Egyptian Journal of Anaesthesia (2015) **31**, 53–58

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Egyptian Journal of Anaesthesia

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Research Article

Comparison of the preemptive analgesia of low dose ketamine versus magnesium sulfate on parturient undergoing cesarean section under general anesthesia

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Received 19 September 2014; revised 18 December 2014; accepted 22 December 2014
Available online 22 January 2015

KEYWORDS

Preemptive;
Low-dose ketamine;
Magnesium sulfate;
Cesarean section

Abstract *Objective:* To investigate the efficacy of the preemptive analgesic effect of low dose ketamine versus $MgSO_4$ on potentiating postoperative analgesia when compared to placebo in patients undergoing cesarean section under general anesthesia.
Methods: This prospective randomized blind study included 60 parturient females scheduled for cesarean section under general anesthesia. They were randomized into three equal groups [20 *patients each*]: group I [*Control*]: received 20 ml normal saline 0.9%, group II [*Ketamine*]: received ketamine 0.3 mg/kg in 20 ml normal saline and group III [$MgSO_4$]: received $MgSO_4$, 30 mg/kg in 20 ml normal saline. Investigated medications infused over 10 min before induction of anesthesia. Fentanyl requirement, mean BP and HR were measured intraoperatively. Pain, sedation and nausea and vomiting were assessed at 2, 6, 12 and 24 h postoperatively. Total postoperative pethidine dose over 24 h was calculated.
Results: MBP and HR showed statistically significantly lower value in group (K) and (M) compared to group (C) at postintubation and postincision readings. Intraoperative fentanyl requirement was statistically higher in (C) groups compared to (K) and (M) groups. The time for first request for postoperative analgesia was longer and the total postoperative pethidine dose over 24 h was lower in (K) group compared to (C) and (M) groups. Postoperative VAS scores at 2 and 6 h postopera-

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2014.12.006

tively showed statistically highly significantly lower values in (K) group compared to (C) and (M) groups. Apgar, postoperative sedation and PONV scores showed no statistically significant differences among the three groups.

Conclusions: Preemptive dose of either ketamine (0.3 mg/kg) or $MgSO_4$ (30 mg/kg) in patients undergoing cesarean section under general anesthesia could suppress the pressor response to endotracheal intubation and skin incision and decreased the intraoperative fentanyl requirement. Ketamine showed a significant preemptive analgesic effect compared to $MgSO_4$ at 2 and 6 h postoperatively.

1. Introduction

The concept of pre-emptive analgesia was introduced by Woolf who demonstrated through experimental studies that peripheral tissue injury causes both central and peripheral sensitization, manifesting as an increase in response to noxious stimuli, and decrease in pain threshold, both at the site of injury and surrounding tissue. Pre-emptive analgesia has been defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from injuries [1].

Although the use of general anesthesia (GA) for cesarean section (CS) has declined while the use of regional techniques has increased, both planned and unplanned CSs continue to be performed under GA when there is a contraindication to regional anesthesia or as in emergency, as GA can be thought to be the quickest anesthesia method in an emergency since it avoids the possibility of a failed regional block [2].

The standard general anesthetics for cesarean section include induction with thiopental and omission of opioids until after delivery of the fetus. This may increase the potential for central hypersensitivity states, with a consequent increase in postoperative pain and analgesic requirement [3,4].

N-Methyl-D-Aspartate (NMDA) receptors are set in a cascade of secondary events in a cell which has been activated. These events lead to intracellular changes which increase the responsiveness of the nociceptive system. These events include development of ''wind up'', facilitation, central sensitization: changes in peripheral receptive fields [5].

Ketamine is an antagonist at (NMDA) receptors, which are considered important in the mechanism of central hypersensitivity [6]. Low dose ketamine (0.15 mg/kg) given before surgical incision reduced the post-operative morphine requirement by 40% in first 24 h after cholecystectomy [7].

Other Therapies that have been tested in pre-emptive trials include NSAIDS, intravenous opioids, peripheral local anesthetics, caudal and epidural analgesia, dextromethorphan and gabapentin. One intravenous adjuvant medication that has shown potential in pre-emptive analgesia is magnesium [8].

Magnesium is of importance in anesthesia practice for several reasons. First, the ion is essential for many biochemical reactions and its deficiency may produce clinically important consequences during anesthesia or in intensive care unit. Second, the extensive use of magnesium sulfate in obstetric practice requires that anesthesiologists be familiar with the pharmacological action of this drug and its interaction with anesthetic agents. Third, few of its properties may be of value in certain areas of anesthetic practice [9].

The present study was designed to study the efficacy of the preemptive analgesic effect of low dose ketamine versus $MgSO_4$ on potentiating postoperative analgesia when compared to placebo in patients undergoing cesarean section under general anesthesia.

2. Methods

After obtaining approval by the Hospital Ethics Committee, 60 ASA I–II parturient female patients (18–40 years old) scheduled for elective cesarean section under general anesthesia (*because of high rate of patient refusal to spinal and epidural analgesia in our hospital*) were enrolled in this randomized double blind study. Patients were excluded if they have history of allergy to either of thiopental, ketamine or magnesium, gestational age less than 36 weeks, candidates with fetal distress, body mass index more than 35 kg/m^2 or history of substance abuse. Also, diabetic patients and those with pregnancy induced hypertension were excluded.

Preoperatively, all patients were instructed for the pain visual analog scale (VAS) for measurement of pain, gave written informed consents and were premedicated against regurgitation and acid aspiration by intravenous H_2 blocker (ranitidine 50 mg) and antiemetic (metoclopramide 10 mg). Upon arrival to the operating room, and after attachment of standard monitors (5-lead ECG, Noninvasive arterial blood pressure monitoring device and pulse oximetry) and after insertion of a wide bore cannula, using the sealed envelope method, parturients were randomly assigned into 3 groups to receive 20 ml of normal saline alone or containing the study drug infused over 10 min before induction of anesthesia:

- Control (C) group (n = 20): received 20 ml normal saline 0.9%.
- Ketamine (K) group (n = 20): received ketamine 0.3 mg/kg in 20 ml normal saline.
- Magnesium sulfate (M) group (n = 20): received $MgSO_4$, 30 mg/kg in 20 ml normal saline.

With the patient placed supine, a wedge inserted under the right hip for left uterine displacement, preoxygenation accomplished with 100% oxygen for 3–5 min while monitors are applied. The patient was prepared and draped for surgery. When the surgeons were ready, a rapid-sequence induction with cricoid pressure was performed using Intravenous 2.5% thiopental (5 mg/kg), followed by succinylcholine 1.5 mg/kg. The patient was intubated under direct vision with a cuffed endotracheal tube lubricated with lidocaine jelly (10%) and

Table 1 Demographic data [Data represented as Median (range) or Mean ± SD].

Parameter	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
Age (year)	30 (22–41)	33 (24–43)	31 (23–43)
BMI (kg/m^2)	32 ± 3	30 ± 3.5	29 ± 3
Operative time (min)	62 ± 15	65 ± 16	59 ± 15
Intraoperative fentanyl requirement (μg)	140 ± 41	110 ± 20*	120 ± 25*

* Statistically significant compared to (C) group ($P < 0.05$).

Table 2 Mean arterial blood pressure [Data represented as Mean ± SD].

Parameter	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
Baseline (mmHg)	88 ± 10	87 ± 12	88 ± 9
Postintubation (mmHg)	94 ± 9	86 ± 6*	85 ± 6*
Postskin incision (mmHg)	101 ± 10	94 ± 12*	93 ± 12*

* Statistically significant compared to (C) group ($P < 0.05$).

was confirmed in place by auscultation and capnography. Lungs were mechanically ventilated to maintain an end-tidal CO_2 pressure at 35–40 mmHg. After neuromuscular recovery from succinylcholine, neuromuscular blockade was achieved with atracurium 0.5 mg/kg and maintained with top-up doses of 0.1 mg/kg when required. Hypnosis was maintained using sevoflurane ±2 vol% in 100 O_2. After the neonate and placenta are delivered, 20–30 IU of oxytocin was added to each liter of intravenous fluid, 0.4 mg methergine IM and 100 μm Fentanyl were given as bolus IV and further fentanyl were given as boluses of 50 μm guided by increase in heart rate and/or blood pressure by more than 20% of the baseline.

At the end of surgery, Ondansetron 4 mg was give as prophylactic for PONV, muscle relaxants were completely reversed by neostigmine 0.05 mg/kg and atropine 0.014 mg/kg and the patient was extubated while awake to reduce the risk of aspiration.

Postoperative analgesia was prescribed as Paracetamol 1 g IV infusion 6 hourly starting at the recovery room and pethidine 50 mg IM if VAS score was ⩾3 at the assessment time or as SOS between the assessment intervals.

The following parameters were evaluated:

- Demographic data of the patients.
- Intraoperative fentanyl requirement.
- Mean arterial blood pressure and heart rate, before induction (baseline), after intubation, after skin incision.
- Pain severity was assessed using visual analogue score (VAS) where (0 = no pain and 10 = worst pain), at 2, 6, 12 and 24 h postoperatively.
- Sedation level was assessed at the same intervals of VAS using a 4-point scale (1 = fully awake; 2 = somnolent, responds to verbal stimuli; 3 = somnolent, responds to tactile stimuli; and 4 = somnolent, responds to painful stimuli).
- Nausea was measured at the same intervals using a categorical scoring system (none = 0, mild = 1, moderate = 2, and severe = 3). Ondansetron 4 mg IV was prescribed for patients who complained of nausea or vomiting.
- Time for the first request for analgesia was recorded and the total dose of pethidine over the 24 h postoperatively was calculated.
- APGAR score of the neonate was assessed by the neonatologist.

2.1. Sample size calculation

Power analysis was performed using one way Analysis of Variance (ANOVA) on time to first analgesic supplementation because it was the main outcome variable in the present study. A previous study [10] showed that the mean of the time to first analgesic supplementation was about 10.22 h with a standard deviation of 8 h in the low dose ketamine group and the mean of the time to first analgesic supplementation was 1.6 h with a standard deviation of 1.01 h in the control group. Taking power of 0.95 and alpha error 0.05, a minimum sample size of 18 patients is calculated for each group. A total number of 20 patients in each group will be included to compensate for the possible dropouts.

2.2. Statistical analysis

Data management and analysis were performed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). The data were statistically presented in terms of Median (range) and Mean ± standard deviation. Comparisons among numerical variables of three groups were done by unpaired Student's t test for parametric data or Kruskal–Wallis test for non-parametric data. All P-values were considered significant when P-values less than 0.05 and highly significant when P-values less than 0.001.

3. Results

There was no statistically significant difference among the three studied groups as regards the demographic data of the patients (age and BMI) and the operative time (Table 1).

Intraoperative fentanyl requirements were less in both the ketamine and magnesium sulfate groups compared to the control group and the difference was highly statistically significant in the K group ($P < 0.001$) and statistically significant in the M group ($P < 0.05$), while it showed no statistically significant difference between (K) and (M) groups (Table 1).

Baseline Mean Arterial Blood Pressure showed **No** statistically significant difference among the three groups, while post-intubation readings showed statistically significantly

Table 3 Heart rate (beat per minute) [Data represented as Mean ± SD].

Parameter	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
Baseline (BPM)	85 ± 5	84 ± 5	85 ± 4
Postintubation (BPM)	99 ± 6	90 ± 4*	90 ± 5*
Postskin incision (BPM)	108 ± 8	93 ± 6*	96 ± 5*

* Statistically significant compared to (C) group ($P < 0.05$).

Table 4 Post-operative VAS [Data represented as Median (Range)].

Parameter	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
2 Hours post-operative	4 (2–5)	2.5 (2–4)*	3 (2–5)
6 Hours post-operative	4 (3–5)	3 (2–4)*	4 (3–5)
12 Hours post-operative	3.5 (2–4)	3 (2–4)	3 (2–4)
24 Hours post-operative	2.5 (1–3)	2 (1–3)	2 (1–3)

* Statistically significant compared to (C) and (M) groups ($P < 0.05$).

Table 5 Time for first analgesic request and total pethidine dose during the first 24 h postoperatively [Data represented as Mean ± SD].

Parameter	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
Time for first analgesic request (min)	33 ± 7	82 ± 12*	36 ± 5
Total dose of pethidine over 24 h (mg)	140 ± 38	82 ± 33*	137 ± 39

* Statistically significant compared to (C) and (M) groups ($P < 0.05$).

Table 6 Apgar score of the neonate [Data represented as Median (Range)].

Timing	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
1 Minute	7 (6–8)	7 (6–8)	7 (6–8)
5 Minutes	8 (7–8)	8 (7–8)	8 (7–8)

No statistically significant difference among the three groups.

Table 7 Post-operative sedation score [Data represented as Median (Range)].

Timing	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
2 Hours post-operative	2 (1–3)	2.5 (1–3)	2 (1–3)
6 Hours post-operative	2 (1–3)	1.5 (1–3)	2 (1–3)
12 Hours post-operative	2 (1–2)	2 (1–2)	2 (1–2)
24 Hours post-operative	1 (1–2)	1 (1–2)	1 (1–2)

No statistically significant difference among the three groups.

lower values ($P < 0.05$) in (K) and (M) groups compared to (C) group. The same pattern of this statistically significant difference was observed in the post-skin incision mean blood pressure, where it was statistically lower ($P < 0.05$) in (K) and (M) groups compared to (C) group. Meanwhile there was No statistically significant difference between (K) and (M) groups as regards the mean blood pressure during the three times of evaluation (Table 2).

Baseline Heart Rate showed **No** statistically significant difference among the three groups, while post-intubation heart rate was statistically highly significantly lower ($P < 0.001$) in (K) and (M) groups compared with (C) groups. Also, post-skin incision heart rate was statistically highly significantly lower ($P < 0.001$) in (K) and (M) groups compared with (C) groups (Table 3).

Table 8 PONV during the 24 h postoperatively [Data represented by number of patients].

Timing	Control group (C) (n = 20)	Ketamine group (K) (n = 19)	$MgSO_4$ group (M) (n = 20)
2 Hours post-operative	9	10	9
6 Hours post-operative	5	6	5
12 Hours post-operative	2	2	2
24 Hours post-operative	0	0	0

No statistically significant difference among the three groups.

Mean VAS score when measured at 2 and 6 h post-operatively showed statistically highly significantly lower values in (K) compared to (C) and (M) groups ($P < 0.001$). But **No** statistically significant difference was observed in VAS score values among the three studied groups at 12 and 24 h post-operatively (Table 4).

The time for the first request for postoperative analgesia showed statistically highly significant longer duration in (K) groups compared to (C) and (M) groups, while there was ***No*** statistically significant difference between the later two groups. Total dose of pethidine required during the first 24 h post-operatively showed highly statistically significantly lower values in (K) group compared to both (C) group and (M) group ($P < 0.001$), while it was statistically **insignificant** between (M) group and the (C) group (Table 5).

There were no statistically significant differences among the three studied groups as regards the Apgar score, post-operative sedation score or post-operative nausea and vomiting (Tables 6–8).

4. Discussion

The results of the present study showed that preemptive injection (*before induction of anesthesia*) of low dose ketamine in cesarean section patients could suppress the pressor response to endotracheal intubation and skin incision and decreased the intraoperative fentanyl requirement together with low pain score during the first 12 h postoperatively, delayed time for the first request for analgesic and decreased total pethidine dose during the first 24 h postoperatively, compared to the control group.

Preemptive infusion of magnesium sulfate was shown to have the same effects intraoperatively, without significant difference on the postoperative pain score, time for the first request for analgesic and total pethidine dose during the first 24 h postoperatively, when compared to the control group.

The results of the present study were in agreement with the findings of Ghazi-Saidi et al., who compared post-operative pain and analgesic requirement in patients undergoing cesarean section with preemptive low-dose ketamine (0.2 mg/kg) versus placebo both administered prior to anesthesia induction. They found that Mean dose of morphine consumption over 24 h postoperatively was less in the ketamine group than in the control group. VAS pain scores were lower in ketamine group compared to the control group [10].

Also the results of the present study were in agreement with the findings of Kwork et al., who compared post-operative pain and analgesic requirement of preemptive low-dose ketamine (0.15 mg/kg) administered preincisional and low-dose ketamine (0.15 mg/kg) administrated after wound closure in patients undergoing gynecological laparoscopic surgery. They found that preincisional ketamine decreased pain over 6 h post-operative, increased time to first analgesic requirement and decreased post-operative analgesic need [11].

Also the results of the present study were in agreement with the findings of Behdad et al., who compared post-operative pain and analgesic requirement in patients undergoing appendectomy under general anesthesia with preemptive low-dose ketamine (0.5 mg/kg) administered 10 min preincisional versus placebo. They found that the VAS score was significantly lower in the ketamine group compared to the control, the time for the first analgesic request was longer in the ketamine group and the total dose of Pethidine injections in the first 24 h post-operatively was lower for the ketamine group [12].

However the results of the present study were in disagreement with the findings of Dahl et al., who compared post-operative pain and analgesic requirement in patients undergoing abdominal hysterectomy under general anesthesia, comparing either preemptive low-dose ketamine (0.4 mg/kg) administered preincisional or low-dose ketamine (0.4 mg/kg) administered after skin closure versus placebo. They found that there were ***no*** significant differences between preemptive ketamine and placebo with respect to pain scores, postoperative opioid analgesic requirements, and incidence of postoperative nausea and vomiting [13].

This disagreement may be explained by the difference in anesthetic drugs used by Dahl et al. who used alfentanil and nitrous oxide 66% which are not used in our hospital.

As regards the intraoperative hemodynamic effects of magnesium sulfate, the results of the present study were in agreement with the findings of Lee et al., who compared intraoperative analgesic requirements and anesthetic depth in patients undergoing cesarean section. Seventy-two patients were randomly assigned to receive intravenous saline (control group) or two doses of magnesium sulfate: (30 mg/kg bolus and 10 mg/kg/h continuous infusion) after induction or (45 mg/kg bolus and 15 mg/kg/h continuous infusion) after induction. They found that both doses of magnesium sulfate attenuated arterial pressure increases during the pre-delivery period and less midazolam to maintain the desired depth of anesthesia compared to the control group [14].

As regards the postoperative analgesic effect of magnesium sulfate, the results of the present study were in line with the findings of Bhatia et al., who studied the effect of placebo versus magnesium sulfate (*preoperative loading dose of* 50 mg/kg *followed by* 15 mg/kg/h *continuous infusion till the end of surgery*) on the analgesic requirement, pain, discomfort, and sleep during postoperative period in patients undergoing open cholecystectomy under general anesthesia. They found that patients in both groups had similar pain scores and morphine requirement during the first 24 h postoperatively [15].

Also the results of the present study best correlate with the findings of Seong-Hoon et al., who studied the effect of intravenous magnesium sulfate infusion (*preoperative loading dose of* 50 mg/kg *followed by* 15 mg/kg/h *continuous infusion for* 6 h) versus placebo on the postoperative pain in patients undergoing abdominal hysterectomy under general anesthesia. They found that cumulative postoperative analgesic and visual analog pain scores at rest and during forced expiration were similar in both groups [16].

Again, the results of the present study were in accordance with those of the study done by Rezae et al., who studied the postoperative analgesic effect of a preoperative single bolus dose of 50 mg/kg intravenous $MgSO_4$ versus normal saline in cesarean section patients and showed significant reduction in postoperative pain and analgesic requirement in comparison with the control group [17].

The results of the present study were in disagreement with the findings of Ryu et al., who studied the effects of magnesium sulfate (50 mg/kg *intravenous as a bolus and then* 15 mg/kg/h *intravenous by continuous infusion*) versus normal saline on anesthetic requirements and postoperative analgesia in patients undergoing gynecological surgeries under remifentanil/propofol total intravenous anesthesia. They found that postoperative pain scores, cumulative analgesic consumption, and shivering incidents were significantly lower in $MgSO_4$ group.

This controversy may be explained by the fact that in this study, a higher dose of $MgSO_4$ bolus than the present study was used with extended infusion till the end of surgery in addition to usage of intraoperative remifentanil infusion [18].

We concluded that Preemptive dose of either ketamine (0.3 mg/kg) or $MgSO_4$ (30 mg/kg) in patients undergoing cesarean section under general anesthesia could suppress the pressor response to endotracheal intubation and skin incision and decreased the intraoperative fentanyl requirement. Ketamine showed a significant preemptive analgesic effect compared to $MgSO_4$ at 2 and 6 h postoperatively.

Conflict of interest

The authors declare that there is no conflict of interest.

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