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Comparative Evaluation of Gabapentin and Memantine for Postoperative Pain Relief in Laparoscopic Cholecystectomy: Correlation with Pupillary Reflex Dilation Using Pupillometry

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KEYWORDS

Gabapentin, Memantine, Postoperative Pain, Laparoscopic Cholecystectomy, Pupillometry, Visual Analogue Scale.

ABSTRACT:

Background: Effective postoperative pain management is crucial for enhanced recovery after laparoscopic cholecystectomy. Gabapentin and memantine, acting via different mechanisms, may reduce pain and opioid requirements. Pupillometry provides an objective measure of nociception.

Objective: To compare the analgesic efficacy of gabapentin and memantine for postoperative pain relief and correlate pain scores with pupillary reflex dilation.

Methods: In this prospective, randomised, controlled study, 120 patients undergoing elective laparoscopic cholecystectomy were allocated into three groups: gabapentin 900 mg (Group G, n=40), memantine 30 mg (Group M, n=40), and control (Vitamin B-complex, Group C, n=40). Postoperative pain was assessed using the Visual Analogue Scale (VAS) at multiple time points up to 24 hours. Pupillary reflex dilation was measured intraoperatively. Rescue analgesic requirements and adverse effects were recorded.

Results: Both gabapentin and memantine significantly reduced VAS scores and total rescue analgesic use compared to control ($p<0.05$). Gabapentin showed slightly superior analgesia with earlier onset and longer duration. Pupillometry correlated positively with VAS scores at all time points (Spearman's $r=0.40–0.70$, $p<0.05$). Adverse effects were minimal and comparable between groups.

Conclusion: Preoperative gabapentin and memantine effectively reduce postoperative pain and rescue analgesic consumption, with gabapentin demonstrating slightly greater efficacy. Pupillometry is a reliable objective tool for nociception assessment in perioperative settings.

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INTRODUCTION

Postoperative pain remains a significant concern following laparoscopic cholecystectomy, affecting patient recovery, satisfaction, and hospital stay [1]. Effective management of postoperative pain is essential to reduce complications, enhance early mobilisation, and improve overall outcomes [2]. Traditionally, opioids have been the mainstay for controlling postoperative pain; however, their use is associated with adverse effects such as nausea, vomiting, respiratory depression, and delayed recovery [3].

Gabapentin, a structural analogue of gamma-aminobutyric acid (GABA), has gained attention for its analgesic and antihyperalgesic properties in perioperative pain management [4]. It acts by modulating voltage-gated calcium channels in the central nervous system, thereby reducing nociceptive transmission [5]. Clinical studies have demonstrated that preoperative administration of gabapentin can reduce postoperative pain scores and opioid consumption, although results vary depending on surgical type, dosage, and timing [6,7].

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been explored as an adjuvant for postoperative pain relief [8]. By inhibiting excitatory glutamatergic neurotransmission, memantine may prevent central sensitisation and reduce the development of acute and chronic postoperative pain [9]. Preliminary studies suggest that memantine may improve analgesia and reduce opioid requirements in various surgical procedures [10,11].

Objective measures of pain, such as pupillometry, offer an innovative approach to assessing nociceptive response and analgesic efficacy [12]. Pupillary reflex dilation correlates with sympathetic activation and has been validated as a reliable indicator of intraoperative and postoperative pain [13]. Combining pharmacological interventions like gabapentin and memantine with objective monitoring can provide more accurate insights into analgesic effectiveness.

This study aims to perform a comparative evaluation of gabapentin and memantine for postoperative pain relief in patients undergoing laparoscopic cholecystectomy and to correlate their analgesic effects with pupillary reflex dilation measured using pupillometry.

MATERIALS AND METHODS

Place of Study:
The study was conducted in the Department of Anesthesiology and Critical Care, Integral Institute of Medical Sciences and Research (IIMS&R), Lucknow, Uttar Pradesh.

Study Design:
This was a prospective, randomised, controlled clinical study.

Study Size:
The sample size was determined using the rule of thumb method. A total of 120 patients were enrolled and randomised into three groups:

- Group A (n=40): Received oral Gabapentin 900 mg
- Group B (n=40): Received oral Memantine 30 mg
- Group C (n=40, Control): Received oral Vitamin B-complex

Study Period:
The study was conducted over 18 months following clearance from the ethics committee.

Inclusion Criteria

- Patients aged between 18–60 years
- American Society of Anesthesiologists (ASA) Grade I and II
- Patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia

Exclusion Criteria

- Patient refusal
- ASA Grade III and IV
- Conversion of laparoscopic to open cholecystectomy
- Known allergy to study drugs
- Morbid obesity

Methodology

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All eligible patients were randomly allocated into three equal groups (n=40 each) using computer-generated randomisation.

- Group A: Received oral Gabapentin 900 mg
- Group B: Received oral Memantine 30 mg
- Group C (Control): Received oral Vitamin B-complex

All patients were visited a day before surgery for pre-anaesthetic evaluation and given standard preoperative advice. Anaesthesia induction was carried out using the standard institutional protocol.

Hemodynamic Monitoring:
Heart rate (HR), non-invasive blood pressure (NIBP), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) were recorded at the following time intervals:

- Pre-induction
- Post-induction
- Pre-incision
- Post-incision
- Every 30 minutes until extubation

Pain Assessment:
Postoperative pain was evaluated using the 10-point Visual Analogue Scale (VAS) at the following time intervals:

- 30 minutes (T1)
- 2 hours (T2)
- 4 hours (T3)
- 6 hours (T4)
- 12 hours (T5)
- 24 hours (T6)

The duration of effective analgesia was defined as the time from completion of surgery to the first rescue analgesic requirement (VAS > 4). Paracetamol 1 g IV (15 mg/kg body weight) was administered as a rescue analgesic. The total number of rescue doses required in the first 24 hours was also documented.

Adverse Effects:
Nausea and vomiting were noted and managed with intravenous Ondansetron 0.1 mg/kg. Other complications, if any, were recorded.

Statistical Analysis

All collected data were entered into Microsoft Excel and analysed using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as numbers and percentages. Intergroup comparisons were made using the Chi-square test for categorical variables and ANOVA for continuous variables. A p-value <0.05 was considered statistically significant, and p <0.001 was considered highly important.

RESULTS AND OBSERVATIONS;

Table 1: Baseline Characteristics of enrolled patients among the groups.

Parameter		**Group G [n=40]**	**Group M [n=40]**	**Group C [n=40]**	**p-value**
Age (years)		**42.35 ± 10.50**	**41.82 ± 9.75**	**43.10 ± 11.25**	**F=0.1496 p=0.8612**
Gender	**Male**	**22 (55.0%)**	**21 (52.5%)**	**20 (50.0%)**	**X=0.2005 p=0.9046**
	Female	**18 (45.0%)**	**19 (47.5%)**	**20 (50.0%)**	
BMI (kg/m²)		**26.24 ± 3.45**	**25.93 ± 3.78**	**27.01 ± 4.22**	**F=0.8434 p=0.4329**
	I	**25 (62.5%)**	**26 (65.0%)**	**24 (60.0%)**	

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ASA Grade	**II**	**15 (37.5%)**	**14 (35.0%)**	**16 (40.0%)**	**X=0.2133 p=0.8988**

Table 2: Patient History and Preoperative Evaluation among the groups.

Parameter		**Group G [n=40]**	**Group M [n=40]**	**Group C [n=40]**	**p-value**
Family History	**Yes**	**3 (7.5%)**	**2 (5.0%)**	**3 (5.0%)**	**X=0.2679 p=0.8747**
	No	**37 (92.5%)**	**38 (95.0%)**	**37(92.5%)**	
Personal History	**Smoking**	**12 (30.0%)**	**10 (25.0%)**	**14 (35.0%)**	**X=0.952 p=0.621**
	Alcohol	**13 932.5%)**	**8 (20.0%)**	**11 (27.5%)**	**X=1.619 p=0.445**

Table 3: General and Systemic Examination among the groups.

Parameter	**Group G [n=40]**	**Group M [n=40]**	**Group C [n=40]**	**p-value**
Pallor	**2 (5.0%)**	**1 (2.5%)**	**0 (0.0%)**	**X=11.38 p=0.6564**
Icterus	**0 (0.0%)**	**1 (2.5%)**	**1 (2.5%)**	
Cyanosis	**1 (2.5%)**	**0 (0.0%)**	**0 (0.0%)**	
Clubbing	**1 (2.5%)**	**0 (0.0%)**	**1 (2.5%)**	
Edema	**1 (2.5%)**	**2 (5.0%)**	**0 (0.0%)**	
Lymphadenopathy	**1 (2.5%)**	**0 (0.0%)**	**0 (0.0%)**	
PR (bpm) (Abnormal)	**1 (2.5%)**	**0 (0.0%)**	**0 (0.0%)**	
BP (mmHg) (Abnormal	**1 (2.5%)**	**0 (0.0%)**	**0 (0.0%)**	
RR (breaths/min) (Abnormal)	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	

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Table 4: Systemic Examination and Airway Assessment among the groups.

Parameter		Group G [n=40]	Group M [n=40]	Group C [n=40]	p-value
CVS (Abnormal)		0 (0.0%)	0 (0.0%)	0 (0.0%)	--
CNS (Abnormal)		0 (0.0%)	0 (0.0%)	0 (0.0%)	--
RS (Abnormal)		0 (0.0%)	0 (0.0%)	0 (0.0%)	--
P/A (Abnormal)		0 (0.0%)	0 (0.0%)	0 (0.0%)	--
Airway Assessment (Mallampati)	I	28 (70.0%),	27 (67.5%),	29 (72.5%),	X=0.2381 p=0.8878
	II	12 (30.0%)	13 (32.5%)	11 (27.5%)	

Table 5: Investigations and Premedication among the groups.

Parameter		Group G [n=40]	Group M [n=40]	Group C [n=40]	p-value
CBC		12.45 ± 1.32	12.78 ± 1.45	12.35 ± 1.41	F=1.042 p=0.3561
LFT	SGOT	24.53 ± 3.21	25.12 ± 3.45	23.91 ± 3.14	F=1.370 p=0.2581
	SGPT	26.74 ± 2.92	27.21 ± 3.03	25.83 ± 2.85	F=2.287 p=0.1061
KFT	Urea	22.34 ± 3.41	23.12 ± 3.72	21.94 ± 3.23	F=1.204 p=0.3037
	Creatinine	0.89 ± 0.12	0.92 ± 0.13	0.87 ± 0.11	F=1.751 p=0.1781
FBS/RBS		90.54 ± 5.63	92.14 ± 5.82	89.87 ± 5.41	F=1.721 p=0.1833
ECG (Abnormal)		0 (0.0%)	0 (0.0%)	0 (0.0%)	--
Chest X-ray (Abnormal)		0 (0.0%)	0 (0.0%)	0 (0.0%)	--

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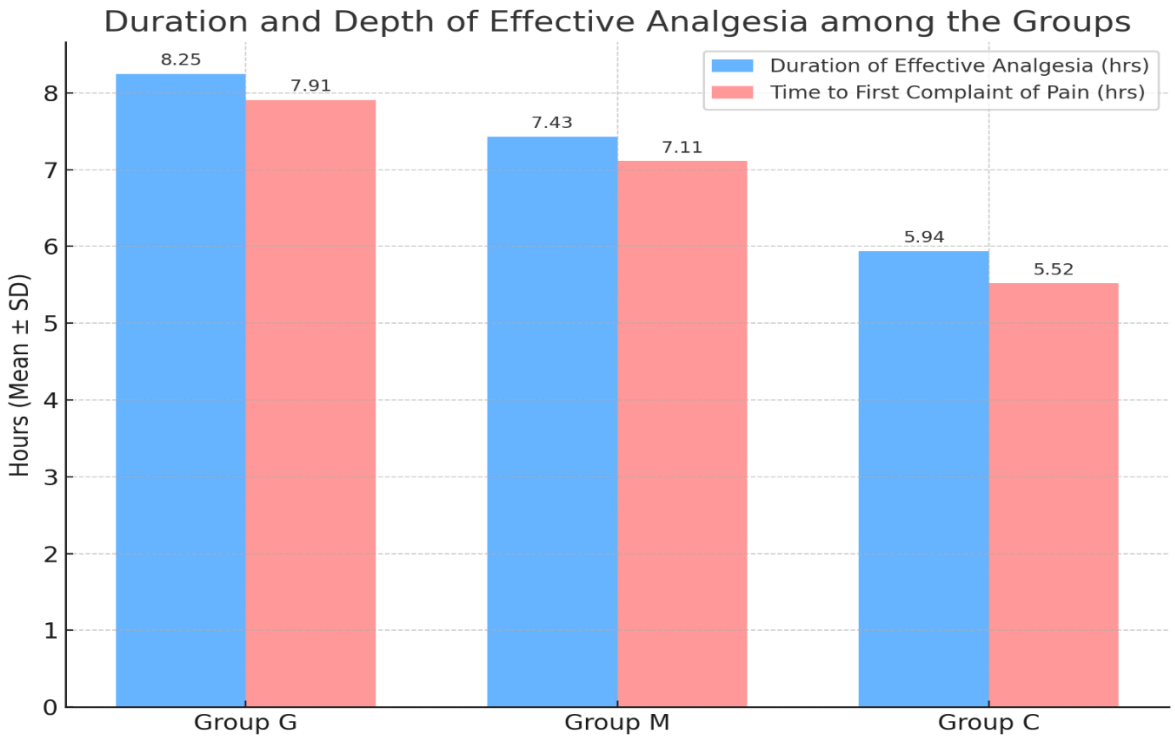

Figure 1: Duration and Depth of Effective Analgesia among the groups.

Table 6: Ramsay Sedation Score at Different Follow-Ups among the groups.

Time Point	Group G [n=40]	Group M [n=40]	Group C [n=40]	p-value
T1 (30 min)	2.85 ± 0.72	2.52 ± 0.66	2.15 ± 0.53	F=11.92 **p<0.0001***
T2 (2 Hr)	2.73 ± 0.66	2.43 ± 0.57	2.06 ± 0.57	F=12.45 **p<0.0001***
T3 (4 Hr)	2.52 ± 0.53	2.36 ± 0.53	1.97 ± 0.46	F=12.42 **p<0.0001***
T4 (6 Hr)	2.36 ± 0.54	2.14 ± 0.43	1.83 ± 0.46	F=12.36 **p<0.0001***
T5 (12 Hr)	2.07 ± 0.43	1.93 ± 0.42	1.62 ± 0.35	F=13.15 **p<0.0001***
T6 (24 Hr)	1.88 ± 0.34	1.72 ± 0.31	1.53 ± 0.21	F=14.40 **p<0.0001***

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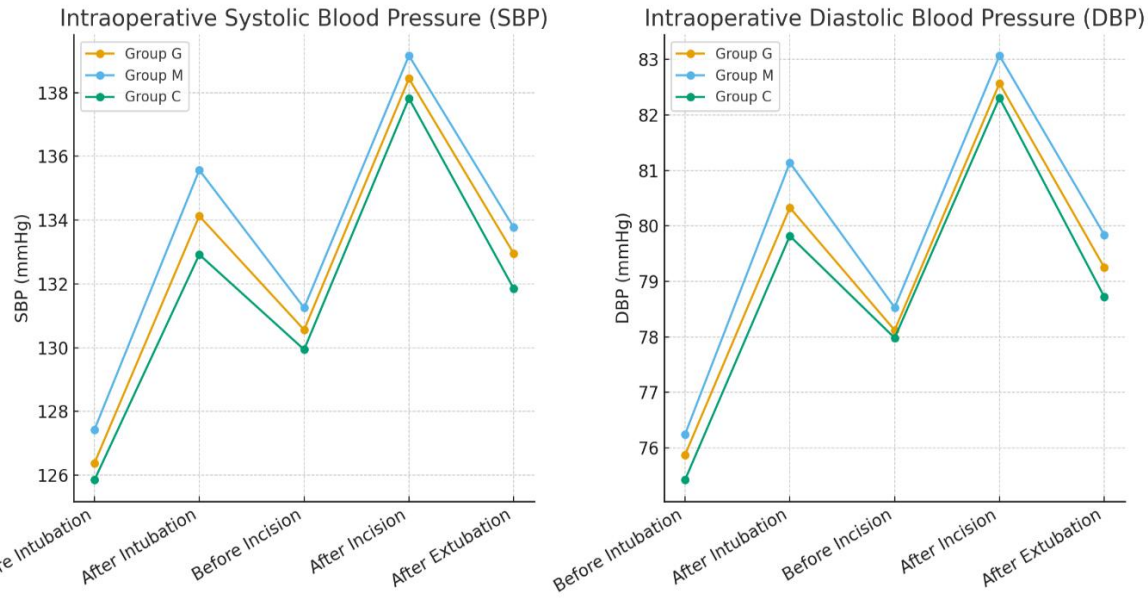
Table:7 Rescue Analgesic Use and Intraoperative Hemodynamic Parameters among the Groups

Parameter	Group G (n=40)	Group M (n=40)	Group C (n=40)	p-value
Rescue Analgesic Use (24 Hours)				
Total Rescue Analgesics Given (Doses)	2.12 ± 0.51	2.47 ± 0.65	3.17 ± 0.87	F=23.83, p<0.0001*
Incidence of Additional Rescue Analgesic Use	15 (37.5%)	18 (45.0%)	25 (62.5%)	X=5.273, p=0.0716
Intraoperative Heart Rate (bpm)				
Before Intubation	78.44 ± 8.22	79.13 ± 7.96	77.85 ± 8.42	F=0.2440, p=0.7839
After Intubation	85.21 ± 7.94	86.55 ± 8.17	84.35 ± 8.52	F=0.7288, p=0.4846
Before Incision	82.77 ± 6.53	83.22 ± 6.86	81.96 ± 7.07	F=0.3502, p=0.7053
After Incision	87.95 ± 8.37	88.72 ± 8.64	86.82 ± 8.93	F=0.4883, p=0.6149
After Extubation	84.36 ± 7.42	85.12 ± 7.77	83.65 ± 8.06	F=0.3595, p=0.6988



Figure;2 Intraoperative Systolic and Diastolic Blood Pressure Changes in Groups G, M, and C"

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Table 8: Intraoperative Hemodynamic Parameters [Mean Arterial Pressure (MAP) and SpO_2] among the groups

Time Point	MAP – Group G (mmHg)	MAP – Group M (mmHg)	MAP – Group C (mmHg)	MAP p-value	SpO_2 – Group G (%)	SpO_2 – Group M (%)	SpO_2 – Group C (%)	SpO_2 p-value
Before intubation	92.65 ± 8.22	93.14 ± 7.95	91.83 ± 8.46	0.7716	98.46 ± 1.03	98.22 ± 1.16	98.06 ± 1.24	0.2951
After intubation	98.46 ± 9.32	99.27 ± 9.08	97.85 ± 9.57	0.7922	97.82 ± 1.24	97.54 ± 1.36	97.25 ± 1.43	0.1708
Before incision	95.48 ± 7.87	95.87 ± 7.56	94.94 ± 8.07	0.8677	98.05 ± 1.12	97.82 ± 1.24	97.57 ± 1.37	0.2316
After incision	101.13 ± 10.24	101.73 ± 10.04	100.83 ± 10.44	0.9231	97.62 ± 1.33	97.47 ± 1.45	97.13 ± 1.54	0.3014
After extubation	97.08 ± 8.55	97.66 ± 8.36	96.43 ± 8.71	0.8128	97.26 ± 1.47	97.03 ± 1.55	96.78 ± 1.62	0.3851

Table 9: Intraoperative Pupillary Dilation and Postoperative Pain (VAS Score) among the Groups

Time Point	Group G [n=40]	Group M [n=40]	Group C [n=40]	p-value
Pupillary Dilation (mm)				
Before intubation	3.24 ± 0.55	3.14 ± 0.46	3.37 ± 0.62	0.1738
After intubation	5.46 ± 0.76	5.83 ± 0.86	6.13 ± 0.95	0.0030*
Before incision	4.72 ± 0.63	5.06 ± 0.76	5.37 ± 0.83	0.0008*
After incision	6.26 ± 0.98	6.57 ± 1.04	6.83 ± 1.18	0.0621
After extubation	4.12 ± 0.52	4.34 ± 0.63	4.56 ± 0.74	0.0101*
VAS Pain Score				
T1 (30 min)	5.83 ± 1.27	6.13 ± 1.34	6.43 ± 1.55	0.1605
T2 (2 hr)	4.72 ± 1.14	5.08 ± 1.25	5.45 ± 1.46	0.0443*
T3 (4 hr)	3.92 ± 1.07	4.23 ± 1.12	4.73 ± 1.37	0.0110*
T4 (6 hr)	3.14 ± 0.98	3.43 ± 1.05	4.02 ± 1.27	0.0020*
T5 (12 hr)	2.54 ± 0.71	2.84 ± 0.93	3.55 ± 1.12	<0.0001*
T6 (24 hr)	1.38 ± 0.53	2.31 ± 0.76	2.87 ± 1.03	<0.0001*

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Table 10: Spearman's Correlation between Visual Analogue Pain Score and Pupillometric Response

Spearman's r Correlation	Group G [n=40]			Group M [n=40]			Group C [n=40]		
Time Point	**r**	**95% CI**	**p-value**	**R**	**95% CI**	**p-value**	**r**	**95% CI**	**p-value**
T1 (30 min)	0.62	0.45 to 0.76	0.01*	0.65	0.48 to 0.78	0.009**	0.70	0.53 to 0.82	0.005**
T2 (2 Hr)	0.58	0.40 to 0.73	0.02*	0.60	0.42 to 0.74	0.015*	0.68	0.51 to 0.80	0.006**
T3 (4 Hr)	0.54	0.36 to 0.70	0.03*	0.57	0.38 to 0.72	0.02*	0.65	0.47 to 0.78	0.007**
T4 (6 Hr)	0.50	0.31 to 0.67	0.04*	0.53	0.34 to 0.69	0.025*	0.61	0.42 to 0.75	0.01*
T5 (12 Hr)	0.46	0.26 to 0.64	0.05*	0.50	0.29 to 0.66	0.03*	0.57	0.37 to 0.72	0.015*
T6 (24 Hr)	0.40	0.19 to 0.60	0.06	0.45	0.23 to 0.63	0.04*	0.52	0.30 to 0.68	0.02*

DISCUSSION

Effective postoperative pain management is crucial in enhancing recovery and reducing complications following laparoscopic cholecystectomy [1,2]. In this study, both gabapentin and memantine demonstrated significant analgesic effects compared to control, as evidenced by reduced Visual Analogue Scale (VAS) scores and lower rescue analgesic consumption. Gabapentin showed slightly better efficacy in early postoperative periods, whereas memantine provided a comparable effect in later hours, consistent with its NMDA receptor antagonism [3,4].

Gabapentin's analgesic efficacy is attributed to its modulation of voltage-gated calcium channels in dorsal horn neurons, leading to decreased release of excitatory neurotransmitters and reduced central sensitisation [5,6]. Previous studies have shown that preoperative gabapentin administration reduces postoperative pain scores and opioid consumption in laparoscopic surgeries [7,8], aligning with our findings of lower VAS scores and fewer rescue analgesic doses in Group G.

Memantine acts primarily through NMDA receptor blockade, which prevents central sensitization and reduces hyperalgesia [9,10]. Our results support earlier clinical studies reporting that memantine provides effective postoperative analgesia and may be beneficial in patients at risk of heightened nociceptive responses [11,12]. The slightly delayed analgesic peak observed with memantine in our study may be due to its pharmacokinetic profile, as oral memantine reaches peak plasma concentration approximately 3–7 hours post-administration [13].

Pupillometry provided an objective measure of nociception and correlated well with subjective VAS scores. Both gabapentin and memantine groups showed reduced pupillary dilation compared to control, reflecting attenuated sympathetic responses to surgical stimuli. Previous literature supports pupillometry as a reliable tool for intraoperative and postoperative pain assessment, with a significant correlation between pupillary reflex dilation and perceived pain intensity [14,15].

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The safety profiles of both drugs were favourable. Adverse effects such as nausea and vomiting were minimal and comparable among groups, consistent with previous studies reporting that gabapentin and memantine are generally well-tolerated in perioperative settings [16,17]. No significant differences in intraoperative hemodynamic parameters or sedation scores were observed, suggesting that these agents do not compromise cardiovascular stability when used at the studied doses [18].

Our study underscores the clinical utility of gabapentin and memantine as adjuncts for postoperative analgesia in laparoscopic cholecystectomy. Gabapentin may be preferred for early pain relief due to its rapid onset, while memantine can provide sustained analgesia via NMDA receptor modulation. The combined use of subjective (VAS) and objective (pupillometry) measures enhances the accuracy of analgesic assessment and may guide individualised pain management strategies [19,20].

Limitations of this study include a single-centre design and a relatively small sample size. Long-term outcomes such as chronic post-surgical pain were not assessed. Future multicentric studies with larger populations are warranted to validate these findings and explore optimal dosing strategies.

CONCLUSION

Preoperative gabapentin (900 mg) and memantine (30 mg) effectively reduce postoperative pain and rescue analgesic use in laparoscopic cholecystectomy. Gabapentin showed slightly better analgesia, while both drugs were well tolerated with stable hemodynamics. Pupillometry correlated with pain scores, supporting its use as an objective nociception monitor.

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