Original Article

Comparison of efficacy of gabapentin and memantine premedication in laparoscopic cholecystectomies for postoperative pain relief – A randomised placebo controlled trial

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ABSTRACT

Background and Aims: The multiplicity of the mechanisms of the pain in laparoscopic cholecystectomy inclines us to the usage of multimodal analgesia. Gabapentin is known for its analgesic efficacy when given as premedication in many surgeries. N-methyl-D-aspartate (NMDA) antagonists are used for both acute and chronic pain, but the use of memantine in the perioperative period is less studied. The aim of this randomised controlled study was to subjectively and objectively compare postoperative pain relief using gabapentin, memantine and placebo as premedication. **Methods:** Sixty-six patients posted for laparoscopic cholecystectomy were randomised into three groups. During the preoperative assessment, the baseline threshold and tolerance values of pain were measured using an algesiometer. Patients were pre-medicated with oral gabapentin 600 mg or memantine 20 mg or placebo an hour before surgery. Following extubation, pain scores were reassessed (both subjectively and objectively) along with Ramsay sedation scores at different time intervals for 4 h postoperatively. **Results:** Gabapentin group had lower Numerical Rating Scale scores at 15 min and 1 h postoperatively when compared to the other two groups. Memantine group had a longer time for the first request for rescue analgesia (50.53 min) compared to gabapentin and placebo. The objective assessment of pain with analgesiometer showed no statistical significance between the three groups for both threshold and tolerance values. Ramsay sedation scores were higher in the gabapentin group compared to the other two. **Conclusion:** Gabapentin provides better postoperative pain relief compared to memantine when given as single dose premedication for laparoscopic cholecystectomy.

Key words: Analgesia, cholecystectomy, gabapentin, laparoscopic, memantine, pain, postoperative

INTRODUCTION

Acute pain after laparoscopic cholecystectomy is a combination of somatic incisional pain, visceral deep intra-abdominal pain, and referred visceral shoulder pain. A combination of opioid and non-opioid analgesic drugs improves analgesic efficacy and reduces the side effects of individual drugs.[1]

Gabapentin is used in laparoscopic cholecystectomy due to opioid-saving effect and less incidence of nausea and vomiting.[1,2] N--methyl-D-aspartate (NMDA) receptor antagonists such as memantine have emerged in the treatment of acute post-operative pain as they have analgesic properties and excellent safety records as quoted in few studies.[3-7]

The primary objective of this study was to compare the effect of gabapentin, memantine and placebo on acute post-operative pain relief. The secondary objectives were to assess time for the request of first analgesic, total analgesic dose, sedation and propofol requirement for induction.

METHODS

This randomised double-blinded controlled study was approved by our Institutional Ethics Committee and was registered in Clinical Trials Registry – India (CTRI/2018/07/014852). The study was conducted in a tertiary care centre from September 2018 to April 2019. Sixty-six patients of both gender aged 18–60 years of American Society of Anesthesiologists (ASA) physical status I or II, posted for elective laparoscopic cholecystectomy under general anaesthesia had participated in this study after informed consent. Patients with uncontrolled diabetes and hypertension, any cardiac or renal ailments, pregnancy, use of anticonvulsants, history of psychiatric disease or drug abuse and morbidly obese were excluded from the study.

The sedation level of patients during preoperative checkup was assessed using Ramsay sedation score (RSS). The patients were then premedicated with one of the three drugs as per the group they were assigned to, based on simple computer-generated randomisation. Patients were pre-medicated with oral gabapentin: Two 300 mg tablets (group G) or memantine: Two 10 mg tablets (group M) or two placebo tablets containing cornstarch (Group C) an hour before surgery by an anaesthesia technician. The sedation score was reassessed, and the patients were wheeled into the operating room.

The Wagner FDX-25 (Wagner Instruments, Greenwich, CT) is a handheld digital algesiometer with a 1-cm² round rubber tip. This tip was applied on the nail-bed of the third finger of the right hand, and the pressure was gradually increased at the rate of 10 kPa/sec. The patients were asked to inform when they started feeling pain (pain threshold) and when they could no longer tolerate the pain (pain tolerance). This objective assessment was done during pre-anesthetic assessment and an hour following premedication. All these assessments were done by an anaesthesia resident who was not aware of the pre-medication.

The patients were explained about the Numerical Rating Scale (NRS) during assessment for the

subjective evaluation of pain. NRS is a 10-point scale ranging from 0 to 10 with 0 considered as no pain and 10 as the worst imaginable pain.

In the operating room, standard monitors including noninvasive blood pressure, pulse oximetry, capnography, electrocardiogram were attached to the patient. An intravenous cannula was secured and connected to lactated ringer's solution. After administration of intravenous (IV) fentanyl 2 µg/kg, the patients were preoxygenated. General anaesthesia was induced with 1% propofol 1.5–2 mg/kg and 0.5 mg/kg of atracurium. The amount of propofol required for loss of verbal response of the patient was noted. The patients were intubated, and anaesthesia was maintained with air-oxygen mixture and isoflurane 1%–2%. Inj. ondansetron 4 mg was given to prevent post-operative nausea and vomiting. At the end of the surgery, the patients were given IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.01 mg/kg for reversing the effect of muscle relaxant. No local anaesthetic was given intraperitoneally or by infiltration. If the duration of surgery was beyond 2 h, or if the unplanned opening of the abdomen took place, the cases were excluded from the study.

Following extubation, the pain was assessed in the post-anaesthesia care unit, at 15 min, 1 h, 2 h and 4 h using NRS and algesiometer. The level of sedation was also recorded during these time intervals by the RSS. Any adverse events like dizziness, nausea and vomiting, headache, epigastric discomfort were noted. In the event of nausea and vomiting, ondansetron 4 mg IV was given.

When the NRS score was ≥4 in the postoperative period, the patients were treated with tramadol 1 mg/kg intramuscularly, and the time for the first request for analgesic was noted in the minutes following extubation. After 15 to 30 min, if the pain still persisted, 25 mg IV boluses of tramadol were given till pain relief (NRS ≤4), and total boluses given were noted.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) (version 20, IBM, Il). The sample size was calculated to be 22 patients in each group by *a priori* analysis, assuming the effect size of 0.4 between the three groups and power of 80% with an alpha of 0.05. The descriptive analysis of normally distributed continuous variables was expressed as mean with standard deviation (S.D). The

categorical variables were expressed as frequencies with percentages and compared using Chi-square test or Fisher Exact test when the expected cell values were <5. The statistical analysis for comparison of continuous variables between the groups was performed using Analysis of Variance (ANOVA) and a two-tailed significance of $P < 0.05$ was considered as a significant difference. Bonferroni *post-hoc* analysis was performed for variables with significant differences between the groups. A two-tailed P value of <0.05 was considered as a significant difference between the groups.

RESULTS

66 patients were assessed for eligibility, randomised and assigned to three groups. 22 patients were allocated to each group, followed up and analysed. All patients were statistically comparable in demographic data including age, height, weight and body mass index (BMI) [Table 1].

There was a significant difference between the groups in NRS scores at 15 min and 1 h postoperatively [Table 2]. But there was no difference between any groups at 2 h and 4 h after extubation. NRS scores were low in the gabapentin group at 15 min and 1 h when compared to the placebo group. The memantine group showed a statistically significant difference in comparison with the placebo group at 15 min following extubation.

Overall, the threshold value was higher in patients in the gabapentin group than in other groups though it was not statistically significant. [Figure 1]. There was no statistically significant difference between baseline tolerance values of algesiometer between the three groups. Even the tolerance values were on the higher side in the gabapentin group than the other two, but there was no statistical significance.

Sedation was more in the gabapentin group compared to placebo and memantine at 15 min, 1 h, 2 h and 4 h post-operatively with P values < 0.5. By posthoc analysis, there was a statistically significant difference at these time points between the gabapentin and placebo group, whereas the memantine group was comparable with the other two [Table 3]. The propofol requirement in Groups C,G and M was 79.55 ± 12.14 mg, 77.73 ± 14.77 mg and 79.09±10.19 mg respectively with $P = 0.88$. The propofol requirement in mg/kg in the Groups C,G and M was 1.31 ± 0.28, 1.27 ± 0.30 and 1.25 ± 0.29 respectively with $P = $

0.75. Overall, the requirement of propofol among the three groups was comparable.

The number of doses of rescue analgesia required and the total dose needed over 4 h was significantly less in the gabapentin group than the memantine and placebo groups. Almost 23% of patients in the placebo group needed more than two doses. About 63% of patients in the gabapentin group did not need rescue analgesia compared to only 14% of patients in the memantine group. The total dose requirement of tramadol was considerably low in the gabapentin group when compared to the other two [Table 4].

The time of request for rescue analgesia was significantly high in the memantine group when compared to the other two. The Kaplan Meyer survival analysis [Figure 2] for the time of the first dose of rescue analgesia shows that almost 50% of patients in the placebo group asked for analgesia by 10 min in the post-operative period. In the gabapentin group, only 8 patients had rescue analgesics within the first 4 h. In the memantine group, most patients needed tramadol after 50 min. No adverse events were noted among the three groups.

DISCUSSION

The results of this study showed that gabapentin is better than placebo and memantine for acute post-operative pain relief. Memantine also showed superiority over the placebo group for post-operative

Table 1: Comparison of demographic data between three groups				
Variable	Group C (Mean±SD)	Group G (Mean±SD)	Group M (Mean±SD)	P
Age (yrs)	38.91±12.12	44.59±13.49	36.18±9.5	0.06
Height (cm)	154.91±5.94	157.27±7.49	155.77±5.78	0.47
Weight (kg)	62.23±13.07	62.77±12.88	65.32±11.87	0.68
BMI (kg/m²)	24.03±1.86	24.78±2.39	24.29±1.79	0.46
Gender (M/F) as numbers	4/18	12/10	6/16	0.102
ASA I/II as numbers	16/6	15/7	17/5	0.802

BMI-Body mass index; ASA-American Society of Anesthesiologists; M-Male; F-Female; SD-Standard deviation

Table 2: Comparison of Numerical Rating Scale scores between three groups				
Time	Group C (Mean±SD)	Group G (Mean±SD)	Group M (Mean±SD)	P
15 min	4.82±1.25	3.14±1.16^	3.82±1.46*	0.00
1 h	3.5±1.33	2.5±0.80^	3.32±1.46	0.02
2 h	2.73±1.07	2.09±0.86	2.32±1.08	0.11
4 h	2.09±0.86	1.59±0.66	1.91±0.92	0.13

^Significant difference between gabapentin and placebo. *Significant difference between memantine and placebo. SD-Standard deviation
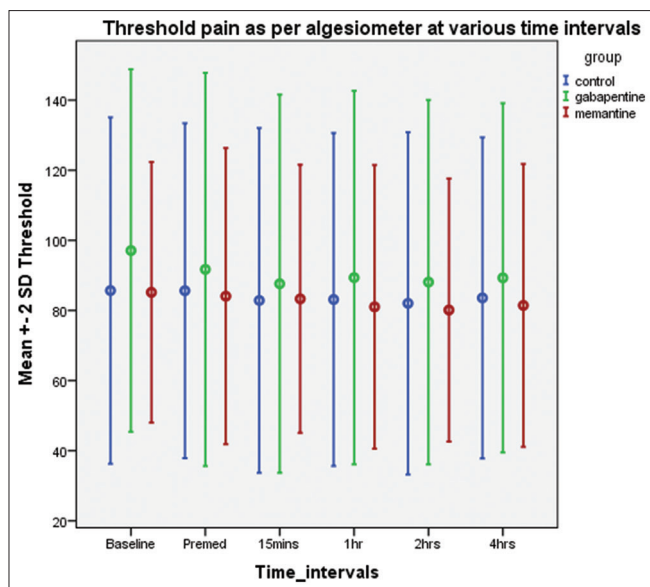
Figure 1: Comparison of pain threshold values of algesiometer among three groups

Figure 2: Kaplan Meyer survival analysis for time for first dose rescue analgesic

Table 3: Comparison of Ramsay Sedation Scale (RSS) score between three groups			
Time	Group C Median (IQL)	Group G Median (IQL)	Group M Median (IQL)	P
Premedication	0 (0-0)	0 (0-0)	0 (0-0)	0
15 min	0 (0-1.25)	2.5 (0-3.0)^	2 (0-3.0)	0.04
1 h	0 (0-1.25)	2.5 (0-3.0)^	2 (0-3.0)	0.03
2 h	0 (0-2.0)	2 (0-3.0)^	0 (0-2.0)	0.03
4 h	0 (0-2.0)	1 (0-3.0)^	0 (0-2.0)	0.01

^Significant difference between gabapentin and placebo. IQL-Interquartile

pain relief. A meta-analysis by Wang *et al.* had concluded that gabapentin reduced pain scores at 12 and 24 h post-operatively in laparoscopic cholecystectomies.[1] In the studies included, the dosage varied from 300 to 1200 mg of gabapentin predominantly given as a single pre-medication dose only. The adverse events of gabapentin are dose-dependent as per the metaanalysis, and hence we used 600 mg of gabapentin.[1] Both our study drugs did not have much drug interactions and lack reaction with hepatic enzymes and plasma proteins. Memantine can be used in doses starting from 5 mg to 30 mg with a gradual increase over a week, and we used 20 mg for this study as per a previous study.[6]

The NRS score showed a decreasing trend in all the three groups over 2 and 4 h post-operatively and was statistically insignificant. This might have been because of the rescue analgesia which was given earlier in the placebo and the gabapentin group (25 min and 39.44 min, respectively). Memantine group, on the other hand, had a longer time for the first request for
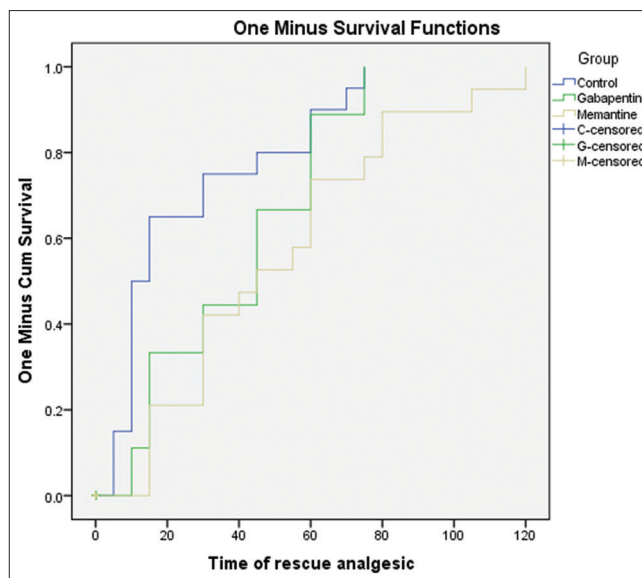
rescue analgesia (50.53 min). Rahimzadeh *et al.*[6] found that when memantine was administered just before induction, visual analogue scores were less at 1 h, 2 h and 6 h postoperatively in dacrocystorhinostomy, and this might have been because of the shorter duration of the procedure. In a study by Taheri *et al.*[8] on the administration of memantine in orthopaedic surgeries, the time of first dose rescue analgesia was prolonged in comparison with dextromethorphan and placebo.

The number of doses of rescue analgesia required within the first 4 h postoperatively were significantly less in the gabapentin group. This might have been due to time-dependent effect of memantine which could be related to several factors. Firstly, the impact of neural transmission via NMDA receptors on pain maintenance may decrease over time. Another reason for the relatively less analgesic effect of memantine might be because of its moderate affinity, strong voltage dependency and rapid unblocking kinetics.[9] Hence, gabapentin has a better analgesic profile than memantine.

The advantage of memantine is that, by inducing sensori-limbic dissociation, it not only protects against pain sensitisation but also against emotional alteration due to pain by its action at the hippocampus.[9] So, inspite of its limitations due to time-limited effectiveness, it can still be considered in pre-medication for short--duration surgeries for augmenting immediate postoperative analgesia.

Table 4: Comparison of the number of doses and total dose of rescue analgesia				
	Group C Mean±SD	Group G Mean±SD	Group M Mean±SD	*P*
Number of Doses of rescue analgesia	1.55±0.96	0.45±0.59^#	1.18±0.73	0.00
Total dose (tramadol in mg)	61.36±28.58	21.59±27.05^#	51.14±24.97	0.00
Time to rescue analgesia as mean (95% CI)	25.0 (14.69-35.30)	39.44 (24.25-54.63)	50.53 (36.58-64.46)*#	0.00

^Significant difference between the placebo group and Gabapentin group, #significant difference between Gabapentin group and Memantine group, *significant difference between the placebo group and Memantine group. CI-Confidence interval; SD-Standard deviation

The total requirement of rescue analgesia or tramadol consumption was significantly low in the gabapentin group than memantine or placebo. To date, there are no studies comparing gabapentin and memantine, but gabapentin has been shown to reduce opioid consumption in several studies.[10-12] The patients on memantine also had lesser tramadol consumption than the placebo group, but this was not statistically significant. Two studies noted that opioid consumption is reduced with memantine in the post-operative period.[6,8] In our study, a single premedication dose reduced tramadol dose requirement only to some extent which is less compared to gabapentin. Few randomised placebo-led trials on memantine have used it over 2 to 3 weeks beginning before surgery with good results of post-operative analgesia.[7] So, in a scheduled surgery, prophylactic oral treatment of memantine when given days in advance might be useful in preventing central sensitisation before incision.

The time to the first dose of rescue analgesia postoperatively was prolonged in the memantine group when compared to the gabapentin group, whereas the number of doses of postoperative rescue analgesia was high in the memantine group as opposed to the gabapentin group. A similar finding was observed in orthopaedic surgeries, when memantine was compared with dextromethorphan and placebo.[8] This discrepant finding of time to first dose rescue analgesia being prolonged, whereas the number of doses of rescue analgesic being high in our study might partly be attributed to the sensori-limbic dissociation induced by memantine.

The objective assessment of pain with algesiometer showed no statistical significance between the groups for both threshold and tolerance values. The algesiometer readings were taken by a single observer to avoid inter-observer variability. Many studies have proven that participants are reliable in making a consistent verbal report of their own threshold value with algesiometer when repeated measurements are done.[13] Sensitisation of the tissue in the repeatedly stimulated area might produce an insignificant difference in the measured variables as in the study by Matin Luginbühl *et al.*[14] Also, algesiometer measures systemic pain and analgesia at the site of testing and not the affected site.[15] That may be the reason for unchanged values of threshold and tolerance over a period of time, even after surgical infliction of pain. Objective assessment tool for quantifying pain threshold might not be useful to quantify the general pain threshold at a different site than the surgical site of injury. Assessment for general pain might not be useful for determining the analgesic requirements of postoperative pain as has been noted in our study.

RSSs were higher in the gabapentin group than the other two in our study. At the end of 4 h post-operatively, the patients in the memantine group and placebo group were fully awake compared to gabapentin. This is because of the sedative effect of gabapentin which has been described by Nain *et al.*[16] In fast-track surgeries, early recovery from anaesthetic effects is needed to prevent the risk of aspiration, early mobility and early enteral feeding. In this aspect, memantine is preferable over gabapentin as the patients become fully awake by 1 h post-operatively.

As per our study, when propofol total dose and dose/kg were taken into consideration, there was no significant difference between the three groups. Considering the hypnotic effect of propofol, which is mediated through gamma aminobutyric acid (GABA) receptor, administration of gabapentin can probably decrease the induction dose of propofol. There are equivocal results with respect to the propofol requirement in studies which used gabapentinoids as premedication.[17] Though the modes of action are different, the NMDA receptor antagonist, ketamine has an additive influence on propofol.[18] But in our study, both the premedication drugs did not reduce the dose requirement of propofol. The requirement of propofol would be more when targeted to entropy level <50 as opposed to clinical criteria with its antecedent side effects. We preferred using the loss of response to verbal command as the end point for induction rather than entropy as proven by certain studies.[19]

The limitations of this study are that only a single preoperative dose of the drugs was used to assess

their efficacy, and therefore the results cannot be extrapolated to multidose regimens. The study was conducted for 4 h post-operatively, and hence the side effect profile of the adjuvant drugs was not studied for a prolonged period of time.

CONCLUSION

In conclusion, gabapentin is preferable as an adjuvant analgesic for laparoscopic cholecystectomy compared to memantine when given as a single preoperative dose. Using an algesiometer for quantifying general pain threshold might not be useful for evaluating and treating acute post-operative pain, which is probably better assessed by subjective methods.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients/have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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