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COMPARATIVE STUDY BETWEEN INTRAVENOUS KETAMINE OR MAGNESIUM SULFATE OR BOTH ON POSTOPERATIVE MORPHINE CONSUMPTION AFTER MAJOR ABDOMINAL SURGERY

By

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ABSTRACT

Background: 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. 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.

Objective: To compare the difference between intravenous Ketamine or Magnesium Sulfate or both on postoperative morphine consumption after major abdominal surgery.

Patients and Methods: This study included 100 patients of both sexes admitted for major abdominal surgery. They were randomly allocated into four equal groups. **Group I:** Control group, **Group II** received only ketamine, **Group III** received only magnesium sulfate and **Group IV** received both ketamine and magnesium sulfate. The following parameters were assessed in the four groups: Heart rate (HR), blood pressure (BP), respiratory rate (RR), end tidal Co2, the severity of pain on modified Ramsay sedation scale, time to first request for analgesia postoperatively, the number of rescue analgesia given, , adverse events, the level of the patient satisfaction and total dose of morphine consumption postoperatively (mg/48h).

Results: This study showed that the hemodynamics of the patients were more stable in (ketamine + magnesium sulfate) and ketamine only group than in magnesium sulfate only group and control group throughout all 48 hours postoperative. Usage of ketamine decreases postoperative pain and analgesic consumption in the first 48 hours after surgery along with longer pain free period compared to patients who were given magnesium sulfate only and control group. Ketamine is highly effective in postoperative pain control in major abdominal surgery without any hazards on patients. The total consumption of morphine, and additional analgesic requirements were less, while the satisfaction level of patients were higher in (ketamine+ magnesium sulfate) and ketamine only group.

Conclusion: Ketamine is one of the most advantageous adjuvant drugs for treating postoperative pain, while magnesium sulfate alone is less effective, with increase in opioid side effect. Combination of ketamine+ magnesium sulfate is better in treating postoperative pain and preserve patient hemodynamics with decrease in opioid side effect.

Key words: Ketamine, magnesium sulfate, postoperative morphine consumption, major abdominal surgery.

INTRODUCTION

Opioid-based analgesia plays a significant role in the control of postsurgical pain; however, use of opioid may lead to significant side effects (e.g., nausea and vomiting) and adverse events (e.g., respiratory depression), which may be associated with significantly longer hospital stays and higher hospital costs in the postsurgical setting *(Hurley and Wu, 2010).*

Since these adverse events occur more often in patients receiving higher doses of opioids, it is important to find ways to reduce opioid use in the postoperative period. 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 reduce opioid use *(Ding et al., 2014).*

Ketamine and Magnesium sulfate are non-opioid analgesics that have been studied as an adjuvant to opioid analgesics. They have been found to have anesthetic, analgesic, and they has been suggested that they may play a role in reducing analgesic requirements during the postoperative period *(Albrecht et al., 2013).*

Effective postoperative pain control is an essential component of the care of the surgical patient. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality. Evidence suggests that surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery. Good analgesia can reduce this deleterious effect *(Ding et al., 2014).*

The aim of this study was to compare the difference between intravenous Ketamine and or Magnesium Sulfate on postoperative morphine consumption after major abdominal surgery as primary outcome and to measure the hemodynamic effects and intensity of pain as secondary outcome.

PATIENTS AND METHODS

After approval of the medical ethical committee at Al-Azhar University Hospitals, department of anesthesiology, 100 patients at the Department of Anesthesiology and Intensive Care were scheduled according to the American Society of Anesthesiologist (ASA) physical status I or II, of either sex, age (30-60) years for major abdominal operation under general anesthesia are enrolled in this prospective controlled double blinded randomized study.

Information about the study was given comprehensively both orally and in written form to the patients. All patients gave their written informed consents prior to their inclusion in the study.

Exclusion criteria:

All patients with cardiovascular, pulmonary, psychological or neurological diseases, patients known to be epileptic, patients who have an increase in intracranial tension, patients with known allergies to the study drug (ketamine-magnesium sulfate), patients with recent NSAID medication, history of current regular use of analgesics, anticonvulsants, antidepressants, or opioids within the last month, patients with any perioperative complications, physical status: ASA III or above, pregnant ladies, body mass index more than 35, coagulation disorder,

history of chronic pain and patients with drug or alcohol abuse, were excluded from the study.

Patients are randomized into the four groups:

All patients received morphine at infusion rate of 0.25 mg/h, and received the studied drugs in the four groups diluted in 50 cc syringe containing a normal saline 0.9 % with infusion rate 1 cm/h.

Control group (Group I): received a bolus dose, and continuous intravenous infusion of normal saline.

Ketamine group (Group II): received a bolus dose of ketamine (0.2 mg/kg) intravenously, followed by continuous infusion of ketamine (0.05 mg/kg/h).

Magnesium group (Group III): received a bolus dose of magnesium sulphate (50 mg/kg) intravenously, followed by continuous infusion of magnesium (10 mg/kg/h).

Ketamine and Magnesium Sulphate group (Group IV): received a bolus dose of ketamine (0.1 mg/kg), and magnesium sulphate (25 mg/kg) intravenously, then continuous infusion of (0.025 mg/kg/h) ketamine + (25 mg/kg/h) magnesium sulphate.

Rescue analgesia: 5 mg morphine IV, followed by pain assessment after 15 minutes if the pain score > 4 piroxicam 20 mg was given intravenously.

All patients were screened for suitability by history including assessment of cardio respiratory status, physical examination for heart, chest. Investigations for CBC, coagulation profile, liver function, kidney function and ECG or specific investigations according to the patients.

Patient monitoring (standard monitoring) by pulse oximetry, ECG, Non-invasive blood pressure monitoring, 5min. interval and capnpgram.

Pre oxygenation with 100% oxygen was done for 3 min. General anesthesia was induced with an injection of Fentanyl (2 μg/kg), Propofol (1-2 mg/kg) followed by Atracurium (0.5 mg/kg) to facilitate orotracheal intubation. Anesthesia was maintained using isoflurane in an air/oxygen mixture. Intermittent boluses of Atracurium were given to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal carbon dioxide; etCO2, between 34 and 38 mm Hg). Ten minutes before the end of surgery, morphine (0.05 mg/kg) was routinely administered IV.

At the end of surgery, anesthesia discontinued, and residual neuromuscular blockade was antagonized with neostigmine (0.08 mg/kg) and atropine (0.02 mg/kg).followed by extubation. When the patients became fully awake; patients transferred to the postanesthesia care unit (PACU). 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 have two separate mechanical infusion devices during the study period.

Heart rate, blood pressure, oxygen saturation, respiratory rate, and end-tidal $PaCO_2$. The severity of pain (with NPRS) were recorded at 0, 30 min, 1hour, 2h, 4h, 6h, 8h, 10h, 12h, 18h, 24h, and every 12 hours to the end point of the study period.

The degree of sedation was assessed using modified Ramsay sedation scale, Time of first request for analgesia postoperatively (hours), Number of rescue analgesic given, Total dose of morphine postoperatively (mg/48h). Adverse events such as nausea, vomiting, pruritus, hypotension, bradycardia and the level of the patient satisfaction will be recorded according to four level satisfaction score: Very satisfied (4), generally satisfied (3), moderately satisfied (2), and unsatisfied (1).

Recorded data were analyzed using the statistical package for the social sciences, version. 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. One way ANOVA test was used to compare means and Fisher exact test was used to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

P-value <0.05 was considered significant.

RESULTS

As regard demographic data among the four groups, there were no statistical differences among them **(Table 1)**.

Table (1): Comparison among groups according to demographic data

Parameters \ Groups		Group I No. = 25	Group II No. = 25	Group III No. = 25	Group IV No. = 25	P-value
Gender	Male	13 (52.0%)	14 (56.0%)	14 (56.0%)	12 (48.0%)	0.931
	Female	12 (48.0%)	11 (44.0%)	11 (44.0%)	13 (52.0%)	
Age	Mean ± SD	43.15 ± 8.53	42.20 ± 8.68	44.00 ± 9.04	41.52 ± 8.78	0.765
	Range	30 – 60	30 – 58	30 – 59	30 – 59	

There was statistically highly significant difference between groups in post-operative heart rate at 1hr, 2hr, 4hr, 6hr,8hr,10hr,12hr,18h and 24hr,and non-significant difference between groups at 30 min,36hr and 48hrfrom postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 2)**.

Table (2): Comparison between groups according to postoperative heart rate (beat/min-Mean ± SD)

Groups / Heart rate (beat/min)	Group I	Group II	Group III	Group IV	P-value
30 min	115.00 ± 14.38	110.00 ± 13.75	112.00 ± 14.00	108.00 ± 13.50	0.332
1 hr	105.00 ± 13.13	88.00 ± 11.00	100.00 ± 12.50	85.00 ± 10.63	< 0.001
2 hr	90.00 ± 11.25	70.00 ± 8.75	95.00 ± 11.88	68.00 ± 8.50	< 0.001
4 hr	85.00 ± 10.63	75.00 ± 9.38	90.00 ± 11.25	70.00 ± 8.75	< 0.001
6 hr	100.00 ± 12.50	66.00 ± 8.25	90.00 ± 11.25	66.00 ± 8.25	< 0.001
8 hr	102.00 ± 12.75	80.00 ± 10.00	91.00 ± 11.38	79.00 ± 9.88	< 0.001
10 hr	90.00 ± 11.25	81.00 ± 10.13	85.00 ± 10.63	78.00 ± 9.75	< 0.001
12 hr	85.00 ± 10.63	75.00 ± 9.38	84.00 ± 10.50	72.00 ± 9.00	< 0.001
18 hr	89.00 ± 11.13	70.00 ± 8.75	87.00 ± 10.88	70.00 ± 8.75	< 0.001
24 hr	80.00 ± 10.00	68.00 ± 8.50	80.00 ± 10.00	65.00 ± 8.13	< 0.001
36 hr	75.00 ± 9.38	70.00 ± 8.75	70.00 ± 8.75	70.00 ± 8.75	0.124
48 hr	75.00 ± 9.38	73.00 ± 9.13	73.00 ± 9.13	71.00 ± 8.88	0.497

There was a statistically significant highly difference between groups in post-operative systolic blood pressure at 2hr, 10hr, 12hr, 18hr and 48hr,and non-significant difference between groups at 30 min, 1hr,4hr,6hr, 8 hr,24hr and 36hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 3)**.

Table (3): Comparison between groups according to postoperative systolic blood pressure (mmHg- Mean ± SD)

Groups / SBP	Group I	Group II	Group III	Group IV	P-value
30 min	150.00 ± 18.75	145.00 ± 18.13	153.00 ± 19.13	140.00 ± 17.50	0.071
1 hr	143.00 ± 16.88	135.00 ± 16.25	137.00 ± 16.88	130.00 ± 16.25	0.054
2 hr	140.00 ± 17.50	125.00 ± 15.63	130.00 ± 16.25	122.00 ± 15.25	< 0.001
4 hr	130.00 ± 16.25	121.00 ± 15.13	126.00 ± 15.75	120.00 ± 15.00	0.089
6 hr	125.00 ± 15.63	118.00 ± 14.75	123.00 ± 15.38	115.00 ± 14.38	0.081
8 hr	130.00 ± 16.25	125.00 ± 15.63	129.00 ± 16.13	125.00 ± 15.63	0.565
10 hr	135.00 ± 16.88	127.00 ± 15.88	130.00 ± 16.25	110.00 ± 13.75	< 0.001
12 hr	134.00 ± 16.75	113.00 ± 14.13	129.00 ± 16.13	115.00 ± 14.38	< 0.001
18 hr	143.00 ± 17.88	125.00 ± 15.63	133.00 ± 16.63	119.00 ± 14.88	< 0.001
24 hr	133.00 ± 16.38	129.00 ± 16.13	130.00 ± 16.13	125.00 ± 15.63	0.0371
36 hr	125.00 ± 15.63	121.00 ± 15.13	122.00 ± 15.25	118.00 ± 14.75	0.443
48 hr	129.00 ± 16.13	115.00 ± 14.38	125.00 ± 15.63	115.00 ± 14.38	0.002

There was a statistically highly significant difference between groups in post-operative diastolic blood pressure at 1hr 2hr, 4hr, 6hr, 10hr, 12hr, 12hr, 18hr, 24hr, 36hr and 48hr and non-significant difference between groups at 30 min and 8hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 4)**.

Table (4): Comparison between groups according to postoperative diastolic blood pressure (mmHg- Mean ± SD)

Groups / DBP	Group I	Group II	Group III	Group IV	P-value
30 min	105.00 ± 13.13	100.00 ± 12.50	101.00 ± 12.63	100.00 ± 12.50	0.455
1 hr	100.00 ± 12.50	90.00 ± 11.25	91.00 ± 11.38	90.00 ± 11.25	0.006
2 hr	95.00 ± 11.88	85.00 ± 10.63	90.00 ± 11.25	84.00 ± 10.50	0.002
4 hr	93.00 ± 11.63	78.00 ± 9.75	88.00 ± 11.00	77.00 ± 9.63	< 0.001
6 hr	97.00 ± 12.13	81.00 ± 10.13	85.00 ± 10.63	80.00 ± 10.00	< 0.001
8 hr	90.00 ± 11.25	86.00 ± 10.75	90.00 ± 11.25	85.00 ± 10.63	0.237
10 hr	95.00 ± 11.88	89.00 ± 11.13	95.00 ± 11.88	70.00 ± 8.75	< 0.001
12 hr	93.00 ± 11.63	80.00 ± 10.00	91.00 ± 11.38	73.00 ± 9.13	< 0.001
18 hr	99.00 ± 12.38	85.00 ± 10.63	88.00 ± 11.00	79.00 ± 9.88	< 0.001
24 hr	98.00 ± 12.25	83.00 ± 10.38	95.00 ± 11.88	80.00 ± 10.00	< 0.001
36 hr	85.00 ± 10.63	80.00 ± 10.00	84.00 ± 10.50	73.00 ± 9.13	< 0.001
48 hr	88.00 ± 11.00	79.00 ± 9.88	81.00 ± 10.13	70.00 ± 8.75	< 0.001

A statistically highly significant difference was found between groups in post-operative O2 saturation at 6hr, 8hr, 10hr and 18hr, and significant difference between groups at 2hr,and non- significant difference between groups at 30 min, 1hr,4hr,12hr,24hr, 36hr and48 from postoperative care unit (PACU) till the end of the first 48 hours after the operation (Table 5).

Table (5): Comparison between groups according to postoperative O2 saturation. (Mean ± SD)

Groups / O_2 Saturation	Group I	Group II	Group III	Group IV	P-value
30 min	95.00 ± 2.30	97.00 ± 1.30	96.00 ± 2.30	97.00 ± 3.50	0.284
1 hr	97.00 ± 2.50	99.00 ± 3.50	99.00 ± 3.60	99.00 ± 3.50	0.101
2 hr	96.00 ± 3.50	99.00 ± 3.60	98.00 ± 2.65	100.00 ± 4.35	0.01
4 hr	97.00 ± 3.80	98.00 ± 4.50	97.00 ± 3.33	98.00 ± 3.58	0.758
6 hr	95.00 ± 1.20	99.00 ± 2.80	96.00 ± 3.59	99.00 ± 4.25	0.001
8 hr	95.00 ± 2.98	98.00 ± 2.36	97.00 ± 2.87	98.00 ± 3.58	0.002
10 hr	93.00 ± 1.25	98.00 ± 2.78	97.00 ± 2.25	99.00 ± 5.65	< 0.001
12 hr	98.00 ± 1.23	98.00 ± 4.35	98.00 ± 3.58	100.00 ± 4.00	0.115
18 hr	96.00 ± 2.89	99.00 ± 4.58	99.00 ± 3.25	100.00 ± 4.25	0.002
24 hr	97.00 ± 3.58	99.00 ± 3.65	99.00 ± 2.99	100.00 ± 4.22	0.108
36 hr	97.00 ± 3.41	99.00 ± 3.74	98.00 ± 3.89	99.00 ± 2.30	0.274
48 hr	99.00 ± 2.15	99.00 ± 2.98	99.00 ± 4.02	99.00 ± 3.58	1

There was a statistically significant highly difference between groups in post-operative respiratory rate at 30min,1hr, 2hr,6hr,8hr,10hr, 12hr and 24hr,and non-significant difference between groups at 4hr,18hr, 36hr and 48hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 6)**.

Table (6): Comparison between groups according to postoperative respiratory rate (RR-Mean ± SD)

Groups / RR	Group I	Group II	Group III	Group IV	P-value
30 min	24.00 ± 3.00	21.00 ± 2.63	23.00 ± 2.88	20.00 ± 2.50	< 0.001
1 hr	20.00 ± 2.50	17.00 ± 2.13	18.00 ± 2.25	16.00 ± 2.00	< 0.001
2 hr	17.00 ± 2.13	15.00 ± 1.88	17.00 ± 2.13	15.00 ± 1.88	< 0.001
4 hr	16.00 ± 2.00	15.00 ± 1.88	16.00 ± 2.00	15.00 ± 1.88	0.092
6 hr	17.00 ± 2.13	16.00 ± 2.00	15.00 ± 1.88	14.00 ± 1.75	< 0.001
8 hr	18.00 ± 2.38	15.00 ± 1.88	17.00 ± 2.13	13.00 ± 1.63	< 0.001
10 hr	17.00 ± 2.63	14.00 ± 1.75	16.00 ± 2.00	14.00 ± 1.75	< 0.001
12 hr	15.00 ± 1.88	14.00 ± 1.75	14.00 ± 1.75	13.00 ± 1.63	0.002
18 hr	14.00 ± 1.75	13.00 ± 1.63	13.00 ± 1.63	13.00 ± 1.63	0.086
24 hr	15.00 ± 1.88	14.00 ± 1.75	14.00 ± 1.75	13.00 ± 1.63	0.002
36 hr	14.00 ± 1.75	14.00 ± 1.75	14.00 ± 1.75	13.00 ± 1.63	0.104
48 hr	14.00 ± 1.75	14.00 ± 1.75	14.00 ± 1.75	13.00 ± 1.63	0.104

There was a statistically significant highly difference between groups in post-operative end tidal CO2 at 2hr, 8hr,10hr, 12hr and 18hr,and significant difference between groups at 24hr, 36hr, 48hr. and non-significant difference between groups at 30 min, 1hr,4hr and 6hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 7)**.

Table (7): Comparison between groups according to postoperative End tidal CO2 (Mean ± SD)

Groups / End Tidal CO_2	Group I	Group II	Group III	Group IV	P-value
30 min	31.00 ± 3.88	30.00 ± 3.75	31.00 ± 3.88	29.00 ± 3.63	0.195
1 hr	29.00 ± 3.63	28.00 ± 3.50	29.00 ± 3.63	27.00 ± 3.38	0.146
2 hr	35.00 ± 4.38	31.00 ± 3.88	33.00 ± 4.13	29.00 ± 3.63	< 0.001
4 hr	32.00 ± 4.00	31.00 ± 3.88	31.00 ± 3.88	30.00 ± 3.75	0.350
6 hr	35.00 ± 4.38	34.00 ± 4.25	35.00 ± 4.38	34.00 ± 4.25	0.720
8 hr	39.00 ± 4.88	31.00 ± 3.88	37.00 ± 4.63	29.00 ± 3.63	< 0.001
10 hr	38.00 ± 4.75	35.00 ± 3.50	38.00 ± 4.75	34.00 ± 3.13	< 0.001
12 hr	39.00 ± 4.88	31.00 ± 3.88	39.00 ± 4.88	30.00 ± 3.75	< 0.001
18 hr	38.00 ± 4.75	35.00 ± 4.38	37.00 ± 4.63	34.00 ± 4.25	0.009
24 hr	40.00 ± 5.00	37.00 ± 4.63	38.00 ± 4.75	36.00 ± 4.50	0.025
36 hr	40.00 ± 5.00	38.00 ± 4.75	39.00 ± 4.88	36.00 ± 4.50	0.027
48 hr	39.00 ± 4.88	38.00 ± 4.75	39.00 ± 4.88	35.00 ± 4.38	0.010

A statistically significant highly difference was received between groups in post-operative Ramsay sedation scale at 2hr,8hr, 10hr, 12hr, 18hr,24hr,36hr and 48hr,and non-significant difference between groups at 30 min, 1hr,4hr and 6hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 8)**.

Table (8): Comparison between groups according to postoperative Ramsay Sedation Scale (Mean ± SD)

Groups / Ramsay Sedation Scale	Group I	Group II	Group III	Group IV	P-value
30 min	1.00 ± 0.13	1.00 ± 0.13	1.00 ± 0.13	1.00 ± 0.13	1
1 hr	1.00 ± 0.13	1.00 ± 0.13	1.00 ± 0.13	1.00 ± 0.13	1
2 hr	2.00 ± 0.25	1.00 ± 0.13	2.00 ± 0.25	1.00 ± 0.13	< 0.001
4 hr	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	1
6 hr	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	1
8 hr	3.00 ± 0.38	2.00 ± 0.25	2.00 ± 0.25	1.00 ± 0.13	< 0.001
10 hr	3.00 ± 0.38	1.00 ± 0.13	3.00 ± 0.38	1.00 ± 0.13	< 0.001
12 hr	3.00 ± 0.38	2.00 ± 0.25	3.00 ± 0.38	1.00 ± 0.13	< 0.001
18 hr	3.00 ± 0.38	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	< 0.001
24 hr	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	1.00 ± 0.13	< 0.001
36 hr	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	1.00 ± 0.13	< 0.001
48 hr	2.00 ± 0.25	2.00 ± 0.25	2.00 ± 0.25	1.00 ± 0.13	< 0.001

Statistically highly significant difference occurred between groups in post-operative rescue analgesia given at 6hr, and significant difference between groups at 1hr, 4hr and 12hr,and non-significant difference between groups at 2hr,10hr, and 36hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 9)**.

Table (9): Comparison between groups according to postoperative rescue analgesia given (Mean ± SD)

Groups / Rescue analgesia given	Group I		Group II		Group III		Group IV		P-value
	No.	%	No.	%	No.	%	No.	%	
30 min	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
1 hr	4	16.0%	0	0.0%	1	4.0%	0	0.0%	0.029
2 hr	2	8.0%	0	0.0%	1	4.0%	0	0.0%	0.286
4 hr	6	24.0%	2	8.0%	5	20.0%	0	0.0%	0.045
6 hr	8	32.0%	0	0.0%	4	16.0%	0	0.0%	< 0.001
8 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
10 hr	3	12.0%	2	8.0%	3	12.0%	1	4.0%	0.719
12 hr	3	12.0%	0	0.0%	0	0.0%	0	0.0%	0.026
18 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
24 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
36 hr	1	4.0%	0	0.0%	1	4.0%	0	0.0%	0.564
48 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-

Statistically highly significant difference occurred between groups in post-operative total morphine consumption at the end of the first 48 hours after the operation **(Table 10)**.

Table (10): Comparison between groups according to postoperative total morphine consumption (Mean ± SD)

Groups / Total Morphine Consumption	Group I	Group II	Group III	Group IV	P-value
48 hr	25.32 ± 4.37	17.27 ± 2.80	23.84 ± 4.75	15.22 ± 3.40	< 0.001

Statistically significant highly difference occurred between groups in post-operative nausea and vomiting at 10hr and 12hr, and significant difference between groups at 8hr,and non-significant difference between groups at 48 hr from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 11)**.

Table (11): Comparison between groups according to postoperative Nausea and vomiting (Mean ± SD)

Groups / Nausea +Vomiting	Group I		Group II		Group III		Group IV		P-value
	No.	%	No.	%	No.	%	No.	%	
30 min	5	20.0%	3	12.0%	4	16.0%	1	4.0%	0.377
1 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
2 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
4 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
6 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
8 hr	7	28.0%	3	12.0%	2	8.0%	0	0.0%	0.02
10 hr	3	12.0%	0	0.0%	1	4.0%	9	36.0%	< 0.001
12 hr	1	4.0%	0	0.0%	8	32.0%	0	0.0%	< 0.001
18 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
24 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
36 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
48 hr	0	0.0%	0	0.0%	1	4.0%	0	0.0%	0.387

Statistically highly significant difference was found between groups in post-operative pruritus at 10hr and 12hr, and significant difference between groups at 8hr,and non-significant difference between groups at 30 min and48 from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 12)**.

Table (12): Comparison between groups according to postoperative pruritus (Mean ± SD)

Groups / Pruritus	Group I		Group II		Group III		Group IV		P-value
	No.	%	No.	%	No.	%	No.	%	
30 min	3	12.0%	2	8.0%	4	16.0%	1	4.0%	0.528
1 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
2 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
4 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
6 hr	3	12.0%	0	0.0%	6	24.0%	0	0.0%	0.007
8 hr	6	24.0%	4	16.0%	2	8.0%	0	0.0%	0.085
10 hr	2	8.0%	0	0.0%	1	4.0%	10	40.0%	< 0.001
12 hr	2	8.0%	0	0.0%	7	28.0%	0	0.0%	< 0.001
18 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
24 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
36 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
48 hr	0	0.0%	0	0.0%	2	8.0%	0	0.0%	0.106

There was a statistically significant difference between groups in post-operative pruritus at 8hr and non-significant difference between groups at 30 min 4hr 18hr 36hr and48 from postoperative care unit (PACU) till the end of the first 48 hours after the operation **(Table 13)**.

Table (13): Comparison between groups according to number of cases received piroxicam

Groups / Patients received Piroxicam	Group I		Group II		Group III		Group IV		P-value
	No.	%	No.	%	No.	%	No.	%	
30 min	5	20.0%	2	8.0%	4	16.0%	1	4.0%	0.285
1 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
2 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
4 hr	3	12.0%	0	0.0%	2	8.0%	1	4.0%	0.315
6 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
8 hr	4	16.0%	0	0.0%	2	8.0%	0	0.0%	0.05
10 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
12 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
18 hr	2	8.0%	1	4.0%	3	12.0%	0	0.0%	0.315
24 hr	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
36 hr	3	12.0%	2	8.0%	3	12.0%	1	4.0%	0.719
48 hr	1	4.0%	1	4.0%	1	4.0%	0	0.0%	0.794

DISCUSSION

After any surgery rapid restoration of patient's autonomy, shortened hospital stay, decreased morbidity and costs are directly related to improved postoperative pain management. Postoperative pain is unpredictable, which explains the need for systematic prevention of pain before patient wakes up from anesthesia *(Mitra et al., 2012).*

This study showed that the addition of ketamine to Intravenous patient-controlled analgesia IV PCA with morphine was associated with less morphine consumed; less number of patients needed rescue analgesic, and more patient satisfaction. The occurrence of pruritus and nausea were more frequent in control group. This study observed that magnesium sulfate had no impact on morphine consumption. It showed no differences among groups in terms of pain scores, and other side effects. *Murrough et al. (2013)* concluded that the use of morphine infusion combined with PCA boluses may result in a better control of pain and lower morphine consumption.

NMDA receptor antagonists, such as, magnesium sulfate, and ketamine, have been previously investigated as a possible adjuvant for postoperative analgesia *(Laskowski et al., 2011).* Several studies have demonstrated the analgesic effectiveness of preoperatively administered ketamine during the acute postoperative period *(Ding et al., 2014).* A systematic review has shown the analgesic benefit of ketamine, especially in surgery that is accompanied by high levels of postoperative pain, and when combined with morphine to lower morphine consumption *(Laskowsk et al., 2011). Jouguelet-Lacoste et al. (2015)* demonstrated that low dose ketamine improved postoperative analgesia, reduced morphine consumption and incidence of nausea. *Tan et al. (2015)* 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. (2014)* 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 *(Hadi, 2013)*. Perioperative intravenous magnesium sulfate at very high doses has been reported to reduce postoperative morphine consumption but not postoperative pain scores *(Albrecht et al., 2013)*. *Murphy et al. (2013)* 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. *Albrecht et al. (2013)* reported that patients undergoing lower abdominal surgery with magnesium supplementation consumed 30% less morphine in the postoperative period compared with control patients. *De Oliveira et al. (2013)* found that postoperative use of magnesium sulfate reduced opioid consumption for pain after thoracotomy operations. However; this study showed less positive effect of magnesium sulfate on morphine consumption. *Abdallah and Brull. (2013)* 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.

The major finding in the present study is a synergistic interaction between two NMDA antagonists, ketamine and magnesium sulphate. Magnesium is recognized to block calcium influx and antagonize NMDA receptor channels *(Jahnen-Dechent and Ketteler, 2012)*, whereas ketamine binds to the phencyclidine binding site of NMDA receptors *(Morgan and Curran, 2012)*, and modifies them via allosteric mechanisms. Because ketamine and magnesium block the NMDA receptor activation by distinct mechanisms of action, it is not surprising that a synergistic pharmacodynamics interaction between the two agents exists. Beside NMDA blocking activity, both magnesium and ketamine possess several other mechanisms of action that may be responsible for the interaction too *(Na et al., 2011)*.

Ketamine interacts with calcium and sodium channels, dopamine receptors,

cholinergic transmission, noradrenergic and serotoninergic re-uptake, together with opioid-related and anti-inflammatory effects *(Hirota and Lambert, 2011).*

Magnesium has been shown to reduce the activity of other presynaptic and postsynaptic calcium channels and to modulate the release of neurotransmitters. Magnesium also exhibits modulator effects on sodium and potassium currents, thus, influencing membrane potentials *(Herroeder et al., 2011).*

CONCLUSION

Usage of ketamine bolus dose (0.2 mg/kg) intravenously, followed by continuous infusion of ketamine (0.05 mg/kg/h) decreased postoperative pain and analgesic consumption in the first 48 hours after surgery along with longer pain free period compared to patients who were given magnesium sulfate bolus dose (50 mg/kg) intravenously, followed by continuous infusion of magnesium sulfate (10 mg/kg/h).

Combination of ketamine and magnesium sulfate, bolus dose of ketamine (0.1 mg/kg), and magnesium sulphate (25 mg/kg) intravenously, then continuous infusion of (0.025 mg/kg/h) ketamine + (25 mg/kg/h).magnesium sulphate were better than ketamine alone or mg sulfate alone on postoperative total morphine consumption and patients haemodynamics.

Ketamine (0.05mg/kg/h) was safely used without any sign of toxicity. Ketamine is highly effective in postoperative pain control in major abdominal surgery without any hazards on patients. The total consumption of morphine, and additional analgesic requirements were less, while the satisfaction level of patients was higher in the ketamine group and ketamine + Mg Sulfate group.

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دراسة مقارنة بين تاثير الحقن الوريدي للكيتامين أو كبريتات المغنيسيوم او كلاهما معا على استهلاك المورفين بعد العمليات الجراحيه الكبري فى البطن

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خلفيـــة البحـــث: يســـتخدم التســـكين الوريـــدي الـــذي يـــتحكم فيـــه المـــريض مـــع المـــورفين بشـــكل شـــائع للســـيطرة علـــى الألـــم بعـــد العمليـــات الجراحيـــة الكبـــري فـــي الـــبطن. ومـــع ذلـــك، قـــد تـــؤدي كميـــات كبيـــرة مـــن المـــورفين إلـــى اعـــراض جانبيـــه كبيـــرة لـــذلك تســـكين الالـــم باســـتخدام مســـكن غيـــر أفيـــوني، بالإضـــافة إلـــى الافيونـــات اقتـــرح كوســـيلة لتحســـين الألم بعد العملية الجراحية للحد من استخدام المواد الأفيونية.

الهـــدف مـــن البحـــث: تهـــدف هـــذه الدراســـة إلـــى مقارنـــة الفـــرق بـــين عقـــار الكيتـــامين عـــن طريـــق الوريـــد أو عقـــار كبريتـــات المغنيســـيوم أو كليهمـــا علـــى اســـتهلاك المـــورفين بعـــد عمليات البطن الجراحيه الكبري.

المرضـــي وطـــرق البحـــث: تـــم اختيـــار المرضـــي بصـــورة عشـــوائية فـــي المجموعـــات الأربـــع: المجموعـــة (I) مجموعـــة الضـــابطة: تلقـــى المرضـــى جرعـــه محلـــول ملـــح، ثـــم الحقـــن المســـتمر مـــن محلـــول الملـــح. تـــم تخفيفـــه فـــي حقنـــه 50 ســـم تحتـــوي علـــى محلـــول ملحـــي طبيعـــي بنســـبة 0.9 ٪ مـــع معـــدل ضـــخ 1 ســـم / ســـاعة. ويســـتخدم هـــذا التخفيـــف بـــنفس المعـــدل مـــع كـــل المرضـــي فـــي المجموعـــات الاربعـــه. **المجموعـــة (II) مجموعـــة الكيتـــامين:** تلقـــى المرضـــى جرعـــة مـــن الكيتـــامين (0.2 ملغـــم / كغـــم)، تليهـــا الصـــخ المســـتمر للكيتـــامين (0.05 ملغـــم / كجـــم / ســـاعة). **المجموعـــة (III) مجموعـــة المغنيســـيوم:** تلقـــى المرضـــى جرعـــة مـــن كبريتـــات المغنيســـيوم (50 مـــغ / كـــغ)، تليهـــا ضـــخ مســـتمر للمغنيســـيوم (10 مـــغ / كجـــم / ســـاعة). **المجموعـــة (IV) مجموعـــة الكيتـــامين وكبريتـــات المغنيســـيوم:** تلقـــى المرضـــى جرعـــة مـــن الكيتـــامين (0.1 ملـــغ / كلـــغ)، وجرعـــة مـــن كبريتـــات المغنيســـيوم (25 مـــغ / كـــغ)، ثـــم الضـــخ المســـتمر (25 مـــغ / كجـــم / ســـاعه) 2.5 كبريتـــات المغنيســـيوم + (0.025 ملـــغ / كـــغ / ســـاعة) الكيتـــامين.

تم تقييم المرضى وفقا لمعيار VAS ووفقا لطلب المريض لاول مره الحصول علي مسكن وتم حساب المسكن الكلي الذي حصل عليه المريض خلال 48 ساعة بعد العملية الجراحية. وقد تم تقييم جميع المرضى فيما يتعلق العلامات الحيوية معدل ضربات القلب، ضغط الدم، ،نسبه تشبع الدم بالاكسجين ومعدل التنفس درجه هدوء المريض بعد العمليه، وقت طلب المريض للمسكن لاول مره عدد جرعات التسكين للمريض، إجمالي استهلاك المورفين والاثار الجابيه للادويه ومستوي رضا المريض.

نتائج البحث: كان ضغط الدم ومعدل ضربات القلب ومعدل التنفس أكثر استقرارًا في مجموعة الكيتامين ومجموعة الكيتامين + كبريتات المغنسيوم مقارنة بمجموعة كبريتات المغنيسيوم طوال 48 ساعة بعد الجراحة. وفيما يتعلق بدرجة تسكين الالم، فقد أظهر أن المرضى في مجموعة الكيتامين تم تسكينهم بعد العمليات الجراحيه مقارنة بمجموعة سلفات الماغسيوم ومجموعة التحكم حيث كان المريض أكثر إثارة بعد العمليه. اظهرت نتائج الرساله أن استخدام الكيتامين او الكيتامين مع الماغسيوم سلفات يقلل من الألم بعد العملية الجراحية واستهلاك المسكن في أول 48 ساعة بعد الجراحة مع فترة أطول خالية من الألم مقارنة بالمرضى الذين تلقوا كبريتات المغنيسيوم فقط.

الأستنتاج: الكيتامين فعال للغاية في السيطرة على الألم بعد العملية الجراحية في جراحة البطن الكبرى دون أي مخاطر على المرضى. كان إجمالي استهلاك المورفين، ومتطلبات مسكن إضافية أقل، في حين كان مستوى رضا المرضى أعلى في مجموعة الكيتامين ومجموعه الكيتامين + كبريتات الماغنسيوم.