administration. The overall trend of pain reduction was significant in both groups. However, the intergroup comparison test showed that often this pain repeats intermittently and its severity changes in the ketorolac group was significantly more than that of the fentanyl group (p -value<0.001) (Fig. 1).

In Table 2, we compare the number of patients who were completely pain-free following the 2 h of the intervention. The number of patients who had a complete pain relief were significantly higher in the ketorolac group (p -value<0.001).

4. Discussion

Annually about 1.2 million people in the world are reported to suffer from renal colic, which accounts for about 1% of hospitalization. In the United States, 2 million people referred to the emergency department are suspected to have renal colic, annually [17]. Renal colic often presents with a severe onset of sudden pain in the flank region that spreads to the front and the thigh. This pain is repeated intermittently in the patients and its severity increases with time [18]. The primary principles of renal colic treatment are to alleviate the pain and treat water and electrolyte imbalance [7,19].

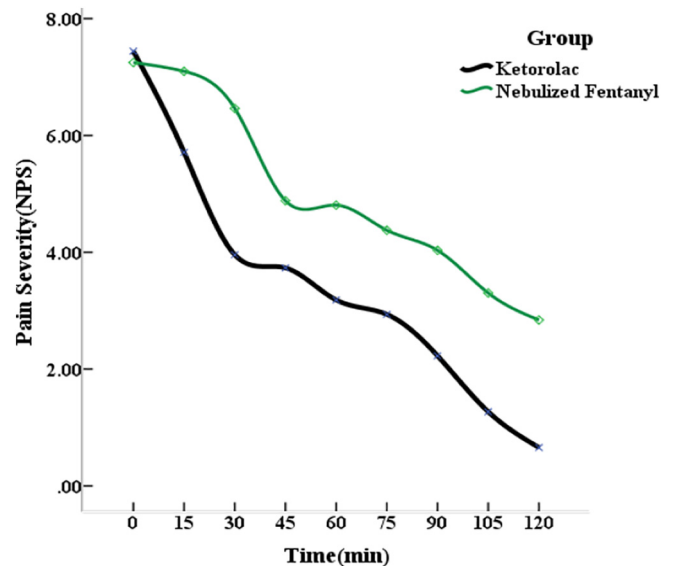


Fig. 1. Comparison of the process of pain reduction in treatment groups. The rate of pain reduction in the ketorolac group was higher than that of the fentanyl nebulizer group.

Table 2
Comparison of pain relief after 2-h of drug administration.

Pain status	Treatment groups Frequency (%)		Chi-Square test P-value
	Nebulized fentanyl	Ketorolac	
No pain	51(54.8)	9(9.7)	0.000
Painful	42(45.2)	84(90.3)	

According to the findings from the present study, the group treated with intravenous ketorolac and fentanyl nebulization was matched for sex distribution, mean age, and mean severity of pain before the treatment. In this study, we attempted to make the treatment procedures in the two groups as similar as possible. These factors, along with the study being double-blind, ensure that the effects observed in the treatment groups are due to the effects of the drugs and the differences observed between the groups are due to the differences in the effects of the drugs [20]. In the present study, a greater number of our patients were male with the male to female ratio of 2.5 which was similar to findings from our study.

In the study of Qasemi Basir et al., out of 500 patients referred to teaching hospitals in Hamadan, 348 were males (69.6%) and 152 females (30.4%). The ratio of male to female was 2.3, which is close to the value reported in our study [21].

In their study, Habibi and colleagues reported that the prevalence of renal colic in the general population was about 12% in males and 4% in females [22], a male to female ratio of 3. In the Shaker et al. study, from a total of 300 patients, male to female ratio reported was 2.5, which is consistent with our study.

In the Qasemi Basir et al. study, the mean age of patients referring to the hospitals in Hamadan was 40.36 years, which is similar to the findings of our study. The mean age of patients referred was 8.11 ± 20.4 years [23]. The mean age in the Shaker et al. study was 39.7 ± 16.8 years in the ketorolac group and 38.4 ± 15.6 years in the morphine group. In the study by Rajaei et al., the mean age of patients was 9.8 ± 2.35 years [8]. However, our study was conducted on the patients aged over 12 years. Imamoglu, Aygün [24], in comparing the effects of intravenous fentanyl with nebulized fentanyl reported an average age of 33.1 ± 10.2 and 35.7 ± 10.8 years in the two group, respectively. The study concluded that nebulized fentanyl is more effective analgesic, with fewer side-effects in patients presenting renal colic as compared to its intravenous (IV) administration. Nonetheless, IV fentanyl is stronger and acts rapidly [25].

In the present study, the mean severity of pain before the treatment was 7.44 ± 1.49 in ketorolac and 7.24 ± 1.74 in nebulized fentanyl group. In the study of Habibi et al., the mean severity of pain in patients with renal colic in the intervention and control groups was 7.8 ± 1.1 and 8 ± 1.0 , respectively. Sirius et al., reported that the primary pain severity in patients in the two groups of the study was 8.08 ± 1.74 and 8.12 ± 1.51 , respectively [26]. In the Etteri et al. Study, the severity of primary pain in patients with renal colic was 8.93. In these studies, visual analogue scale was used to evaluate the intensity of the pain whereas, we utilized numeric pain rating scale in our study.

The results of this study showed that pain reduction in the ketorolac group was significant 15 min after the administration of the drug, but no such findings were seen in nebulized fentanyl group.

In both the groups, the overall trend of pain reduction was significant, but the decrease in the ketorolac group was significantly more than that of the fentanyl group.

To our knowledge, no previous studies have compared the analgesic efficacy of nebulized fentanyl and ketorolac in renal colic patients. Kim, Jang [27] conducted a study to compare the post-operative effects of IV fentanyl and IV ketorolac in eye surgery patients. The results from the study indicated that fentanyl has superior analgesic outcomes over ketorolac. Furthermore, ketorolac was significantly associated with the greater incidence of postoperative nausea and vomiting, despite the

administration of antiemetic agents. The nature of this study was entirely different from that of ours, nonetheless, the outcomes of our study contradicts the one presented by Kim and colleagues [28]. A study has also reported that combinational effects of NSAID (ketorolac) and opioid (fentanyl) are superior as compared opioid alone, in terms of analgesia and postoperative nausea and vomiting [26]. Etteri et al. showed that concomitant administration of ketorolac and fentanyl had the same therapeutic effects whether administered intravenously or inhaled [29]. Several studies have also compared the effects of nebulized fentanyl with intravenous morphine to relieve acute colic, such as the ones presented by Furryk et al. [19,30], Farahmand et al. [18] and Deaton et al. 21 (cited above). Overall, the results of these studies suggest that the efficacy and safety of intravenous morphine and nebulized fentanyl are similar for pain relief in patients with renal colic. Shaker et al. report the superiority of intravenous ketorolac over morphine against renal colic. Holdgate has shown that pain relief from NSAID is better than morphine and there is less need for salvage therapy [31].

A study by Safdar et al. showed that combination of morphine and ketorolac is more effective for the management of renal colic than with solo use of these agents [32]. In a study by Wood et al., it has been shown that pain relief after pethidine or ketorolac is significant, but the ability to return to routine work after ketorolac is better [33].

As can be concluded from the above studies, in general, ketorolac reduces the pain effectively and rapidly in patients with acute colic compared to opioids, including morphine. Therefore, since previous studies have equated the analgesic effects of nebulized fentanyl and morphine whereas, ketorolac is known to be more effective than morphine, it can be hypothesized that ketorolac is likely to have superior analgesic effects than fentanyl [34].

IV ketorolac is one of the few NSAIDs whose IV administration is Food and Drug Administration approved [35]. Ketorolac is characterized by significantly lesser side-effects as compared to opioids. However, it reduces renal blood flow and decreases glomerular filtration and is therefore, not recommended in patients with renal failure. Also, this drug is not recommended in patients with a history of bleeding or active bleeding diseases and can lead to increased bleeding. Our study does not report the side effects or combinational effects of these two analgesics. Our pain measurement data was self-reported by the patients. Adding further variables could help researchers to reach a better conclusion.

5. Conclusion

Both intravenous ketorolac and nebulized fentanyl were able to significantly reduce the severity of pain, but the amount of pain reduction was greater in the ketorolac-treated patients. Further studies and optimization of the doses along with the optimization of nebulization time should be conducted.

Contributors' statement page

Dr. Barezai: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Alireza Kalantari and Dr. Peyman Astaraki: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Rasoul Salimi: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Ethical approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

From the under 16 years old was given by a parent or legal guardian.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Credit author statement

Bareza rezaei: Conceptualization, Methodology, Software, Visualization, Investigation

Rasoul Salimi: Data curation, Writing- Original draft preparation, Supervision

Alireza Kalantari: Software, Validation

Peyman Astaraki: Writing- Reviewing and Editing

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study. All the fees were provided by research center fund and deployed accordingly.

References

- [1] Mora B, Giorni E, Dobrovits M, Barker R, Lang T, Gore C, et al. Transcutaneous electrical nerve stimulation: an effective treatment for pain caused by renal colic in emergency care. *J Urol* 2006;175(5):1737–41.
- [2] Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol* 2003;170(6):2202–5.
- [3] Holdgate A, Oh CM. Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol* 2005;174(2):572–5.
- [4] Troxel S, Jones A, Magliola L, Benson J. Physiologic effect of nifedipine and tamsulosin on contractility of distal ureter. *J Endourol* 2006;20(8):565–8.
- [5] Davenport K, Timoney AG, Keeley FX. Conventional and alternative methods for providing analgesia in renal colic. *BJU Int* 2005;95(3):297–300.
- [6] REZA KB, Safarinezhad M, Markazi MN, Valimanesh H, Abd EM. The comparison of the efficacy of common pain management in acute renal colic; 2004.
- [7] Alizadeh R, Fard ZA. Renal effects of general anesthesia from old to recent studies. *J Cell Physiol* 2019;234(10):16944–52.
- [8] Rajaei M, Noorian K, Madineh S. Comparing the efficacy and adverse effects of tramadol and sodium diclofenac with pethedine in the treatment of renal colic. *Armaghane danesh* 2013;18(1):1–9.
- [9] Alizadeh R, Aghsaie Fard Z. Renal impairment and analgesia: from effectiveness to adverse effects. *J Cell Physiol* 2019;234(10):17205–11.
- [10] Aghsaiefard Z, Alizadeh R, Bagheri N. Association between neutrophil gelatinase-associated lipocalin (NGAL) and iron profile in chronic renal disease. *Arch Physiol Biochem* 2020:1–5.
- [11] Aganovic D, Prcic A, Kulovac B, Hadziosmanovic O. Clinical decision making in renal pain management. *Acta Informatica Medica* 2012;20(1):18–21.
- [12] Peng PW, Sandler AN. A review of the use of fentanyl analgesia in the management of acute pain in adults. *Anesthesiology* 1999;90(2):576–99.
- [13] Mohammadzadeh I, Mohammadi M, Khodabakhsh E. The effect of nebulized salbutamol plus magnesium sulfate in comparison with nebulized salbutamol plus normal saline in acute asthmatic attack in children. *J Babol Univ Med Sci* 2014;16(3):7–12.
- [14] Yaster M, Kost-Byerly S, Maxwell LG. Opioid agonists and antagonists. pain in infants, children, and adolescents. Philadelphia: Lippincott Williams and Wilkins; 2003; 181–224.
- [15] Bartfield JM, Flint RD, McErlean M, Broderick J. Nebulized fentanyl for relief of abdominal pain. *Acad Emerg Med* 2003;10(3):215–8.
- [16] Miner JR, Kletti C, Herold M, Hubbard D, Biros MH. Randomized clinical trial of nebulized fentanyl citrate versus iv fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* 2007;14(10):895–8.
- [17] Schoenfeld EM, Pekow PS, Shieh M-S, Scales Jr CD, Lagu T, Lindenauer PK. The diagnosis and management of patients with renal colic across a sample of US hospitals: high CT utilization despite low rates of admission and inpatient urologic intervention. *PLoS One* 2017;12(1):e0169160-e.
- [18] Farahmand S, Shiralizadeh S, Talebian M-T, Bagheri-Hariri S, Arbab M, Basirghafouri H, et al. Nebulized fentanyl vs intravenous morphine for ED patients with acute limb pain: a randomized clinical trial. *Am J Emerg Med* 2014;32(9):1011–5.
- [19] Furyk JS, Grabowski WJ, Black LH. Nebulized fentanyl versus intravenous morphine in children with suspected limb fractures in the emergency department: a randomized controlled trial. *Emerg Med Australas* 2009;21(3):203–9.
- [20] Marusteri M, Bacarea V. Comparing groups for statistical differences: how to choose the right statistical test? *Biochemia medica* 2010;20(1):15–32.
- [21] Ghasemi Basir H, Mosavi Bahar S. A survey of epidemiologic factors in patients with urinary stones in Hamadan. *Avicenna J Clin Med* 2016;23(2):157–63.
- [22] Habibi A, Najafi SM, Hossein BAA. Comparison of two drug regimens diclofenac sodium with fluids and diclofenac sodium with restricted fluids in reducing pain in patients with renal colic; 2015.
- [23] Mehrabi S, Hadinia A. Comparison of fentanyl and combination of pethedine and midazolam for pain control during extracorporeal shock wave lithotripsy. *J Shahrekord Univ Med Sci* 2011;13.
- [24] Imamoglu M, Aygün A, Bekar O, Erdem E, Cicek M, Tatti O, et al. A retrospective analysis of nebulized versus intravenous fentanyl for renal colic. *Am J Emerg Med* 2017;35.
- [25] Soares LGL, Martins ML, Uchoa R. Intravenous fentanyl for cancer pain: a “fast titration” protocol for the emergency room. *J Pain Symptom Manage* 2003;26(3):876–81.
- [26] Pazoki S, Goodarzi D, Yavari M, Babayee E, Piraste S. Evaluation of the effects of oral ketamine as an adjuvant drug in treatment of renal colic. *J Arak Univ Med Sci* 2008;11(2):56–63.
- [27] Kim JH, Jang SY, Kim MJ, Lee SY, Yoon JS. Comparison of pain-relieving effects of fentanyl versus ketorolac after eye amputation surgery. *Korean J Ophthalmol* 2013;27(4):229–34.
- [28] Kim SY, Kim EM, Nam K-H, Chang DJ, Nam SH, Kim KJ. Postoperative intravenous patient-controlled analgesia in thyroid surgery: comparison of fentanyl and ondansetron regimens with and without the nonsteroidal anti-inflammatory drug ketorolac. *Thyroid* 2008;18(12):1285–90.
- [29] Eteri M, Maj M, Maino C, Valli R. Intranasal ketorolac and opioid in treatment of acute renal colic. *Emerg Care J* 2018;14(1).
- [30] Imamoglu M, Aygun A, Bekar O, Erdem E, Cicek M, Tatti O, et al. A retrospective analysis of nebulized versus intravenous fentanyl for renal colic. *Am J Emerg Med* 2017;35(5):757–63.
- [31] Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *Bmj* 2004;328(7453):1401.
- [32] Safdar B, Degutis LC, Landry K, Vedere SR, Moscovitz HC, D’Onofrio G. Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. *Ann Emerg Med* 2006;48(2):173–81 [e1].
- [33] Wood VM, Christenson JM, Innes GD, Lesperance M, McKnight RD. The NARC (Non-steroidal Anti-inflammatory in Renal Colic) trial. Single-dose intravenous ketorolac versus titrated intravenous meperidine in acute renal colic: a randomized clinical trial. *Can J Emerg Med* 2000;2(2):83–9.
- [34] Amri Maleh MDP. Comparison of efficacy of transdermal fentanyl patch and intravenous morphine on postoperative pain of esophageal cancer surgery with trans-hiatal approach. *J Babol Univ Med Sci* 2014;16(9):7–13.
- [35] Kossick MA. Intravenous acetaminophen and intravenous ketorolac for management of pediatric surgical pain: a literature review. *AANA J* 2014;82(1):53.