Comparison of the effects of magnesium and ketamine on postoperative pain and morphine consumption. A double-blind randomized controlled clinical study[1]

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ABSTRACT

PURPOSE: To compare the effects of magnesium sulfate and ketamine on postoperative pain and total morphine consumption in a placebo-controlled design.

METHODS: One hundred and twenty women scheduled for total abdominal hysterectomy were included in this prospective, randomized, double-blind study. Postoperatively, when the Numeric Pain Rating Scale (NPRS) was four or more, IV-PCA morphine was applied to all patients. The patients were randomized into three groups: Group K ketamine, Group M magnesium, and Group C saline received as infusion. Total morphine consumption for 48h, pain scores, adverse effects, and patients' satisfaction were evaluated.

RESULTS: Total morphine consumption was significantly lower in Group K (32.6±9.2 mg) than in Group M (58.9±6.5 mg) and in Group C (65.7±8.2 mg). The satisfaction level of patients in Group K was higher than the other two groups ($p<0.05$). Pruritus and nausea were observed more frequently in Group C.

CONCLUSİON: The addition of ketamine to IV-PCA morphine reduces the total consumption of morphine without psychotic effects; however, magnesium did not influence morphine consumption.

Key words: Analgesia, Patient-Controlled. Morphine. Magnesium Sulfate. Ketamine.

Introduction

Intravenous patient-controlled analgesia (IV-PCA) with morphine is commonly used for postoperative pain control following major abdominal surgery. However, large amounts of morphine may lead to significant adverse events, such as respiratory depression, nausea, vomiting, or hypotension[1].

Multimodal analgesia using a non-opioid analgesic, in addition to an opioid analgesic, has been suggested as a way to improve postoperative pain control and to reduce opioid use[2-5].

Since the mechanism of action differs from that of opioids, ketamine may be a useful adjunct to improve the management of perioperative pain. The potential benefit of adding ketamine to IV-PCA with morphine has been reported by a number of studies across several types of surgery[5-12].

Magnesium sulfate has also been previously investigated as a possible adjuvant for postoperative analgesia[13-23]. However; relatively few studies have been conducted on the effects of postoperative intravenous magnesium administration (as an infusion) over a 24-hour period[17,21-23].

The current prospective, randomized study aimed to compare the effects of magnesium sulfate and ketamine on postoperative pain and total morphine consumption in a placebo-controlled design. We also assessed the occurrence of adverse effects and the level of patient satisfaction.

Methods

The investigation was approved by the Ethics Committee of Zekai Tahir Burak Training and Research Hospital, (ETIC 864/2013), according to the principles outlined in the Declaration of Helsinki. After obtaining approval from the hospital ethics committee**,** written informed consent was obtained from all patients.

This randomized (computerized), double-blind, placebo-controlled, clinical study was conducted at the Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey, from May 2013 to May 2014.

One hundred and twenty patients belonging to American Society of Anesthesiologist (ASA) physical status I and II, age 30-60 years, scheduled to undergo elective open total abdominal hysterectomy (TAH) for fibroid disease, or uterine myomectomy under general anesthesia were enrolled in the study.

The exclusion criteria were patients with severe hepatic, renal, cardiovascular impairment, neurological or psychiatric disorders, with allergy to the study drugs, and with history of chronic pain, drug or alcohol abuse. Those with history of current regular use of analgesics, anticonvulsants, antidepressants, or opioids within the last month were excluded from the study.

Patients were randomly allocated into one of three equal groups (n = 40) with a computerized random number generator: group K (ketamine bolus 0.2 mg/kg followed by infusion of 0.05 mg/kg/h, group M (magnesium bolus 50 mg/kg followed by 10 mg/kg/h infusion), and group C (normal saline). Study drugs were started in the postoperative period and continued for 48 h.

During the preoperative visit, the patients were informed about the purpose, and the use of the patient-controlled analgesia (PCA) device (Abbott Pain Management Providerc, Abbot Laboratories, North Chicago, IL, USA).

All patients were premedicated with midazolam (0.15 mg/kg, IV) 45 min before surgery. On arrival in the operating room, routine monitorization including electrocardiography (ECG), pulse oximetry (SpO_2), and noninvasive blood pressure (NIBP) were implemented.

General anesthesia was induced with thiopental sodium (5 mg/kg) and fentanyl (1 µg/kg). Tracheal intubation was facilitated with 0.6 mg/kg of rocuronium. Maintenance of anesthesia was accomplished by sevoflorane, 50% N_2O in O_2. Mechanically controlled ventilation was adjusted to maintain end-tidal PCO_2 near 35 mmHg. Additional muscle relaxant and fentanyl were administered during the operation according to clinical need and the discretion of the attending anesthesiologist. However, in the last 20 min of the operation, fentanyl was not applied.

All surgeries were performed by a single surgical team with the same way. Ten minutes before the end of surgery, morphine (0.05 mg/kg) and ondansetron (4 mg) were routinely administered. At the end of surgery, anesthesia was discontinued, and residual neuromuscular blockade was antagonized with neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). The trachea was extubated, when the patient became fully awake. Patients were transferred to the postanesthesia care unit (PACU).

In the PACU, a physician, blinded to the groups, evaluated the severity of pain by using a Numeric Pain Rating Scale (NPRS, 0 = no pain, 10 = worst pain). When a NPRS score of 4 was reached, or the patient requested analgesic, a bolus dose of morphine 0.01 mg/kg was administered, and then the IV-PCA device containing

morphine 1 mg/mL was connected to the patients (bolus = 0.01 mg/kg, lock-out interval = 15 min, and continous background infusion = 0.03 mg/kg/h)[24]. It was continued throughout the 48 h study period.

Patients were randomly allocated into three equal groups (n = 40) with a computerized random number generator in a double-blinded manner:

1. Ketamine group (Group K), patients received a bolus dose of ketamine (0.2 mg/kg), and followed by continuous infusion of ketamine (0.05 mg/kg/h),

2. Magnesium group (Group M), patients received a bolus dose of magnesium (50 mg/kg), and followed by continuous infusion of magnesium (10 mg/kg/h),

3. Control group (Group C), patients received a bolus dose, and continuous infusion of normal saline.

The bolus doses of the study drugs were administered, and their infusions were started simultaneously with the initiation of the IV-PCA morphine. All studied solutions were continued until 48 h postoperatively via an infuser. Thus, patients had two separate mechanical infusion devices during the study period.

The severity of pain (with NPRS) was recorded at 2, 4, 6,12, 24, and 48 h after surgery. Patients received tenoxicam 20 mg (IV) as rescue analgesia, if pain was not adequately controlled (pain score >3 on the NPRS)[24]. The total number of rescue analgesic doses were noted in the 48 h period.

The degree of sedation was assessed using modified Ramsay sedation scale at 2-6-12-24 and 48 h after PCA device had been started.

Adverse events such as nausea, vomiting, pruritus, hypotension, bradycardia, hypoventilation, constipation, headache, dizziness, nightmare, sedation (Ramsay sedation score >3), and hallucination were also recorded. The complications were treated according to each individual case.

The satisfaction level of the patients was divided into one of four levels: very satisfied (4), generally satisfied (3), moderately satisfied (2), and unsatisfied (1).

Total morphine consumption, the number of rescue analgesic given, and the level of the patient satisfaction were recorded at 48 h after surgery.

Demographic characteristics such as age, ASA, and duration of surgery were also recorded for all patients.

The physicians collecting the postoperative data, as well as the patients, were unaware of the infused solutions.

The primary endpoint was total morphine consumption 48 h after surgery. The secondary outcome measures were the pain scores, the presence of adverse effects, and the patient satisfaction levels.

Statistical analysis

The morphine consumption by PCA at the end of 48 hours was the primary outcome variable on which sample size estimation was based at the beginning of the study. A sample size of 25 per group was required to detect a difference in morphine consumption between treatments at a two-sided 5% significance level with a power of 90%[25].

Data were expressed as mean ± standard deviation (SD), or number (%) of patients. For the statistical analysis, SPSS version 13.0 (SPSS Inc. Illinois) was used. A one-way ANOVA was used to compare the continuous variables among the groups. If a significant difference was noted, to know which group differs from which others, post hoc Tukey was used. Categorical variables were analyzed using the chi-square test or Fisher exact test, as appropriate. P value of less than 0.05 was considered statistically significant. The Bonferroni Correction was applied for all possible multiple comparisons controlling Type I error.

Results

In the present study, a total of 120 patients met the inclusion criteria, and consented for the study. Patients were randomized to one of three groups (Figure 1). There were no dropouts or loss to follow-up. There were no significant differences among the three groups with respect to demographic data or the duration of the operation (Table 1).

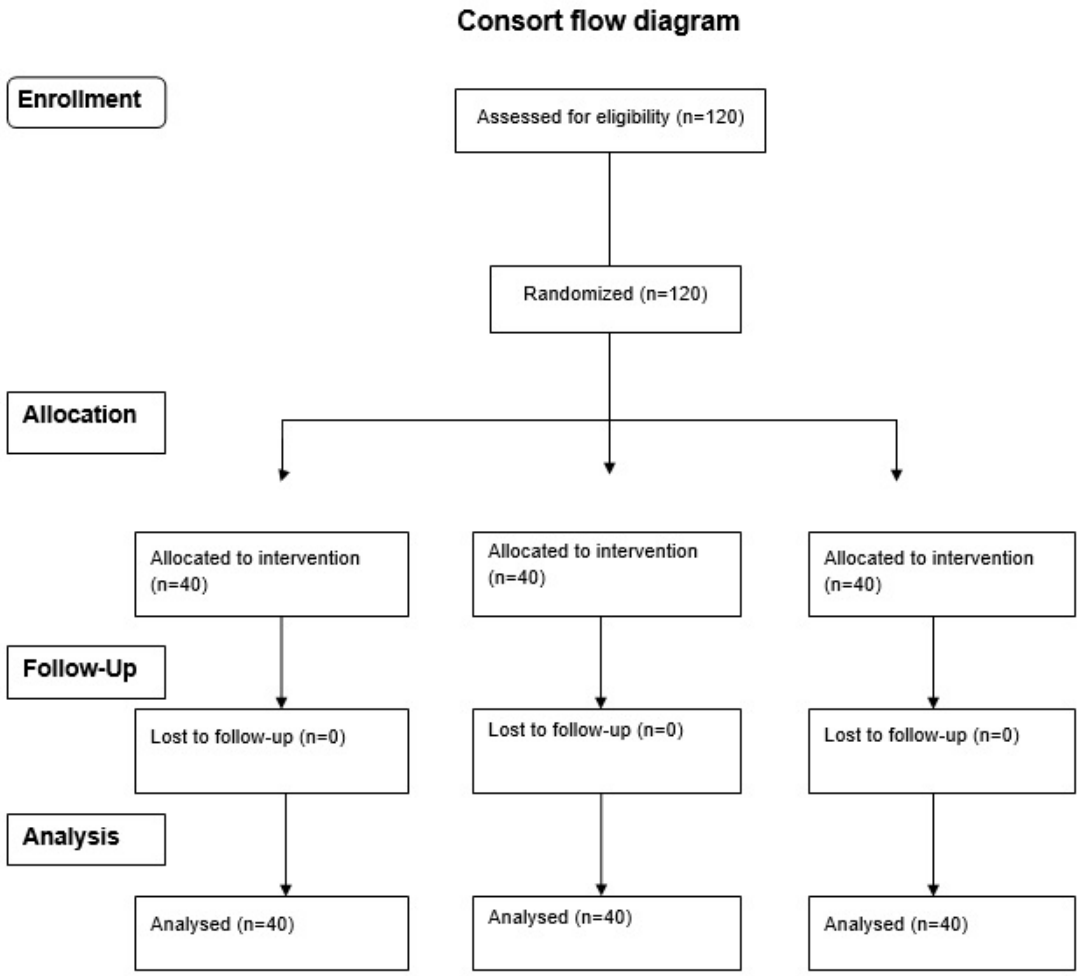

FIGURE 1 - The flow chart of the study.

TABLE 1 - Demographic characteristics of patients and duration of surgery**.**

	Group C (n=40)	Group M (n=40)	Group K (n=40)
Age (years)	58.45±5.71	56.81±5.12	59.35±4.96
Weight (kg)	70.85±12.51	69.05±11.12	68.52±10.02
Duration of surgery (hours)	1.53±0.23	1.57±0.20	1.56±0.12

Data are the mean ± SD. There were no significant differences among the groups.

The mean morphine consumption doses after 48 h was lowest in the ketamine group ($p<0.05$). There was no statistically significant difference between the control group and magnesium group ($p>0.05$). The NPRS at all time points were similar among the three groups (Table 2).

TABLE 2 - Morphine consumption (48h after surgery), and Numeric Pain Rating Scores.

		Group C (n=40)	Group M (n=40)	Group K (n=40)	P
Morphine consumption (mg)		65.7±8.2	58.9±6.5	32.6±9.2*	0.015*
NPRS	2 h	6.6±1.9	6.4±1.6	6.2±0.6	0.39
	6 h	4.4±0.9	4.1±1.7	4.0±1.1	0.47
	12 h	3.9±1.1	3.6±0.7	3.5±1.7	0.25
	24 h	3.1±1.0	2.8±0.3	2.7±0.5	0.31
	48 h	2.8±0.5	2.6±0.9	2.5±1.1	0.42

Data are the mean ± SD. A one-way analysis of variance was used to compare the continuous variables among the groups with a post hoc Bonferroni multiple comparisons test. *$p<0.05$; *vs* Group C and Group M.

The postoperative 48h; rescue analgesic was given to 16/40 patients (40%) in Group C, 12/40 patients (30%) in Group M, and 5/40 patients (12.5%) in Group K. Additional analgesic requirements were less in Group K ($p<0.05$). The level of the patient satisfaction was higher in Group K compared to Group M and Group C (Group K, Group M, and Group C: 3.4±0.2, 2.3±0.8, and 2.4±0.5, respectively) ($p<0.05$).

The incidence of adverse events such as hypotension, bradycardia, vomiting, nightmare, hallucination, and dizziness were comparable among the groups. However, pruritus (p=0.012), and nausea (p=0.015) were observed more frequently in Group C than in the other two groups (Table 3).

TABLE 3 - Adverse events.

	Group C (n=40)	Group M (n=40)	Group K (n=40)
Hypotension	3 (7.5%)	1 (2.5%)	0
Bradycardia	2 (5%)	1(2.5%)	0
Nausea	10 (25%)*	6 (15%)	5 (12.5%)
Vomiting	3 (7.5%)	1 (2.5%)	1(2.5%)
Pruritus	5 (12.5%)*	1 (2.5%)	0
Dizziness	0	0	1(2.5%)
Hallucination	0	0	1(2.5%)
Nightmare	0	0	0

Data are expressed as the number and proportion (%) of patients in each group. *p<0.05; *vs* Group K and Group M.

Discussion

This study showed that the addition of ketamine to IV-PCA with morphine was associated with less morphine consumed, less number of patient needed rescue analgesic, and more patient satisfaction. The occurrence of pruritus and nausea were more frequent in morphine alone group. In our study, we observed that magnesium sulfate had no impact on morphine consumption. We did not find any differences among groups in terms of pain scores, and other side effects.

Intravenous patient-controlled analgesia (IV-PCA) with morphine is commonly used for postoperative pain control after major abdominal surgery. White *et al*.[26] concluded that the use of morphine infusion combined with PCA boluses may result in a better control of pain and lower morphine consumption. Therefore, in our study, we used this method. In addition, rescue analgesia with tenoxicam (20 mg, IV) was given[27].

Different drugs have been used as an adjuvant in order to reduce morphine consumption. The N-methyl D-aspartate (NMDA) receptor is found in many parts of the body, including the nerve endings, and it plays a well-defined role in pain modulation. NMDA receptor antagonists, such as, magnesium sulfate, and ketamine, have been previously investigated as a possible adjuvant for postoperative analgesia[13].

Several studies have demonstrated the analgesic effectiveness of perioperatively administered ketamine during the acute postoperative period[2-4]. A systematic review has shown the analgesic benefit of ketamine, especially in surgery that is accompanied by high levels of postoperative pain[2], and when combined with morphine to lower morphine consumption[8].

Nesher *et al*.[11] reported that IV-PCA with a subanesthetic dose of ketamine and morphine following transthoracic lung and heart surgery resulted in lower pain scores, morphine consumption, and incidence of nausea-vomiting without increasing side effects.

Zakine *et al*.[12] compared ketamine infusion during the intraoperative period alone with that for the perioperative period (intraoperative plus postoperative, 48h). The authors demonstrated that low dose ketamine improved postoperative analgesia, reduced morphine consumption and incidence of nausea. Remerand and colleagues[10] demonstrated that an IV bolus at the beginning of surgery followed by a 24h infusion decreased morphine consumption in patients undergoing total hip arthroplasty. Akhavanakbari *et al*.[28] showed that adding ketamine to morphine in IV-PCA reduced pain score and morphine consumption.

In this study, ketamine has been used only for the postoperative period without pre- or perioperative administration. In line with the previous studies, we found that the morphine consumption was less in ketamine group, and the use of the low dose (0.05 mg/kg/h) of ketamine was not associated with any psychotic effects. These results were also confirmed in a previous study[3].

Perioperative intravenous magnesium sulfate at very high doses has been reported to reduce postoperative morphine consumption but not postoperative pain scores[15]. Murphy *et al*.[29] found that the perioperative infusion of magnesium sulfate was associated with a decrease in postoperative opioid consumption;

nevertheless, the decrease in opioid consumption was not associated with a decrease in opioid related side effects (eg, postoperative nausea and vomiting). In addition, they also found that perioperative magnesium sulfate infusion was associated with a decrease in visual analog scale pain scores up to 4-6 hours after surgery.

Ryu *et al*.[30] gave magnesium sulfate (50mg/kg bolus followed by 15mg/kg/h) or placebo intraoperatively to patients undergoing total abdominal hysterectomy under general anesthesia. They found that postoperative PCA morphine use and pain scores were lower in the magnesium group at 24 and 48 h, and PONV incidence was also lower than with placebo. Tramer *et al*.[15] reported that patients undergoing lower abdominal surgery with magnesium supplementation consumed 30% less morphine in the postoperative period compared with control patients. Ozcan *et al*.[21] found that postoperative use of magnesium sulfate reduced opioid consumption for pain after thoracotomy operations. However; in our study, we did not find any positive effect of magnesium sulfate on morphine consumption. Lysakowski *et al*.[31], in a systemic review of randomized trials, reached different conclusions as to whether magnesium sulfate is a useful adjuvant to postoperative analgesia. Their trials do not provide convincing evidence that perioperative magnesium sulfate has favorable effects on postoperative pain intensity and analgesic requirement.

Unlugenc *et al*.[23] compared the effects of magnesium sulfate with ketamine on postoperative analgesia and morphine consumption. They found that both drugs significantly reduced morphine consumption during the first 24 hours. In this study, the total morphine consumption was significantly lower in ketamine group, but we did not find any favorable effects of magnesium sulfate on morphine consumption. Postoperative pain scores were similar in all groups. The incidence of nausea and pruritus were more common in morphine alone group.

This study had some limitations. The present study was that pain scores were not recorded after the postoperative first 48 hours. Moreover, we evaluated the pain intensity only at rest. The analgesic effects of the study drugs on postoperative mobilization, and hospital discharge time were not evaluated. These effects should be addressed in future studies.

Conclusions

Patients in morphine alone group experienced more nausea and pruritus than in the other groups. The total consumption of morphine, and additional analgesic requirements were less, while the satisfaction level of patients were higher in the ketamine group. Ketamine is still one of the most advantageous adjuvant drugs for treating postoperative pain.

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