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# Intra Peritoneal S Ketamine reduces Postoperative Analgesic Requirements in Morbidly Obese Patients A Controlled Study

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## Abstract

### Background

This study was designed to evaluate the role of intraperitoneal S (+) ketamine in peripheral NMDA receptors blockade, and whether it reduces the postoperative analgesic requirements after bariatric surgery in morbidly obese patients in comparison with intraperitoneal lidocaine.

### Patients and Methods

The study included 45 patients, and a standardized general anesthetic technique including fentanyl, propofol, isoflurane, and vecuronium for muscle relaxation were used. At the end of surgery, patients were divided into three groups ,15 patients each, S (+) Ketamine 0.5 mg /kg diluted in 50 ml saline was injected intra peritoneally in (ketamine group), 50 ml of 1% lidocaine in saline was injected intra peritoneally in (lidocaine group), 50 ml of normal saline was injected intra peritoneally in (saline group). Parameters were evaluated time of first request of analgesia in minutes ,postoperative shoulder pain and arm pain for 24 hours(VAS score), and the amount of post operative mepridine (mg) consumed in 0-6.6-12,12-18,18-24, hours after extubation.

### Results

Times of the first request of postoperative analgesia were 60(10), 50(5), 20(5) minutes, in Intra peritoneal S Ketamine group, Intra peritoneal lidocaine group, and Intra peritoneal Saline group respectively. It was statistically longer in Ketamine group and Lidocaine group than Saline group, with statistically longer duration in Ketamine group than Lidocaine group.

However the amount of mepridine was statistically higher in Lidocaine group and Saline group than in Ketamine group, at 6, 8,12,18,24 hours postoperatively, it was statistically higher in Saline group than in Lidocaine group.

Both the incidence postoperative shoulder pain, and the visual analogue score were significantly higher in Lidocaine group and Saline group than in Ketamine group, but it was statistically higher in Saline group than in Lidocaine group.

### Conclusion

Peripheral (peritoneal) NMDA receptors blockade by S (+) Ketamine was involved in reduction of postoperative pain, and analgesic requirement following bariatric surgery.

Keywords: Intraperitoneal; S Ketamine; Morbidly obese

## Introduction

Bariatric surgery at the upper extremes of weight can be associated with serious postoperative complications [1].The complications are postoperative hypoventilation, hypoxia, hypercapnia, and postoperative pain [2]. The incidence of postoperative shoulder pain following laparoscopic surgery may reach up to 80% as discussed by Collins KM et al., and it represents a major cause for high unanticipated admission rate up to 12.1 % [3].

Experimentally, intra peritoneal administration of NMDA receptor antagonists decreased the nociception observed during the late phase of the formalin test [4]. Animal studies have shown that S ketamine has approximately four times more affinity for phencyclidine binding area in NMDA receptors as compared to (R-) ketamine [5]. Increased affinity for the receptor ,combined with similar pharmacokinetics suggests that S (+) ketamine could be clinically interesting drug [6], in rats and mice S(+) ketamine has 1.5-3 times higher hypnotic potency and 3 times higher analgesic potency as compared with – ketamine being twice more potent than racemic mixture as said by Koga et al.

Aim of this study was to assess the analgesic effects of intra peritoneal ketamine S (+) (NMDA receptors antagonist), and compare its analgesic effect with intra peritoneal 0.1 % Lidocaine.

## Patients and Methods

The study include 45 morbidly obese patients (BMI>40) ,ASA I,II admitted to surgical ICU in new Kasr El Ani Hospital ,after laparoscopic bariatric surgery with absence of primary cardiac or chest disease. After the approval of ethics committee, written consents from patients preoperatively were taken.

Patients were divided into 3 groups, 15 patients each, the first group was S (+) ketamine group (K group), the second group was lidocaine group (L group) and the third group was normal saline group (S group).

## Exclusion Criteria

Were Cardiac disease, Diabetes mellitus, Gross anemia, Hemoglobinopathies, Polycythemia, Hepatic disease, Ischemic cerebrovascular disease, Renal disease, Respiratory insufficiency, Severe systemic hypertension.

For premedication midazolam 0.05 mg/kg IV was given 15 minute before induction.

Induction of anesthesia was achieved by 2.5-3 mg /kg propofol injected intravenously on 3-5 minute to prevent sudden drop of blood pressure, fentanyl 1µg/kg iv. Tracheal intubation with cuffed endotracheal tube was facilitated with 0.1mg/kg vecuronium. Nasogastric tube was inserted.

## Maintenance of Anesthesia

Anesthesia was maintained with 50% O2 in air with 1.3 MAC of isoflurane, and then 0.05 mg/Kg vecuronium.
Ventilation was adjusted to maintain end tidal CO2 between 30-35mmHg 6 ml/kg/hour IV crystalloid solution was given, monitoring included non invasive blood pressure measurement, SO2 (O2 saturation), end tidal CO2, and ECG.
A small about 1 cm elliptical sub umbilical incision was used to introduce the Vress needle towards the pelvis with patients in the Trendelenburg position.

Pneumoperitoneum was achieved by insufflation of CO2 at rate 1 L /min for the first minute, then at rate of 3-4 L/minute with a maximum intra-abdominal pressure of 15 mmHg. Introduction of a safety reusable metal trocar through the previous incision was done .The camera scope was then introduced and the pelvis was inspected for any site of bleeding. Patients were put in anti- Trendelenburg position with rising of the right shoulder. At the end of the surgical procedure, patients were randomly allocated into one of the three equal groups. In (K group) S (+) Ketamine 0.5 mg / kg diluted in 50 ml saline was injected intra peritoneally, in (L group) 50 ml 1% lidocaine in saline was injected, in S group 50 ml of normal saline was injected intra peritoneally. In the three studied groups, intra peritoneal injection was guided by camera under both copulae of the diaphragm, and patients kept in the Trendelenburg position till the end of intraperitoneal injection (10-15 minute). Pain was assessed using Visual Analogue Scale (VAS), where zero score corresponds to no pain. All patients were admitted to postoperative surgical ICU, where they were monitored by O2 saturation, ECG, blood pressure. CPAP of 5- 10 cm H2O was used via face mask.

Post operative pain was initially managed with bolus of 0.5 mg /kg IV mepridine and increased gradually to 1 mg/kg IV mepridine if there was inadequate analgesia, (VAS) was repeated every 6 hours for the first 24 hours, mepridine was given in a dose of 0.25 mg IV, and it was increased gradually after 15 minutes if there was in adequate analgesia. The following parameters were evaluated in all studied groups:

1. Time of first request of analgesia (time elapsed from extubation to the first analgesic dose).

2. The amount of postoperative mepridine was consumed in 0-6 h,6-12 h,12-18 h,18-24h,,and 0-24 following extubation.

3. The incidence and severity of postoperative shoulder pain for 24 hours, it represents the mean of pain scores measured at 0-6, 6-12, 12-18, and 18-24 hours postoperatively.

## Statistical Analysis

Data are expressed as mean and (SD). One way ANOVA was used to detect both time to first request of analgesia and the variability in the VAS in between the studied groups, with post hoc Newman-Keules test. Chi-squared or Fisher exact test were used, as appropriate, to compare incidences of side effects and postoperative pain in different groups. All significant results were carried out the 5% level.

## Results

Patient's characteristics and operative details were comparable among the three groups (Table 1).

Times of the first request of postoperative analgesia were 60(10), 50(5), 20(5) minutes, in Intra peritoneal S (+) Ketamine group (K group), Intra peritoneal lidocaine group (L group), and Intra peritoneal Saline group (S group) respectively. It was statistically longer in K group and L group than S group, with statistically longer duration in K group than L group (Table 2).

However the amount of mepridine was statistically higher in group L, and group S than in group K, at 6, 8,12,18,24 hours postoperatively, it was statistically higher in group S than group L (Table 2).

Both the incidence postoperative shoulder pain, and the visual analogue score were significantly higher in group L and group S than group K, but it was statistically higher in group S than in group L (Table 2).

Table (1): patients and operative data .values are mean (SD).

| | K group (n=15) | L group (n=15) | S group (n=15) |
|---|---|---|---|
| Age (years) | 24 ,1(6.5) | 23(7.4) | 22 .2 (8.1) |
| Sex (male /female) | 8/7 | 9/6 | 7/8 |
| Weight ( kg) | 130(25) | 128(26) | 126(27) |
| Height (cm) | 170(10) | 169(11) | 168(12) |
| BMI(kg/m2) | 43 (1.9) | 42(2.7) | 42 (2.8) |
| ASAI/II | 10/5 | 11/4 | 12/3 |
| Duration of surgery(minutes) | 120(25) | 125(20) | 122(22) |

K group = Intra peritoneal S (+) ketamine group; L group = Intra peritoneal lidocaine group, S group = Intra peritoneal saline group.

Table 2: post operative analgesic requirements, time to first request of analgesia, incidence, and severity of post operative shoulder pain. Values are means (SD) or number and percent % of patients.

| | K group (n=15) | L group (n=15) | S group (n=15) |
|---|---|---|---|
| Time to first request of postoperative mepridine (min) | 60(10) | 50(5) * | 20(5)* † |
| Dose of mepridine (mg) | | | |
| 0-6 h | 80 (5.3) | 120(12.2) * | 150 (8.2) *† |
| 6-12h | 60 (4.5) | 100(10.4) * | 130 (5.4) *† |
| 12 -18h | 40 (5.4) | 85 (15.3) * | 100 (10.1) *† |
| 18-24h | 25 (3.5) | 60 (5.2) * | 80 (7.5) *† |
| 0-24h | 205 (4.6) | 365( 10.3) * | 460 (7.8) *† |
| Incidence % of postoperative shoulder pain | 3 (20%) | 7(46.7%)* | 12 (80%)*† |
| Visual analogue shoulder pain score | 2 (0.4) | 4(0.9) * | 6.4(0.6) *† |

K Group = Ketamine S (+) group; L group =lidocaine group; S group= normal saline group.
* Comparison was between the three groups.
†comparison was between lidocaine group (L group), and saline group (S group).

## Discussion

The present study demonstrated that intra peritoneal S (+) ketamine was associated with reduction of both postoperative shoulder pain, and the analgesic requirements in patients underwent laparoscopic bariatric surgery. The efficacy of intra peritoneal Ketamine S (+) was superior to the intra peritoneal lidocaine. N-methyl –D-aspartate (NMDA)receptor activation is considered one of the mechanism of postoperative pain, and the hypersensitivity through both peripheral (intraperitoneal) ,and central effects (intravenous route) [7]. Peripheral NMDA receptors are important in normal visceral pain transmission, and may provide a noval mechanism for development of peripheral sanitization, and visceral hyperalgesia [8]. At the same time, N-methyl-D aspartate (NMDA) activation plays an important role in wind up. Activation of NMDA receptors increases intracellular calcium concentration in spinal neurons and activates both phospholipase C (PLC), and phospholipase A2 (PLA2), activation of NMDA receptors also induces nitric oxide synthetase, resulting in formation of nitric oxide (NO). Both prostaglandin and nitric oxide facilitate the release of excitatory amino acids in the spinal cord [9]. In the present study intra peritoneal Ketamine S (+) reduced postoperative shoulder pain, and reduced the total dose of required mepridine, this could be explained by peripheral blockade of peripheral NMDA receptors. Many studies observed the role of intra peritoneal NMDA receptors blockade [10] demonstrated the anti nociceptive effects in mice of intra peritoneal N methyl –D aspartate receptor antagonists in the formalin test.

Davidson et al. [11] demonstrated that peripheral NMDA and non NMDA glutamate receptor contribute to nociceptive behavior in the rat formalin test. Nadeson et al. concluded that S (+) ketamine can potentiate the effects of fentanyl by an interaction at the level of the spinal cord even when ketamine was given via the intra peritoneal route in rats. Borner et al. [12] concluded that the application of intra articular S (+) ketamine (peripheral NMDA receptors antagonism) after arthroscopic knee surgery led to a significant decrease of postoperative analgesic demand.

## Conclusion

Peripheral (peritoneal) NMDA receptors blockade by S (+) Ketamine was involved in reduction of postoperative pain, and analgesic requirement following bariatric surgery.

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