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Original Article / Özgün Araştırma

Does the Method and Timing of Intravenous Ketamine Administration Affect Postoperative Morphine Requirement After Major Abdominal Surgery?

İntravenöz Ketamin Uygulama Yöntemi ve Zamanı Büyük Abdominal Cerrahi Sonrası Morfin Gereksinimini Etkiler mi?

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Abstract / Özet

Objective: Single intravenous bolus administration and postoperative or perioperative infusions are the most preferred methods of ketamine. Nevertheless, there is no clear explanation on the ideal ketamine administration method. In this study, we aimed to compare the effects of the most common ketamine administration methods and administration time on postoperative opioid consumption.

Methods: Fifty-two patients undergoing colectomy for colon cancer were randomly assigned into four groups. Group 1 was the control group. Group 2 received only a single intravenous bolus dose of 0.5 mg kg^{-1} ketamine at induction. Group 3 received 0.5 mg kg^{-1} intravenous ketamine bolus at induction and perioperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}. Group 4 received a bolus of 0.5 mg kg^{-1} intravenous ketamine at induction and perioperative and postoperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}. Postoperatively, visual analogue scale pain scores, side effects, and morphine consumption were recorded.

Results: There was no statistically significant difference in postoperative pain scores. Total morphine consumption was found to be significantly lower in Group 4 compared to the other groups (p=0.03, p=0.004, p=0.03, respectively). During the 1st, 2nd, and 4th hours in the postoperative period, patient-controlled analgesia morphine consumption was significantly lower in Group 4 compared to the control group (p<0.01).

Conclusion: Preoperative single-bolus dose or intraoperative low-dose ketamine infusion does not decrease postoperative morphine consumption; however, per- and postoperative 48-hour ketamine infusion has a significant effect in decreasing morphine consumption without decreasing the incidence of side effects in patients undergoing major abdominal surgery.

Key Words: Ketamine, postoperative analgesia, colectomy, morphine

Amaç: Tek doz intravenöz bolus uygulama, postoperatif veya peroperatif infüzyon yoluyla verilmesi ketaminin en çok tercih edilen uygulama yöntemlerindendir. Bununla beraber, ideal ketamin uygulama yöntemi konusunda net bir konsensus bulunmamaktadır. Bu çalışmada, en sık kullanılan ketamin uygulama yöntemleri ve zamanlarının postoperatif opioid tüketimi üzerine olan etkilerini karşılaştırmayı amaçladık.

Yöntemler: Kolon kanseri için kolektomi ameliyatı geçirecek 52 hasta randomize olarak 4 gruba ayrıldı. Grup 1 kontrol grubuydu. Grup 2 indüksiyonda 0,5 mg kg^{-1} tek bolus doz intravenöz ketamin aldı. Grup 3 indüksiyonda 0,5 mg kg^{-1} bolus intravenöz ketamini takiben 0,25 mg kg^{-1} sa^{-1} hızda peroperatif intravenöz ketamin infüzyonu aldı. Grup 4 indüksiyonda 0,5 mg kg^{-1} bolus intravenöz ketamini takiben 0,25 mg kg^{-1} sa^{-1} hızda peroperatif ve postoperatif dönemde intravenöz ketamin infüzyonu aldı. Postoperatif ağrı skorları, yan etkiler ve morfin tüketimleri kaydedildi.

Bulgular: Postoperatif ağrı skorlarında istatistiksel olarak anlamlı bir fark yoktu. Grup 4'de diğer gruplarla karşılaştırıldığında toplam morfin tüketimi daha az bulundu (p=0,03, p=0,004, p=0,03, gruplarda sırasıyla). Postoperatif 1, 2 ve 4. saatlerde hasta kontrollü analjeziyle morfin tüketimi Grup 4'de kontrol grubundan anlamlı olarak daha düşüktü (p<0,01).

Sonuç: Preoperatif tek bolus doz yada intraoperatif düşük doz ketamin infüzyonu postoperatif morfin tüketimini azaltmamışken, per- ve postoperatif 48 saatlik ketamin infüzyonu uygulaması büyük abdominal cerrahi geçiren hastalarda yan etki insidansını artırmadan morfin tüketiminde anlamlı bir azalmayla sonuçlanmıştır.

Anahtar Kelimeler: Ketamin, postoperatif analjezi, kolektomi, morfin

Introduction

Postoperative pain occurs through several anatomical and biochemical pathways. When the N-methyl-D-aspartate receptors (NMDAR) in the central nervous system are stimulated with afferent nociceptive inputs, the neuronal sensitization process is activated, and thus, pain perception increases. NMDAR activation does not only increase cellular response to painful stimulus, it also reduces the neuronal sensitivity against opioid receptor agonists (1). Activation of

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NMDAR is also the main mechanism of the hyperalgesia that is induced by opioids (2). Besides inhibiting central sensitization, using NMDAR antagonists with opioids also prevents tolerance that may develop against opioid analgesia (3).

Multimodal analgesia aims to improve efficiency by blocking different nociceptive pathways; therefore, when agents are administered in this way, their dose requirement and side effects can be reduced accordingly. Ketamine, which is a non -competitive NMDAR antagonist, has analgesic characteristics when it is used in subanaesthetic doses. However, several studies hypothesizing that subanaesthetic doses of ketamine may reduce the postoperative opioid requirement have reported controversial results. It has been reported that a low dose of ketamine administered intravenously (IV) as a part of multimodal analgesia after cesarean section did not have an additional postoperative analgesic effect (4). It has been indicated that adding ketamine to remifentanil infusion as an adjuvant does not lead to a decrease in pain severity after cholecystectomy, time to first analgesic requirement, and morphine consumption during the first 24 hours (2). However, some randomized and controlled studies have concluded that ketamine decreases postoperative opioid consumption and incidence of opioid-related side effects (5-9). These controversial outcomes may have been resulted from the methodology of the studies, heterogeneity of study populations, differences in patient-controlled analgesia (PCA) protocols or pain measurement methods, and the method of ketamine administration (10). There are several ways to administer ketamine, but the intravenous route has been reported to be the optimal method (11). Single intravenous bolus administration and postoperative or perioperative infusions are the most preferred methods. Nevertheless, meta-analyses did not bring a clear explanation on the ideal ketamine administration method (12, 13).

This prospective, randomized, double-blind study aimed to compare the effects of the most common ketamine administration methods-i.e., single bolus or infusion-and administration time (pre-induction, continuous infusion during preoperative and/or postoperative period) on postoperative opioid consumption.

Methods

After Marmara University Medical School ethics committee approval and patients' written informed consent, 52 patients, aged 30-70 years, American Society of Anesthesiology physical status I or II, undergoing colectomy for colon cancer under general anaesthesia were randomly assigned into four groups in this prospective, randomized, double-blinded, placebo-controlled study. Group allocation was determined by drawing white, closed envelopes containing group numbers. The patients, the anaesthesia team, and the team managing the postoperative analgesia were blinded to the study groups. A different anaesthesiologist prepared the solutions. Group 1 was the control group and received peri- and postoperative saline infusion. Group 2 received only a single-bolus dose of 0.5 mg kg^{-1} ketamine IV at induction and saline infusion peri- and postoperatively. Group 3 received 0.5 mg kg^{-1} ketamine bolus IV at induction and perioperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1} and postoperative saline infusion. Group 4 received a bolus of 0.5 mg kg^{-1} ketamine IV at induction and perioperative and postoperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}.

All patients were instructed about the use of a PCA device and a 100-mm visual analog scale (VAS) the day before the operation. Exclusion criteria were patients' refusal, history of psychiatric disorders, altered mental status, alcohol abuse, opioid abuse or chronic opioid treatment, uncontrolled hypertension, renal or hepatic insufficiency, inability to use a PCA device, pregnancy, allergy to ketamine or morphine, and history of seizure or intracranial hypertension.

All patients were premedicated with 0.07 mg kg^{-1} midazolam and 0.5 mg atropine intramuscularly administered 45 min before surgery. A central venous catheter, peripheral venous catheters, an arterial catheter, and urinary Foley catheters were inserted. Patients were continuously monitored for heart rate (ECG), oxygen saturation (SpO_2), end-tidal CO_2 pressure, invasive arterial blood pressure, and central venous pressure.

General anaesthesia was induced with thiopental sodium 5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} IV. Endotracheal intubation was performed in all patients. Anaesthesia was maintained with 1 MAC isoflurane and 70% N_2O in oxygen. Residual neuromuscular blockade was reversed with neostigmine 0.03 mg kg^{-1} and atropine 0.015 mg kg^{-1} IV.

Postoperatively in the recovery room, pain intensity was assessed using a 0-100-mm VAS, and IV morphine bolus was administered to keep the VAS score ≤30. Then, IV PCA with 1 mg mL^{-1} morphine solution was started to deliver a 1.5-cc bolus dose with a 10-min lockout time. PCA was continued for 48 h after surgery. No other analgesics were used during the study. During follow-up, in case of patients' VAS ≥30, 2 mL morphine was loaded from a PCA device.

Postoperatively at 1, 2, 4, 8, 12, 24, 36, and 48 Hours, VAS scores, side effects (nausea and vomiting, pruritus, sedation with a 4-point scale, respiratory depression, psychomimetic side effects, such as hallucination and nightmares), and morphine consumption were recorded. Ondansetron 4 mg IV was used for the treatment of nausea and vomiting.

Statistical analysis

A reduction of 30% in postoperative morphine consumption was considered clinically significant. In order to obtain a power of 80% and significance level of 5%, the sample size for each study group was calculated as 13 patients or more.

Table 1. Patient characteristics (mean±SD)

	Group 1 (n=13)	Group 2 (n=13)	Group 3 (n=13)	Group 4 (n=13)
Age (year)	60.87±7.9	56.77±9.0	56.81±9.7	57.1±15.7
Weight (kg)	66.12±14.1	73.55±12.2	78.45±11.8	67.4±10.4
Male: female	4:4	5:4	7:4	4:6

p>0.05. Group 1: control group. Group 2: single-bolus dose of 0.5 mg kg^{-1} ketamine IV at induction. Group 3: bolus dose of 0.5 mg kg^{-1} ketamine IV at induction and perioperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}. Group 4: a bolus of 0.5 mg kg^{-1} ketamine IV at induction and perioperative and postoperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}

Table 2. Postoperative VAS scores (mm) (mean±SD)

	Group 1 (control, n=13)	Group 2 (n=13)	Group 3 (n=13)	Group 4 (n=13)	p
1st hour	41.00±22.26	51.22±27.81	40.00±22.00	38.40±30.38	0.7075
2nd hour	35.62±17.08	48.55±29.50	34.72±15.40	37.10±26.76	0.5411
4th hour	22.25±12.89	37.22±25.64	23.72±11.74	25.60±31.05	0.4689
6th hour	14.87±5.96	23.44±13.23	22.09±8.12	23.50±28.85	0.6893
8th hour	16.75±6.54	16.55±7.03	16.82±7.58	11.00±28.85	0.8170
12th hour	14.14±6.12	13.44±3.00	17.45±6.15	11.00±7.12	0.1101
24th hour	12.87±5.71	12.22±6.03	13.45±8.23	14.90±6.98	0.8551
36th hour	11.50±7.98	14.55±7.10	10.82±9.63	16.70±13.07	0.5231
48th hour	10.37±5.99	13.55±13.39	11.82±10.62	7.77±7.88	0.6323

p>0.05. Group 1: control group. Group 2: single-bolus dose of 0.5 mg kg^{-1} ketamine IV at induction. Group 3: bolus dose of 0.5 mg kg^{-1} ketamine IV at induction and perioperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}. Group 4: a bolus of 0.5 mg kg^{-1} ketamine IV at induction and perioperative and postoperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}; VAS: visual analog scale

Table 3. Morphine loading dose and total morphine consumption (mg) (mean±SD)

	Group 1 (n=13)	Group 2 (n=13)	Group 3 (n=13)	Group 4 (n=13)
Morphine bolus dose	8.25±2.91	5.66±3.04	8.81±2.85	8.70±6.16
Total PCA morphine consumption	101.87±53.31	115.61±43.48	98.37±49.16	61.77±35.38*

*p<0.05 compared with other groups. Group 1: control group. Group 2: single-bolus dose of 0.5 mg kg^{-1} ketamine IV at induction. Group 3: bolus dose of 0.5 mg kg^{-1} ketamine IV at induction and perioperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}. Group 4: a bolus of 0.5 mg kg^{-1} ketamine IV at induction and perioperative and postoperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}; PCA: patient-controlled analgesia

Table 4. Side effects n (%)

	Group 1 n=13	Group 2 n=13	Group 3 n=13	Group 4 n=13
Nausea-vomiting	1 (7.7)	3 (23)	1 (7.7)	1 (7.7)
Nightmares	1 (7.7)	0 (0)	3 (23)	4 (30.7)
Hallucination	-	-	-	-

p>0.05. Group 1: control group. Group 2: single-bolus dose of 0.5 mg kg^{-1} ketamine IV at induction. Group 3: bolus dose of 0.5 mg kg^{-1} ketamine IV at induction and perioperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}. Group 4: a bolus of 0.5 mg kg^{-1} ketamine IV at induction and perioperative and postoperative ketamine infusion at a rate of 0.25 mg kg^{-1} h^{-1}

Demographic characteristics of the patients were compared statistically by one-way analysis of variance (ANOVA), while time-dependent variables were compared by two-way analysis of variance, and non-parametric data were analyzed by Kruskal-Wallis test. A p<0.05 was considered statistically significant, and the Tukey-Kramer test was used as the post hoc test.

Results

The demographic characteristics of the patients did not differ between groups (Table 1). There was no statistically significant difference in postoperative pain scores between the groups (Table 2). There was no significant difference in the amount of initial morphine requirement in the recovery room (Table 3).

Total PCA-morphine consumption was found to be significantly lower in Group 4 compared to the other groups (p=0.03, p=0.004, p=0.03, respectively). However, no significant difference was found between Group 1, Group 2, and Group 3 regarding total morphine consumption. During the 1st, 2nd, and 4th hours in the postoperative period, PCA morphine consumption was significantly lower in Group 4 compared to the control group (p<0.01). The incidence of nightmares was recorded in 7.7%, 0%, 23%, and 30.7% of patients in each group, respectively (Table 4) (p>0.05). No hallucinations were reported in any of the groups, and there was no statistically sig-

nificant difference in the incidence of nightmares, nausea and vomiting, pruritus, or sedation scores. Respiratory depression was not recorded in any patients.

Discussion

In this clinical study, we observed that low-dose ketamine decreased postoperative opioid requirements only when administered as an IV bolus at induction and IV infusion during the perioperative and postoperative 48 hours, without decreasing the incidence of opioid side effects.

Many studies conducted about the analgesic effect of IV low-dose ketamine have revealed controversial results. IV bolus ketamine has been reported to decrease morphine consumption in patients having severe acute pain due to trauma (14, 15). Argiriadou et al. (16) concluded that compared to a placebo group, intraoperative ketamine infusion was more effective in post-thoracotomy pain management. As ketamine provides early knee mobilization, it has been reported as a useful adjuvant for perioperative multimodal analgesia in patients undergoing arthroplasty (17). Another randomized, placebo-controlled study stated the opioid-sparing effect of preemptive IV bolus ketamine (18). On the other hand, Lopez-Alvarez et al. (19) indicated that morphine consumption and postoperative pain scores were higher in the group in which ketamine was administered. However, in this study, ketamine was only administered at induction; then, the patients received remifentanil infusion during the surgery. Sveticic et al. (20) concluded that combining ketamine with PCA-morphine administration did not provide any additional benefits; so, they did not suggest ketamine usage in routine practice. In this study, patients received PCA with a bolus of morphine plus ketamine 1.5 mg each after major orthopaedic surgery. This result may be related to the sole use of ketamine in the postoperative period. In a meta-analysis of 35 randomized, controlled studies conducted in children, all of the included studies, except 2 of them, planned to examine the effects of single-bolus dose ketamine or single bolus plus intraoperative IV infusion (21). Ketamine was infused for 24 hours in one of the two studies mentioned above. The patients in this study received postoperative IV paracetamol, rectal morniflumate, and IV nalbuphine infusion. However, the pain management in the postoperative period is recommended to evaluate using the PCA method, because IV PCA provides superior pain relief compared with conventional on-demand analgesia (22, 23). In the second study, morphine consumption within 72 hours was evaluated using IV PCA without postoperative ketamine infusion, and it was found that perioperative infusion affected neither postoperative pain scores nor opioid consumption.

Such controversial outcomes may have resulted from different factors, such as heterogeneity of the study population and differences in PCA protocols or pain measurement methods; however, the most important reason for these controversial results is the methodological differences in ketamine administration. Previous studies have focused on ketamine regarding its administration time (during preoperative, perioperative, or postoperative period), use of different doses, and administration method, such as IV, intra-articular, or intramuscular. However, there have not been any studies analyzing both administration time and methods regarding ketamine. The current study examined the effects of using single preoperative IV low-dose ketamine bolus and administering IV infusion during the peri- and postoperative periods on total morphine consumption as a part of multimodal analgesia. No statistical difference was found between the groups regarding pain scores during the study period. Similar pain scores were achieved with significantly lower total morphine consumption in Group 4 than the other groups. There was no difference in the PCA-morphine consumption at the postoperative 1st and 2nd hours between the group having a single-bolus dose and the one receiving peri- and postoperative ketamine infusion. However, the group having peri- and postoperative ketamine infusion consumed only 46% of the total morphine consumed by the group that received single-bolus dose ketamine. This can be attributed to the short duration of action of ketamine. Therefore, administering IV single-bolus dose ketamine did not affect the opioid consumption except for the first 2 postoperative hours. Ketamine, which is a short-acting anaesthetic agent, can be adequately effective only if it is administered as IV infusion.

In the present study, there was no increase in the incidence of behavioral, psychotomimetic, or neurological complications in patients receiving ketamine. In the postoperative period, even patients having ketamine infusion for 48 hours did not develop hallucinations. Moreover, nightmare incidence did not show a significant difference between groups. This may have resulted from use of low-dose ketamine-not from duration of infusions.

The limitation of our study is the number of patients in the groups (13 patients in each group). Although this is enough to detect a 30% decrease in morphine consumption, it may be different for the incidence of side effects. The incidence of hallucinations, which is insignificantly higher in Group 4, may be significant with a higher number of patients.

Conclusion

According to the results of the present study, the administration method of low-dose ketamine as an adjuvant in postoperative multimodal analgesia affects opioid consumption. Preoperative single-bolus dose or intraoperative low-dose ketamine infusion does not decrease postoperative morphine consumption; however, peri- and postoperative 48-hour ketamine infusion has a significant effect in decreasing morphine consumption without increasing the incidence of side effects in patients undergoing major abdominal surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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