Research Article

A comparative study of low dose ketamine versus magnesium sulfate for local wound infiltration after cesarean section

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Abstract
Introduction: Spinal anesthesia is the safest during lower abdominal operations. Long acting local anesthetics administered to the wound site or under the skin after surgery have been demonstrated to be effective for postoperative analgesia. The infiltration of wounds with local anesthetics seems not only to provide analgesia. It may also help to reduce the up-regulation of peripheral nociceptors that manifest as increased sensitivity to pain. It has suggested that regional anesthetic techniques can reduce postoperative stress response. Some additives to local anesthetics can hasten the onset of nerve block, prolong block duration, or reduce toxicity. Magnesium has been used as an effective adjuvant in postoperative pain and as its role as a physiological blocker of NMDA receptors in sensitization process and hyperalgesia suppression. Another NMDA antagonist, Ketamine, has been raised to not only alleviate the patients' pain but also to lessen their needs for systemic opioid. Methods: A total of 100 parturients underwent elective Caesarean sections were randomized into two equal groups of 50 patients each using computer generated table. Ketamine group(K) received postoperative incisional local infiltration with a total volume of 20 ml of 10 ml bupivacaine 0.5%, 25 mg ketamine (0.5 ml) plus saline 0.9% (9.5 ml) and magnesium sulfate group(M) who received post operative incisional local infiltration with a total volume of 20 ml of 10 ml bupivacaine 0.5 %, 750 magnesium sulfate (7.5 ml) plus saline 0.9% (2.5 ml). Results: We found that the use of magnesium sulfate in a dose of (750 mg) as an adjuvant to bupivacaine provided better post operative analgesia than usage of low dose ketamine in a dose of (25 mg) as an adjuvant to bupivacaine in subcutaneous infiltration in cesarean wound .
Keywords: cesarean section, bupivacaine, ketamine, local wound infiltration, magnesium sulfate, postoperative analgesia, postoperative pain.

Introduction
The definition of pain by the International Association for the Study of Pain (IASP) is as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [Wright & Aydede, 2017]. In the last decade, the number of caesarean deliveries worldwide has risen dramatically. By 2007, the cesarean section rates has risen over 32%, making it the most common surgical procedure perfo-rmed in hospitals [Hamiliton et al., 2009]. Severe acute post cesarean delivery pain is associated with persistent pain and postpartum depression for eight weeks after delivery and the risk of thromboembolic disease, which increases during pregnancy, is likely to further exacerbate by immobility due to the pain during the puerperium [Kodali & Oberoi, 2014]. Long acting local anesthetics administered to the wound site or on/under the skin after surgery have been demonstrated to be effective for post-operative analgesia. It has been reported that, in addition to general or regional anesthesia, local anesthetic infiltration is useful for postoperative analgesia in cases of delivery by caesarean section [Aydogmus et al., 2014]. It has been reported that magnesium administered to the surgical area reduced postoperative analgesia consumption. Magnesium is known to antagonize the expression of inflammatory mediators (histamine, sero-tonin, and cytokines) in peripheral tissues consumption. These mediators are respon-sible for nociceptors excitation which in

turn may influence the overall post-operative outcome [Demiroglu et al., 2016]. The addition of ketamine to a local anesthetic in peripheral or neuraxial anesthetic and analgesic techniques improves or prolongs pain relief with a decrease in drug-related side effects (sedation, pruritus, or adverse psychological reactions) mainly because the required drug doses are reduced. These effects may be explained by blockade of central and peripheral NMDA receptors and/or an antinociceptive action complementary to that of the other drugs used [Taurá et al., 2003].

Patient and methods

This prospective, randomized double-blinded study was conducted in Anesthesiology department, Minia university hospital for obstetric and gynecological diseases during the period from April 2017 to November 2017 after obtaining approval from the ethical committee and consent from the patients. One hundred healthy parturients aged 18-40 years old, ASA physical status II scheduled for elective cesarean section under spinal anesthesia were included in the study. This is a prospective randomized double blinded study. The studied drugs were prepared by the supervisor as similar sterile coded two syringes (10 ml) labeled A or B in the form of 20 ml volume. For the method of randomization, patients were randomly allocated into two groups, 50 patients in each one, using computer generated table and randomization sequence was hidden in closed envelopes that held by the supervisor who also prepared the studied medications used but not involved in the clinical management or data collection. Blood pressure, and oxygen saturation were monitored upon arrival to the operating room and subsequently every 5 minutes as usual monitoring in CS operations using [*Mindray monitor, model: IMEC12-China*]. 20 or 18 gauge cannulae were inserted for administration of drugs and fluids then intravenous crystalloid was administrated at 6 mL/kg as a preload. Patients were positioned in the sitting position and under strict aseptic precautions, spinal anesthesia was performed with 2-2.5 ml of 0.5 % heavy bupivacaine was injected into subarachnoid space through L3-L4 or L4-L5 interspace using a midline approach using a 25 G spinal needle after flow of cerebrospinal fluid. All patients in this study were positioned similarly during the entire surgical procedure in supine position with left lateral position to avoid the aortocaval compression. A supplemental oxygen was delivered to the parturient through nasal cannula at flow rate 3-4 (L/min). When the patient experienced either a decrease in systolic blood pressure >20% from baseline values or a mean arterial blood pressure <60 mm Hg, intravenous ephedrine 6 mg was administered. When the heart rate decreased to <60 bpm, intravenous atropine 0.2 mg was administered. Surgery perfored in all cases with Pfannenstiel incision. After delivery of the baby and umbilical cord clamping, 15-30 IU of oxytocin diluted in 1000 ml of 0.9% saline, and prophylactic antibiotics were administered intravenously. By the end of the surgery & immediately after skin closure, each patient in this study received postoperatively at the incision site a subcutaneous local infiltration of 20 ml total volume containing either: Group (K): 25 mg ketamine (0.5 ml) [Ketam, E.I.P.I.CO., Egypt] + 10 ml of bupivacaine 0.5 % [Sunnypivacaine, Egypt] and adding saline 0.9% [Otsuka Ateco Pharma, Egypt] (9.5 ml) till reaching the total volume (20 ml). Or group (M): 750 mg magnesium sulfate (7.5ml) [Magnisol, Memphis, Egypt] + 10 ml of bupivacaine 0.5% and adding saline 0.9% (2.5ml) till reaching the total volume (20 ml). After completing the study, the key was opened by the supervisor.

Sample size: Before the study, the number of patients required in each group was determined after a power calculation according to data obtained Pilot study. In that study, 1st analgesic request in group A was 6±1.6 and in group B was 7±1.9 hr. A sample size of 50 patient in the group was determined to provide 80% power for independent samples T test at the level of 5% significance using G Power 3.19.2 software.

Methods of statistical analysis: The collected data were coded, tabulated, and statistically analyzed using SPSS program

(Statistical Package for Social Sciences) software version 24. Descriptive statistics were done for parametric quantitative data by mean, standard deviation and minimum& maximum of the range, and for non-parametric quantitative data by median and interquartile range, while they were done for categorical data by number and percentage. Analyses were done for parametric quantitative data between the two groups using independent samples T test, and for non-parametric quantitative data using Mann Whitney test between the two groups. Analyses were done for qualitative data using Chi square test (if number per cell >5), and Fisher exact test (if number per cell<5). Analyses were done for non-parametric quantitative data using Wilcoxon signed rank test. The level of significance was taken at (P value < 0.05).

Results

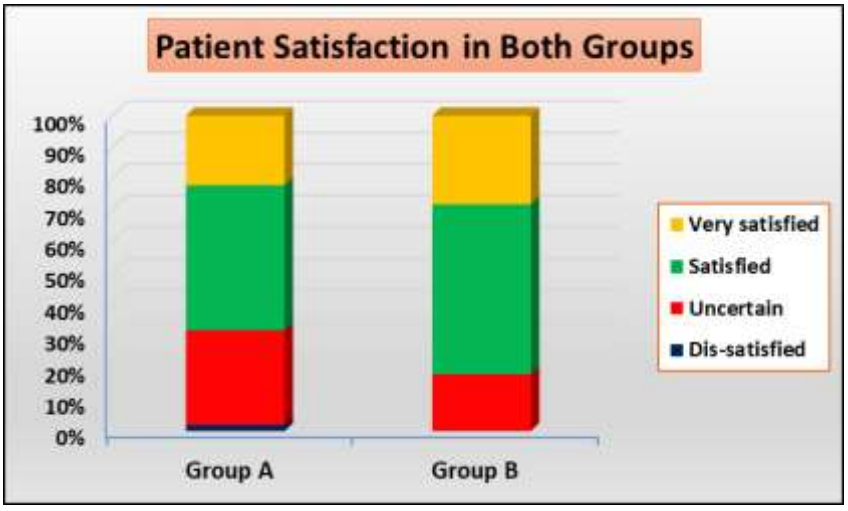
The time to first analgesic request was significantly longer in $MgSo_4$ group when compared to the ketamine group. Also the total amount of postoperative 24 hr analgesics requirement was significantly lower (table 1).

Variable	Group K (n=50)	Group M (n=50)	P value
1st analgesia request **Range (hr)** **Mean ± SD**	 (4-12) 5.9±1.6	 (4-16) 7.1±2.2	0.003*
Analgesic doses (paracetamol) **Range (gm)** **Mean ± SD**	 (1-3) 2.4±0.7	 (1-3) 1.9±0.7	0.001*
Analgesia frequency **One** **Two** **Three**	 5(10%) 22(44%) 23(46%)	 14(28%) 27(54%) 9(18%)	0.004*

The postoperative visual analogue pain scale score was significantly lower in $MgSo_4$ group in comparison to ketamine group at 8, 12& 20 hrs (table 2).

Time	Group A (n=50)	Group B (n=50)	P value
4 h **Median** **IQR**	 2 (0-2)	 1 (0-2)	0.147
8 h **Median** **IQR**	 2 (1-3)	 1 (1-2)	0.009*
12 h **Median** **IQR**	# 3 (2-3)	# 2 (1-3)	0.002*
16 h **Median** **IQR**	 2 (1-3)	# 2 (1-3)	0.557
20 h **Median** **IQR**	# 3 (2-3)	# 2 (1-3)	0.012*
24 h **Median** **IQR**	 1 (1-2)	 1 (1-2)	0.154

Patient satisfaction score was insignificantly higher in patients in $MgSo_4$ group than ketamine group patients (figure 1).



For sedation score, there weren't any signs of sedation could be observed on any case in both groups; and this was beneficial to keep early maternal – fetal bonding. As regard to complications and RBS at 6th hr ,there were statistically insignificant between the two groups (table 3).

	Group A (n=50)	Group B (n=50)	P value
RBS **Range (mg/dl)** **Mean ± SD**	 (72-140) 115±15.9	 (70-143) 110.2±16.3	0.139
($)Sedation score **Median** **IQR**	 0 (0-0)	 0 (0-0)	1
Complaint **No Complaints** **Visceral pain** **Headache**	 36(72%) 9(18%) 5(10%)	 38(76%) 8(16%) 4(8%)	0.894

Discussion

The results of the current research detected that local wound infiltration with magnesium sulfate or ketamine added to bupivacaine had an effect; as reflected by postoperative analgesia, delayed 1st request of rescue analgesia, lower analgesic consumption and attenuated and blent post-operative stress response particularly with magnesium sulfate in parturients underwent elective C.S. under spinal anesthesia. Hemodynamics like SBP & DBP & MAP & HR showed no significant difference between both groups. Our findings agrees with the observations of Hazarika et al., 2017, who studied the effect of local infiltration of 500 mg of magnesium sulfate as adjuvant to 20 ml of 0.25% bupivacaine versus 500 mg of mgso4 as adjuvant to 20 ml of 0.25% ropivacaine on sixty adult patients underwent Postlumbar lamin-ectomy and founded a significant decrease in VAS and consumption of nalbuphin; also, the time to first analgesic consumption was signifi-cantly longer. The time to first analgesic consumption was significantly longer in the mgso4 – bupivacaine combination group (7.3± 0.46 h) compared to other group. The BM group result correlated with our $mgso_4$ addition to bupivacaine result (7.1±2.2 h).

Our findings agrees with the observations of Mohamed et al., 2018, who performed double-blinded study included ninety patients scheduled for total abdominal hysterectomy and were randomly assigned into three groups to receive local wound

infiltration with 40 mL of 0.25% bupivacaine (group C), plus 2 mg/kg ketamine (group K) or 2 μg/kg dexmedetomidine (group D) in first analgesic reuest and Vas score.

This result is in consistence with Al-hakim and Alidreesi, 2010, who studied adding pubivacaine as local anesthetic in wound infiltration for post cesarean section pain management. At this study, Thirty patients were assigned randomly to receive either 20ml of 0.5% bupivacaine or 20ml normal saline solution (group A - placebo group) that was injected in the subcuticular tissue and fascia before closure of the skin this result differed from ours may be this is owing to type of anesthesia, bupivacaine dosage.

Nesioonpour et al., 2013, who used local infiltration of bupivacaine in patients undergoing inguinal hernia repair under spinal anesthesia was compared with placebo in randomized clinical trial. The patients were randomly divided to two groups of 30 including the case group who received 10 cc of 0.5 % bupivacaine and the control group who received 10 cc of normal saline in the operation site before surgical incision. The Rescue time (hr) in bupivacaine (Mean± SD) 12.67 ± 5.43while in placebo one was 4.20 ± 2.29; this result was longer than ours - although there were no bupivacaine's additives- may be due to deprivation of uterine contractions element.

Also our study was in agreement with, Dal et al., 2007, who studied the efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy; Group I received: 2 ml i.v. saline, group II received i.v. ketamine (0.5 mg/kg) and group III received a local peritonsillar infiltration of ketamine (0.5 mg/kg). And concluded that low dose ketamine (0.5 mg·kg) given i.v. or by peritonsillar infiltration intraoperatively provides an alternative analgesia without significant side-effects in children undergoing adenotonsillectomy. With consideration that the first time for analgesic requirement was so earlier than ours, and this may be due to absence of bupivacaine as a powerful anesthetic agent.

A study which in agree with ours that done by Tverskoy et al., 1996, to study Ketamine enhancement effect when was added to local anesthetic and analgesic effects of bupivacaine by peripheral mechanism; this study was done in postoperative patients who underwent uni and bilateral herniorrhaphy. The patients were randomly assigned to one of two groups. One group at the end of the surgery received the infiltration with a solution of bupivacaine 0.5% and ketamine 0.3%, the other group received the infiltration with a solution of bupivacaine 0.5% only. In patient with unilateral herniorrhaphy, the addition of ketamine for wound infiltration enhanced the duration of infiltration anesthesia (206± 76 versus 343±108 min, $P<0.02$). The results indicate that ketamine acting via a peripheral mechanism can profoundly enhance anesthetic and analgesic actions of a local anesthetic administered for infiltration anesthesia.

A diversity in results were found in Honarmand et al., 2008, who studied the preventative analgesic effect of preincisional peritonsillar infiltration of two low doses of ketamine for postoperative pain relief in children following adenotonsillectomy. Patients were divided into three groups of 25 each and received a local peritonsillar infiltration of 0.9% saline (group S), ketamine 0.5 mg/kg (group K1), or ketamine 1 mg/kg (group K2). All medications were 2 ml in volume which was applied in 1 ml per tonsil 3 min prior to tonsillectomy. During 24 h after surgery, 16 patients in group S and no patients in groups K1 or K2 needed analgesics (During 24 $P< \pm 0.001$). The first time for analgesic requirement in group S was (1.9±2.2) $P<$ 0.001 versus groups K1 and K2). This difference in result with ketamine group owing to absence of bupivacaine and type of procedure.

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