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# EFFECT OF INTRAOPERATIVE KETAMINE VS MAGNESIUM SULPHATE ON INCIDENCE OF CHRONIC POSTSURGICAL PAIN IN PATIENTS UNDERGOING MODIFIED RADICAL MASTECTOMY

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**ABSTRACT** **Background:** Chronic postsurgical pain (CPSP) following modified radical mastectomy (MRM) is a clinically significant complication affecting patient recovery and quality of life. The transition from acute to chronic pain is largely mediated through central sensitization via N-methyl-D-aspartate (NMDA) receptors. Both ketamine and magnesium sulphate function as NMDA receptor antagonists and have been investigated as preventive analgesic agents. **Aim:** To evaluate the effect of intraoperative ketamine versus magnesium sulphate on the incidence of CPSP in patients undergoing modified radical mastectomy. **Materials and Methods:** This prospective, randomized, double-blind, interventional study was conducted at a tertiary care hospital following approval from the institutional ethics and scientific committee. Sixty patients scheduled for MRM were randomly allocated into two equal groups (n=30 each). Group A received intraoperative ketamine and Group B received magnesium sulphate as intravenous infusions. The primary outcome was the incidence of CPSP at six months postoperatively. Secondary outcomes included time to first rescue analgesia, total analgesic consumption, patient satisfaction (Likert scale), quality of life (EuroQoL-5D), and postoperative complications.**Results:** The incidence of CPSP was comparable between groups: 16.7% in Group A versus 13.3% in Group B ($p = 0.718$). Mean time to first rescue analgesia was similar in both groups (15.05 ± 6.68 hours in Group A vs 15.30 ± 6.67 hours in Group B; $p = 0.899$). Haemodynamic parameters, patient satisfaction scores, and quality-of-life assessments were comparable between groups ($p > 0.05$), and postoperative complication rates did not differ significantly. **Conclusion:** Both ketamine and magnesium sulphate have been equally effective in reducing the incidence of CPSP following MRM. Both agents were haemodynamically safe and can be effective components of preventive multimodal analgesia for MRM surgery.

**KEYWORDS :** Ketamine; Magnesium sulphate; Chronic postsurgical pain; Modified radical mastectomy; NMDA receptor antagonists; Postoperative analgesia

## INTRODUCTION

Effective perioperative pain management is a major clinical concern, as inadequately treated acute pain frequently transits to persistent pain, thereby increasing patient morbidity following surgery.[1,2] Tissue trauma and inflammation during surgery trigger the release of inflammatory mediators, which sensitize peripheral nociceptors. Repetitive C-fibre stimulation leads to progressive increases in dorsal horn neuronal excitability a phenomenon known as 'wind-up'-resulting in central and peripheral sensitization that amplifies and sustains postoperative pain.[1,3] This mechanism is primarily mediated through NMDA receptors and plays a fundamental role in the transition from acute to chronic postsurgical pain. An understanding of these central sensitization mechanisms has shifted perioperative pain management toward multimodal and preventive analgesic strategies. Preventive analgesia refers to interventions applied at any point during the perioperative period that reduce postoperative pain and analgesic requirements beyond the expected pharmacological duration of the agents used.[4,5]

Both ketamine and magnesium sulphate act as non-competitive NMDA receptor antagonists.[4] Perioperative administration of these agents has been associated with anti-hyperalgesic and anti-allodynic properties, reduced anaesthetic and opioid requirements, and improved postoperative analgesia.[6,7,8,9]

Ketamine exerts its analgesic effect through high-affinity blockade of NMDA receptors in the dorsal horn, thereby preventing wind-up and central sensitization. However, its use requires careful dose selection owing to the risk of psychotomimetic side effects and postoperative delirium.[6] Magnesium sulphate reduces nociceptive transmission by blocking calcium influx through NMDA receptor channels, providing membrane stabilization with a more gradual and sustained analgesic profile.[10,11] Its analgesic efficacy has been variable across studies, potentially owing to differences in dosing regimens, surgical procedures, and its limited penetration of the blood–brain barrier.[12]

Although both agents are well established in acute postoperative pain management, comparative data regarding their efficacy in prevention of incidence of chronic post – surgical pain remains limited.[13,14] This randomized clinical study was therefore undertaken to compare the analgesic efficacy of low-dose intraoperative intravenous ketamine and magnesium sulphate in patients undergoing MRM, with particular emphasis on the incidence of CPSP.[15,16]

## MATERIALS AND METHODS

This prospective, randomized, double-blind, interventional study was conducted in the Department of Anaesthesiology and Pain Medicine following approval from the Institutional Scientific and Ethics Committee. The study was registered in the Clinical Trials Registry of India (CTRI//2025/05/087427).

### Sample size calculation

Sample size was calculated using by the SPSS software version 20.0 based on the study by Thakur et al.,[17] which compared the effects of preoperative ketamine and magnesium sulphate on post-operative analgesia in patients undergoing laparoscopic cholecystectomy. A minimum sample size of 74 patients was estimated using comparison of two independent means, with 80% statistical power and an - error probability of 0.05%.

### Inclusion criteria

Female patients aged 18–65 years, ASA physical status I or II, scheduled for elective MRM, and willing to participate in the study were enrolled.

### Exclusion criteria

Patients were excluded if they had BMI > 25 kg/m², any history of psychiatric illness, pregnancy or breastfeeding, known neuropathic disorders, chronic pain medication use, or a known contraindication or allergy to ketamine or magnesium sulphate.

Patients were randomized into two groups using computer-generated random number tables with allocation concealment via sealed opaque envelopes. **Group A** received Inj. Ketamine 0.5 mg/kg diluted in 100 mL normal saline administered intravenously over 10 minutes after induction, followed by a continuous infusion of 0.15 mg/kg/hr until extubation. **Group B** received Magnesium sulphate 50 mg/kg diluted in 100 mL normal saline administered intravenously over 10 minutes after induction, followed by a continuous infusion of 8 mg/kg/hr until

extubation.

Study drug solutions were prepared by a resident anaesthesiologist not involved in subsequent data collection. All outcome parameters were recorded by an observer blinded to group allocation.

**Anaesthetic protocol**

Pre-anaesthetic evaluation was performed one day prior to surgery and written informed consent was obtained. Standard ASA monitors were applied on arrival to the operating theatre, intravenous access was secured, and premedication with intravenous midazolam 1 mg and pentazocine 0.5 mg/kg was administered. Anaesthesia was induced with propofol 2 mg/kg IV and neuromuscular blockade achieved with atracurium 0.5 mg/kg IV. Following tracheal intubation, anaesthesia was maintained with isoflurane in a nitrous oxide–oxygen mixture (70:30). Study drug infusions were commenced as per group allocation. Fifteen minutes prior to extubation, intravenous paracetamol 1 g and ondansetron 4 mg were administered.

Haemodynamic parameters – heart rate (HR), blood pressure (BP), $SpO_2$ were recorded at baseline, post-induction, and at 15-minute intervals intraoperatively.

**Postoperative assessment**

All patients were monitored in the post-anaesthesia care unit (PACU) for 24 hours. The following parameters were assessed:

- Haemodynamic parameters (HR, BP, $SpO_2$) until 24 hours postoperatively
- Pain intensity using Visual Analogue Scale (VAS) at 0, 1, 2, 3, 4, 8, 12, and 24 hours at rest
- Time to first rescue analgesia
- Patient satisfaction score using Likert scale
- Postoperative complications: nausea, vomiting, hallucinations, pruritus, respiratory depression, and decreased urine output

**Long-term follow-up**

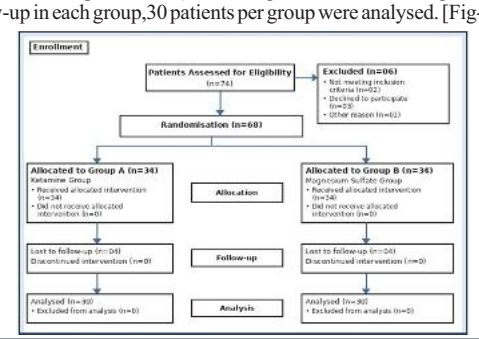
Patients were contacted by telephone at 1, 3, and 6 months postoperatively. Chronic post – surgical pain (CPSP) was defined as pain that develops after a surgical procedure, persists for at least 3 months beyond the expected healing period, is distinct from any pre-existing pain condition,and is not attributable to other causes such as infection or malingnancy, and it was evaluated using the Visual Analogue Scale and DN4 Questionnaire (Douleur Neuropathique 4). Quality of life was assessed at 6 months using the EuroQoL-5D scale a validated five-domain instrument evaluating mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each domain rated on a three-level scale and patient satisfaction using the Likert scale at 6 months.

**Statistical analysis**

Data were entered in Microsoft Excel and analysed using SPSS software version 20. Continuous variables are expressed as mean ± standard deviation (SD); categorical variables as frequency and percentage. Between-group comparisons of continuous data were performed using the unpaired Student's t-test, and of categorical data using Chi-square or Fisher's exact test. Intragroup comparisons used the paired t-test. Non-normally distributed data were analysed using the Mann–Whitney U test. A $p$-value < 0.05 was considered statistically significant.

**RESULTS**

A total of 74 patients were assessed for eligibility,6 were excluded and 68 randomised equally into Group A (Ketamine, n=34) and Group B (Magnesium Sulphate, n=34);following 4 losses to following 4 losses to follow-up in each group,30 patients per group were analysed. [Fig-1]




**[Fig-1] Consort Diagram**

Demographic characteristics (mean age, sex, weight, and ASA physical status) were comparable between the two groups ($p$ > 0.05) [Table-1].

**[Table-1]: Demographic profile. p-value <0.05 was considered as statistically significant**

| Parameters | Group A (Mean±SD) | Group B (Mean±SD) | p-value (Student's paired t-test) |
|---|---|---|---|
| Age (years) | 42.83 ± 9.33 | 40.47 ± 9.17 | 0.326 |
| BMI (kg/m²) | 22.11 ± 1.92 | 22.07 ± 1.83 | 0.826 |
| American Society of Anaesthesiologists (ASA) | | | |
| Grade II | 30 (100%) | 30 (100%) | 1 |

The incidence of CPSP was 16.7% in Group A and 13.3% in Group B, with no statistically significant difference ($p$ = 0.718), indicating comparable long-term outcomes [Table-2].

**[Table-2]: Incidence of Chronic Postsurgical Pain (CPSP) between Group A and Group B. Chi-square=0.131, p=0.718.**

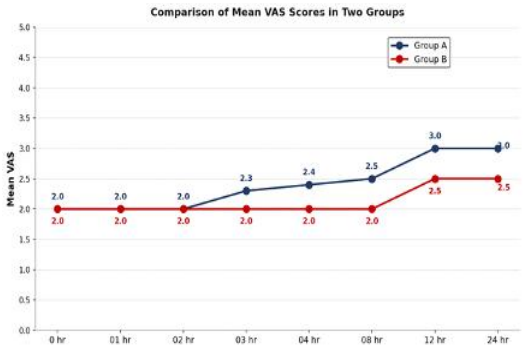
| Chronic Postsurgical Pain (CPSP) | Group A | | Group B | | Chi-Square Value | p-value |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| No Chronic Pain (<=4) | 25 | 83.3 | 26 | 86.7 | 0.131 | 0.718 |
| Chronic Pain (>4) | 05 | 16.7 | 04 | 13.3 | | |
| Total | 30 | 100 | 30 | 100 | | |

Mean time to first rescue analgesia was 15.05 ± 6.68 hours in Group A and 15.30 ± 6.67 hours in Group B, with no significant difference between groups ($p$ = 0.899) [Table-3].

**[Table-3]: Duration of analgesia and rescue analgesic consumed in 24 hours.**

| Parameters | Group A (n=30) | Group B (n=30) | p-value |
|---|---|---|---|
| Time to First Rescue Analgesia (Hours) | 15.05 ± 6.682 | 15.30 ± 6.677 | 0.899 |
| Total Postoperative Analgesic Consumption (mg) | 70.11 ± 44.33 | 112.74 ± 34.86 | <0.05 |

VAS scores were comparable during the early postoperative period (0–2 hours), with both groups maintaining a mean score of approximately 2.0 ($p$ > 0.05). From the third postoperative hour onward, Group B demonstrated significantly lower VAS scores, reaching statistical significance at 3 hours ($p$ = 0.046), 4 hours ($p$ = 0.003), and from 8 to 24 hours ($p$ = 0.0001), indicating more sustained analgesia with magnesium sulphate [Table -4].




**[Table -4 ] P-Values: 0 hr=0.317; 1 hr=0.150; 2 hr=0.081; 3 hr=0.046; 4 hr=0.003; 8 hr=0.0001; 12 hr=0.0001; 24 hr=0.0001** ***VAS = Visual Analogue Scale. Values in red indicate statistical significance (p < 0.05).***

Quality-of-life assessment using the EuroQoL-5D questionnaire at 6 months evaluated five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Distribution of patients across all domains was comparable between groups, with no statistically significant differences ($p$ > 0.05). [Table/Fig-5,6].

**[Table-5]: Postoperative Mean DN4 Scores (Neuropathic Pain) at Follow-up Intervals. DN4 Score (Douleur Neuropathique 4 Questionnaire).**

| Time Interval | Group A | | Group B | | P Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| 15 Days | 5.83 | ± 0.531 | 5.52 | ± 0.491 | 0.900 |
| 1 Month | 5.77 | ± 0.504 | 5.41 | ± 0.390 | 0.830 |
| 3 Month | 5.23 | ± 0.728 | 5.03 | ± 0.765 | 0.304 |
| 6 Month | 3.60 | ± 0.770 | 3.57 | ± 0.728 | 0.864 |

**[Table-6]: Different Dimensions (EQ-5D Domain). Data are number (%). Chi-square test applied.**

| Variable | | Group A (n=30) | | Group B (n=30) | | Chi-Square Value | p-value |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| I. Mobility | Problem | 30 | 100 | 22 | 73.3 | 9.231 | 0.002 |
| | No Problem | 00 | 00 | 08 | 26.7 | | |
| II. Self-Care | Problem | 29 | 96.7 | 26 | 86.7 | 1.964 | 0.161 |
| | No Problem | 01 | 3.3 | 04 | 13.3 | | |
| III. Usual Activity | Problem | 14 | 46.7 | 18 | 60 | 1.071 | 0.301 |
| | No Problem | 16 | 53.3 | 12 | 40 | | |
| IV. Pain Discomfort | Problem | 13 | 43.3 | 17 | 56.7 | 1.067 | 0.302 |
| | No Problem | 17 | 56.7 | 13 | 43.3 | | |
| V. Anxiety Depression | Problem | 16 | 53.3 | 19 | 63.3 | 0.617 | 0.432 |

Postoperative complications nausea and vomiting was observed in only 3 patients in the ketamine group. No hallucinations and respiratory depression were observed in either group ($p > 0.05$).

## DISCUSSION

The incidence of CPSP in the present study was 16.7% in Group A (ketamine) and 13.3% in Group B (magnesium sulphate), with no statistically significant intergroup difference ($p = 0.718$). The reported incidence of CPSP following MRM ranges from 25% to 60%,[18] which is substantially higher than observed in either group, suggesting that both agents contribute to a reduction in CPSP. However, neither drug demonstrated superiority over the other in preventing long-term pain. Dullenkopf et al.[19] reported that a single intraoperative ketamine bolus (0.15–0.5 mg/kg) was insufficient to reduce CPSP. Etezadi et al.[20] similarly found that a single bolus of magnesium sulphate (20–50 mg/kg) did not reduce CPSP at 3 months. Taken together, these findings suggest that single-dose administration of either drug cannot sustain NMDA receptor blockade across the sub-acute recovery phase, during which wind-up continues to propagate.

Peyton et al.[21] found no significant reduction in CPSP at 6 months despite using a prolonged perioperative ketamine infusion (0.5 mg/kg bolus followed by 0.25 mg/kg/hr intraoperatively and 0.1 mg/kg/hr for 24 hours). This may reflect the limitations of a pilot study design with a small sample size.

Guo et al.[22] used S-ketamine (0.5 mg/kg bolus followed by 0.5 mg/kg/hr infusion) and reported a significant reduction in CPSP at 3 months (18.2% vs. 43.8%). The pharmacological advantage of S-ketamine—approximately 3–4 times more potent than racemic ketamine due to higher NMDA receptor affinity—along with a higher infusion rate likely explains the more pronounced benefit compared to our study.

Kang et al.[16] reported reduced CPSP incidence at 1 and 3 months using a ketamine bolus (0.5 mg/kg) with low-dose infusion (0.12 mg/kg/hr), but this benefit was not sustained at 6 months. In the present study, a modestly higher infusion rate (0.15 mg/kg/hr) was used, and reduced CPSP was observed at 6 months. This positions our protocol between the low-dose infusion and the high-potency approach.[16,22] Suggesting that a moderate increase in infusion intensity may sustain long-term prevention without increasing the risk of dissociative side effects.

Hassan et al.[23] evaluated a combined ketamine–magnesium sulphate regimen (ketamine 0.5 mg/kg and magnesium sulphate 50 mg/kg boluses, followed by infusions of 0.12 mg/kg/hr and 8 mg/kg/hr respectively, continued for 24 hours postoperatively) and found no significant reduction in chronic neuropathic pain. This observation, combined with the results of the present study, suggests that to achieve meaningful prevention of CPSP, clinicians may need to move toward higher-potency agents such as S-ketamine, or significantly intensified dosing regimens maintained throughout the high-risk inflammatory window.

During the early postoperative period (0–2 hours), VAS scores were comparable between both groups (mean approximately 2.0; $p > 0.05$). From the third postoperative hour onward, Group B demonstrated progressively lower VAS scores, which became highly significant from the fourth hour ($p = 0.003$) through 24 hours ($p = 0.0001$). This temporal pattern is consistent with the mechanistic differences between the two agents: ketamine provides an intense early NMDA blockade with pre-emptive suppression of wind-up, while magnesium sulphate offers more gradual membrane stabilization that yields superior sustained analgesia in the recovery phase. These findings align with observations by Helmy et al.[26] and Heydari et al.,[25] who noted that the most pronounced VAS score differences between ketamine and comparators occur within the first 12 postoperative hours.

Total analgesic consumption was significantly lower in Group A (70.11 ± 44.33 mg vs. 112.74 ± 34.86 mg; $p < 0.05$), consistent with studies by Zakine et al.[7] and Kamel et al.[24] Ketamine's ability to suppress central sensitization via dorsal horn NMDA receptor blockade prevents the progressive amplification of pain signals ('wind-up'), thereby reducing the overall analgesic burden. This is also in keeping with De Oliveira et al.,[6] who reported a 30–40% reduction in opioid consumption with ketamine, along with lower early postoperative pain scores and prolonged time to rescue analgesia.

Levaux et al.[27] and Hassan et al.[23] collectively suggest that while magnesium sulphate may not match ketamine's immediate analgesic intensity, its role in stabilizing resting membrane potential provides a smoother, more prolonged recovery curve. When combined with ketamine, magnesium may contribute to additional analgesic sparing.
The absence of a prolonged duration of analgesia in the ketamine group in the present study was unexpected, as it contrasts with findings from Jain et al.,[13] who reported that ketamine nearly doubled the initial duration of analgesia compared to magnesium sulphate (67 min vs. 30 min). The basis for this discrepancy is unclear and may relate to differences in surgical context, patient population, or baseline sensitization.

Thakur et al.[17] reported reduced morphine consumption in both the magnesium (6.5 ± 2 mg) and ketamine (7.2 ± 2 mg) groups compared to controls (10.2 ± 2 mg; $p < 0.05$), consistent with the opioid-sparing properties observed in the present study.

The literature and our findings together support a temporal model of NMDA antagonist-mediated analgesia: ketamine provides a pre-emptive, high-intensity blockade effective in the immediate postoperative phase, while magnesium sulphate acts as a stabilizing agent that smooths the middle-to-late recovery period. The combination of both agents may represent an optimal opioid-sparing strategy by leveraging their complementary temporal profiles.

All haemodynamic parameters remained stable and comparable between groups intraoperatively and postoperatively, confirming that both agents are haemodynamically safe. This is consistent with findings from Jain et al.,[13] Talukdar et al.,[14] and Etezadi et al.,[20] and reflects a key clinical advantage: NMDA antagonists attenuate the haemodynamic response to surgical stress without myocardial depression.

Patient satisfaction scores and quality of life (EuroQoL-5D) were comparable between groups, and no significant differences in postoperative complications were observed.

## LIMITATIONS

- Inclusion of only ASA I and II patients undergoing MRM limits the generalizability of findings to other patient groups and surgical procedures.
- Psychological, genetic, and individual factors influencing pain perception and chronification were not assessed.
- The study was conducted at a single centre with a relatively small sample size; multi-centre studies with larger cohorts are warranted to confirm these findings.

## CONCLUSION

Both ketamine and magnesium sulphate are equally efficacious in

reducing chronic postsurgical pain when administered as intraoperative bolus and infusion regimens for MRM. Both agents are haemodynamically safe adjuncts for multimodal preventive analgesia and effectively attenuate the sympathetic stress response to surgical trauma without the risks associated with high-dose opioids. Although they share a common pathway of NMDA receptor modulation, they exhibit distinct and complementary analgesic profiles: ketamine produces rapid-onset, intense analgesia with superior reduction in total analgesic consumption, while magnesium sulphate provides more prolonged and sustained postoperative pain control. Leveraging these complementary temporal benefits may form the basis of an optimal preventive analgesic regimen for patients undergoing major breast surgery.

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