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ORIGINAL ARTICLE

Perioperative low-dose ketamine improves postoperative analgesia following Cesarean delivery with general anesthesia

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Abstract

Objective: *In* this study, the effect of perioperative uses of low dose ketamine on post-operative wound pain and analgesic consumption in patients undergoing elective Cesarean section was evaluated.

Methods: In randomized, double blind clinical trial, 52 women with American Society of Anesthesiologists (ASA) class I-II identification undergoing elective Cesarean section in general anesthesia were enrolled. In the ketamine group (group K), a ketamine bolus of 0.5 mg kg^{-1} IV was administered at the time of induction of general anesthesia. After induction, a ketamine infusion of 0.25 mg kg^{-1} h^{-1} was started and discontinued at the end of surgery. Patients allocated to the control group (group C) were given identical volumes of saline. The cumulative dose of morphine consumption after surgery was measured as the primary outcome of this study. Secondary outcomes were pain control assessed by numeric rating scale (NRS) and need for rescue analgesia and incidence of side effects.

Results: The mean 24-h morphine consumption was lower in group K ($p = 0{,}001$). At 15 min postoperatively, NRS values were lower in group K than group C ($p = 0{,}001$). There was no difference among groups regarding the need for supplemental analgesia (rescue diclofenac doses) ($p > 0.05$).

Conclusions: Perioperative uses of low dose ketamine decreased post-operative opioid requirements, which was observed long after the normal expected duration of ketamine.

Keywords

Caeserean section, perioperative ketamine, postoperative analgesia

History

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Introduction

Cesarean section (CS) is the most common surgical procedure performed in hospitals and the number is increasing [1]. Although regional anesthesia is preferred as an anesthetic method in CS, general anesthesia has also been used because of its rapid induction, less hypotension and cardiovascular instability and better control of airways [2].

Postoperative pain is the greatest concern for women undergoing CS [3]. Good pain relief will provide maternal comfort as well as may permit improved mother-child bonding, early abulation and discharge and reduce the risk of deep vein thrombosis [4]. Also, the presence of severe pain during the 36 hours after delivery was noted to be associated with three-fold increased like hood of developing postpartum depression [5].

Systemic administration of opioids is a commonly used modality for immediate post-Cesarean delivery pain relief, particularly after general anesthesia [6]. Currently, non-steroidal anti-inflammatory drugs, local anesthetics, α2-adrenaline receptor antagonists, and ketamine, have been used to enhance the effects of opioids and reduce complications of opioids that can occur when large doses of opioids are used alone [7–9]. Ketamine, a pencyclidine derivative, is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptor is a non-specific cation channel that contributes to excitatory synaptic transmission [10]. Therefore, ketamine has a potential for altering synaptic plasticity and central nervous system facilitation of pain processing [11]. Potentiation of opioid-induced analgesia and the opioid sparing effect of ketamine had been reported in several studies [12,13]. However, the results from various studies are controversial. The aim of this trial was to investigate whether low dose ketamine administered perioperatively decreases postoperative pain following CS under general anesthesia or reduce the need for analgesics in the postoperative period.

Materials and methods

This was a single center, randomized, double blind, placebo-controlled study conducted in the Umraniye education and

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Research Hospital between May 2011 – April 2012. Ethical approval (No: 09.2011.0049) was provided by Ethics Committee of the Marmara University, Istanbul, Turkey (Chairperson: Haner Dreskeneli, Professor), on 03 March 2011 and complied with Helsinki Declaration including current revisions and Good Clinical Practice guidelines. After institutinal review board approval and written informed consent from each study participant, 62 American Society of Anesthesiologists (ASA) physical status I-II women scheduled for elective CS were recruited. Inclusion criteria included nulliparous, 18–35 years, gestation 37–40 weeks, general anesthesia. Exclusion criteria included history of pelvic surgery, chronic pelvic pain known allergy to any of the planned perioperative medications, cardiovascular problems, diabetes mellitus and evidence of intrauterine growth restriction. Indications for CS were cephalopelvic disproportion, breech position, placenta praevia or maternal request.

No pre-anesthetic medication was prescribed. Once they consented to participate in the study and signed the written informed consent, they were instructed for pain assessment on a numeric rating scale (NRS) with zero being no pain and 10 representing worst pain imaginable.

Patients were assigned to a control or ketamine group through random allocation using a computer-generated random number table. For bolus dose, 10 ml of normal saline was used in group C and 10 ml ketamine (5 mg ml^{-1}) in group K. For infusion during maintenance, 50 ml of normal saline was prepared in group C and 50 ml of ketamine (2 mg ml^{-1}) in group K. In the ketamine group, a ketamine bolus of 0.5 mg kg^{-1} IV was administered at the time of induction of general anesthesia. After induction, a ketamine infusion of 10 μg kg^{-1} min^{-1} was started and discontinued at the end of surgery. Patients allocated to the control group were given identical volumes of saline. Study drugs were prepared by an anesthesiologist independent of the study. The participant's, care givers, and those assessing the outcomes were blinded to group assignment.

An intravenous 0.9% NaCl infusion was started in the operation room in all patients. Heart rate, non-invasive blood pressure, pulse oximetry and bispectral index (BIS) were monitored routinely before induction of anesthesia. After preoxygenation, anesthesia was induced with 4 mg kg^{-1} thiopental; and tracheal intubation was facilitated with rocuronium 0.6 mg kg^{-1}. Anesthesia was maintained with 50% oxygen in N_2O and end-tital sevoflurane concentration 1.2–1.3% to provide the BIS value lower than 60. Following Pfannenstiel incision, the uterus was exteriorized and after delivery, 20 ml IU oxytocin, 0.1 mg kg^{-1} morphine chloride were given intravenously. Umbilical venous blood samples were drawn from a clamped section of the umbilical cord for an arterial blood gas (ABG) analysis including pH (acidity), pCO2, (partial pressure of carbon dioxide), pO2 (partial pressure of oxygen), taking care to ensure that the same machine was used in all cases. APGAR scores at 1 and 5 min were recorded by the pediatrician in attendance. Residual neuromuscular block was reversed with 2.5 mg neostigmine and 1 mg atropine at the end of the operation. All of the patients were extubated when fully awake. The patients evaluated the intensity of their pain with the NRS, starting with as soon as they responded to verbal stimuli in the post-anesthesia care unit (PACU; 15 min) and post-operative 2, 6, 12, 18, and 24 h. If the NRS value was >4 in the PACU, the patients were treated with incremental dose intravenous doses up to 0.05 mg kg^{-1}. Patients with modified Aldrete score >8 were considered eligible to be discharged from PACU [14].

Post-operative analgesia was provided intravenously with patients controlled analgesia (PCA) at concentration 0.5 mg $kg^{-1.}$ The PCA was set to deliver a 1 mg bolus, with a 10-min lock-out time without basal infusion. Rescue analgesia with 75 mg diclofenac sodium intramuscularly was allowed if the patient could not obtain adequate pain relief from the PCA regimen.

The cumulative dose of morphine consumption after surgery was measured as the primary outcome of this study. Secondary outcomes were pain control assessed by NRS and need for rescue analgesia and incidence of side effects.

A previous study showed that morphine consumption after CS is 38 ± 14 mg [15]. To detect a 30% decrease in post-operative morphine consumption, we calculated that 26 patients would be required for each group with $\alpha = 0.05$ and power 80%. 5 patients were added to each group to account for possible missing data from potential causes.

Statistical analysis

All statistical analyses were performed with Statistical Package for Social Sciences (SPSS, Chicago, IL) for Windows 15.0 software. An unpaired Student's t test to compare the parametric values of the two groups, the Mann–Whitney U test to compare the non-parametric values of the two groups were performed. Non-parametric data was compared within groups using the Friedman's S test and the the Wilcoxon signed-rank test. Values for qualitative variables were compared using the Continuity Correction (Yates) test and the Fisher's Exact test. A p value <0.05 was deemed to indicate statistical significance.

Results

Patients recruitment is shown in Figure 1. In total, 52 participants were included in the analysis: 26 in the ketamine group and 26 in the control group. Patients' characteristics and operative details did not differ between the groups (Table 1).

The APGAR scores at 1 and 5 minutes were similar between groups. All neonates had scores >7 at 5 min. Even though the umbilical venous blood pH was slightly lower in group K compared to group C, this difference was not statistically significant (Table 2).

At 15 min post-operatively, NRS values were lower in group K compared to group C ($p = 0.001$). There were no differences at 2, 6, 12, 18, 24 h among groups ($p > 0.05$; Table 3).

Morphine consumption obtained at 0–6 hours interval ($p = 0{,}001$), 6–12 hours interval ($p = 0{,}001$), 12–18 hours interval ($p = 0{,}001$), 18–24 hours interval ($p = 0.001$), and cumulative morphine consumption at 24 hours ($p = 0{,}001$) hours were significantly lower in group K compared to group C (Table 4).

There was no difference among groups regarding the need for supplemental analgesia (rescue diclofenac doses)

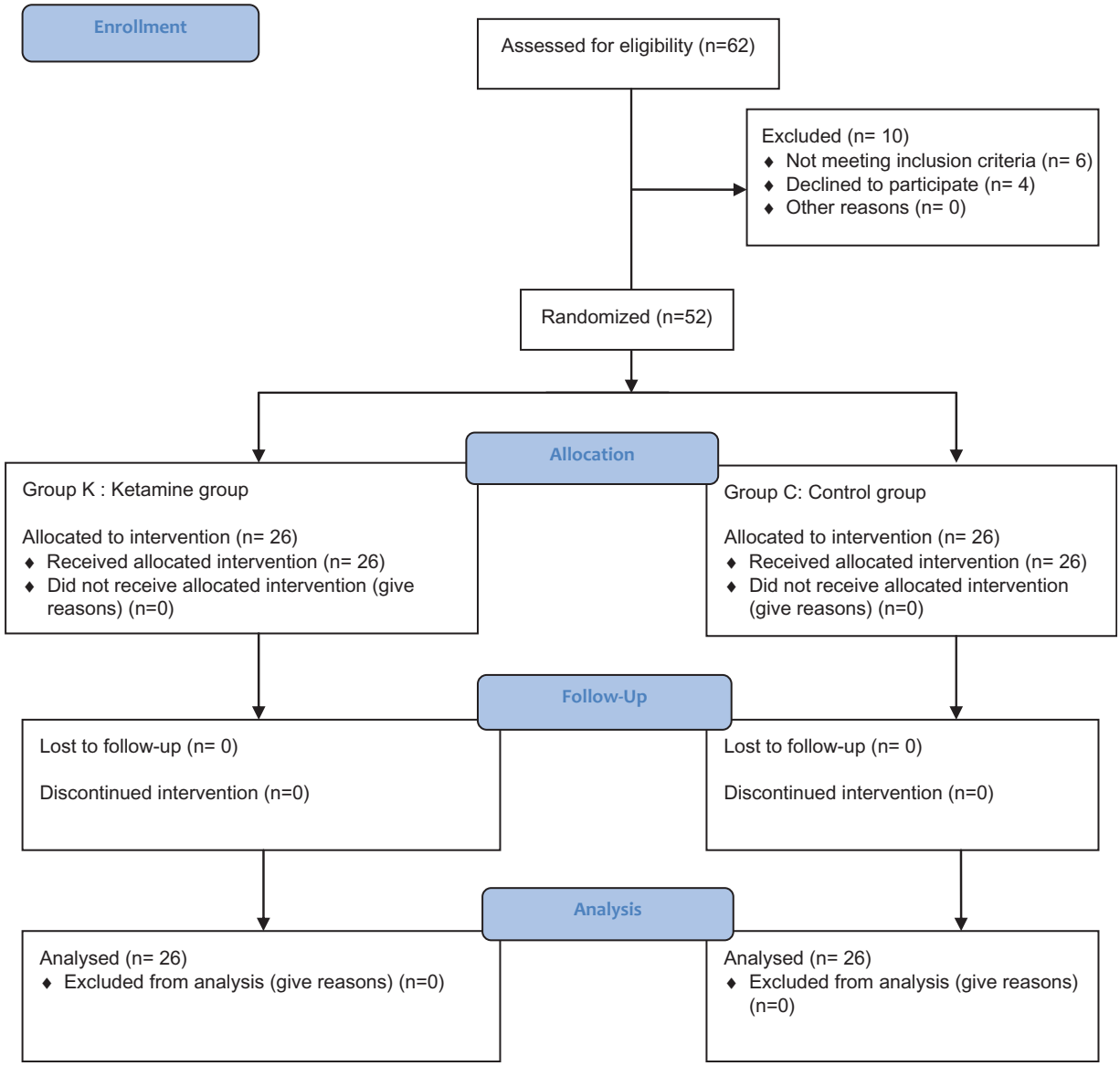

Figure 1. Flow diagram showing patient recruitment and flow.

Table 1. Patient characteristics.

Characteristics	Group K ($n=26$)	Group C ($n=26$)	p value
Age (years)	29.1 ± 2.2	29 ± 2.2	0.8
Weight (kg)	80.1 ± 5.2	80.3 ± 5.1	0.9
Operation time (min)	40.6 ± 2.5	40.4 ± 2.7	0.7
Gestational age (weeks)	38.9 ± 1	38.9 ± 0.9	0.9
Educational level			
• Primary school	8 (30.8%)	7 (26.9%)	0.9
• High school	15 (57.7%)	16 (61.5%)	
• University	3 (11.5%)	3 (11.5%)	
Economic class			
• Low	5 (19.2%)	4 (15.4%)	0.9
• Middle	19 (73.1%)	20 (76.9%)	
• High	2 (7.7%)	2 (7.7%)	
Indication for CS			
• Breech position	11 (42.3%)	12 (46.2%)	0.7
• Cephalopelvic disproportion	9 (34.6%)	8 (30.8%)	
• Placenta previa	4 (15.4%)	2 (7.7%)	
• Maternal request	2 (7.7%)	4 (15.4%)	

Values are given as mean ± SD or number (%).

($p>0.05$; Table 5). Side effects encountered during the treatment are presented in Table 5. The most common side effect was post-operative nausea and vomiting (PNV) in all groups, followed by pruritus. Four patients group C, five patients in group K required intervention for PNV ($p>0.05$). Four patients in group C and five patients from group K required no intervention for mild pruritus ($p>0.05$; Table 5). Nystagmus, hallucination and diplopia did not occur in either group.

Discussion

The analgesic efficacy of low dose ketamine administered peri-operatively was studied with 52 patients in double blind randomized controlled manner using a patient-controlled analgesia system. In the present study, we observed that the peri-operative using low dose ketamine decreased post-operative analgesic consumption. Additionally, NRS value at 15 min in the group K was significantly lower than in the group C. Maternal side effects were minimal and APGAR scores were not affected.

Table 2. Changes in fetal parameters.

Characteristics	Group K ($n=26$)	Group C ($n=26$)	p value
APGAR Score 1 min	8.46 ± 0.51	8.44 ± 0.50	0.8
APGAR Score 5 min	9.65 ± 0.49	9.63 ± 0.49	0.8
Umbilical venous blood gas values			
pH	7.29 ± 0.03	7.30 ± 0.02	0.2
PCO_2 (mmHg)	44.33 ± 3.72	45.55 ± 4.18	0.3
PO_2 (mmHg)	34.40 ± 5.28	32.78 ± 6.02	0.3

Values are given as mean ± SD.

Table 3. NRS values for the first 24 h after surgery.

Time	Group K ($n=26$)	Group C ($n=26$)	p value
NRS 15 min	3.65 ± 1.29	7.15 ± 1.49	0.001
NRS 2 hr	2.38 ± 0.64	2.38 ± 0.64	1
NRS 6 hr	1.23 ± 0.91	1.07 ± 0.97	0.5
NRS 12 hr	1.04 ± 0.72	1.15 ± 0.73	0.5
NRS 18 hr	0.73 ± 0.67	0.77 ± 0.51	0.7
NRS 24 hr	0.42 ± 0.50	0.46 ± 0.51	0.7

Values are given as mean ± SD.

Table 4. Post-operative morphine consumption (mg) at different time intervals.

Time	Group K ($n=26$)	Group C ($n=26$)	p value
0–6 hr interval	11.3 ± 2.1	16.7 ± 2.4	0.001
6–12 hr interval	4.8 ± 1.1	7.2 ± 1	0.001
12–18 hr interval	5.04 ± 1.5	6.5 ± 1.6	0.001
18–24 hr interval	3.85 ± 1	5.9 ± 1.1	0.001
Cumulative morphine consumption at 24 hours	25 ± 3.7	36.4 ± 3.6	0.001

Values are given as mean ± SD.

Table 5. Rescue diclofenac dose required and drug-related side effects throughout the study.

	Group K ($n=26$)	Group C ($n=26$)	p value
Rescue Diclofenac	10 (38.5%)	13 (50%)	0.7
PNV	4 (15.4%)	5 (19.2%)	1
Pruritus	4 (3.8%)	5 (19.2%)	1

Values are given as number (%).

Although advances have been made in the understanding of pathophysiology of post-operative pain, new analgesics and delivery techniques, some patients still suffer from moderate to severe post-operative pain because of individual variability and limitation from side effects [16]. The systemic administration of high doses of opiates has been associated with side effects as nausea, vomiting, sedation, and respiratory depression which may impair the early bonding process between the mother and the newborn [17,18]. The analgesic of choice requires minimal transfer in breast milk, little or no effect on neonates, minimal maternal side effects and minimal or no interference with caring for the newborn or discharge from hospital. This lead us to a multimodal analgesia therapy, with goal of obtaining synergistic or additive analgesia with fewer side effects by combining lesser amounts of each drug with different mechanism of action. In that case, using low doses of ketamine as an adjuvant drug for local anesthesia or opioids in multimodal pain therapy is increasing gradually [19,20].

Many clinical trials have investigated the use of ketamine for the post-operative pain management during the past 15 years [21]. Reports regarding the effectiveness of the NMDA antagonist ketamine to reduce post-operative hyperalgesia and acute and long lasting pain are inconsistent [21,22]. Single treatment comparisons in human clinical trials may be problematic in addressing the issue of preventive analgesia. Single administration of an analgesic before surgical incision may result in having analgesia wear off before the end of surgery [15,23]. Perhaps continuous preventive analgesia during surgical stimulation may be needed to provide effective analgesia [24]. In that case, we provided continuous infusion of ketamine during the surgery. Most studies demonstrating ketamine's opioid sparing effects in intra-abdominal procedures were conducted in patients receiving general anesthesia with a bolus ketamine dose (0.15–1 mg kg^{-1}) followed by an infusion (0.1–0.5 mg kg^{-1} h^{-1}) [25,26]. The authors suggested that complete blockade of the nociceptive input and NMDA receptor activation may be necessary for a definitive analgesic effect [27].

Optimal dosage is another controversial area. Because of their side effects, low dose ketamine can be administered in clinical practice. The low-dose ketamine is defined as a bolus dose of less than 2 mg kg^{-1} when given intramuscularly or less than 1 mg kg^{-1} when administered via IV or epidural route. For continuous IV administration, low dose ketamine is defined as a rate $\leq$20 μg kg^{-1} min^{-1} [28].A 2006 Cochrane review concluded: ketamine in sub-anesthetic doses is effective in reducing morphine requirements in the first 24 h after surgery [29]. In the present study, nystagmus, hallucination and diplopia did not occur; but sub-therapeutic doses of ketamine can cause hallucinogenic effects. However, it was infrequently a reason for discontinuing the regimen owing to side effects [30].

Ketamine has an analgesic effect at plasma concentrations of $\geq$100 ng/ml, and the plasma concentration is maintained at this level or higher up to 1–2 h after operation when administered at a dose of 1 mg/kg [31,32] We did not measure the plasma concentration of ketamine , but our initial loading bolus 0.5 mg kg^1 and it was followed by 10 μg kg^{-1} min^{-1} until the end of surgery; thus, the plasma concentration of ketamine was high enough to have a direct analgesic effect at 2 h after surgery. Cumulative morphine consumption obtained at 6, 12, 18 and 24 h after surgery were significantly lower in the ketamine group compared to the control group, the ketamine administered in this study was considered to have preventive analgesic effect.

The developing rhesus macaque brain was sensitive to apoptotic action of ketamine at both fetal and neonatal age, and exposure duration of 5 h was sufficient to induce a significant neuroapototic response [33] Therefore, it is necessary to keep the potential neuroapototic effect of ketamine in mind, during organogenesis [33,34]. APGAR score is a good index of neonatal well-being and may correlate with subsequent neurological damage [35]. Like other studies APGAR scores were similar in both groups [36,37].

The incidence of PNV was similar in all groups. Recently a small dose of ketamine has been shown to decrease PNV, but a similar decrease was not seen in our study, as the nature of surgery might have masked the antiemetic property at small doses [38].

Ketamine is known to alter the neuroplasticity and reduced the development of chronic pain syndromes [39]. One limitation of our study is that we did not follow-up the patients to evaluate whether chronic pain was reduced with the small dose of ketamine. Future research should also focus on long-term effects of ketamine in reducing the incidence of chronic pain syndromes.

In conclusion, low-doses of ketamine may be considered as a useful and safe adjunct in perioperative pain management. Ketamine displays anti-hyperalgesic and analgesic effects, and no major dysphoric adverse effects at low doses. When used correctly, ketamine is an inexpensive and versatile drug.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

1. Mayor S. 23% of babies in England are delivered by caesarean section. BMJ 2005;330:806.
2. Hughes SC, Levinson G, Rosen MA. Anesthesia for cesarean section. In: Schneider SM, Levinson G, ed. Anesthesia for obstetrics. 3rd ed. Baltimore: William & Wilkes; 2002:201.
3. Carvalho B, Cohen SE, Lipman SS, et al. Patient preferences for anesthesia outcomes associated with Cesarean delivery. Anesth Analg 2005;101:1182–7.
4. Yost NP, Bloom SL, Sibley MK, et al. A hospital-sponsored quality improvement study of pain management after cesarean delivery. Am J Obstet Gynecol 2004;190:1341–6.
5. Eisenach JC, Pan PH, Smiles R, et al. Persistent pain after caesarean section and vaginal birth: a cohort study. Int J Obstet Anesth 2010;19:4–9.
6. Jenkins JG, Khan MM. Anaesthesia for Caesarean section: a survey in a UK region from 1992 to 2002. Anaesthesia 2003;58:1114–18.
7. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmetodomitine versus morphine for postoperative analgesia after major inpatient surgery. AnesthAnalg 2004;98:153–8.
8. Weinbroum AA. Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res 2012;65:411–29.
9. Cassulo J, Wallin G, Högström S, et al. Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. Anesth Analg 1985;98:153–8.
10. Paoletti P, Neyton J. NMDA receptor subunits: function and pharmacology. CurrOpinPharmacol 2007;1:39–47.
11. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology 2005;103:813–20.
12. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand 2005;49: 1405–28.
13. Dahmani S, Michelet D, Abback PS, et al. Ketamine for perioperative pain management in children: a meta-analysis of published studies. Pediatr Anaesth 2011;21:636–52.
14. Aldrete JA. The post-anesthesia recovery score revisited. J ClinAnesth 1995;7:89–91.
15. Bilgen S, Köner O, Türe H, et al. Effects of three different doses of ketamine prior to general anaesthesia on postoperative pain following Caesarean delivery: a prospective randomised study. Minerva Anestesiol 2012;78:442–9.
16. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute post-operative pain management: Evidence from published data. Br J Anaesth 2002;89:4009–23.
17. McDonnell JG, Curley G, Carney J, et al. The analgesic efficicacy of transversusabdominis plane block after Cesarean delivery: a randomised controlled trial. Anesth Analg 2008;106:186–91.
18. Harrison D, Sinatra R, Morgese L, Chung J. Epidural narcotic and patient-controlled analgesia for Cesarean section pain relief. Anesthesiology. 1988;68:454–7.
19. Weinbroum AA. Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res 2012;65:411–29.
20. Stephan A, Dodd S, Dodd P. Perioperative analgesia. Aust Prescrire 2004;27:152–4.
21. Elia N, Tramer MR. Ketamine and postoperative pain-a quantitative systemic review of randomised trials. Pain 2005;113:61–70.
22. Carstensen M, Moller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomised trials. Br J Anaesth. 2010; 104:401–6.
23. Reza FM, Zahra F, Esmaeel F, Hossein A. Preemptive analgesic effect of ketamine in patients undergoing elective Caesarean section. Clin J Pain 2010;26:223–6.
24. Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362–79.
25. Zakine J, Samareq D, Lorne E, et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg 2008;106:1856–61.
26. Guillou N, Tangury M, Seguin P, et al. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg 2003;97: 843–7.
27. Aida S, Yamakura T, Baba H, et al. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology 2000;92: 1624–30.
28. Becke K, Albrecht S, Schmitz B, et al. Intraoperative low-dose S-ketamine has no preventive effects on postoperative pain and morphine consumption after major urological surgery in children. Paediatr Anaesth 2005;15:484–90.
29. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;(1): CD004603.
30. Sveticic G, Eichenberger U, Curatolo M. Safety of mixture of morphine with ketamine for postoperative patient –controlled analgesia: an audit with 1026 patients. ActaAnaesthesiolScand 2005;49:870–5.
31. NganKee WD, Khaw KS, Ma ML, et al. Postoperative analgesic requirement after Cesarean section: comparison of anesthetic induction with ketamine or thiopental. AnesthAnalg 1997;85: 1294–8.
32. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth 1981;53:27–30.
33. Brambrink AM, Evers AS, Avidan MS, et al. Ketamine-induced neuroapoptosis in fetal and neonatal rhesus macaque brain. Anesthesiology 2012;116:372–84.
34. Lois F, De Kock M. Something new about ketamine for pediatric anesthesia? Curr Opin Anaesthesiol 2008;21:340–4.
35. Braveman FR, Scavone BM, Wong CA, Santos AC. Obstetrical anaesthesia. In: Barash PG, Cullen BF, Steolting RK. Cahalan MC, Stock MC, ed. Clinical anaesthesia. 6th ed. Philadephia: Lippincott Williams and Wilkins; 2009:1137–70.
36. Sen S, Ozmert G, Aydın ON, et al. The persisting analgesic effect of low dose intravenous ketamine after spinal anaesthesia for Caesarean Section. Eur J Anaesthesiol 2005;22:518–23.
37. Lavand'homme PM, Roelants F. Ketamine effect on postoperative pain according to the presence of a perioperative temporal summation. Anesthesiology 2009;107:A215.
38. Chandrakantan A, Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anaesth 2011;107:127–40.
39. Voscopoulos C, Lema M. When dose acute pain become chronic? Br J Anaesth 2010;105:169–85.