European Review for Medical and Pharmacological Sciences 2023; 27: 8860-8867

Subcutaneous wound infiltration of ketamine is superior to bupivacaine in terms of pain perception and opioid consumption after cesarean section: a double-blinded randomized placebo-controlled clinical trial

H. AKSOY[1], G. GÖKAHMETOĞLU[2], M. AK[1], Ü. AKSOY[3]

[1]Department of Obstetrics and Gynecology, Kayseri City Hospital, Kayseri, Turkey
[2]Department of Anesthesiology and Reanimation, Kayseri City Hospital, Kayseri, Turkey
[3]Department of Obstetrics and Gynecology, Kayseri Memorial Hospital, Kayseri, Turkey

Abstract. – OBJECTIVE: The aim of the present study was to evaluate the analgesic efficiency of SC ketamine, either alone or in combination with bupivacaine, following CS by means of postoperative pain and opioid need.

PATIENTS AND METHODS: One hundred and twenty women were allocated into 4 groups in this prospective, double-blind, placebo-controlled, randomized trial. Group K (Ketamine, n=30) received SC 1 mg/kg ketamine. Group B (Bupivacaine, n=30) received SC 20 mL bupivacaine 0.5%. Group KB (Ketamine+Bupivacaine, n=30) received SC ketamine 1 mg/kg plus SC 20 mL bupivacaine 0.5%. Group P (Placebo, n=30) received SC 30 mL 0.9% saline (placebo).

RESULTS: VAS scores at resting and on coughing and analgesic consumptions were compared. Visual analogue scale (VAS) pain scores at rest and coughing, at 15 and 60 minutes, and 2, 6 and 12 hours, and total opioid necessity were measured. VAS scores at rest in Group P were higher than in Group KB at the 6th hour, while lower in Group K and Group KB than in Groups B or P at the 12th hour. Patients receiving placebo had higher coughing VAS scores than those receiving ketamine or ketamine+bupivacaine at 2nd, 6th and 12th hours. Patients in Groups P and B required higher doses of morphine than those in groups K or KB.

CONCLUSIONS: Subcutaneous ketamine, either alone or in combination with bupivacaine, provides a better postoperative pain relief and reduces postoperative opioid consumption when compared to use of bupivacaine alone.

Key Words:
Ketamin, Bupivacaine, Visual analogue scale, Ceserean section.

Introduction

Cesarean section (CS) is the most commonly performed surgery in the USA, with a reported[1,2] rate of 32.3% of all deliveries. The percentage has been dramatically increased all through the world in recent years. However, the most considerable concern of patients undergoing CS is postoperative pain[3], which might hinder the bonding between the mother and the newborn and initiation of early breastfeeding. Moreover, delay in ambulation and discharge may result in a delayed interval of hospitalization and enhanced risk of thromboembolic complications. Consequently, prompt and adequate postoperative pain alleviation has obtained much interest in line with the increasing CS rates. Though opioids are the mainstay postoperative pain alleviation, various approaches, including local anesthesia, have been described for pain management after CS.

Local anesthetic agents are commonly used through the subcutaneous (SC) route for alleviating postoperative pain[4], both for pre- or post-incisional neuronal blockade[5] and for pre- and post-incisional wound infiltration[6]. Different infiltration methods are revealed[7] to reduce pain and lessen opioid demand after various surgical methods. Wound infiltration of analgesics is widely used because it achieves similar pain control compared to the intramuscular (IM) and intravenous (IV) routes, as well as the fact that clinicians could avoid side effects related to IM or IV administrations[8].

Ketamine inhibits the reuptake of noradrenaline and 5-hydroxytryptamine, interrupts

Corresponding Author: Mehmet Ak, MD, Ph.D; e-mail: ak-mehmet@hotmail.com

cholinergic transmission, and interacts with N-methyl-D-aspartate (NMDA) receptor complexes[9]. Ketamine has been used as postoperative analgesic drug for pre-emptive analgesia[10,11]. In postoperative pain control, administration of ketamine epidurally or intrathecally is beneficial. It has been postulated[12] that ketamine is very effective for pathological pain conditions, in which receptor-controlled ion channels had been initiated by a constant nociceptive stimulus, not for pre-emptive analgesia. Recent reports[13-18] have concentrated on the local ketamine infiltration in various surgical procedures including circumcision[13], appendectomy[14], tonsillectomy[15,16], arthroplasty[17,] and cholecystectomy[18]. Though the clinical efficacy of various local anesthetics' instillation following CS[19-21] and abdominal hysterectomy[22] has been investigated[19-22], wound infiltration of ketamine after CS is quite limited in the literature[23,24]. The ideal method of pain alleviation after cesarean surgery remains elusive at this time. Previously published reports[5,6,25,26] demonstrated the efficacy of incisional infiltration after CS. The local anesthetic infiltration to the surgical incision site may allow the use of a decreased dose of opioids and, thereby, reduce its adverse outcomes. Cochrane Database systematic review[27] also indicated local analgesic infiltration to be of benefit in cesarean section. Although various wound infiltration techniques of local anesthetic agents have been defined, there is a paucity of literature reporting the SC infiltration of ketamine for cesarean surgery.

The purpose of the present study was to evaluate the analgesic efficiency of SC ketamine, either alone or in combination with bupivacaine, following CS by means of postoperative pain and opioid need.

Patients and Methods

Study Design

A prospective, placebo-controlled, double-blind, randomized study was conducted between June 2014 and May 2015 in our Obstetrics and Gynecology Department. All patients signed an informed consent form and consented to the study. This study was registered to Clinical Trials (NCT02515422, https://clinicaltrials.gov/).

Singleton pregnant women who had been scheduled for elective cesarean delivery were included in the study. Inclusion criteria included singleton term pregnancies between 38-41st weeks of gestation, age ≥ 18 years, ASA physical status I-II, and the lack of any important obstetrical problems. Exclusion criteria included multiple pregnancies, active labor, obstetric difficulties, intrauterine fetal deaths, unstable patients, clinically significant medical or surgical situations requiring special care or intraoperative complications which required extraordinary surgical procedures, special request for general anesthesia, known allergy or sensitivity to drugs used in the study, anxiety or depression throughout surgery, any systemic diseases (renal or hepatic insufficiency, thyroid diseases, chronic hypertension, epilepsy, psychiatric disorders, or intracranial hypertension), or medications which may alter the pain perception, history of opioid use, failure to understand VAS. No participants received any drugs that could change the perception of pain in the last seven days prior to cesarean section. All participants were informed of the operation by the same physician who performed the cesarean sections. The participants completed a questionnaire evaluating sociodemographic characteristics and past medical history. The preoperative examinations involved anesthesia counseling and ultrasonic assessment. Afterwards, the pregnants were randomly assigned into four groups using a computer-aided random number chart with 35 patients in each group.

Patients, anesthetists, surgeon, and other staff were blinded to the contents of the medications. As shown in Figure 1, Group K (Ketamine, n=30) received SC 1 mg/kg ketamine (Ketalar®, Pfizer Drug Company, USA). Group B (Bupivacaine, n=30) received SC 20 mL bupivacaine 0.5% (Marcaine®, AstraZeneca Drug Company, Turkey). Group KB (Ketamine+Bupivacaine, n=30) received SC ketamine 1 mg/kg plus SC 20 mL bupivacaine 0.5%. Group P (Placebo, n=30) received SC 30 mL 0.9% saline (placebo).

All procedures were carried out by the same experienced surgeon, using the consistent operation technique to exclude additional variables. The baseline arterial blood pressure, oxygen saturation electrocardiogram, and heart rate were monitored prior to anesthesia induction. Spinal anesthesia was managed at the L3-4 or L4-5 interspinous level by a 25G spinal needle. Hyperbaric bupivacaine 0.5% 8-10 mg with fentanyl 20 μg combined was injected intrathecally over 20 s to accomplish a T4 sensorial block, and then the

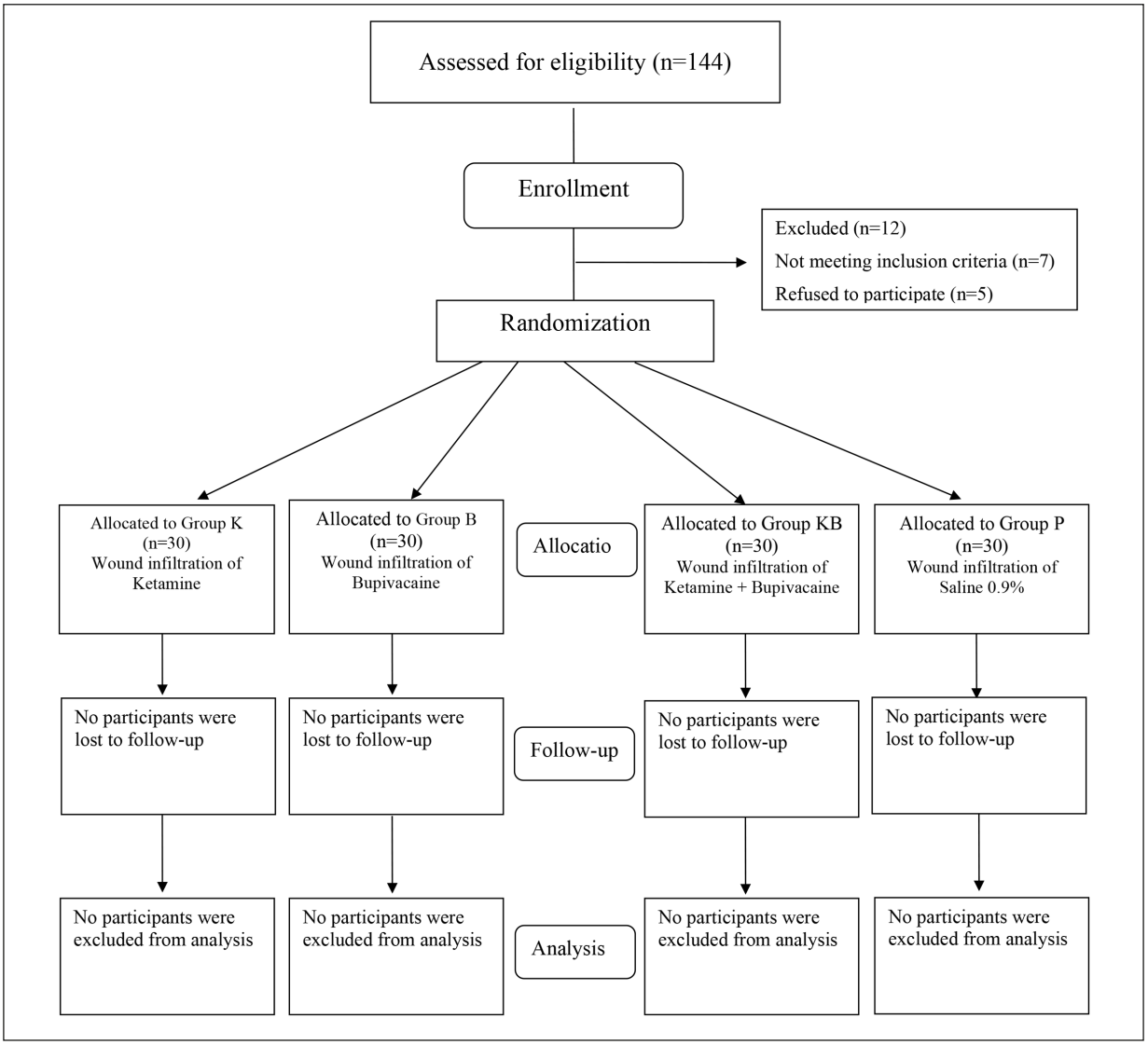

Figure 1. Flowchart of the study.

surgery was consented to continue. There were four separate syringes for four different treatment groups labeled G1, G2, G3, and G4 representing each study group. Following the completion of operations, patients were transferred to the anesthesia recovery room, where they received routine postoperative care. Pain management after cesarean section was achieved through a patient-controlled IV analgesia device releasing morphine.

During the postoperative period, pain assessments were documented using a standard 10-cm VAS, throughout the postoperative 15 and 60 minutes, 2, 6 and 12 hours, by the patients grading the pain from 0 (no pain at all) to 10 (worst pain) at rest and on coughing by an anesthetist blinded to study groups. If VAS score was ≥ 4, 75 mg diclofenac sodium (Dikloron®, Deva Drug Company, Istanbul, Turkey) was injected intramuscularly. The total diclofenac sodium dose did not exceed 150 mg in 24 hours. Total morphine consumption in PCA was also recorded.

The groups were compared by means of basal and provoked VAS scores and postoperative opioid consumption. The primary outcome of this study was postoperative opioid consumption, and the secondary outcome was VAS scores.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v.18 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using the Shapiro-Wilk's test. The variance homogeneity assumption was tested with Levene's test. Parametric tests (Independent-samples *t*-test and post-hoc Tukey test) were applied to data of normal distribution, and non-parametric tests (Mann–Whiney U-test and Kruskal-Wallis' test) were applied to data of questionably normal distribution. Bonferroni post-hoc analysis was used for multiple comparison tests. The results for all items were expressed as mean±SD, assessed within a 95% reliance and at a level of p=0.05 significance. While determining sample size, reference values were received from the study by Honarmand et al[14] and found that minimum of 30 patients were needed in each group for significant difference between groups for 80% power at type I error of 0.05. Analyses were performed by G-Power 3.1.7 (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany).

Results

A total of 144 pregnant women were screened prior to the recruitment. Twenty-four women were excluded due to the following reasons: 5 refused to participate, 7 did not meet the inclusion criteria (2 were at the age <18, and 5 were preterm births), and 12 were excluded (4 multiple pregnancies, 3 acute fetal distress, 3 general anesthesia, 1 epilepsy patient and 1 inability to score VAS). A total of 120 pregnant women were involved in the study, each group consisted of 30 patients. The flow chart diagram of the study is shown in Figure 1. As for the demographic characteristics, the studied groups did not differ from each other, as presented in Table I.

Resting VAS scores at 15, 60 minutes, and 2-hour time intervals were not significantly different, whereas they were significantly different at 6 and 12 hours among the groups (p=0.039 and <0.001, respectively) (Table II). Bonferroni correction revealed that the mean resting VAS score in Group P was significantly higher than Group KB at the 6th hour interval, while resting VAS score in Group K was lower than that in groups B and P at the 12th hour. Additionally, the mean VAS score was lower in group KB than in groups B or P at the 12th-hour interval.

Coughing VAS scores at the 15th and 60th-minute intervals were comparable (p=0.238 and 0.209, respectively); at the 2nd, 6^{th,} and 12th-hour controls, there were significant differences among study groups (p=0.013, 0.040 and <0.001, respectively). With reference to the results of Bonferroni correction, patients receiving placebo had significantly higher coughing VAS scores at 2nd hour than those receiving ketamine or ketamine+bupivacaine. Similarly, patients receiving placebo had significantly higher coughing VAS scores at the 6th hour than those receiving ketamine+bupivacaine. At the 12th hour, coughing VAS scores of patients administered ketamine or ketamine+bupivacaine were significantly lower than that of patients administered bupivacaine or placebo. Postoperative resting and coughing VAS scores are shown in Figures 2 and 3, respectively, with the respective mean and standard deviation values. Also, the total VAS scores were higher in the group P than in the groups K and KB.

Additional analgesic requirements did not significantly differ among study groups (p=0.088) (Table II). However, total morphine consumption was significantly different among the groups (p<0.001). Accordingly, group P necessitated higher doses of opioids than those in groups K or KB. Also, group B necessitated higher doses of opioids than groups K or KB.

Table I. Demographic and clinical characteristics of the groups

	Group K (n = 30)	Group B (n = 30)	Group KB (n = 30)	Group P (n = 30)	p
Age	28.83 ± 5.75	28.97 ± 5.08	28.60 ± 4.46	28.27 ± 6.02	0.961[a]
BMI	28.79 ± 3.20	29.04 ± 3.31	29.07 ± 4.76	28.97 ± 3.58	0.992[a]
Gravidity	2.53 ± 1.07	2.77 ± 1.30	2.73 ± 0.98	2.63 ± 1.33	0.869[b]
Parity	2.40 ± 1.07	2.63 ± 1.16	2.47 ± 0.73	2.33 ± 1.12	0.708[b]
Gestational age	39.03 ± 1.19	39.13 ± 1.17	39.07 ± 0.69	39.13 ± 0.78	0.972[b]

All data were expressed as mean ± standard deviation (SD). [a]One Way ANOVA (with Bonferroni corrected); [b]Kruskal-Wallis' test (Mann-Whitney U test for post-hoc analysis). $p < 0.05$ was considered statistically significant.

Table II. Demographic and clinical characteristics of the groups

	Group K (n = 30)	Group B (n = 30)	Group KB (n = 30)	Group P (n = 30)	*p*
Resting VAS scores					
15 minutes	0.07 ± 0.37	0.20 ± 0.66	0.30 ± 0.88	0.50 ± 0.97	0.162
60 minutes	0.97 ± 1.47	1.40 ± 2.40	0.93 ± 1.28	1.27 ± 1.64	0.676
2 hours	1.93 ± 1.96	1.87 ± 1.55	1.60 ± 1.43	2.43 ± 1.63	0.270
6 hours	2.23 ± 1.52	2.17 ± 1.72	1.67 ± 1.35[a]	2.83 ± 1.56	**0.039**
12 hours	0.70 ± 1.18[b]	2.17 ± 1.78	0.83 ± 1.05	1.93 ± 1.31	**< 0.001**
Coughing VAS scores					
15 minutes	0.13 ± 0.73	0.37 ± 1.10	0.50 ± 1.57	0.80 ± 1.52	0.238
60 minutes	1.13 ± 1.76	1.83 ± 2.56	1.23 ± 1.48	2.03 ± 1.87	0.209
2 hours	2.23 ± 2.22	2.90 ± 1.82	2.17 ± 1.78	3.57 ± 1.50	**0.013**
6 hours	2.80 ± 1.67	2.90 ± 1.86	2.33 ± 1.49[a]	3.57 ± 1.55	**0.040**
12 hours	1.00 ± 1.44[b]	2.97 ± 1.65	1.23 ± 1.30	2.73 ± 1.23	**< 0.001**
Total VAS scores	13.20 ± 9.00	18.77 ± 11.80	12.80 ± 8.93	21.67 ± 9.70[c]	**0.001**
Total morphine consumption	9.03 ± 3.16	12.51 ± 4.32	8.46 ± 3.60	15.09 ± 3.82[c]	**< 0.001**
Additional analgesic require	0.40 ± 0.56	0.53 ± 0.68	0.30 ± 0.47	0.67 ± 0.61	0.088

All data were expressed as mean ± standard deviation (SD). [a]$p < 0.05$ *vs*. Group P ; [b]$p < 0.05$ *vs*. Group B and Group P; [c]$p < 0.05$ *vs*. Group K and Group KB. VAS: visual analog scale. $p < 0.05$ was considered statistically significant.

Discussion

Intraincisional ketamine administration, either alone or in combination with bupivacaine, has been proposed for various abdominal or extra-abdominal surgical procedures. Jha et al[28] compared the surgical site infiltrations of bupivacaine with ketamine and defined that ketamine was stronger than bupivacaine for additional analgesic needs, still sleep, and timely continuation of feeding.

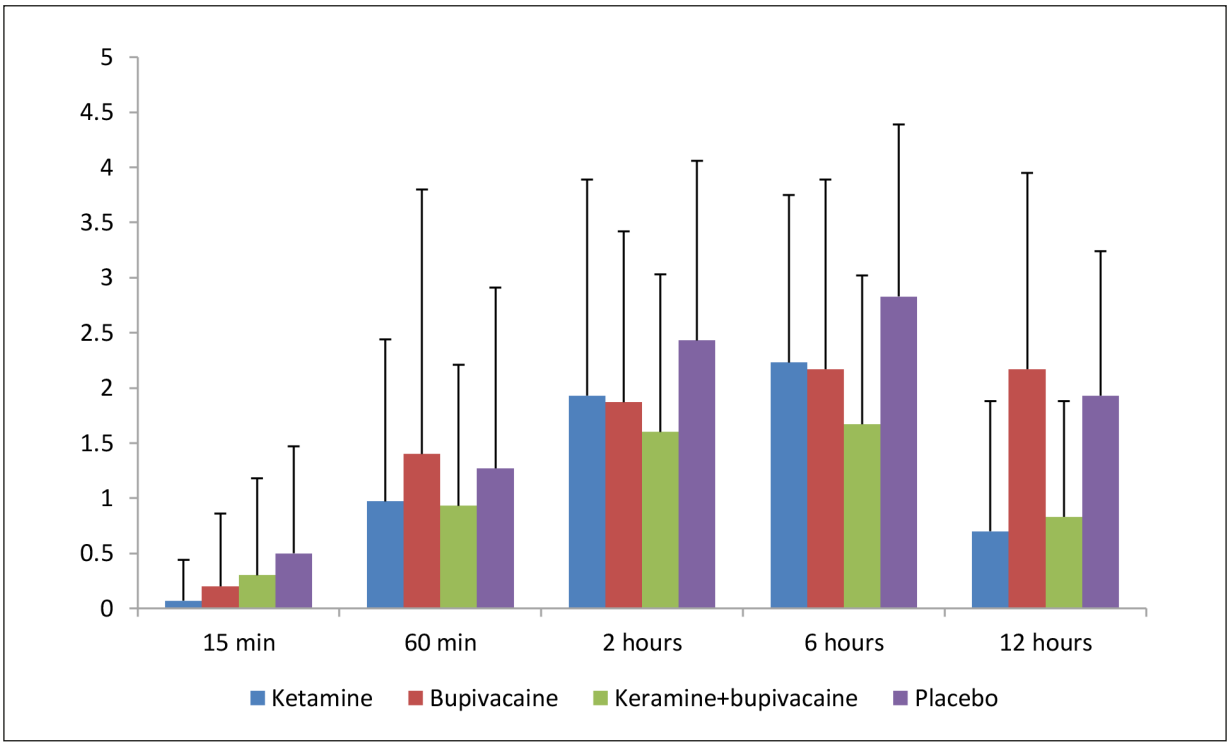

Figure 2. Postoperative resting VAS score. Mean and standard deviation values.

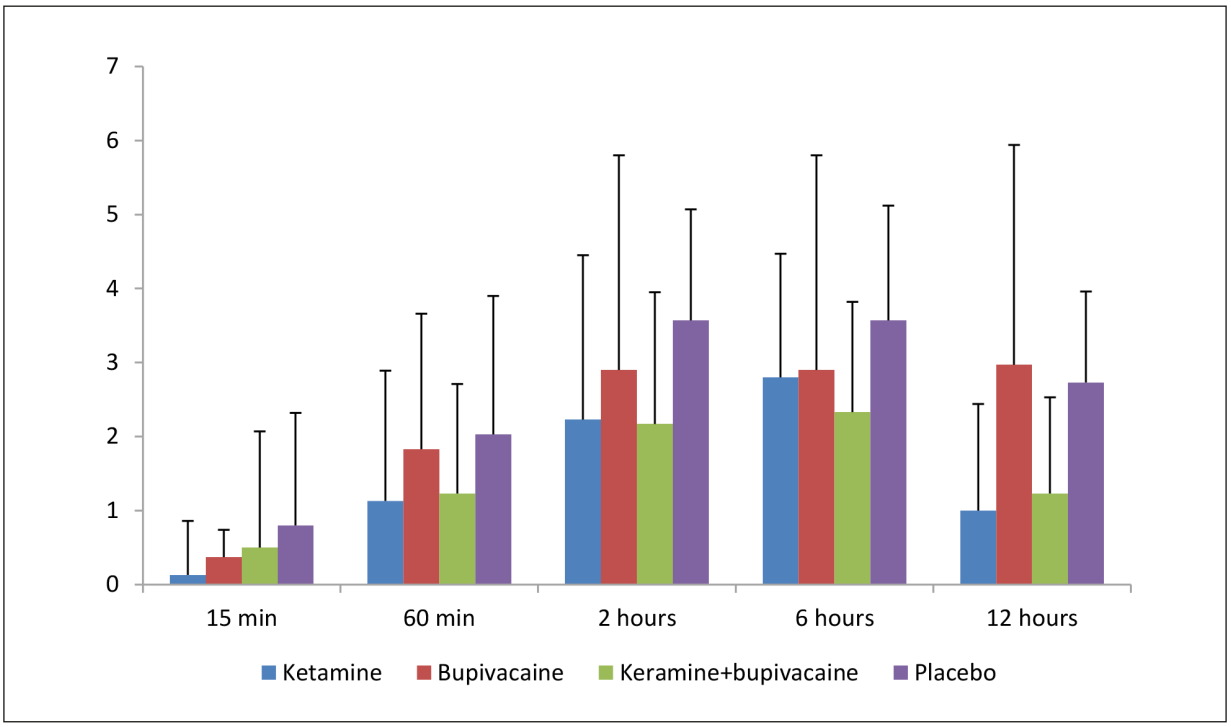

Figure 3. Postoperative coughing VAS score. Mean and standard deviation values.

Tan et al[13] compared SC ketamine and saline in patients undergoing circumcision surgery and suggested that preincisional SC ketamine could overwhelm postoperative pain. Wound infiltration of ketamine for abdominal surgeries has also been described by a set of reports. Tverskoy et al[29] concluded that adding ketamine enhanced the duration of infiltration anesthesia and analgesia in patients undergoing both uni- or bilateral herniorrhaphy. Grace et al[30] reported promising results of low-dose ketamine with a local anesthetic agent without compromise of analgesia, emergence, or satisfaction in patients undergoing postpartum tubal ligation. Honarmand et al[14] compared SC and IV ketamine given 15 minutes before appendectomy and reported that both administration routes reduced the postoperative pain and the amount of opioid use. Safavi et al[18] assessed the effectiveness of ketamine administration on postoperative pain relief after open cholecystectomy and concluded that both SC and IV use of ketamine before surgery provided adjunct analgesia during postoperative 24 hours. However, SC use of ketamine for CS has been reported by only two previously published articles, which were different in study design and the method of administration from our study[23,24].

We compared the wound infiltrations of ketamine and bupivacaine, either alone or in combination, and with placebo. In the present study, both resting and coughing VAS scores were found to be significantly lower in patients administered wound infiltration of ketamine at 6th and 12th hour control points. The VAS scores at earlier postoperative periods were comparable between the groups at rest and on coughing. Moreover, total postoperative morphine use was significantly decreased in Ketamine and Ketamine+Bupivacaine groups when compared to Bupivacaine and Control groups; although additional analgesic requirements did not differ among study groups. At this point, using PCA morphine due to ethical concerns, which allowed patients to use morphine to get their VAS scores down, to relieve the postoperative pain, might have resulted in similar VAS scores at earlier time periods between the groups and this could be considered as a treatment bias.

Zohar et al[23] compared groups that were administered SC bupivacaine and bupivacaine+ketamine through a PCA device. In contrast to our results, VAS scores, at either rest or on coughing, were similar at all time intervals, and total postoperative morphine consumptions were compara-

ble between the groups; hence, they reported that adding ketamine to local anesthetic in patients receiving regional anesthesia did not present any benefit for opioid need. Bahaeen et al[24] compared SC ketamine administration before and after skin incision with a control group and concluded that patients who were given ketamine before or after CS had decreased pain intensity and lowered analgesic need than the placebo. Although Honarmand et al[14] reported that VAS scores of patients receiving ketamine, either IV or SC, before appendectomy were significantly lower than that of patients receiving saline solution, at all-time intervals, VAS scores in our study, did not differ amongst study groups at early time intervals. However, only VAS scores of the 6th and 12th hour at resting and 2nd-, 6th-, and 12th-hour VAS scores on coughing were lower in patients taking SC ketamine alone or together with bupivacaine. Accordingly, we may conclude that SC wound infiltration of ketamine is an efficacious method in relieving delayed, not acute, postoperative pain after CS.

Conclusions

We propose that wound infiltration of ketamine, either alone or with bupivacaine, offers better postoperative pain control and reduces postoperative opioid consumption when compared to the use of bupivacaine alone. However, further studies examining the pharmacodynamics and pharmacokinetic characteristics and the side-effect profile of wound infiltration ketamine in cesarean patients are required.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

H. Aksoy and U. Aksoy designed the study, M. Ak and H. Aksoy collected the data, and M. Ak, G. Gokahmetoglu, and H. Aksoy analyzed the data and wrote the manuscript. M. Ak and H. Aksoy contributed to the study design and wrote the manuscript. All authors read and approved the final manuscript.

Funding

No financial support or funding was received for this paper.

Ethics Approval

All interventional procedures in this study were performed in accordance with both ethical and Helsinki Declaration standards, with the approval of the Ethics Committee of the Erciyes University Medicine Faculty (2014/99).

Informed Consent

Informed consent was obtained from all participants.

ORCID ID

Hüseyin Aksoy: 0000-0003-3467-3783
Günhan Gökahmetoğlu: 0000-0001-8281-2667
Mehmet Ak: 0000-0003-3384-0586
Ülkü Aksoy: 0000-0003-1010-9248

References

1) Lavender T, Hofmeyr GJ, Neilson JP, Kingdon C, Gyte GM. Caesarean section for non-medical reasons at term. Cochrane Database Syst Rev 2012; 3: CD004660.
2) Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman SJ. Births: final data for 2008. Natl Vital Stat Rep 2010; 59: 3-71.
3) Carvalho B, Cohen SE, Lipman SS, Fuller A, Mathusamy AD, Macario A. Patient preferences for anesthesia outcomes associated with cesarean delivery. Anesth Analg 2005; 101: 1182-1187.
4) Novy MJ. The normal pueperium. In: Pernoll ML, ed. Current Obstetrics & Gynecologic Diagnosis and Treatment. Connecticut: Appleton & Lange 1991; 260.
5) Ganta R, Samra SK, Maddineni VR, Furness G. Comparison of the effectiveness of bilateral ilioinguinal nerve block and wound infiltration for postoperative analgesia after caesarean section. Br J Anaesth 1994; 72: 229-230.
6) Kumar Das A, Wig J, Dhaliwal L. Preincisional local infiltration of bupivacaine and a mixture of bupivacaine and morphine for pain following lower segment cesarean section (a comparative evaluation). J Anaesthesiol Clin Pharmacol 1999; 15: 317-320.
7) Patridge BL, Stabile BE. The effects of incisional bupivacaine on postoperative narcotic requirement, oxygen saturation and length of stay in the postoperative unit. Acta Anaesthesiol Scand 1990; 34: 486-491.
8) Negro S, Martín A, Azuara ML, Sánchez Y, Barcia E. Stability of tramadol and haloperidol for continuous subcutaneous infusion at home. J Pain Symptom Manage 2005; 30: 192-199.

9) Hirota K, Lambert DG. Ketamine: Its mechanism(s) of action and unusual clinical use. Br J Anaesth 1996; 77: 441-444.

10) Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg 1994; 78: 205-209.

11) Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997; 84: 1086-1090.

12) Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonists (Ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. Anesth Analg 1995; 81: 63-68.

13) Tan PH, Cheng JT, Kuo CH, Tseng FJ, Chung HC, Wu JI, Hsiao HT, Yang LC. Preincisional subcutaneous infiltration of ketamine suppresses postoperative pain after circumcision surgery. Clin J Pain. 2007; 23: 214-218.

14) Honarmand A, Safavi M, Karaky H. Preincisional administration of intravenous or subcutaneous infiltration of low-dose ketamine suppresses postoperative pain after appendectomy. J Pain Res 2012; 5: 1-6

15) Tekelioglu UY, Apuhan T, Akkaya A, Demirhan A, Yildiz I, Simsek T, Gok U, Kocoglu H. Comparison of topical tramadol and ketamine in pain treatment after tonsillectomy. Paediatr Anaesth 2013; 23: 496-501.

16) Ugur KS, Karabayirli S, Demircioğlu Rİ, Ark N, Kurtaran H, Muslu B, Sert H. The comparison of preincisional peritonsillar infiltration of ketamine and tramadol for postoperative pain relief on children following adenotonsillectomy. Int J Pediatr Otorhinolaryngol 2013; 77: 1825-1829.

17) Kadic L, Niesten E, Heijnen I, Hofmans F, Wilder-Smith O, Driessen JJ, Malefijt MC. The effect of addition of pregabalin and s-ketamine to local infiltration analgesia on the knee function outcome after total knee arthroplasty. Acta Anaesthesiol Belg 2012; 63: 111-114.

18) Safavi M, Honarmand A, Nematollahy Z. Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: a randomized, double-blind, placebo-controlled study. Pain Med 2011; 12: 1418-1426.

19) Fredman B, Shapiro A, Zohar E, Feldman E, Shorer S, Rawal N, Jedeikin R. The analgesic efficacy of patient-controlled ropivacaine instillation after cesarean delivery. Anesth Analg 2000; 91: 1436-1440.

20) Behdad S, Sekhavat L, Ayatollahi V, Meshkat F, Mortazavi A. Comparison of postoperative analgesic effect of tramadol and bupivacaine subcutaneous infiltration in patients undergoing cesarean section. Acta Clin Croat 2013; 52: 93-97.

21) Jabalameli M, Safavi M, Honarmand A, Saryazdi H, Moradi D, Kashefi P. The comparison of intraincisional injection tramadol, pethidine and bupivacaine on postcesarean section pain relief under spinal anesthesia. Adv Biomed Res 2012; 1: 53.

22) Zohar E, Fredman B, Phillipov A, Jedeikin R, Shapiro A. The analgesic efficacy of patient controlled bupivacaine wound instillation after total abdominal hysterectomy with bilateral salpingooophorectomy. Anesth Analg 2001; 93: 482-487.

23) Zohar E, Luban I, Zunser I, Shapiro A, Jedeikin R, Fredman B. Patient-controlled bupivacaine wound instillation following cesarean section: the lack of efficacy of adjuvant ketamine. J Clin Anesth 2002; 14: 505-511.

24) Behaeen K, Soltanzadeh M, Nesioonpour S, Ebadi A, Olapour A, Mehdi Aslani SM. Analgesic effect of low dose subcutaneous ketamine administration before and after cesarean section. Iran Red Crescent Med J 2014; 16: e15506.

25) Trotter TN, Hayes-Gregson P, Robinson S, Cole L, Coley S, Fell D. Wound infiltration of local anaesthetic after lower segment caesarean section. Anaesthesia 1991; 46: 404-407.

26) Nguyen NK, Landais A, Barbaryan A, M'barek MA, Benbaghdad Y, McGee K, Lanba P. Analgesic efficacy of pfannenstiel incision infiltration with ropivacaine 7.5 mg/mL for caesarean section. Anesthesiol Res Pract 2010; 2010: 542375.

27) Bamigboye AA, Hofmeyr GJ. Local anaesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief. Cochrane Database Syst Rev 2009; (3): CD006954.

28) 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: 401-406.

29) Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I. Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients. Neurosci Lett 1996; 215: 5-8.

30) Grace RF, Lesteour T, Sala T, Stewart J. A randomized comparison of low-dose ketamine and lignocaine infiltration with ketamine-diazepam anaesthesia for postpartum tubal ligation in Vanuatu. Anaesth Intensive Care 2001; 29: 30-33.