Review Article

Efficacy of memantine premedication in alleviating postoperative pain- A systematic review and meta-analysis

ABSTRACT

Many premedication agents with opioid-sparing properties have been used in patients undergoing various elective surgeries. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has been used by many researchers as an opioid-sparing strategy. Various databases like PubMed, Scopus, Cochrane Library, and clinicaltrials.gov were searched after registering the review protocol in PROSPERO for randomized-controlled trials (RCTs) that investigated the efficacy and safety of memantine premedication in adult patients undergoing various elective surgeries. The risk of bias (RoB-2) scale was used to assess the quality of evidence. From the 225 articles that were identified after a database search, 3 studies were included for a qualitative systematic review and a quantitative meta-analysis. The pooled analysis revealed that the use of memantine provided better pain scores at 2nd (mean difference: -0.82, 95% CI: -1.60, -0.05, $P = 0.04$) with significant heterogeneity ($P = 0.06$; $I^2 = 71\%$), and 6 hours postoperatively (mean difference: -1.80, 95% CI: -2.23, -1.37, $P < 0.00001$), but not at 1 hour. The sedation scores at 1 hour were higher in the memantine group but comparable in the 2nd hour. The number of doses of rescue analgesia and nausea/vomiting in the postoperative period was comparable in both groups. The results of this review suggest that memantine premedication could provide better pain scores in the immediate postoperative period with acceptable adverse effects. However, the current evidence is insufficient to suggest the routine use of memantine as a premedication before elective surgeries.

Key words: Acute pain, memantine, *N*-Methyl-D-Aspartate, postoperative, premedication

Introduction

Despite several advances in the management of acute pain, nearly 20%–50% of patients experience moderate to severe pain in the first 24 hours after surgery.[1,2] Opioids are essentially the cornerstone of acute postoperative pain management. However, the problems with its use are postoperative nausea/vomiting (PONV), respiratory depression, somnolence, constipation, and addiction potential.[3,4] Therefore, anaesthesiologists are in constant search of adjuncts that not only provide opioid-sparing, effective analgesia but also have minimal adverse effect profiles.

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N-methyl-D-aspartate (NMDA) receptors are the target receptors for the excitatory neurotransmitter glutamate, which is released in response to unpleasant peripheral inputs.[5] The activation of NMDA receptors has been linked to opioid receptor dysfunction, neuropathic pain, and hyperalgesia.[6] NMDA receptors are expressed in the central nervous system and also outside the CNS.[7] Activation of the NMDA receptor leads to a wind-up phenomenon and causes central sensitization. The activation of NMDA receptors also leads to peripheral sensitization and has been implicated in visceral pain.[8]

Ketamine, a phencyclidine, is the commonly used NMDA-receptor antagonist which has been used for procedural sedation, acute pain, and complex chronic pain management.[9] The dissociative analgesia and psychomimetic symptoms are known concerns with the use of ketamine but this is seen at doses more than 1 mg/kg. At doses of 0.1–0.3 mg/kg bolus or 1 mg/kg/hour infusion, which is also known as the analgesic dose of ketamine, such adverse events are uncommon.[10] In a systematic review by Karlow *et al.*,[11] the authors concluded that ketamine is non-inferior to morphine when used judiciously in the management of acute pain in the emergency department. In a Cochrane review by Brinck *et al.*,[12] the authors concluded that ketamine reduces postoperative analgesic consumption and pain intensity with reduced nausea/vomiting in the postoperative period.

Magnesium, ketamine, amantadine, memantine, and dextromethorphan are other drugs that belong to the NMDA-receptor antagonist family. Memantine is a derivative of amantadine and is available as an oral preparation. In the year 2000, US FDA approved the use of memantine for Alzheimer's disease. Another indication of its use is a complex regional pain syndrome, phantom limb pain, fibromyalgia, and postmastectomy pain. Memantine has a low affinity for NMDA-receptor antagonist action and does not lead to psychomimetic symptoms or dissociation at doses of 20–60 mg/day.[13,14] The use of memantine as an opioid-sparing adjunct when administered as a premedication preoperatively has been investigated in many studies with variable success.[15,16] This systematic review and meta-analysis aimed to investigate the efficacy and safety of preoperative oral memantine premedication as a part of multimodal analgesia in patients undergoing various elective surgeries in adults by comparing it with a control group or placebo.

Methods

This systematic review was registered with the international prospective register of systematic reviews (PROSPERO registration number: CRD42023404008) and was reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[17]

The search for relevant keywords was done from databases starting from January 2000 till February 2023. The strategy included searches of PubMed/MEDLINE, Scopus, Cochrane Library (CENTRAL), and clinicaltrials.gov. The search strategy for the PubMed database was as follows: "Memantine" AND "Acute pain" OR "Postoperative pain".

Participants (inclusion and exclusion criteria)

RCTs in which oral memantine was compared with a placebo or a control group in patients undergoing elective surgeries and non-cardiac surgeries in adults were included. Studies in which there were no control groups, case reports/series, editorials, review articles, or conference abstracts were excluded.

RCTs in which oral memantine premedication was compared to a placebo or a control medication in patients undergoing elective surgery were carefully searched for in the database findings. Two authors independently examined the titles and abstracts, removing any duplicates. After careful consideration by both authors, who also read the entire text, the studies were chosen. An independent third author addressed discrepancies and inconsistencies, if any. Each reviewer separately extracted the data using a predefined approach. The study characteristics and study results were evaluated in the completed publications. Details like the name of the author, publication year, study design, number of participants, country, age, surgeries performed, primary and secondary outcomes, and conclusions were gathered.

Intervention and comparators

Adult patients undergoing elective on-cardiac surgeries were premedicated with oral memantine premedication which was compared with either a placebo or a control group.

Outcomes: Primary and secondary

The primary outcomes were pain scores at various time intervals. The secondary outcomes were sedation scores, postoperative opioid consumption, patients requiring rescue analgesia, adverse events like postoperative nausea/vomiting (PONV), and quality of recovery (QoR).

Methodological quality assessment

The methodological quality and risk of bias of the included RCTs were assessed using the Revised Cochrane risk-of-bias assessment for RCTs (RoB 2). To assess bias, six areas were taken into account: randomization bias, deviation from intended intervention bias, missing data bias, outcome measurement bias, selection bias for reported results, and overall bias.[18]

Data extraction

From the publications, reference data, populations, and results were taken out and inserted into pre-designed tables. For data extraction, the two authors (— and --) used a systematic procedure. Data on the study's design, number of arms, main finding, participant demographics, sample size, the procedure performed, and experimental intervention were acquired (oral memantine premedication).

Data synthesis and analysis

The distinction between a therapeutic or negative effect being present or absent was recovered as a dichotomous result. For continuous data, we computed means and standard deviations (SDs). The confidence intervals (CIs) or *P* values that were associated with the variations in means between the two groups were used to calculate the SDs if they were not explicitly mentioned. If trials were clinically homogenous in terms of demographic and control group, pooling of the available was performed. When adequate numbers of adequately homogenous studies were extracted based on inclusion criteria, Review Manager software was used to conduct the meta-analysis (version 5.4.1).[19]

Dichotomous variables were evaluated using the Mantel-Haenszel method, and the risk ratio and its corresponding 95% confidence interval (CI) were calculated. The mean difference (MD) with the associated 95% CI for continuous variables with units-unified was calculated using the inverse variance method. The I2 statistic, which was defined as 0%–40%-might not be important, 30%–60%-may represent moderate heterogeneity, 50%–90%-may indicate significant heterogeneity, and 75%–100%-considerable heterogeneity, was used to assess the heterogeneity between trials.[20]

The results were compared with the random effects model and fixed effects model, and ultimately the reliability of the combined results was analyzed following the degree of consistency of the results. For the meta-analysis, the fixed effects model was employed when $P > 0.01$ and I2 <50% and the random effects model when $P < 0.01$ and I2 >50%.[21] For the reporting of dichotomous outcomes, risk ratios (RR) with 95% CI were used. Different opioids were converted to intravenous (IV) morphine equivalent for comparison between the trials.

Sensitivity and sub-group analysis

The robustness of the pooled estimates for outcomes that included data from three or more studies was evaluated by sequentially removing data from each study and by reanalyzing the remaining data to ensure that the pooled effect sizes were not the result of single study domination. A sub-group analysis will be performed if there is both placebo or an active control group (some other premedication drug).

Publication bias

Funnel plots of effect sizes against standard errors for outcomes will be examined for asymmetry if there are more than 10 studies that fulfill inclusion criteria.[22] The Egger bias test will be used as a corresponding statistical test with $P < 0.10$ indicating asymmetry.[23]

Results

Results of literature search

We searched PubMed/Medline, CENTRAL, Scopus, and clinicaltrials.gov for RCTs comparing oral memantine premedication with control in patients undergoing elective non-cardiac surgeries. We identified 225 articles by searching the above-mentioned databases and registries. After removing duplicates and also articles that were not relevant, we identified 14 articles for scrutiny. A total of nine studies were considered eligible. From these six studies were excluded (study with no control group-1, review articles-3, active control group-0, unrelated primary and secondary outcomes-3). Finally, we included 3 studies which included 224 patients for analysis (112 patients in the memantine group and 112 in the control group),[24-26] depicted in the PRISMA flowchart [Figure 1]. All the included studies with study characteristics are summarized in Table 1. The PRISMA checklist is provided as Supplementary File 1.

Risk of bias

The risk of bias within the trials according to ROB2 is depicted in Figure 2a. The summary plot of the quality assessment is shown in Figure 2b. The bias from the randomization process was low in three studies.[24-26] Bias due to deviations from intended interventions (allocation concealment) was low in all 3 studies.[24-26] Bias arising due to missing outcome data was low in one study[26] and there was no information in two studies.[24,25] Bias in the measurement of outcome was low in all three studies.[24-26] Bias arising due to the selection of reported results was low in all three studies.[24-26] The overall bias was low.

Primary outcome meta-analysis

The three studies which fulfilled the inclusion criteria are summarised here. Taheri *et al.*[24] randomized 180 patients undergoing elective lower limb orthopedic surgery into three groups (60 patients in each group). Patients in group 1 received 30 mg memantine, patients in group 2 received 45 mg dextromethorphan, and patients in group 3 received a placebo 2.5 hours before surgery. Pain scores and sedation scores (at 6, 12, 24, 36, and 48 hours), and PONV were

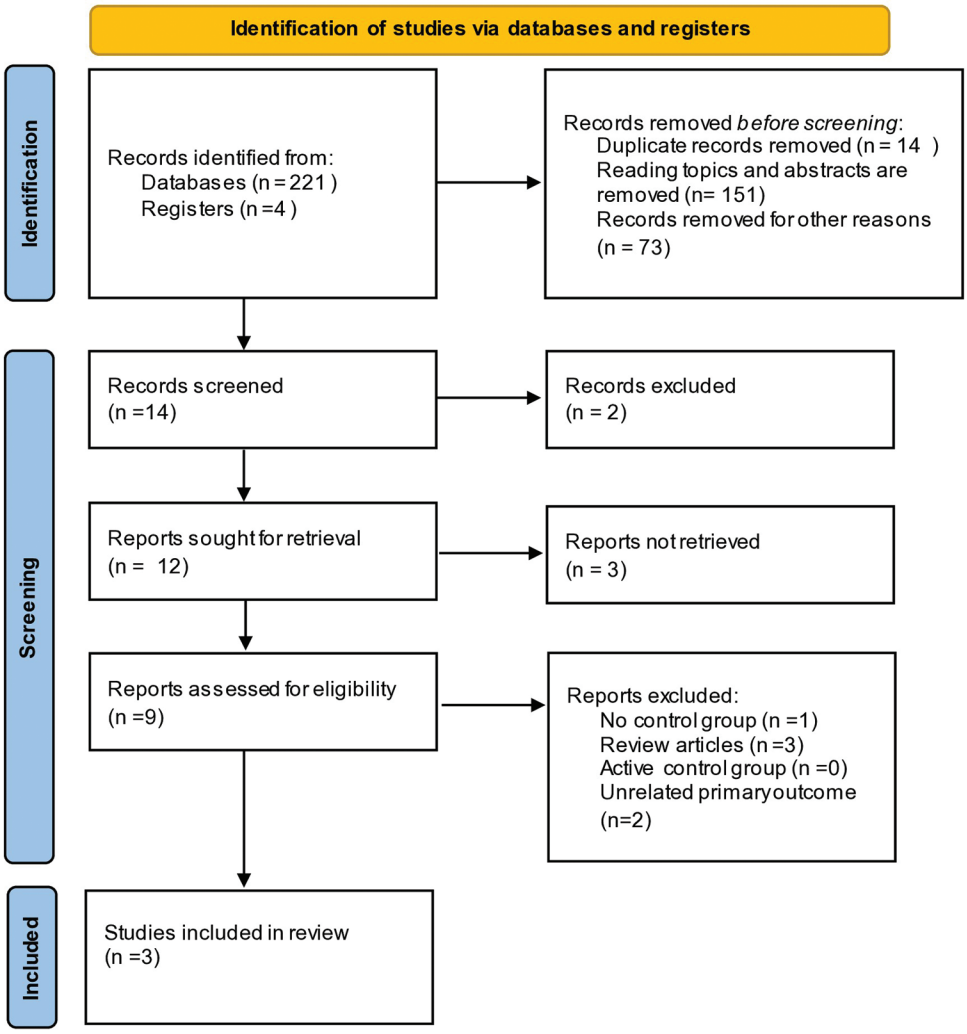

Figure 1: PRISMA flowchart

compared postoperatively. The authors also compared opioid consumption at 48 hours and patient satisfaction at the end of 48 hours.

Rahimzadeh *et al.*[25] randomized 60 patients undergoing dacryocystorhinostomy under standard general anesthesia protocol. One group received 20 mg of memantine before surgery (30 patients) and the patients in the other group received a placebo (30 patients). Pain scores and sedation scores were noted and compared at 1, 2, and 6 hrs after surgery. Demographic data and adverse events like PONV were also compared.

Karri *et al.*[26] randomized 66 patients undergoing laparoscopic cholecystectomy into three groups: group 1 patients received 600 mg oral gabapentin, group 2 patients received 20 mg oral memantine, and group 3 patients received a placebo 1 hour before surgery. Post extubation, pain scores at 15 min, 1,2, and 4 hours were assessed and compared using NRS and algesiometer. Sedation scores were also noted at the same time intervals. Rescue analgesia (NRS > 4) was with IV tramadol 1 mg/kg. The number of doses of rescue analgesia, total rescue analgesia, and time to rescue analgesia was also compared. Adverse events like dizziness, PONV, headache, and epigastric discomfort were also compared. The efficacy for compared only for 4 hours postoperatively.

Meta-analysis of pain scores at 1, 2, and 6 hour

Three studies reported pain scores at the end of the first postoperative hour (112 patients in the memantine group and 112 patients in the control group).[24-26] At the end of 1 hour, pain scores were comparable between the memantine and control group (MD: −0.85, 95% CI: -2.04, 0.34, $P = 0.16$). A random effect model revealed considerable heterogeneity ($P = 0.009$; $I^2 = 86\%$) [Figure 3a].

Two studies reported pain scores at the end of 2 hours (52 patients in the memantine and control group, each).[25,26] At the end of 2 hours, pain scores were significantly less

Table 1: Summary of all the included studies

Authors/ year	Country	Type of study	Surgery	Number of patients	Comparator	Dose of memantine used	Primary outcomes	Secondary outcome	Conclusions
Taheri *et al.*/2017[24]	Iran	Double-blind clinical trial	Orthopaedic	100 (60 in memantine group, 60 in dextromethorphan group, 60 as control)	Dextromethorphan 45 mg and placebo	30 mg	Comparison of postoperative pain scores	Sedation scores, PONV	Memantine is effective in reducing postoperative pain scores when compared to 45 mg dextromethorphan and placebo
Rahimzadeh *et al.*/2017[25]	Iran	Double-blind clinical trial	Dacryocystorhinostomy (DCR)	60 (30 in memantine group, 30 in placebo)	Placebo	20 mg	Comparison of postoperative pain scores	Sedation scores, adverse effects	Single dose, preoperative memantine is effective in reducing postoperative pain after DCR
Karri *et al.*/2021[26]	India	Randomised, placebo-controlled trial	Laparoscopic cholecystectomy	66 (22 in memantine group, 22 in gabapentin group, 22 in placebo)	Gabapentin 600 mg and placebo	20 mg	Comparison of postoperative pain scores	Sedation scores, time to rescue analgesia, number of doses of rescue analgesia	Gabapentin is a better adjuvant analgesic for laparoscopic cholecystectomy compared to memantine as a single preoperative dose.

in the memantine group when compared to the control group (MD: −0.82, CI: −1.60, −0.05, $P = 0.04$). A random effect model was applied which was suggestive of significant heterogeneity ($P = 0.06$; $I^2 = 71\%$) [Figure 3b].

Two studies reported pain scores at the end of 6 hours (45 patients in the memantine and control group, each).[24,25] Pain scores were significantly less in the memantine group after 6 hours when compared to the control (MD: −1.80, 95% CI: −2.23, −1.37, $P < 0.00001$). However, heterogeneity was not applicable as one study had 100% of weight as the details of standard deviation were not provided by the second study [Figure 3c].[24]

Meta-analysis of sedation scores

Two studies reported sedation scores at the end of 1 hour (52 patients in the memantine and control group, each).[25,26] On pooled analysis, it was revealed that the sedation scores at the end of 1 hour were significantly more in the memantine group than in the control group (MD: 1.73, 95% CI: 0.82, 2.64, $P = 0.0002$). Based on a fixed effect model, there was moderate heterogeneity ($P = 0.21$; $I^2 = 36\%$) [Figure 4a]

Two studies reported sedation scores at the end of 2 hours (52 patients in the memantine and control group, each).[25,26] On pooled analysis, it was revealed that the sedation scores at the end of 2 hours were comparable between both groups (MD: 0.07, 95% CI: −0.38, 0.53, $P = 0.76$). Based on a fixed effect model, there was no heterogeneity between the studies ($P = 0.85$; $I^2 = 0\%$) [Figure 4b].

Meta-analysis of the total dose of rescue analgesia

Two studies reported a total dose of rescue analgesia postoperatively (82 patients in the memantine and control group, each).[24,26] Pooled analysis revealed that the doses of rescue analgesia were comparable between both groups (MD: −7.57, 95% CI: −20.39, 5.25, $P = 0.25$). A random effect model revealed considerable heterogeneity ($P < 0.00001$; $I^2 = 99\%$) [Figure 5a].

Meta-analysis of PONV

Two studies reported PONV (52 patients in the memantine and control group, each).[25,26] Pooled analysis revealed comparable PONV between memantine and control (MD: 0.82, 95% CI: 0.24, 2.81, $P = 0.75$). However, heterogeneity was not applicable as one study had 100% of weight (as there were no PONV events in the other group) [Figure 5b].

As there were only three studies in quantitative analysis, publication bias was not estimated.

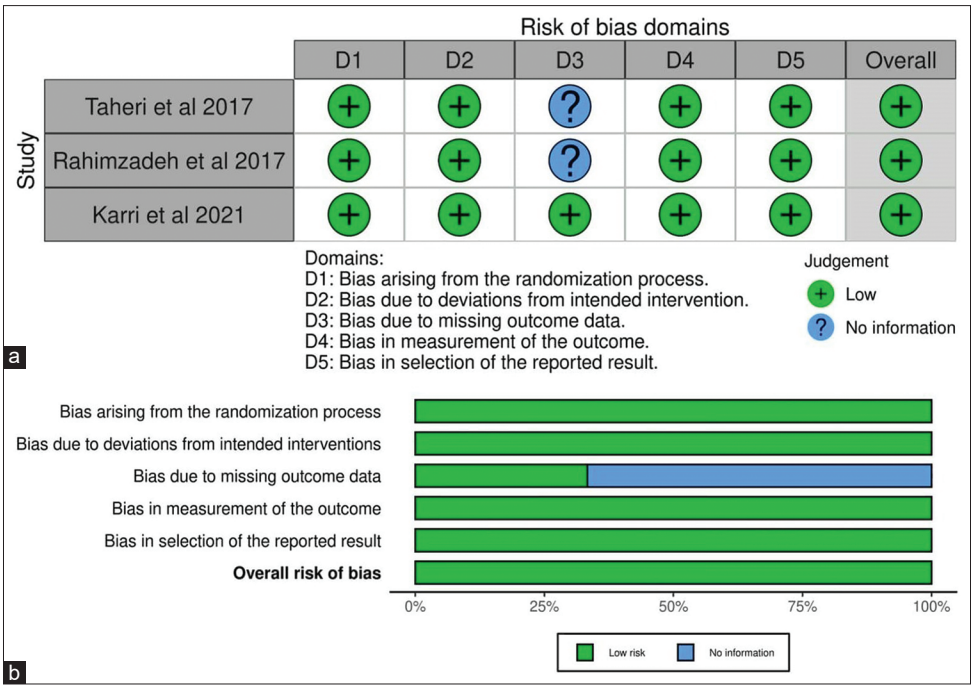

Figure 2: (a) Traffic light plot. (b) Summary plot

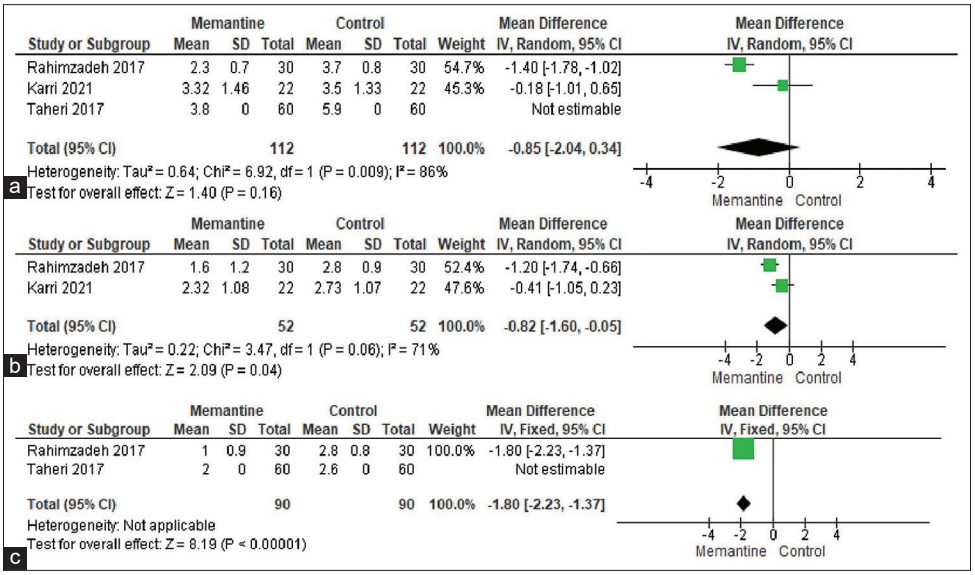

Figure 3: (a) Forest plot showing comparison between pain scores at 1 hour. (b) Forest plot showing comparison between pain scores at 2 hours. (c) Forest plot showing comparison between pain scores at 6 hours

Discussion

Summary of results

This systematic review and meta-analysis investigated the efficacy and safety of oral memantine premedication before various surgeries in providing opioid-sparing analgesia. The pooled analysis revealed that the use of memantine provided better pain scores at 2nd and 6 hours postoperatively, but not at 1 hour. This was at the cost of higher sedation scores in the first postoperative hour with comparable sedation scores from 2nd hour. However, the number of doses of rescue analgesia (in terms of IV morphine) and PONV were comparable in both groups. To the best of our knowledge, this is the first systematic review that has attempted to investigate the efficacy of oral memantine premedication in adults before surgery.

Several studies have demonstrated that low-dose ketamine (up to 0.1 mg/kg) is useful in managing acute pain especially when opioids are contraindicated, rapid onset of analgesia

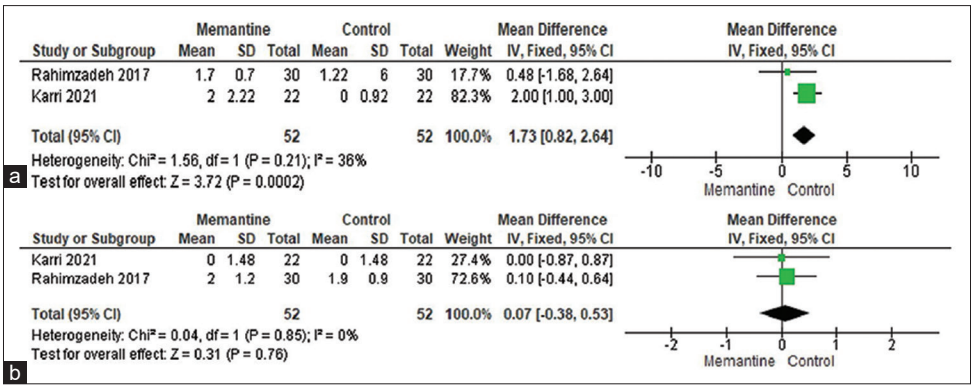

Figure 4: (a) Forest plot showing comparison between sedation scores at 1 hour. (b) Forest plot showing comparison between sedation scores at 2 hours

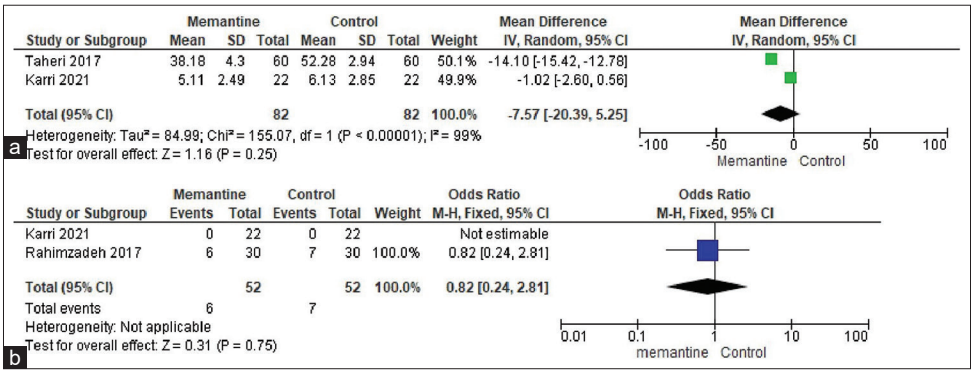

Figure 5: (a) Forest plot showing comparison between total dose of rescue analgesia. (b) Forest plot showing comparison between PONV scores

is required, or pain is persistent despite conventional analgesic modalities.[27,28] Although there are many NMDA receptors available, ketamine has been widely used in acute postoperative pain as the anaesthesiologists are familiar with its use as a result of its extensive application in general anesthesia and procedural sedation in combination with other drugs in several areas.[29-32] However, the common adverse effects of ketamine like dissociation, and psychomimetic effects interferes with its use regularly.[33] This is despite the existing availability of consensus guidelines on the use of IV ketamine infusions for acute pain management made available by the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists.[10]

Several NMDA antagonists like magnesium sulfate, amantadine, dextromethorphan, and memantine were explored by several researchers for various surgeries to investigate their safety and analgesic efficacy.[34-38] In a randomized, double-blind, controlled trial by Schley *et al.*,[39] the authors randomized 19 patients undergoing acute traumatic amputation of the upper extremity under brachial plexus block (continuous ropivacaine infusion for at least 7 days). There were 10 patients in the memantine group who received 20–30 mg per day of oral memantine for 4 weeks and the 9 patients in the control group received a placebo. the authors concluded that memantine can reduce the intensity of phantom limb pain and might also prevent the development of phantom limb pain.

Morel *et al.*[15] randomized 40 females with breast cancer undergoing mastectomy into two groups. One group received 5–20 mg/day of oral memantine for 2 weeks before surgery which was continued at a dose of 20 mg/day for another two weeks after surgery. The other group received a placebo for a similar duration. Post-mastectomy pain was compared in both groups at the end of 3 months. The analysis revealed that patients receiving memantine showed a significant difference in post-mastectomy pain intensity at three months, less rescue analgesia, and a better emotional state. Shanthanna *et al.*[40] conducted a randomized-controlled, factorial-design, pilot study to compare NMDA antagonists (IV ketamine and oral memantine) with a placebo and IV steroid (dexamethasone) with placebo in patients undergoing video-assisted thoracic surgeries. Patients were allotted 27 eligible patients randomly in 4 groups viz., NMDA active with steroid placebo, NMDA placebo with steroid active, NMDA and steroid both active, and both NMDA and steroid placebo. As per the methodology, 0.5 mg/kg ketamine was administered as a bolus followed by 0.1 mg/kg/hour for 24 hours started postoperatively in the NMDA active group. From postoperative day-1, patients received 5 mg BD memantine for a week, and 10 mg BD for the second week, and was continued for 4 weeks.

The patients in the placebo group received a placebo preoperatively and postoperatively for 4 weeks. Out of the 27 patients, four patients had pain at rest and two patients had pain at movement. The authors discontinued the trial due to the non-availability of trial medications.

In an interesting study by Martin *et al.*,[41] the authors randomized 60 patients who were treated for chronic neuropathic pain with 0.4–0.5 mg/kg IV ketamine infusion (over 2 hours) into two groups. In one group, patients received 90 mg/day oral dextromethorphan, in another group the patients received 20 mg/day oral memantine, and in the third group, patients received a placebo, all for 12 weeks. This limited sample-sized study concluded on analysis of various outcomes that oral dextromethorphan temporarily extended ketamine pain relief over one month, with improved cognition in patients who received memantine. This is an interesting premise in postoperative patients in which intraoperatively the patients receive an analgesic dose of ketamine and postoperatively, the planned NMDA antagonist for an extended duration, depending on the type of surgery.

Limitations

There were several limitations in this review. The number of RCTs was less thus leading to an overall small sample size. Although in all studies, patients received a single dose of memantine, the dose was not consistent. Moreover, the type of surgeries for which memantine was investigated was of varying severity which could have affected overall pain assessment. A pooled analysis of pain scores was possible for up to 6 hours only and not beyond due to methodological limitations. Several outcomes like patient satisfaction, quality of recovery, length of stay, and cost of hospitalization were not investigated in the included studies. Memantine is a safe NMDA-receptor antagonist with negligible adverse effects and therefore well-designed and adequately powered studies need to be conducted to encourage its use as an opioid-sparing premedication. However, the strength of this review is that all the studies included are RCTs with a low bias.

Conclusion

This systematic review and meta-analysis demonstrate better pain relief postoperatively with a preoperative single dose memantine premedication at 2 and 6 hours with comparable adverse events with a placebo. There is insufficient evidence at present to advocate the routine use of memantine as a premedication before various surgeries. Future studies with robust methodology and adequate sample size need to explore the role of memantine premedication for various surgeries.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mitra S, Carlyle D, Kodumudi G, Kodumudi V, Vadivelu N. New advances in acute postoperative pain management. Curr Pain Headache Rep 2018;22:35.
2. Gerbershagen HJ, Aduckathil S, van Wijck AJM, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: A prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013;118:934–44.
3. Johnson Q, Borsheski RR, Reeves-Viets JL. Pain management mini-series. Part I. A review of management of acute pain. Mo Med 2013;110:74-9.
4. Stephan BC, Parsa FD. Avoiding opioids and their harmful side effects in the postoperative patient: Exogenous opioids, endogenous endorphins, wellness, mood, and their relation to postoperative pain. Hawaii J Med Public Health 2016;75:63-7.
5. Jewett BE, Thapa B. Physiology, NMDA receptor. 2022 Dec 11. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
6. Zhou HY, Chen SR, Pan HL. Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. Expert Rev Clin Pharmacol 2011;4:379-88.
7. Bozic M, Valdivielso JM. The potential of targeting NMDA receptors outside the CNS. Expert Opin Ther Targets 2015;19:399–413.
8. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: A review. Anesth Analg 2003;97:1108–16.
9. Silverstein WK, Juurlink DN, Zipursky JS. Ketamine for the treatment of acute pain. CMAJ 2021;193:E1663. doi: 10.1503/cmaj. 210878.
10. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, *et al*. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43:456–66.
11. Karlow N, Schlaepfer CH, Stoll CRT, Doering M, Carpenter CR, Colditz GA, *et al*. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the emergency department. Acad Emerg Med 2018;25:1086-97.
12. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, *et al*. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev 2018;12:CD012033.
13. Nair AS, Sahoo RK. Efficacy of memantine hydrochloride in neuropathic pain. Indian J Palliat Care 2019;25:161-2.
14. Kurian R, Raza K, Shanthanna H. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. Eur J Pain 2019;23:1234-50.
15. Morel V, Joly D, Villatte C, Dubray C, Durando X, Daulhac L, *et al*. Memantine before mastectomy prevents post-surgery pain: A randomized, blinded clinical trial in surgical patients. PLoS One 2016;11:e0152741.
16. Rahimzadeh P, Imani F, Faiz S, Mohsenpour A, Nasiri A. The effect of premedication with oral memantine on pain control after orthopedic surgery. J Anesth Pain 2013;3:216-22.
17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

19. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020. Available from: http://revman.cochrane.org. [Last accessed on 2023 Apr 09].
20. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi: 10.1136/bmj.d5928.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
22. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. J Clin Epidemiol 2001;54:1046-55.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
24. Taheri M, Mirkheshti A, Manafi Rasi A, Adili Y. Comparing the use of memantine with dextromethorphan and placebo to reduce pain before orthopedic surgery. J Cell Mol Anesth 2017;2:157-64.
25. Rahimzadeh P, Imani F, Nikoubakht N, Koleini Z, Faiz SHR, Sayarifard A. A comparative study on the efficacy of oral memantine and placebo for acute postoperative pain in patients undergoing dacryocystorhinostomy (DCR). Anesth Pain Med 2017;7:e45297.
26. Karri SR, Jayaram K, Kumar A, Durga P. Comparison of efficacy of gabapentin and memantine premedication in laparoscopic cholecystectomies for postoperative pain relief - A randomised placebo controlled trial. Indian J Anaesth 2021;65:539-44.
27. Thompson T, Whiter F, Gallop K, Veronese N, Solmi M, Newton P, *et al*. NMDA receptor antagonists and pain relief: A meta-analysis of experimental trials. Neurology 2019;92:e1652-62.
28. Kreutzwiser D, Tawfic QA. Expanding Role of NMDA receptor antagonists in the management of pain. CNS Drugs 2019;33:347-74.
29. De Kock MF, Lavand'homme PM. The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. Best Pract Res Clin Anaesthesiol 2007;21:85-98.
30. Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of ketamine in acute postoperative pain management: A narrative review. Biomed Res Int 2015;2015:749837.
31. Ghojazadeh M, Sanaie S, Paknezhad SP, Faghih SS, Soleimanpour H. Using ketamine and propofol for procedural sedation of adults in the emergency department: A systematic review and meta-analysis. Adv Pharm Bull 2019;9:5-11.
32. Khajavi M, Emami A, Etezadi F, Safari S, Sharifi A, Shariat Moharari R. Conscious sedation and analgesia in colonoscopy: Ketamine/Propofol combination has superior patient satisfaction versus fentanyl/propofol. Anesth Pain Med 2013;3:208-13.
33. Bell RF, Kalso EA. Ketamine for pain management. Pain Rep 2018;3:e674.
34. King MR, Ladha KS, Gelineau AM, Anderson TA. Perioperative dextromethorphan as an adjunct for postoperative pain: A meta-analysis of randomized controlled trials. Anesthesiology 2016;124:696-705.
35. Yazdani J, Aghamohamadi D, Amani M, Mesgarzadeh AH, Maghbooli Asl D, Pourlak T. Effect of preoperative oral amantadine on acute and chronic postoperative pain after mandibular fracture surgery. Anesth Pain Med 2016;6:e35900. doi: 10.5812/aapm. 35900.
36. Snijdelaar DG, Koren G, Katz J. Effects of perioperative oral amantadine on postoperative pain and morphine consumption in patients after radical prostatectomy: Results of a preliminary study. Anesthesiology 2004;100:134-41.
37. Asadollah S, Vahdat M, Yazdkhasti P, Nikravan N. The effect of magnesium sulphate on postoperative analgesia requirements in gynecological surgeries. Turk J Obstet Gynecol 2015;12:34-7.
38. Peng YN, Sung FC, Huang ML, Lin CL, Kao CH. The use of intravenous magnesium sulfate on postoperative analgesia in orthopedic surgery: A systematic review of randomized controlled trials. Medicine (Baltimore) 2018;97:e13583.
39. Schley M, Topfner S, Wiech K, Schaller HE, Konrad CJ, Schmelz M, *et al*. Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. Eur J Pain 2007;11:299-308.
40. Shanthanna H, Turan A, Vincent J, Saab R, Shargall Y, O'Hare T, *et al*. N-Methyl-D-aspartate antagonists and steroids for the prevention of persisting post-surgical pain after thoracoscopic surgeries: A randomized controlled, factorial design, international, multicenter pilot trial. J Pain Res 2020;13:377-87.
41. Martin E, Sorel M, Morel V, Marcaillou F, Picard P, Delage N, *et al*. Dextromethorphan and memantine after ketamine analgesia: A randomized control trial. Drug Des Devel Ther 2019;13:2677-88.

Supplementary File 1

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1,2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5,6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 8
Study characteristics	17	Cite each included study and present its characteristics.	Page 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 9-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8,9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12
	23b	Discuss any limitations of the evidence included in the review.	Page 14
	23c	Discuss any limitations of the review processes used.	Page 12,14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	--
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	In title page.
Competing interests	26	Declare any competing interests of review authors.	In title page.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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