Int J Clin Exp Med 2016;9(2):2969-2976
www.ijcem.com /ISSN:1940-5901/IJCEM0017409

Original Article

The comparative study on the combination of ketorolac tromethamine and sufentanil for postoperative analgesia in patients receiving traumatic lower limb surgery: a randomized controlled trial

Wei Xu[1*], Nu Zhang[1*], Mengya Ni[1], Bin Wang[3], Hao Fang[1,2]

[1]Department of Anesthesiology, Jinshan Hospital Fudan University, 1508 Longhang Road, Shanghai 201508, China; [2]Department of Anesthesiology, Zhongshan Hospital Fudan University, 180 Fenglin Road, Shanghai 200032, China; [3]Department of Mathematics and Statistics, University of South Alabama, 411 University BLVD N, Mobile 36688, AL, USA. [*]Equal contributors and co-first authors.

Received October 7, 2015; Accepted December 18, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Postoperative pain can cause a series of physiological and psychological changes, also impact systems of human body. Intravenous analgesia mainly with opioids, has been widely used in clinical practice and well accepted by patients. However, the adverse events, which may be caused by opioids influence and restrict its application. In the present study, we conducted a single-center, controlled randomized clinical trial to investigate whether the use of toradol combined with sufentanil could exert equivalent postoperative analgesic effect as with sufentanil alone in adults receiving general anesthesia after traumatic orthopedic surgery with reduced dosage of opioids. The primary endpoint was the patients' pain scores after surgery. The secondary endpoint was the Ramsay sedation scale. Total dosage of analgesics during the analgesia period, side effects, adverse events and vital signs during the study were also observed. Sixty-three patients completed the study and the outcomes for these patients were analyzed. Statistical analysis showed the combination of ketorolac tromethamine and sufentanil for postoperative analgesia in patients receiving traumatic orthopedic surgery can not only play a favourable analgesic and sedative effect, but also significantly reduce the dosage of sufentanil, with relatively less related adverse events accompanied.

Keywords: Clinical trial, ketorolac tromethamine, sufentanil, patient-controlled, dosage of opioids

Introduction

Following body temperature, pulse, respiration and blood pressure, pain has become the fifth vital sign and receives more and more attention. Postoperative pain, in particular, can cause a series of physiological and psychological changes, anxiety, fear and insomnia. It also affects the respiration, circulation, digestion, immune, endocrine and coagulation system, leading to delayed wound healing, infection and other complications. Appropriate postoperative analgesia is helpful in alleviating or eliminating postoperative discomfort, reducing the incidence of adverse events and complications, promoting postoperative recovery and improving the quality of survival. Currently, postoperative patient-controlled analgesia (PCA) technique, mainly including epidural analgesia and intravenous analgesia [1], is widely used in clinical practice. Intravenous analgesia is well accepted by the patients and easy to handle. Thus, it is the most common postoperative analgesia method in clinical practice nowadays. Opioids like fentanyl and sufentanil, are the main drugs applied for intravenous analgesia. The advantages of this application include rapid onset, favorable analgesic effect, fast clearance, and appropriate controllability [2]. However, nausea, vomiting and other adverse events, to a certain extent, limit its application [3-5].

Ketorolac tromethamine (Toradol) is the first non-steroidal anti-inflammatory drug (NSAID) available for injection. It is characterized by a strong analgesic effect, a moderate anti-inflammatory effect, mild adverse reactions and no

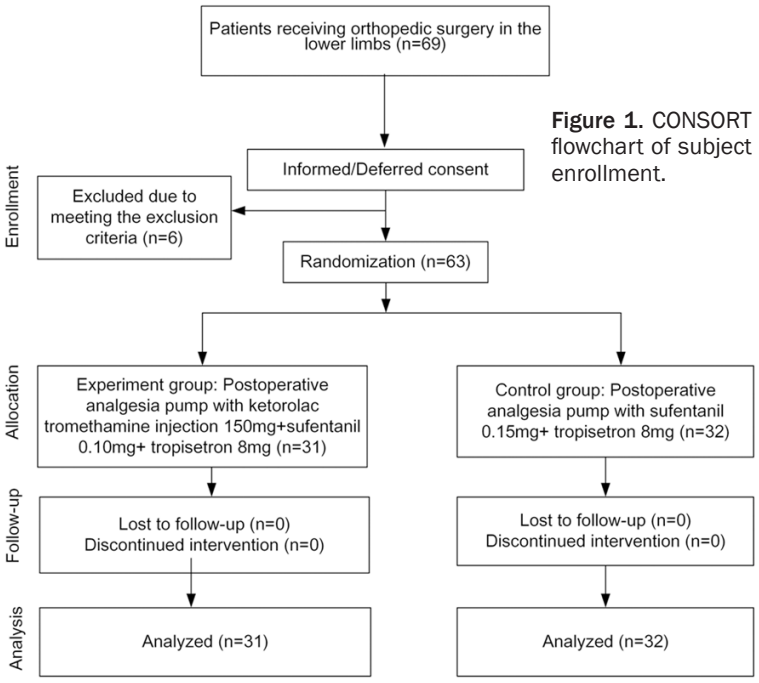

Figure 1. CONSORT flowchart of subject enrollment.

injection pain [6-8]. Currently, it has been reported to be applied in laparoscopic [9, 10], lumbar vertebral [11], cardiac [12] and pediatric surgeries [13, 14]. The postoperative effect is similar to that of morphine, pethidine and other opioids. In addition, patients using Toradol and opioids in combination take less time to pass gas, take solid food again and stop PCA than individuals only using opioids, without increasing the risk of viscera damage [15-17]. However, few studies on patients with severe postoperative pain after traumatic orthopedic surgery have been reported [18-20]. The postoperative pain following the lower limb trauma surgery, especially the tibia and fibula operation, is much more severe than other patterns of surgeries. Thus, the drug effect on analgesia after this type of surgery may vary from others'. On the Basis of existing results, the present study aimed to explore an ideal drug used for intravenous analgesia. We hoped to obtain the advantages of different drugs and avoid the corresponding shortcomings by applying two drugs in combination. As most of the previous studies mainly focused on morphine and fentanyl, rarely involving a control of sulfentanil, our null hypothesis was that ketorolac tromethamine combined with sufentanil could exert equivalent postoperative analgesic effect as sufentanil alone in adults receiving general anesthesia after traumatic orthopedic surgery while the dosage of opioids is reduced. The analgesic, sedative effect, adverse events and the reduction of opioids dosage were compared and analyzed. This study was conducted in a tertiary hospital with vast population undergoing orthopaedic surgery, making it possible to recruit enough patients in a relatively short period.

Methods

This study has been approved by Ethic Committee in Jinshan Hospital Fudan University. Subjects were selected from patients receiving orthopedic surgery in the lower limbs (installation or removal of the internal fixation device due to femoral and tibiofibular fractures) in Jinshan Hospital Fudan University in the period from July 2015 to August 2015. The patients (F:M 1:1) aged 18-70, ASA I to II, body mass index (BMI) 19 to 26 kg/m^2, suffered with moderate-level pain or above once after the surgery (Visual Analogue Scale, VAS>3) were recruited. Informed consents have been gained from all the subjects involved. All enrolled subjects showed normal in cardiac, hepatic, renal and coagulation function, by preoperative test. Intravenous analgesic pump was employed for postoperative analgesia.

Exclusion criteria [21]

Pregnant and lactating women; Allergic to NSAIDs and allergic constitution; A history of asthma; Intraoperative accidents or greatly prolonged operation duration; A history of peptic ulcer or bleeding in 6 months; Administration of NSAIDs in 2 weeks; current administration of drugs that interacts with Toradol (such as phenytoin, carbamazepine, tubocurare and other non-depolarizing muscle relaxants); Patients with delirium or those unable to depict treatment response; Coagulation disorders; Participants involved in clinical trials on other drugs in recent 3 months; Patients with poor compliance; Intraoperative blood loss ≥1500 ml.

Table 1. Demographic characteristics of patients

	Group S	Group K
n	32	31
Age (year)	48.56±11.84	49.90±11.11
Gender (M/F)	17/15	16/15
ASA I/II	13/19	14/17
BMI (Kg/m^2)	22.11±2.02	22.48±1.94
MAP (mmHg)	74.51±6.91	73.80±7.46
Operation duration (min)	96.50±87.98	92.65±49.31
Intraoperative propofol dosage (mg)	144.22±85.41	131.29±39.92
Intraoperative sufentanil dosage (μg)	24.44±7.03	24.13±8.78

In total, 69 patients were assessed for eligibility. Due to the exclusion criteria (11), which are ≥1500 ml intraoperative blood loss, 6 subjects were excluded. Thus, 63 subjects were enrolled and proceeded to finish this trial finally. They were randomized into two groups, one group with treatment of Toradol combined with sufentanil as experiment (Group K, n=31), and another group with treatment of only sufentanil as control (Group S, n=32) (**Figure 1**).

Anesthesia methods [22]

All the subjects received general anesthesia with the same criterion. Intravenous induction: injection of sufentanil 0.4 μg/kg, propofol 2 mg/kg. When the patients were well sedated, rocuronium 0.6 mg/kg was injected. 90 seconds later, tracheal intubation was performed and mechanical ventilation was applied with an anesthesia machine. VT was controlled at 8 to 10 ml/kg, and ventilation frequency 10 to 14 times/min. During the surgery, PET CO_2 was maintained at 35 to 40 mmHg. The concentration of inhaled oxygen was 50% to 60%. During the surgery, sevoflurane was inhaled for anesthesia maintenance. MAC was maintained at 1.0. Sufentanil was intermittently injected. Rocuronium was used to maintain muscle relaxant. HR was controlled between 60 bpm to 90 bpm, noninvasive mean arterial BP 60 mmHg to 90 mmHg. When the skin closure was begun, stop inhaled and intravenous anesthesia. When the patients were recovered with enough tidal volume and had swallowing reflex or when patients were awake, remove the endotracheal catheter. The patients were sent to the post anesthesia care unit (PACU). During the whole operation process, the total dosage of sufentanil was remained at about 0.6 μg/kg. For all the subjects who met the inclusion criteria of this study, patient controlled intravenous analgesia (PCIA) pump was connected at the end of the surgery.

When entering into the study, each enrolled patient would receive a random number, which was generated by computer and a set of drugs bound to the specific number. The drugs for the two groups look the same, thus patients cannot distinguish. Intraoperative anesthesia and the preparation of the analgesia pump were performed by one physician. Postoperative follow-up was completed by another physician who was completely unaware of the treatment.

Intervention [23]

After the operation, PCA solution was prepared by a designated researcher. And the patients were guided to use PCA by a designated researcher. Group S: PCIA medication: sufentanil 0.15 mg (sufentanil injection: 1 ml: 0.05 mg, Yichang Human Well Pharmaceutical Co., LTD.) + tropisetron 8 mg (tropisetron hydrochloride injection: 2 ml: 5 mg, Yichang Human Well Pharmaceutical Co., LTD.), diluted to 150 ml. Group K: PCIA medication: ketorolac tromethamine injection 150 mg + sufentanil 0.10 mg + tropisetron 8 mg, diluted to 150 ml.

The pain score was evaluated when patients regained consciousness. Patients suffering with moderate or more severe pain (i.e. intolerable pain, when painkillers were needed) were enrolled. Indicators of pain and sedation, vital signs, total dosage of opioids applied, and adverse events were observed and recorded within 48 h after the administration (7 time points: 0 h, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h).

Once the application of PCIA device was confirmed correct, patients with intolerable pain (the analgesia method was not effective by pressing the PCIA pump 12 times within 1 h), should be given 50 mg of pethidine for intramuscular injection to alleviate the pain. Drug was considered non-therapeutic-effective if the prescribed dose of the study drug within 24 h cannot exert the analgesic effect, or other drugs were necessary for analgesia.

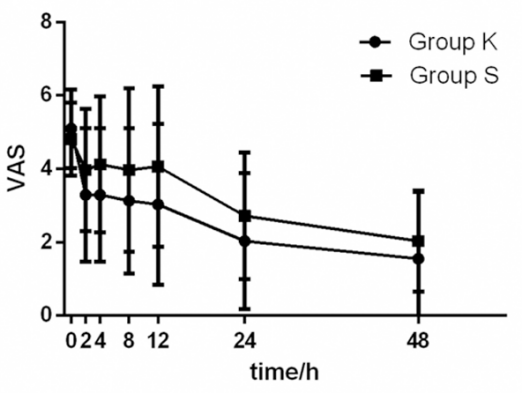

Figure 2. Comparison of the pain scores (VAS) between two groups after surgery.

Exclusion and drop-out criteria

After the re-review, the subjects did not meet the inclusion criteria or met the exclusion criteria; Other analgesic drugs were used during the study, which impacted the observation of the analgesic effect; The treatment was not complete because of adverse events; The observation indicators were not finished due to poor compliance; The investigators believed the patients' health and life would be threatened if they continued this study.

Outcomes

Primary endpoint: pain score (VAS), which was observed from 0 to 48 h after surgery.

Secondary endpoint: ramsay sedation scale, which was observed from 0 to 48 h after surgery.

Other observational variables: total dose of analgesics during the analgesia period within 48 h (0 h, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h) after the surgery, adverse events and vital signs during the study.

Pain was assessed by using VAS. The sedation score at each time point was provided and recorded by employing Ramsay sedation scale. The total dosage of drug administration, the times of effective pressing and ineffective pressing were recorded by researchers. Adverse events included nausea, vomiting, dizziness, drowsiness itching and urinary retention, in the two groups of patients were recorded as well. Blood pressure (BP), heart rate (HR) and blood oxygen saturation (SpO_2) were recorded before, 0, 2 h, 4 h, 8 h, 12 h, 24 h, and 48 h after the surgery.

Randomization and blinding

Stata 10 statistical software was used for randomization.

Single-blind: each enrolled patient would receive a random number, which was generated by computer and a set of drugs bound to the specific number. The drugs distributed to the two groups were the same in appearance, thus they are not distinguishable to the enrolled patients. Intraoperative anesthesia and the preparation of the analgesia pump were performed by one physician. Postoperative follow-up was completed by another physician who was completely unaware of the treatment.

Statistical analysis

Stata 10 statistical analysis software was used. Quantitative data are presented as mean ± SD, and categorical variables are presented as frequency (percentage). Student t test was used for the continuous variables. We used a rank-based nonparametric method for analyzing the longitudinal data to compare the treatment effects in terms of VAS and Ramsay sedation scales. The time effect and their interaction effect were also evaluated. The R package nparLD is used for computing and the *p*-values for the modified ANOVA-type statistics using the Box approximation for the whole-plot factors and their interaction were reported [32, 33]. The differences of the adverse events of nausea and vomiting were assessed for the two groups by fitting a logistic regression model. A significance level of 0.05 was used in hypothesis testing.

Results

The differences in age, gender, BMI, MAP, operation duration, intraoperative propofol dosage and intraoperative sufentanil dosage were not statistically significant between the two groups of patients (P>0.05), as shown in **Table 1**.

The VAS scores in Group K at time points after 2 hours were slightly lower than those in Group S. However, there was no statistically significant differences in analgesic (P=0.06, **Figure 2**) and sedative (P=0.08, **Figure 3**) effects between the two groups. The computed effec-

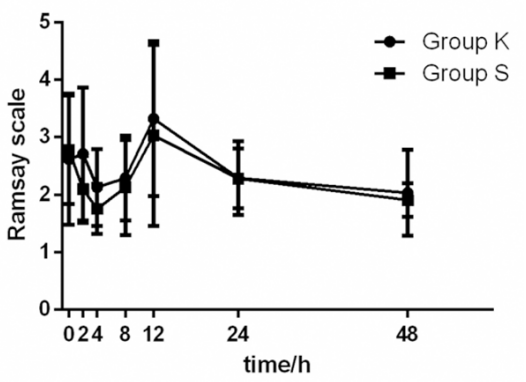

Figure 3. Comparison of the sedation scores (Ramsay scale) between two groups after surgery.

Table 2. Totalopioids dosage at each time point in two groups of patients

Time (h)	Dosage in Group S (μg, n=32)	Dosage in Group K (μg, n=31)	Significance of difference*
0	0	0	-
2	4.20±0.42	3.03±0.68	Yes
4	8.83±1.05	5.91±0.78	Yes
8	17.08±2.37	11.55±1.05	Yes
12	25.11±3.80	17.10±1.59	Yes
24	49.52±6.12	34.13±3.20	Yes
48	96.89±11.51	64.40±9.68	Yes

*Yes: comparison between the two groups, P<0.05.

tive sizes of the VAS and Ramsay scores are 0.296 and 0.053, respectively. The time effect is significant (P<0.0001), while there was no significant interaction effect between the treatment and time (**Tables 3** and **4**). The differences in dosage of opioids were statistically significant (P<0.05, **Table 2**).

The percentage of nausea was significantly higher in Group S than in Group K (P=0.017), while the percentage of vomiting was higher in Group S than in Group K but not significant (P=0.271, **Tables 5** and **6**). The time effect was significant for both postoperative adverse events-the percentages significantly dropped as time going on (P=0.029 for vomiting and P=0.002 for nausea). Neither itching nor urinary retention was observed in the two groups.

Discussion

The results of this study showed the combination of ketorolac tromethamine and sufentanil exerted similar analgesic and sedative effects when compared with sufentanil alone for postoperative analgesia. However, the combination of ketorolac tromethamine and sufentanil can significantly reduce the dosage of sufentanil and opioids-related adverse reactions, like nausea, vomiting (**Tables 2**, **5**, **6**).

The potential mechanism is ketorolac inhibits arachidonic acid to transform into prostacyclin and prostaglandins by inhibiting the activity of cyclooxygenase, in order to decrease the secretion of prostaglandin at the site of tissue injury or inflammation. The sensitivity of the afferent nerve terminals at local lesions is inhibited. Thus, the impact on the whole body is reduced [24]. Referred the study by Diblasio et al. [25], the present study also showed that a reduction of 30% of the normal sufentanil concentration, when combined with ketorolac tromethamine, can exert the same analgesic and sedative effect, even better. Meanwhile, the dosage of PCA drug was not increased. Therefore, the possibility of side effects was decreased. The results confirmed the hypothesis in the study design.

Ng. A et al. compared ketorolac and parecoxib (selective cox-2 inhibitor). After induction, they intravenously injected ketorolac 30 mg and parecoxib 40 mg, respectively. It was reported that ketorolac was more effective than parecoxib for analgesia within 4 h after surgery. Therefore, the dosage of opioids and its side effects was reduced [26, 27]. Smith LA. et al. also demonstrated the analgesic effect of the oral administration of ketorolac 10 mg was similar to the muscular injection of ketorolac 30 mg [28]. In addition, intramuscular injection of ketorolac can achieve the analgesic effect similar to that of morphine. The effect of ketorolac 30 mg was equivalent to that of morphine 4 mg. Moreover, ketorolac was superior to cox-2 inhibitors in postoperative analgesia [29, 30]. Since orthopedic trauma causes great damage to the tissues, leading to severe and persistent pain and discomfort. The recovery also lasts a relatively long time. Lower limb surgery, in particular, needs a long term of postoperative braking, which usually results in more lasting discomfort. Therefore, favorable postoperative analgesia can promote postoperative recovery and improve the quality of survival. Sufentanil alone can relieve pain [31]. However, this greatly increases the possibility of side effects like nausea and vomiting, which further impact postoperative recovery. The combination of

Table 3. Nonparametric longitudinal data analysis results for VAS scores

	df	Rank Means	Relative Treatment Effect (P)
Wald-Type Statistics			
Group	1	3.169	0.0750
Time	5	235.944	<0.0001
Group: Time	5	5.587	0.3485
ANOVA-Type Statistics			
Group	1	3.169	0.0750
Time	6	48.715	<0.0001
Group: Time	6	1.599	0.1787
Modified ANOVA-Type Statistic for the Whole-Plot Factors			
Group	(1, 60.6)	3.169	0.0801

Table 4. Nonparametric longitudinal data analysis results for Ramsay sedation scales

	df	Rank Means	Relative Treatment Effect (P)
Wald-Type Statistics			
Group	1	3.524	0.0605
Time	6	98.248	<0.0001
Group: Time	6	9.278	0.1585
ANOVA-Type Statistics			
Group	1	3.524	0.0605
Time	6	13.584	<0.0001
Group: Time	6	2.003	0.0784
Modified ANOVA-Type Statistic for the Whole-Plot Factors			
Group	(1, 55.5)	3.524	0.0657

Table 5. Percentage of vomiting at each time point in two groups

Time	Group S	Group K
0	6% (2/32)	10% (3/31)
2	9% (3/32)	6% (2/31)
4	6% (2/32)	3% (1/31)
8	9% (3/32)	3% (1/31)
12	0	0
24	6% (2/32)	0
48	0	0

Table 6. Percentage of nausea at each time point in two groups

Time (h)	Group S	Group K
0	9% (3/32)	3% (1/31)
2	9% (3/32)	0
4	13% (4/32)	6% (2/31)
8	3% (1/32)	0
12	0	0
24	3% (1/32)	0
48	0	0

ketorolac and sufentanil can not only exert a strong analgesic effect, but also makes up the side effect of sufentanil. This is ideal for postoperative analgesia.

This study is limited to postoperative analgesia after orthopaedic surgery of the lower limbs. Different types of orthopaedic surgery were not included. If multiple gradient concentrations of opioids had been designed, the dosage of opioids can be reduced at utmost, so as to avoid the complications, improve patients' comfort, and shorten the hospital stay.

Conclusion

The combination of ketorolac tromethamine and sufentanil exerts similar analgesic and sedative effects when compared with sufentanil alone for postoperative analgesia in patients receiving traumatic orthopedic surgery. It can not only significantly decrease the dosage of sufentanil, but also reduce the possibility of related adverse events.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hao Fang, Department of Anesthesiology, Jinshan Hospital Fudan University, 1508 Longhang Road, Shanghai 201508, China; Department of Anesthesiology, Zhongshan Hospital Fudan University, 180 Fenglin Road, Shanghai 200032, China. E-mail: fanghao_dr@163.com; Dr. Bin Wang, Department of Mathematics and Statistics, University of South Alabama, 411 University BLVD N, Mobile 36688, AL, USA. E-mail: bwang@southalabama.edu

References

[1] Gritsenko K, Khelemsky Y, Kaye AD, Vadivelu N, Urman RD. Multimodal therapy in perioperative analgesia. Best Pract Res Clin Anaesthesiol 2014; 28: 59-79.

[2] Macintyre PE, Huxtable CA, Flint SL and Dobbin MD. Costs and consequences: a review of discharge opioid prescribing for ongoing management of acute pain. Anaesth Intensive Care 2014; 42: 558-574.

[3] Pergolizzi JV, Taylor R and Raffa RB. Intranasal ketorolac as part of a multimodal approach to postoperative pain. Pain Pract 2015; 15: 378-88.

[4] Simon SM and Schwartzberg LS. A review of rapid-onset opioids for breakthrough pain in patients with cancer. J Opioid Manag 2014; 10: 207-215.

[5] Jones T, Lookatch S, Grant P, McIntyre J and Moore T. Further validation of an opioid risk assessment tool: the Brief Risk Interview. J Opioid Manag 2014; 10: 353-364.

[6] Kossick MA. Intravenous acetaminophen and intravenous ketorolac for management of pediatric surgical pain: a literature review. AANA J 2014; 82: 53.

[7] Iorno V, Landi L, Di Pasquale R, Cicenia S and Moschini V. Comparison of intravenous ketorolac with or without paracetamol in postoperative pain control following ambulatory surgery. Curr Med Res Opin 2013; 29: 1685-1690.

[8] Gobble RM, Hoang HL, Kachniarz B and Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. Plast Reconstr Surg 2014; 133: 741-755.

[9] Lee SJ, Calderon B, Gardner GJ, Mays A, Nolan S, Sonoda Y, Barakat RR and Leitao MM. The feasibility and safety of same-day discharge after robotic-assisted hysterectomy alone or with other procedures for benign and malignant indications. Gynecol Oncol 2014; 133: 552-555.

[10] Hwang B, Kwon J, Kim E, Lee D, Kim T and Kim H. Oxycodone vs. fentanyl patient-controlled analgesia after laparoscopic cholecystectomy. Int J Med Sci 2014; 11: 658.

[11] Gianesello L, Pavoni V, Barboni E, Galeotti I and Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. J Neurosurg Anesthesiol 2012; 24: 121-126.

[12] Oliveri L, Jerzewski K and Kulik A. Black box warning: is ketorolac safe for use after cardiac surgery? J Cardiothorac Vasc Anesth 2014; 28: 274-279.

[13] Chan DK and Parikh SR. Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. Laryngoscope 2014; 124: 1789-1793.

[14] Mohammed BS, Engelhardt T, Cameron GA, Hawwa AF, Helms PJ and McLay JS. Development of an enantiomer selective microsampling assay for the quantification of ketorolac suitable for paediatric pharmacokinetic studies. Biopharm Drug Dispos 2013; 34: 377-386.

[15] Carney DE, Nicolette LA, Ratner MH, Minerd A and Baesl TJ. Ketorolac reduces postoperative narcotic requirements. J Pediatr Surg 2001; 36: 76-79.

[16] Grimsby GM, Andrews PE, Castle EP, Nunez R, Mihalik LA, Chang YH and Humphreys MR. Long-term renal function after donor nephrectomy: secondary follow-up analysis of the randomized trial of ketorolac vs placebo. Urology 2014; 84: 78-81.

[17] Lowder JL, Shackelford DP, Holbert D and Beste TM. A randomized, controlled trial to compare ketorolac tromethamine versus placebo after cesarean section to reduce pain and narcotic usage. Obstet Gynecol 2003; 189: 1559-1562.

[18] Banerjee P and Rogers BA. Systematic review of high-volume multimodal wound infiltration in total knee arthroplasty. Orthopedics 2014; 37: 403-412.

[19] Baratta JL, Gandhi K and Viscusi ER. Perioperative pain management for total knee arthroplasty. J Surg Orthop Adv 2014; 23: 22-36.

[20] Young AC and Buvanendran A. Pain management for total hip arthroplasty. J Surg Orthop Adv 2014; 23: 13-21.

[21] Banerjee P. The efficacy of multimodal high-volume wound infiltration in primary total knee replacement in facilitating immediate post-operative pain relief and attainment of early rehabilitation milestones. Eur J Orthop Surg Traumatol 2014; 24: 571-577.

[22] Hwang B, Kwon J, Kim E, Lee D, Kim T and Kim H. Oxycodone vs. fentanyl patient-controlled analgesia after laparoscopic cholecystectomy. Int J Med Sci 2014; 11: 658.

[23] Daniels S, Melson T, Hamilton DA, Lang E and Carr DB. Analgesic efficacy and safety of a novel injectable formulation of diclofenac compared with intravenous ketorolac and placebo after orthopedic surgery: a multicenter, randomized, double-blinded, multiple-dose trial. Clin J Pain 2013; 29: 655-663.

[24] Varrassi G, Marinangeli F, Agro F, Aloe L, De Cillis P, De Nicola A, Giunta F, Ischia S, Ballabio M and Stefanini S. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. Anesthes Analges 1999; 88: 611-616.

[25] Diblasio CJ, Snyder ME, Kattan MW, Russo P. Ketorolac: safe and effective analgesia for the management of renal cortical tumors with partial nephrectomy. J Urol 2004; 171: 1062-1065.

[26] Ng A, Temple A, Smith G and Emembolu J. Early analgesic effects of parecoxib versus ketorolac following laparoscopic sterilization: a randomized controlled trial. Br J Anaesth 2004; 92: 846-849.

[27] Chapa HO, Antonetti AG and Bakker K. Ketorolac-mepivacaine lower uterine block for in-office endometrial ablation: a randomized, controlled trial. J Reprod Med 2010; 55: 464-468.

[28] Smith LA, Carroll D, Edwards JE, Moore RA and McQuay HJ. Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. Br J Anaesth 2000; 84: 48-58.

[29] Gan TJ, Daniels SE, Singla N, Hamilton DA and Carr DB. A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: a multicenter, double-blind, randomized, multiple-dose study. Anesth Analg 2012; 115: 1212-1220.

[30] Grimsby GM, Conley SP, Trentman TL, Castle EP, Andrews PE, Mihalik LA, Hentz JG and Humphreys MR. A double-blind randomized controlled trial of continuous intravenous Ketorolac vs placebo for adjuvant pain control after renal surgery. Mayo Clin Proc 2012; 87: 1089-1097.

[31] Han JB, Keller EE and Grothe RM. Postoperative gastrointestinal bleeding in orthognathic surgery patients: its estimated prevalence and possible association to known risk factors. J Oral Maxillofac Surg 2014; 72: 2043-2051.