Original Article

Effects of preincisional analgesia with surgical site infiltration of ketamine or levobupivacaine in patients undergoing abdominal hysterectomy under general anesthesia; A randomized double blind study

ABSTRACT

Context: Postoperative pain management remains a cornerstone in patient's management to ensure a better quality of life. Preemptive analgesia is reported to inhibit the persistence of postoperative pain.

Aims: The aim of this study is to assess the analgesic effectiveness of preincisional infiltration of ketamine following elective abdominal hysterectomy as compared to levobupivacaine.

Settings and Design: This was a prospective, randomized, double-blind study.

Subjects and Methods: This study included 48 patients undergoing abdominal hysterectomy under general anesthesia. They were randomized into two equal groups; Group K received subcutaneous infiltration of 20 ml containing ketamine 2 mg/kg and Group L received subcutaneous infiltration of 20 ml of levobupivacaine 0.25% along the Pfannenstiel incision 5 min before incision. Postoperative pain was assessed using visual analog scale (VAS) at rest and on coughing with evaluation of additional opioid analgesic requirements.

Statistical Analysis Used: Numerical variables were presented as mean and standard deviation or median and range as appropriate. The intergroup differences were compared using the independent-sample Student's *t*-test or Mann–Whitney test for numerical variables.

Results: VAS score decreased significantly in Group L from 10 to 24 h and in Group K from 8 to 24 h as compared to the immediate postoperative reading. VAS score in ketamine group was significantly lower than that in the levobupivacaine group 8, 10, and 24 h postoperatively. Ketamine group showed delayed request of additional opioid analgesia ($P < 0.001$) with significantly less opioid consumption ($P < 0.001$) as compared to levobupivacaine. The total dose of meperidine consumed during the 24 postoperative h was significantly smaller in ketamine group ($P < 0.001$).

Conclusion: Surgical site infiltration of ketamine is a promising preemptive analgesic method in the lower abdominal surgery with minimal sedation and adverse effects.

Key words: general anesthesia; ketamine; levobupivacaine; surgical site infiltration

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Introduction

Postoperative pain management has become a major quality of life issue.[1] Unfortunately, adequate postoperative analgesia is achieved in a minority of patients.[2] Adverse physiological alterations due to insufficient postoperative analgesia may eventually lead to increased morbidity and mortality.[3] Delayed postoperative mobilization caused by pain reduces quality of life and delays return to normal daily activities.[4,5]

Preemptive analgesia (treating pain before its onset) was described in the beginning of the last century.[6] Preemptive analgesia is intended to decrease acute pain after tissue injury, prevent pain-related pathologic modulation of the central nervous system, and inhibit the persistence of postoperative pain.[1]

The use of preemptive analgesia has been reported in different surgeries including cesarean delivery, abdominal hysterectomy, and open cholecystectomy.[7] Postoperative pain varies according to many variables including age, sensitivity to pain, type and duration of surgery, and type of analgesia used, making the optimal management of pain problematic.[8]

Ketamine is a noncompetitive antagonist of n-methyl-d-aspartate (NMDA) receptor which plays an important role in pain modulation.[9,10] Stubhaug *et al*.[10] showed that ketamine decreases acute postoperative pain by inhibiting C-fiber activity. Preincisional infiltration of ketamine prolongs the time to first analgesic requirement and also decreases the total amount of analgesics used postoperatively.[11]

Levobupivacaine is the pure S(−)-enantiomer of racemic bupivacaine. Clinically, levobupivacaine has been shown to have the same efficiency as bupivacaine at comparable doses and concentrations and produce similar anesthetic characteristics.[12] Levobupivacaine has been found to have lower risk of cardiovascular and central nervous system toxicity than bupivacaine.[13]

The aim of this study was to assess the effectiveness of preincisional infiltration of ketamine for attenuation of postoperative pain following elective abdominal hysterectomy as compared with levobupivacaine infiltration.

Subjects and Methods

After approval of the Institutional Ethical Committee, this randomized, double-blind study included 48 patients American Society of Anesthesiologists (ASA) Physical Status I, II undergoing elective abdominal hysterectomy under general anesthesia. They were recruited from the Obstetrics and Gynecology Department at Kasr El Aini Hospital between September 2015 and April 2016. A written informed consent was obtained from each participant on the day of surgery by an anesthesiologist. Trial registration: Pan African Clinical Trial Registry, http://www.pactr.org. PACTR201509001245595, registered on August 23, 2015.

Exclusion criteria were patients with allergy to study drugs, cardiovascular disease (hypertension, tachycardia, congestive heart failure, and coronary artery disease), decompensated liver, renal failure, and duration of surgery more than 120 min.

Using computer-generated random list, the participants were randomized into two equal treatment groups. Group K (ketamine $n = 24$) received subcutaneous infiltration of ketamine 2 mg/kg and Group L (levobupivacaine $n = 24$) received subcutaneous infiltration of 20 ml of levobupivacaine 0.25%. All medications were diluted with sterile 0.9% saline solution to 20 ml volume and similar syringes and were infiltrated subcutaneously along the skin wound edges (Pfannenstiel incision) 5 min before skin incision.

Heart rate (HR), noninvasive arterial blood pressure (systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure [MAP]), end-tidal carbon dioxide, and peripheral oxygen saturation level were monitored in the operating room.

Anesthesia was induced by propofol 10% 2 mg/kg, 3 μg/kg fentanyl, and 0.5 mg/kg of atracurium for facilitation of tracheal intubations. Anesthesia was maintained by 1.2% isoflurane. Mechanical ventilation with air in oxygen (1:1) was set to maintain normocapnia. An anesthetist who was not involved in the conduct of anesthesia prepared the study drugs. The study drugs were infiltrated subcutaneously by a surgeon who was not involved in group assignment into the incisional site region after induction of anesthesia and all surgical incisions were done only after 15 min from the study drug administration. At the end of surgery, volatile anesthetics were discontinued, neuromuscular blockade was reversed by intravenous (IV) neostigmine mg/kg and IV atropine 0.02 mg/kg, and extubation was performed when airway reflexes had returned.

During the postoperative period, pain was assessed by a blinded observing physician at 0, 1, 2, 4, 6, 8, 12, 24 h using visual analog scale (VAS) where 0 = no pain and 10 = the worst pain possible. VAS scores at rest and on coughing were assessed. In addition, the patients were assessed for level

of sedation using sedation scale (0 = awake; 1 = drowsy but responsive to verbal orders; 2 = drowsy but responsive to physical stimulus; 3 = sleepy but responsive to painful stimulus), HR, and MAP. The time from induction of anesthesia to discontinuation of anesthesia was considered as the anesthetic time and the time from the first surgical incision till the last skin suture was considered to be the operative time. All these data were recorded by a physician blinded to the study protocol.

In postoperative care unit, all patients received the same analgesic regimen consisting of administration of 1 g propacetamol intravenously every 8 h, and if the VAS score was >4. Meperidine 0.4 mg/kg was given intravenously if the VAS score did not decrease within 10 min. If the VAS score did not decrease within 10 more min, meperidine 0.2 mg/kg was given to the patient with maximum dose of 2 mg/kg in any 4 h. The total meperidine consumption and time to the first additional meperidine need were recorded. Finally, occurrence of adverse effects such as nausea, vomiting, dizziness, hallucination, and allergic reactions was recorded in the postoperative period. In case of vomiting, ondansetron 4 mg was given intravenously.

Statistical analysis of the data was performed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical variables were presented as mean and standard deviation or median and range as appropriate. The intergroup differences were compared using the independent-sample Student's *t*-test or Mann–Whitney test for numerical variables. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. All tests were two-sided. A $P < 0.05$ was considered statistically significant.

Results

No patients were excluded from the study after enrollment. Intention-to-treat analysis was performed, and data from all 48 women were analyzed [Figure 1]. The two groups were comparable regarding age, weight, ASA class, and duration of anesthesia and surgery [Table 1].

Table 2 shows that the VAS score at rest decreased significantly in Group L starting from 10 h postoperatively up to 24 h. In Group K, VAS score decreased significantly from 8 to 24 h as compared to the immediate postoperative reading. VAS score

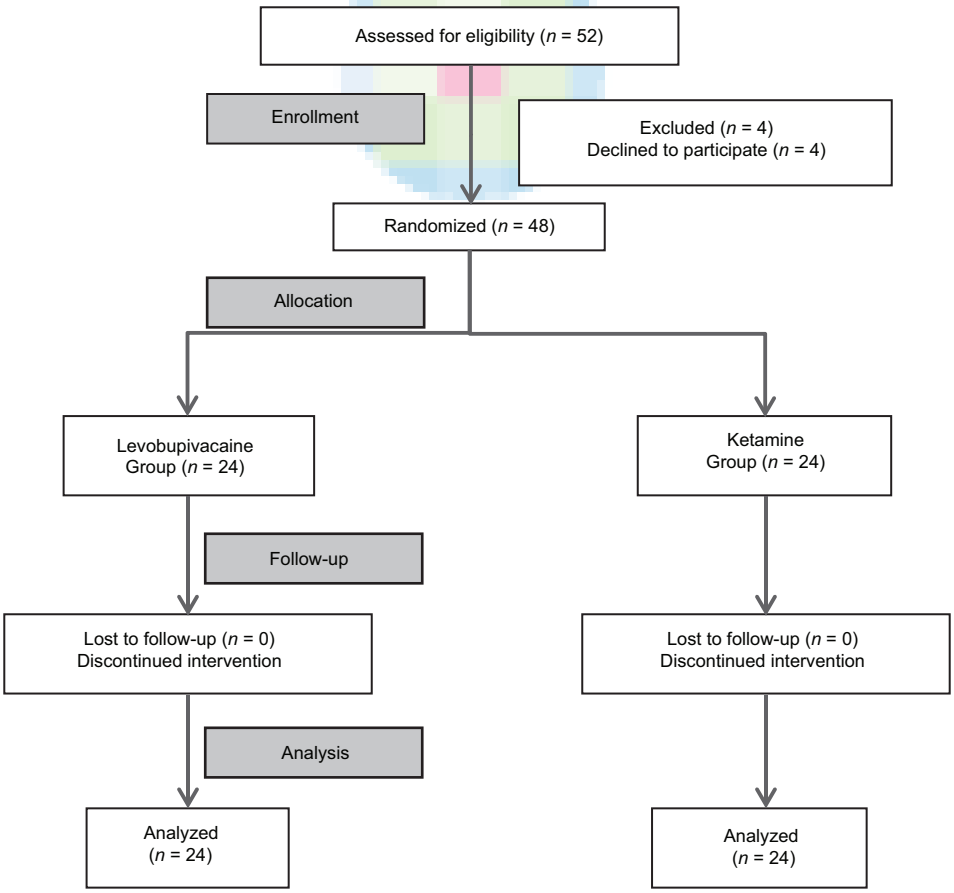

Figure 1: CONSORT flow diagram

in ketamine group was significantly lower than that in the levobupivacaine group 8, 10, and 24 h postoperatively. The time-to-first request of additional analgesia was significantly longer in ketamine group ($P < 0.001$). The total dose of meperidine consumed during the 24 postoperative h was significantly smaller in ketamine group ($P < 0.001$) [Table 3].

There were no clinically significant changes in blood pressure and HR throughout the 24 postoperative h in the two groups [Figures 2 and 3]. Sedation was limited to maximally score 1 as shown in Table 4 in the two groups up to 8 h postoperatively, with no significant difference between the two groups. Afterward, sedation score was zero in all patients.

Postoperative adverse effects of levobupivacaine were limited to one case of nausea and another case of dizziness. Ketamine-related adverse effects were two cases of nausea, one case of vomiting and one case of dizziness.

Discussion

The results of this study indicate that preincisional surgical site infiltration using both ketamine and levobupivacaine can provide adequate postoperative pain relief up to 24 h postoperatively following abdominal hysterectomy under general anesthesia. Both drugs were safe with minimal sedation and limited adverse events. Ketamine appeared to have a longer analgesic duration compared to levobupivacaine. It delayed requesting and decreased consumption of additional analgesia.

The concept of preemptive or preincisional analgesia focuses on prevention of central sensitization triggered by surgical incision; however, other factors have been advocated to exaggerate acute and long-term postoperative pain as a result of central sensitization. These include noxious intraoperative stimuli as retraction, postoperative inflammatory processes, and ectopic neural activity.[14]

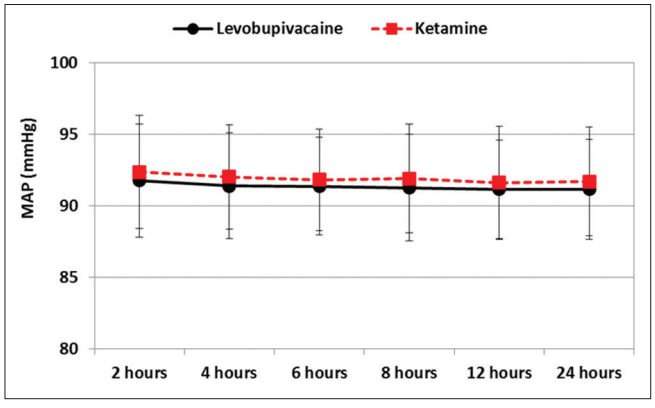

Figure 2: Changes of mean arterial pressure during the 24 postoperative h in the two studied groups; data are presented as mean ± standard deviation

In the current study, we tested the hypothesis that ketamine, having multiple mechanisms of action, may be effective when administered by subcutaneous injection at the surgical site before incision. The analgesic effect of ketamine may involve the block of other sources of pain. It is a NMDA receptor antagonist that can reverse central sensitization and reduce wind-up and consequently decreases postoperative pain.[15] It has been shown to have a local anesthetic effect mediated by a depression of sodium-channel function.[16] The analgesic effect of ketamine may be increased due to its

Table 1: Baseline characteristics of the two studied groups

	Group L ($n=24$)	Group K ($n=24$)	*P*
Age (years)	48.4±5.6	47.0±5.9	0.399
Weight (kg)	76.3±5.6	78.5±6.0	0.177
ASA Class I/II	18/6	19/5	0.731
Duration of surgery (min)	94.6±9.3	91.7±10.3	0.309
Anesthetic time (min)	37.9±3.1	37.8±3.4	0.860

Data are expressed as mean and SD or numbers. SD: Standard deviation, ASA: American Society of Anesthesiologists

Table 2: Visual analog score in the 24 postoperative h in the two studied groups

	Group L ($n=24$)	Group K ($n=24$)	*P*
Immediate	2 (1-3)	2 (1-3)	0.609
2 h	2 (1-3)	2 (1-3)	0.808
4 h	2 (1-3)	2 (1-3)	0.144
6 h	2 (1-3)	2 (1-3)	0.206
8 h	2 (0-2)	1 (0-2)*	0.046
10 h	2 (0-2)*	1 (0-2)*	0.048
12 h	1 (0-2)	1 (0-1)	0.161
24 h	1 (0-2)*	0 (0-1)*	<0.001

*Significantly lower than the immediate postoperative reading, data are expressed as median and range

Table 3: Pattern of additional analgesic requirements during the postoperative period in the two studied groups

	Group L ($n=24$)	Group K ($n=24$)	*P*
Time of first analgesic demand (min)	127.7±5.7	158.3±7.9	<0.001
Total meperidine consumption (mg)	105.8±9.3	90.2±5.8	<0.001

Data are expressed as mean±SD. SD: Standard deviation

Table 4: Number and percentage of patients with sedation score in the two studied groups

	Group L ($n=24$), *n* (%)	Group K ($n=24$), *n* (%)	*P*
Immediate	5 (20.8)	8 (33.3)	0.517
2 h	2 (8.3)	6 (25.0)	0.245
4 h	1 (4.2)	3 (12.5)	0.609
6 h	1 (4.2)	2 (8.3)	1.000
8 h	0	1 (4.2)	1.000

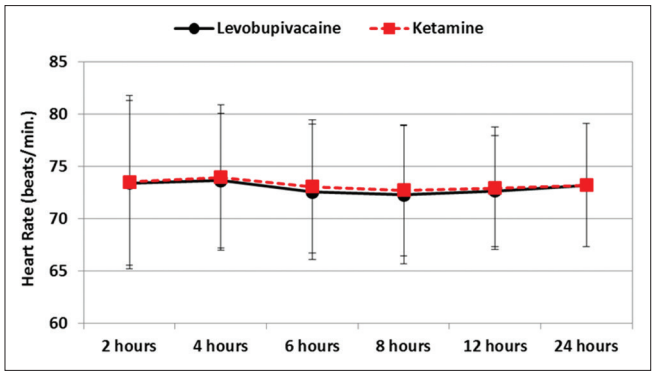

Figure 3: Changes of heart rate during the 24 postoperative hours in the two studied groups; data are presented as mean ± standard deviation

anti-proinflammatory effect. It interacts with inflammatory cells recruitment, cytokines production, and inflammatory mediator regulation.[17]

Investigators were concerned whether the analgesic effect of ketamine is mainly a result of an antihyperalgesia, or specific analgesia.[18] Pain level appears to reflect an increased nociceptive input in addition to pain sensitization process. Glutamate through the NMDA receptors plays a major role in this phenomenon of neuronal plasticity that leads to pain hypersensitivity that could facilitate chronic pain development. By an action on NMDA receptors, opioids also induce, in a dose-dependent manner, an enhancement of this postoperative hypersensitivity. Thus, ketamine the NMDA receptors antagonist can exert its antihyperalgesic effect to decrease this central sensitization in the postoperative period.[19]

On the other hand, the action of local anesthetic is restricted to block of nerve impulse conduction by inhibition of sodium channels at the nerve endings and along the axon.[20] In the current study, we compared ketamine with levobupivacaine owing to its longer duration of action (approximately 14–16 h) which diminishes the clinical importance of adding epinephrine.[21] Ketamine has the additional advantage of being inexpensive, widely available, noninvasive and does not require additional laboratory work.

Several previous studies in adults and children have demonstrated postoperative analgesic efficacy of local anesthetic infiltration of surgical site including laparoscopic gynecology,[22] orthopedic surgery,[23,24] and hernia repair.[25,26] Moreover, randomized trials reported that preemptive injection of levobupivacaine provides more effective postoperative analgesia in patients undergoing lumbar discectomy and laparoscopic cholecystectomy.[27,28]

In a recent randomized trial, surgical site infiltration with liposomal bupivacaine was compared to transversus abdominis plane blocks for pain relief after total abdominal hysterectomy through a Pfannenstiel incision. Surgical site infiltration provided superior pain relief at rest and on coughing and reduced opioid consumption for up to 48 h.[29] Other studies did not find any advantage of local infiltration in many types of surgery.[30-32]

Postoperative analgesic efficacy of surgical site infiltration of ketamine has been demonstrated in few previous studies, mostly in pediatric population. In a group of fifty children undergoing palatoplasty, ketamine produced similar analgesic effect compared to bupivacaine up to 12 h; then pain intensity was lower with ketamine 24 h postoperatively with reduction of requirement of rescue analgesic.[33]

A prospective, randomized, double-blind study compared postoperative analgesic efficacy of preincisional peritonsillar infiltration of ketamine and ropivacaine in children undergoing tonsillectomy. Ketamine was as effective as ropivacaine in pain relief, but ropivacaine was superior in reduction of time to first analgesic demand.[34] In a similar study, ketamine was equivalent to tramadol in pain reduction. It was safe with limited instances of postoperative nausea, vomiting, and dysphagia.[35] These results confirmed the findings of prior systematic review including four studies of local ketamine infiltration with tonsillectomy.[36]

A recent meta-analysis of ten studies concluded that perioperative ketamine peritonsillar infiltration in children can relieve postoperative pain within 1 h but not at 2 h and reduces analgesic requirement.[37] In forty adults undergoing circumcision surgery, preincisional subcutaneous ketamine infiltration was found to suppress postoperative pain.[11]

However, earlier studies found no beneficial postoperative analgesic effects of preemptive ketamine administered intravenously in small doses in adults undergoing abdominal hysterectomy,[38] total mastectomy,[39] and cruciate ligament repair.[40]

Conclusion

We can conclude that ketamine appears to be a promising preemptive analgesic through surgical site infiltration in lower abdominal surgery. It has comparable effect to levobupivacaine with longer duration of action and minimal adverse effects.

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Conflicts of interest

There are no conflicts of interest.

References

1. Grape S, Tramèr MR. Do we need preemptive analgesia for the treatment of postoperative pain? Best Pract Res Clin Anaesthesiol 2007;21:51-63.
2. Sommer M, de Rijke JM, van Kleef M, Kessels AG, Peters ML, Geurts JW, *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. Eur J Anaesthesiol 2008;25:267-74.
3. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North America 2005;23:21-36.
4. Bernucci F, Carli F. Functional outcome after major orthopedic surgery: The role of regional anesthesia redefined. Curr Opin Anaesthesiol 2012;25:621-8.
5. Parvizi J, Miller AG, Gandhi K. Multimodal pain management after total joint arthroplasty. J Bone Joint Surg Am 2011;93:1075-84.
6. Crile GW. The kinetic theory of shock and its prevention through anociassociation (Shockless operation). Lancet 1913;11:7-16.
7. Møiniche S, Mikkelsen S, Wetterslev J, Dahl JB. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. Br J Anaesth 1998;81:377-83.
8. Pan PH. Post cesarean delivery pain management: Multimodal approach. Int J Obstet Anesth 2006;15:185-8.
9. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: A review of current techniques and outcomes. Pain 1999;82:111-25.
10. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997;41:1124-32.
11. Tan PH, Cheng JT, Kuo CH, Tseng FJ, Chung HC, Wu JI, *et al.* Preincisional subcutaneous infiltration of ketamine suppresses postoperative pain after circumcision surgery. Clin J Pain 2007;23:214-8.
12. Glaser C, Marhofer P, Zimpfer G, Heinz MT, Sitzwohl C, Kapral S, *et al.* Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg 2002;94:194-8.
13. Foster RH, Markham A. Levobupivacaine: A review of its pharmacology and use as a local anaesthetic. Drugs 2000;59:551-79.
14. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: Risk factors and protective factors. Expert Rev Neurother 2009;9:723-44.
15. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage 2000;20:358-73.
16. Frenkel C, Urban BW. Molecular actions of racemic ketamine on human CNS sodium channels. Br J Anaesth 1992;69:292-7.
17. Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: State of the art. Acta Anaesthesiol Belg 2011;62:47-58.
18. Persson J. Wherefore ketamine? Curr Opin Anaesthesiol 2010;23:455-60.
19. Richebé P, Rivat C, Rivalan B, Maurette P, Simonnet G. Low doses ketamine: Antihyperalgesic drug, non-analgesic. Ann Fr Anesth Reanim 2005;24:1349-59.
20. Heavner JE. Local anesthetics. Curr Opin Anaesthesiol 2007;20:336-42.
21. Burlacu CL, Buggy DJ. Update on local anesthetics: Focus on levobupivacaine. Ther Clin Risk Manag 2008;4:381-92.
22. El Hachem L, Small E, Chung P, Moshier EL, Friedman K, Fenske SS, *et al.* Randomized controlled double-blind trial of transversus abdominis plane block versus trocar site infiltration in gynecologic laparoscopy. Am J Obstet Gynecol 2015;212:182.e1-9.
23. Gurbet A, Bekar A, Bilgin H, Ozdemir N, Kuytu T. Preemptive wound infiltration in lumbar laminectomy for postoperative pain: Comparison of bupivacaine and levobupivacaine. Turk Neurosurg 2014;24:48-53.
24. Ozyilmaz K, Ayoglu H, Okyay RD, Yurtlu S, Koksal B, Hanci V, *et al.* Postoperative analgesic effects of wound infiltration with tramadol and levobupivacaine in lumbar disk surgeries. J Neurosurg Anesthesiol 2012;24:331-5.
25. Nesioonpour SH, Akhondzadeh R, Pipelzadeh MR, Rezaee S, Nazaree E, Soleymani M. The effect of preemptive analgesia with bupivacaine on postoperative pain of inguinal hernia repair under spinal anesthesia: A randomized clinical trial. Hernia 2013;17:465-70.
26. Gurnaney HG, Maxwell LG, Kraemer FW, Goebel T, Nance ML, Ganesh A. Prospective randomized observer-blinded study comparing the analgesic efficacy of ultrasound-guided rectus sheath block and local anaesthetic infiltration for umbilical hernia repair. Br J Anaesth 2011;107:790-5.
27. Gurbet A, Bekar A, Bilgin H, Korfali G, Yilmazlar S, Tercan M. Pre-emptive infiltration of levobupivacaine is superior to at-closure administration in lumbar laminectomy patients. Eur Spine J 2008;17:1237-41.
28. Cantore F, Boni L, Di Giuseppe M, Giavarini L, Rovera F, Dionigi G. Pre-incision local infiltration with levobupivacaine reduces pain and analgesic consumption after laparoscopic cholecystectomy: A new device for day-case procedure. Int J Surg 2008;6 Suppl 1:S89-92.
29. Gasanova I, Alexander J, Ogunnaike B, Hamid C, Rogers D, Minhajuddin A, *et al*. Transversus abdominis plane block versus surgical site infiltration for pain management after open total abdominal hysterectomy. Anesth Analg 2015;121:1383-8.
30. Tam T, Harkins G, Wegrzyniak L, Ehrgood S, Kunselman A, Davies M. Infiltration of bupivacaine local anesthetic to trocar insertion sites after laparoscopy: A randomized, double-blind, stratified, and controlled trial. J Minim Invasive Gynecol 2014;21:1015-21.
31. Tüzel E, Kiziltepe G, Akdogan B. The effect of local anesthetic infiltration around nephrostomy tract on postoperative pain control after percutaneous nephrolithotomy. Urolithiasis 2014;42:353-8.
32. Leelanukrom R, Suraseranivongse S, Boonrukwanich V, Wechwinij S. Effect of wound infiltration with bupivacaine on postoperative analgesia in neonates and infants undergoing major abdominal surgery: A pilot randomized controlled trial. J Anesth 2012;26:541-4.
33. Jha AK, Bhardwaj N, Yaddanapudi S, Sharma RK, Mahajan JK. A randomized study of surgical site infiltration with bupivacaine or ketamine for pain relief in children following cleft palate repair. Paediatr Anaesth 2013;23:401-6.
34. Farmawy MS, Rashad MM. Preemptive analgesia by peritonsillar ketamine versus ropivacaine for post-tonsillectomy pain in children. Egypt J Anaesth 2014;30:1-5.
35. Ugur KS, Karabayirli S, Demircioğlu Rİ, Ark N, Kurtaran H, Muslu B, *et al*. The comparison of preincisional peritonsillar infiltration of ketamine and tramadol for postoperative pain relief on children following adenotonsillectomy. Int J Pediatr Otorhinolaryngol 2013;77:1825-9.
36. Dahmani S, Michelet D, Abback PS, Wood C, Brasher C, Nivoche Y, *et al.* Ketamine for perioperative pain management in children: A meta-analysis of published studies. Paediatr Anaesth 2011;21:636-52.
37. Tong Y, Ding XB, Wang X, Ren H, Chen ZX, Li Q. Ketamine peritonsillar infiltration during tonsillectomy in pediatric patients: An updated meta-analysis. Int J Pediatr Otorhinolaryngol 2014;78:1735-41.
38. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg 2000;90:1419-22.
39. Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J. Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesth Analg 1999;89:444-7.
40. Menigaux C, Fletcher D, Dupont X, Guignard B, Guirimand F, Chauvin M. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg 2000;90:129-35.