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Original Article

Intraoperative Intravenous Ketamine Alone Versus Ketamine Combined with Magnesium Sulphate for Postoperative Analgesia After Laparoscopic Cholecystectomy: A Randomised Comparative Study

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ABSTRACT

Background: Pain after laparoscopic cholecystectomy has visceral, parietal and referred shoulder components and is often underestimated. Ketamine and magnesium sulphate both antagonise the N-methyl-D-aspartate (NMDA) receptor but at different sites, so their combination may act synergistically and spare opioid. We compared an intraoperative infusion of ketamine alone with the same infusion combined with magnesium sulphate. **Materials and Methods**: Sixty adults aged 18–65 years of American Society of Anaesthesiologists (ASA) physical status I or II undergoing elective laparoscopic cholecystectomy under general anaesthesia were allocated by computer-generated randomisation to Group Ket (ketamine 0.3 mg/kg bolus then 0.15 mg/kg/h until extubation, with saline as a blinded placebo infusion, n = 30) or Group KetMag (the same ketamine regimen plus magnesium sulphate 50 mg/kg over 10 minutes then 10 mg/kg/h until extubation, n = 30). Anaesthesia was standardised. Pain was scored on a visual analogue scale (VAS) at 1, 2, 4, 8, 12, 18 and 24 hours; rescue analgesia was paracetamol 1 g with tramadol 100 mg for VAS > 5 and fentanyl 0.5–1 µg/kg for VAS ≥ 8. Primary outcomes were postoperative pain scores and 24-hour rescue opioid consumption; secondary outcomes were time to ambulation, haemodynamics and Ramsay sedation score. **Results**: The groups were comparable for age, sex, ASA grade and duration of surgery. VAS scores were significantly lower with the combination through the first eight hours — at 2 hours 4.53 ± 1.04 versus 6.53 ± 0.51 (mean difference 2.00, 95% CI 1.58–2.42) and at 8 hours 2.87 ± 0.73 versus 4.40 ± 0.50 (mean difference 1.53, 95% CI 1.21–1.85; both $p < 0.001$) — and again at 24 hours. At 12 and 18 hours the direction reversed, scores being modestly higher in the combination group. Twenty-four-hour rescue fentanyl consumption was 14.27 ± 21.43 µg with the combination versus 35.80 ± 35.53 µg with ketamine alone (mean difference 21.5 µg, 95% CI 6.4–36.7; $p = 0.006$). By four hours no patient in the combination group required rescue analgesia, against 73.3% in the ketamine group ($p < 0.001$). Ambulation occurred earlier with the combination (8.40 ± 1.22 versus 9.07 ± 1.26 h; $p = 0.041$). Sedation scores, oxygen saturation and heart rate were comparable, and no patient developed a clinically significant adverse event. **Conclusion**: Adding magnesium sulphate to an intraoperative low-dose ketamine infusion improved early analgesia after laparoscopic cholecystectomy, cut 24-hour

rescue opioid consumption by about 60% and allowed earlier ambulation, without added sedation or haemodynamic instability. The benefit was clearest during the first eight hours; the unexpected reversal at 12 and 18 hours needs confirmation before the combination is assumed to help throughout the first postoperative day.

Keywords*: Magnesium sulphate; Laparoscopic cholecystectomy; Postoperative pain; Opioid-sparing.*

INTRODUCTION

Laparoscopic cholecystectomy is often described as minimally invasive, and by the standards of open biliary surgery it is. That description can mislead. Pain after the procedure has three distinct sources — visceral pain from manipulation of the gallbladder bed, parietal pain at the port sites, and referred shoulder-tip pain from diaphragmatic irritation by residual carbon dioxide — and the mixture is not always well controlled by the analgesia routinely prescribed [1,2]. Poorly relieved pain delays mobilisation, prolongs stay after what should be a same-day or next-day discharge, and is a common reason patient are dissatisfied with an otherwise uncomplicated operation [3].

The obvious remedy, more opioid, brings its own costs: nausea and vomiting, sedation, respiratory depression, ileus and, with larger perioperative doses, opioid-induced hyperalgesia [4,5]. Multimodal analgesia — combining agents that act at different points in the nociceptive pathway so that no single drug has to be pushed to its toxic range — has become the accepted answer, and the search for effective non-opioid adjuncts has moved to the centre of perioperative pain research [6].

Ketamine occupies an unusual place in that search. Introduced in 1964 as a dissociative anaesthetic, it has been rediscovered as an analgesic at doses far below those needed for anaesthesia. As a non-competitive NMDA receptor antagonist it blunts central sensitisation and the spinal wind-up phenomenon that amplifies postoperative pain, and at subanaesthetic doses it does so with little sedation [7]. A Cochrane review of perioperative intravenous ketamine found consistent reductions in postoperative opioid consumption and pain scores across a wide range of operations [8], confirming an earlier quantitative review that reached the same conclusion [16].

Magnesium is the other NMDA antagonist available to anaesthetists, and it works differently. Rather than binding within the channel as ketamine does, magnesium ions block the channel in a voltage-dependent manner, and magnesium additionally antagonises calcium entry at presynaptic terminals [9,10]. The evidence for magnesium used alone has been judged inconsistent, which is part of why the combination is of interest [15]. Because the two drugs act at separate sites on the same receptor complex, their effects may be more than additive. Liu and colleagues demonstrated exactly this superadditive modulation in receptor studies [10], and clinical trials of the combination in scoliosis and open bariatric surgery have reported reduced early morphine consumption compared with ketamine alone [11,12]. Later work in breast cancer surgery found the same opioid-sparing effect [13].

Whether the combination helps in laparoscopic cholecystectomy specifically is less clear. The pain here is shorter-lived and more visceral than in spinal or bariatric surgery, the opioid requirement is smaller to begin with, and there is correspondingly less room for an adjunct to demonstrate benefit. We therefore compared an intraoperative low-dose ketamine infusion with the same infusion combined with magnesium sulphate, measuring postoperative pain scores and rescue opioid consumption over the first 24 hours, together with time to ambulation, sedation and haemodynamic stability.

MATERIALS AND METHODS

Design, setting and ethics

This prospective, randomised, comparative study was conducted in the Department of Anaesthesiology and Critical Care Medicine, Subbaiah Institute of Medical Sciences, Shivamogga, Karnataka, over 18 months. The protocol was approved by the Institutional Ethics Committee [IEC-SUIMS/43/Apr/23]. Written informed consent was obtained from every participant.

Participants

Adults aged 18–65 years of ASA physical status I or II scheduled for elective laparoscopic cholecystectomy under general anaesthesia were eligible. Patients were excluded if they had a known allergy to either study drug, were pregnant, had a current psychiatric disorder or any respiratory disorder, or had a difficult intubation.

Randomisation, blinding and drug regimens

Patients were allocated in a 1:1 ratio using a computer-generated randomisation chart. Study infusions were prepared identically in appearance so that the observer recording postoperative outcomes remained unaware of allocation:

Group Ket received ketamine 0.3 mg/kg intravenously as a bolus after intubation, followed by an infusion of 0.15 mg/kg/h until extubation, delivered through one intravenous line; 100 mL of 0.9% saline was infused through a second line as a blinded placebo in place of magnesium.

Group KetMag received the identical ketamine bolus and infusion through one line, together with magnesium sulphate 50 mg/kg over 10 minutes followed by 10 mg/kg/h until extubation through the second line.

Anaesthetic technique

Patients fasted for six to eight hours. On arrival in theatre, electrocardiography, non-invasive blood pressure and pulse oximetry were established and baseline values recorded; two 18 G cannulae were sited so that anaesthetic and study drugs could be given separately. Premedication was glycopyrrolate 0.01 mg/kg, midazolam 0.05 mg/kg and ondansetron 0.10 mg/kg intravenously. After preoxygenation with 100% oxygen for three to five minutes, anaesthesia was induced with propofol 2 mg/kg and fentanyl 2 µg/kg, and vecuronium 0.1 mg/kg was given for relaxation. The trachea was intubated and volume-controlled ventilation instituted at a tidal volume of 8 mL/kg. Anaesthesia was maintained with low-flow oxygen–nitrous oxide and isoflurane at 1 MAC, with vecuronium 0.05 mg/kg top-ups as required. Both groups received intraoperative fentanyl 1 µg/kg hourly. Neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, and patients were extubated on meeting standard criteria and transferred to the postoperative ward once the modified Aldrete score reached 9.

Outcome measures

The primary outcomes were postoperative pain scores and total rescue opioid consumption in the first 24 hours. Pain was assessed on a 10 cm visual analogue scale (0 = no pain, 10 = worst pain) on arrival in the post-anaesthesia care unit and at 30 minutes and 1, 2, 4, 8, 12, 18 and 24 hours. Rescue analgesia followed a fixed protocol: for VAS above 5, paracetamol 1 g intravenously with tramadol 100 mg; for VAS of 8 or more, fentanyl 0.5–1 µg/kg. Secondary outcomes were time to ambulation and duration of hospital stay. Ramsay sedation score [17], heart rate, systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded intraoperatively (every 5 minutes for the first 15 minutes and every 15 minutes thereafter) and at each postoperative assessment. Ondansetron 4 mg was given for troublesome nausea or vomiting. All patients were observed in the post-anaesthesia care unit by an anaesthesiologist for 24 hours.

Sample size and statistical analysis

The sample size was derived from the 24-hour morphine consumption reported by Jabbour and colleagues, in which the mean was 44.68 mg (SD 19.79) with ketamine alone and 32.03 mg (SD 14.56) with ketamine plus magnesium [11]. Using the standard formula for comparing two means with a two-sided α of 0.05 and 80% power, 30 patients per group were required, giving a total of 60. Data were entered in Microsoft Excel and analysed with SPSS. Categorical variables are presented as frequencies and percentages and compared with the chi-square test; continuous variables are presented as mean ± standard deviation and compared with the independent-samples t test, with mean differences and 95% confidence intervals reported for the principal outcomes. A two-sided p value below 0.05 was taken as significant.

RESULTS

All 60 randomised patients completed the study and were analysed in their allocated groups.

Baseline and intraoperative characteristics

The groups were comparable in every respect measured (Table 1). The largest age band in both groups was 51–60 years (24 patients overall, 40.0%), and the overall distribution did not differ (p = 0.52). Women predominated (40 of 60, 66.7%; p = 0.27), and 37 patients (61.7%) were ASA grade I (p = 0.42). The mean duration of surgery was 80.97 ± 11.01 minutes in Group Ket and 77.07 ± 12.56 minutes in Group KetMag (mean difference 3.90 min, 95% CI −2.20 to 10.00; p = 0.21).

Table 1. Baseline and intraoperative characteristics of the two groups

Characteristic	Group Ket (n = 30)	Group KetMag (n = 30)	p value
Age 20–30 years, n (%)	4 (13.3)	6 (20.0)	0.52
Age 31–40 years, n (%)	10 (33.3)	5 (16.7)	
Age 41–50 years, n (%)	5 (16.7)	5 (16.7)	
Age 51–60 years, n (%)	11 (36.7)	13 (43.3)	
Age 61–70 years, n (%)	0 (0.0)	1 (3.3)	
Male, n (%)	8 (26.7)	12 (40.0)	0.27

Characteristic	Group Ket (n = 30)	Group KetMag (n = 30)	p value
Female, n (%)	22 (73.3)	18 (60.0)	
ASA grade I, n (%)	20 (66.7)	17 (56.7)	0.42
ASA grade II, n (%)	10 (33.3)	13 (43.3)	
Duration of surgery (min)	80.97 ± 11.01	77.07 ± 12.56	0.21

Values are n (%) or mean ± SD. Categorical variables compared by chi-square test, duration of surgery by independent t test. Mean difference in duration 3.90 min (95% CI −2.20 to 10.00). ASA, American Society of Anesthesiologists.

Postoperative pain scores

Pain relief in the first eight hours was clearly better with the combination (Table 2, Figure 1). At one hour the mean VAS was 5.27 ± 1.14 in Group KetMag against 6.53 ± 0.51 in Group Ket (mean difference 1.26, 95% CI 0.80–1.72; $p < 0.001$). The gap widened at two hours — 4.53 ± 1.04 versus 6.53 ± 0.51 (mean difference 2.00, 95% CI 1.58–2.42; $p < 0.001$) — and persisted at four hours (4.00 ± 0.64 versus 5.47 ± 0.51; mean difference 1.47, 95% CI 1.17–1.77) and eight hours (2.87 ± 0.73 versus 4.40 ± 0.50; mean difference 1.53, 95% CI 1.21–1.85; both $p < 0.001$).

Table 2. Postoperative visual analogue scale scores

Time	Group Ket	Group KetMag	Mean difference (95% CI)	p value
1 h	6.53 ± 0.51	5.27 ± 1.14	1.26 (0.80 to 1.72)	< 0.001*
2 h	6.53 ± 0.51	4.53 ± 1.04	2.00 (1.58 to 2.42)	< 0.001*
4 h	5.47 ± 0.51	4.00 ± 0.64	1.47 (1.17 to 1.77)	< 0.001*
8 h	4.40 ± 0.50	2.87 ± 0.73	1.53 (1.21 to 1.85)	< 0.001*
12 h	3.60 ± 0.50	3.93 ± 0.69	−0.33 (−0.64 to −0.02)	0.038*
18 h	2.60 ± 0.50	3.93 ± 0.69	−1.33 (−1.64 to −1.02)	< 0.001*
24 h	2.60 ± 0.50	1.87 ± 0.51	0.73 (0.47 to 0.99)	< 0.001*

*Values are mean ± SD. Independent-samples t test. A positive mean difference favours Group KetMag (lower pain); negative values at 12 and 18 h indicate higher scores in Group KetMag. *Statistically significant.*

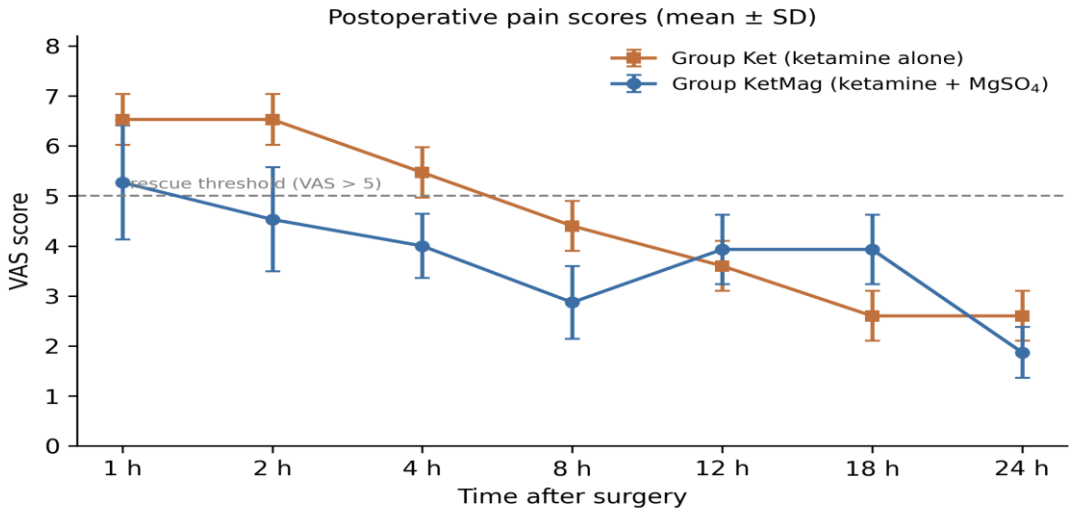

Figure 1. Postoperative visual analogue scale scores (mean ± SD). Pain was significantly lower in the ketamine–magnesium group through the first eight hours and again at 24 hours; at 12 and 18 hours the direction reversed. The dashed line marks the VAS > 5 rescue threshold.

The pattern then reversed. At 12 hours the mean VAS was 3.93 ± 0.69 in Group KetMag against 3.60 ± 0.50 in Group Ket (mean difference −0.33, 95% CI −0.64 to −0.02; p = 0.038), and at 18 hours 3.93 ± 0.69 against 2.60 ± 0.50 (mean difference −1.33, 95% CI −1.64 to −1.02; p < 0.001) — that is, scores were higher in the combination group at both these points. By 24 hours the advantage had returned to the combination (1.87 ± 0.51 versus 2.60 ± 0.50; mean difference 0.73, 95% CI 0.47–0.99; p < 0.001). Mean scores in both groups remained at or below the rescue threshold of 5 from four hours onwards.

Rescue analgesia and opioid consumption

Total rescue fentanyl consumption over 24 hours was 14.27 ± 21.43 µg in Group KetMag against 35.80 ± 35.53 µg in Group Ket, a mean reduction of 21.5 µg or about 60% (95% CI 6.4–36.7; p = 0.006) (Table 3, Figure 2).

Table 3. Rescue opioid consumption over 24 hours and time to ambulation

Outcome	Group Ket	Group KetMag	Mean difference (95% CI); p
Total rescue fentanyl (µg)	35.80 ± 35.53	14.27 ± 21.43	21.53 (6.37 to 36.69); p = 0.006*
Time to ambulation (h)	9.07 ± 1.26	8.40 ± 1.22	0.67 (0.03 to 1.31); p = 0.041*

*Values are mean ± SD. Independent-samples t test. *Statistically significant.*

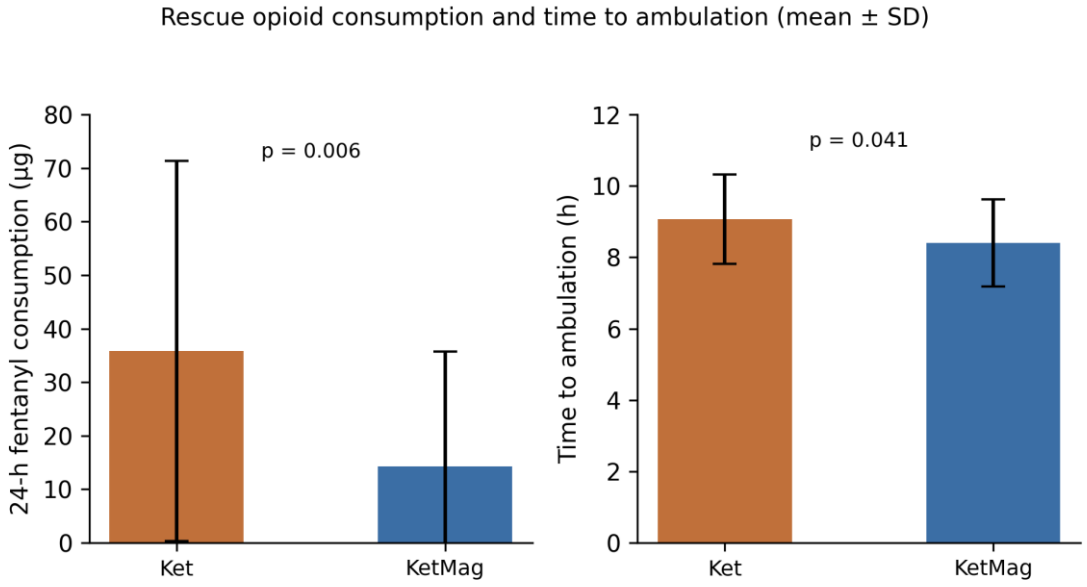

Figure 2. Total rescue fentanyl consumption over 24 hours and time to ambulation (mean ± SD). The combination reduced opioid requirement by about 60% (p = 0.006) and shortened time to ambulation by approximately 40 minutes (p = 0.041).

The pattern of rescue requirement over time was equally striking (Table 4, Figure 3). At 30 minutes every patient in both groups received some rescue analgesia, though the mix differed: fentanyl was needed by 16 patients (53.3%) in Group Ket against 10 (33.3%) in Group KetMag, with the remainder receiving paracetamol and tramadol (p = 0.11). At one hour all 30 patients in Group Ket required paracetamol with tramadol, whereas 16 patients (53.3%) in Group KetMag needed nothing (p < 0.001). At two hours the corresponding figures were 30 (100%) and 8 (26.7%) requiring rescue (p < 0.001); at four hours 22 (73.3%) and none (p < 0.001); and at eight hours 10 (33.3%) and none (p = 0.01). Neither group required any rescue analgesia at 12, 18 or 24 hours.

Table 4. Rescue analgesia administered at each assessment

Time	Rescue agent	Group Ket, n (%)	Group KetMag, n (%)	p
30 min	Fentanyl	16 (53.3)	10 (33.3)	0.11
	Paracetamol + tramadol	14 (46.7)	20 (66.7)	
1 h	Paracetamol + tramadol	30 (100.0)	14 (46.7)	< 0.001*
	None required	0 (0.0)	16 (53.3)	

Time	Rescue agent	Group Ket, n (%)	Group KetMag, n (%)	p
2 h	Paracetamol + tramadol	30 (100.0)	8 (26.7)	< 0.001*
	None required	0 (0.0)	22 (73.3)	
4 h	Paracetamol + tramadol	22 (73.3)	0 (0.0)	< 0.001*
	None required	8 (26.7)	30 (100.0)	
8 h	Paracetamol + tramadol	10 (33.3)	0 (0.0)	0.01*
	None required	20 (66.7)	30 (100.0)	
12, 18, 24 h	None required	30 (100.0)	30 (100.0)	—

*Chi-square test. Rescue protocol: paracetamol 1 g with tramadol 100 mg for VAS > 5; fentanyl 0.5–1 µg/kg for VAS ≥ 8. *Statistically significant.*

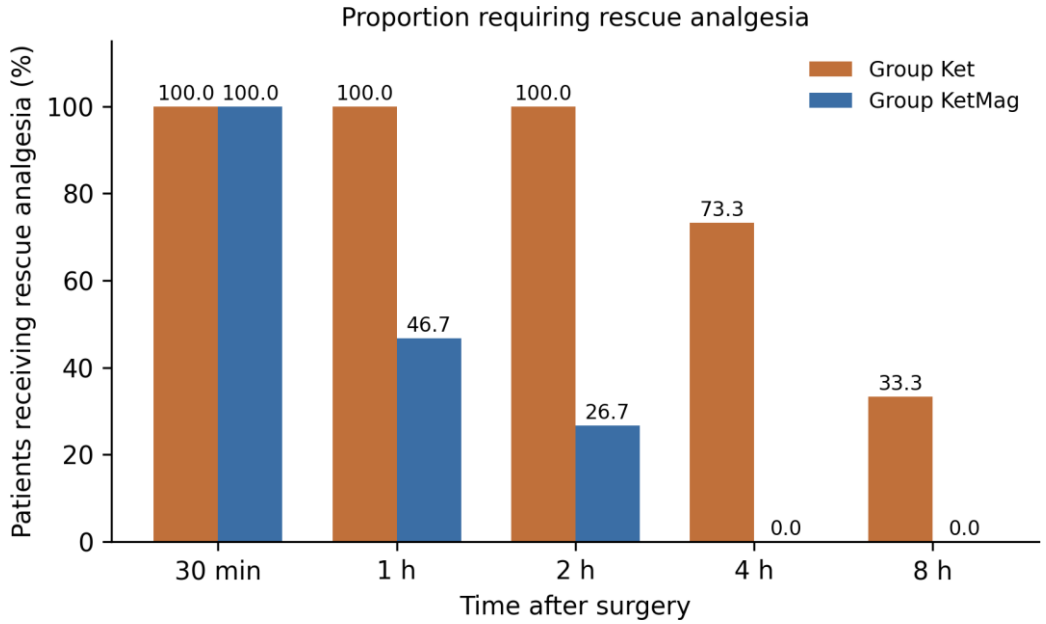

Figure 3. Proportion of patients receiving rescue analgesia at each assessment. By four hours no patient in the ketamine–magnesium group required rescue analgesia, compared with 73.3% in the ketamine group (p < 0.001).

Table 5. Intraoperative haemodynamic variables (selected time points)

Variable / time	Group Ket	Group KetMag	p value
SBP baseline (mmHg)	123.40 ± 7.11	123.13 ± 8.11	0.89
SBP 15 min (mmHg)	113.33 ± 6.16	109.00 ± 9.44	0.04*
SBP 30 min (mmHg)	111.53 ± 6.81	105.53 ± 8.97	0.005*
SBP 60 min (mmHg)	112.13 ± 6.39	107.07 ± 9.96	0.02*
SBP post extubation (mmHg)	120.60 ± 7.35	115.27 ± 9.38	0.01*
DBP 15 min (mmHg)	70.80 ± 6.08	67.53 ± 5.57	0.03*
DBP 120 min (mmHg)	64.07 ± 5.69	69.60 ± 7.98	0.003*
DBP post extubation (mmHg)	62.53 ± 6.87	73.93 ± 6.64	< 0.001*
MAP 15 min (mmHg)	84.87 ± 4.55	81.33 ± 6.44	0.01*

Variable / time	Group Ket	Group KetMag	p value
MAP 30 min (mmHg)	82.60 ± 4.30	79.20 ± 6.09	0.01*
MAP post extubation (mmHg)	81.93 ± 5.36	87.60 ± 7.07	< 0.001*
Heart rate baseline (/min)	80.07 ± 5.00	78.60 ± 4.98	0.26
Heart rate post extubation (/min)	65.93 ± 3.96	64.87 ± 4.18	0.31
SpO_2 baseline (%)	97.67 ± 0.71	97.47 ± 0.73	0.28
SpO_2 post extubation (%)	98.40 ± 0.72	98.20 ± 0.66	0.27

*Values are mean ± SD. Independent-samples t test. Selected time points shown; heart rate and SpO_2 were non-significant at every time point. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. *Statistically significant.*

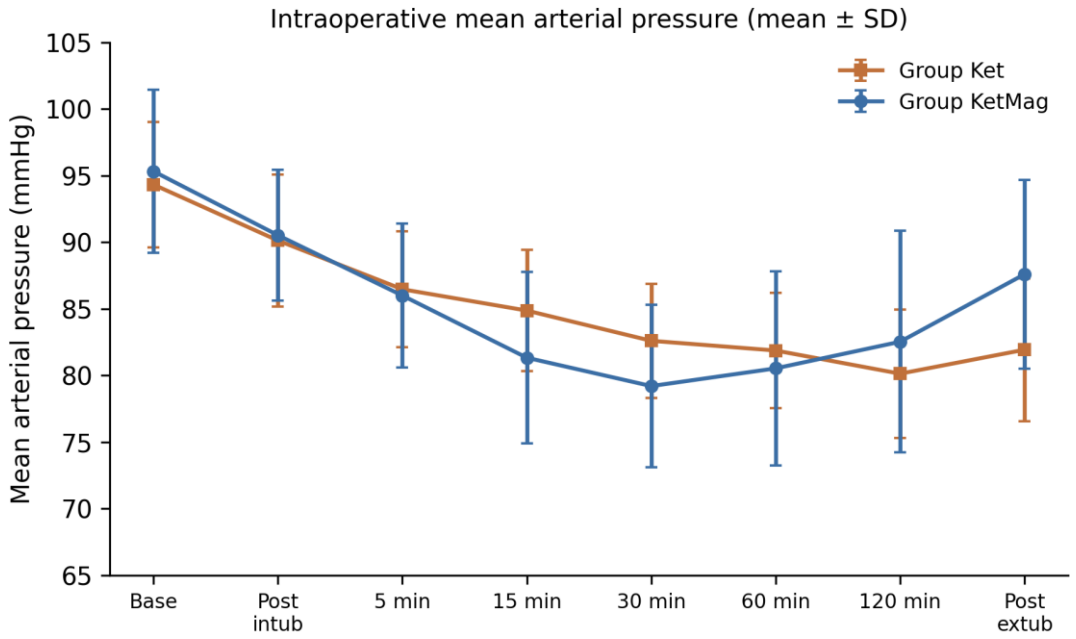

Figure 4. Intraoperative mean arterial pressure (mean ± SD). Values were lower in the combination group at 15 and 30 minutes and higher after extubation; all remained within a clinically acceptable range and none required intervention.

Ambulation

Patients in Group KetMag mobilised earlier, at a mean of 8.40 ± 1.22 hours against 9.07 ± 1.26 hours in Group Ket (mean difference 0.67 h, 95% CI 0.03–1.31; p = 0.041) (Table 3, Figure 2).

Haemodynamics, oxygenation and sedation

Intraoperative systolic pressure was lower in Group KetMag at 15, 30 and 60 minutes and after extubation (p = 0.04, 0.005, 0.02 and 0.01 respectively), while mean arterial pressure was lower at 15 and 30 minutes and higher after extubation (all p ≤ 0.01) (Table 5, Figure 4). Diastolic pressure differed at 15 minutes, 120 minutes and after extubation, the most marked difference being post-extubation (73.93 ± 6.64 versus 62.53 ± 6.87 mmHg; p < 0.001). All these values remained within a clinically acceptable range and no patient required a vasopressor, an antihypertensive or any other intervention. Intraoperative heart rate and oxygen saturation did not differ at any time point (p = 0.21–0.31 and 0.08–0.71 respectively). Postoperatively, systolic pressure was consistently lower in Group KetMag at every time point (p < 0.001), while diastolic pressure did not differ at any point (p = 0.56–0.94). The Ramsay sedation score was 2.13 ± 0.35 in Group Ket and 2.30 ± 0.47 in Group KetMag at 30 minutes (p = 0.12), and was exactly 1.00 in every patient in both groups at all subsequent

assessments, indicating that neither regimen produced residual sedation. No patient in either group experienced hallucinations, nightmares or other psychomimetic effects requiring treatment (Table 6).

Table 6. Postoperative blood pressure and Ramsay sedation score

Variable / time	Group Ket	Group KetMag	p value
SBP 1 h (mmHg)	130.00 ± 3.34	118.73 ± 5.54	< 0.001*
SBP 8 h (mmHg)	122.93 ± 4.48	111.53 ± 2.68	< 0.001*
SBP 24 h (mmHg)	121.53 ± 4.22	117.27 ± 3.92	< 0.001*
DBP 1 h (mmHg)	64.40 ± 8.57	64.27 ± 5.19	0.94
DBP 24 h (mmHg)	70.00 ± 9.46	69.53 ± 5.28	0.81
Ramsay sedation score, 30 min	2.13 ± 0.35	2.30 ± 0.47	0.12
Ramsay sedation score, 1–24 h	1.00 ± 0.00	1.00 ± 0.00	—

*Values are mean ± SD. Independent-samples t test. Ramsay score was 1 (alert, oriented) in every patient in both groups from 1 hour onward, so no test was possible. *Statistically significant.*

DISCUSSION

Adding magnesium sulphate to an intraoperative low-dose ketamine infusion produced better analgesia through the first eight hours after laparoscopic cholecystectomy, reduced 24-hour rescue fentanyl consumption by roughly 60%, and allowed patients to mobilise about 40 minutes sooner — all without additional sedation, respiratory depression or haemodynamic instability. In a procedure where the goal is early discharge, those are the outcomes that matter.

The opioid-sparing result is the most robust finding and sits squarely within the existing literature. Jabbour and colleagues found that the ketamine–magnesium combination reduced early morphine consumption after scoliosis surgery and again after open bariatric surgery, in the latter case by a substantial margin over ketamine alone during the first 24 hours [11,12]. Mohamed Elsayed and Essam reported the same opioid-sparing effect in cancer breast surgery [13]. That the effect appears in a shorter, less painful, predominantly visceral operation — where the total opioid requirement is small and the room for improvement correspondingly narrow — strengthens rather than weakens the case for a genuine pharmacological interaction.

That interaction has a clear mechanistic basis. Ketamine blocks the NMDA receptor channel non-competitively, while magnesium produces a voltage-dependent block at a distinct site and additionally limits presynaptic calcium entry [9,10]. Liu and colleagues showed that the two act superadditively on receptor function rather than merely summing [10], which predicts exactly what we observed: an effect larger than ketamine alone at a ketamine dose low enough to avoid psychomimetic side effects. The complete absence of hallucinations or excess sedation in our series supports the practical corollary — that magnesium allows the analgesic benefit of ketamine to be obtained without escalating its dose.

The pattern of rescue requirement illustrates the clinical meaning of this better than the consumption figures do. By four hours, no patient in the combination group needed any rescue analgesia at all, while nearly three-quarters of the ketamine-alone group still did. For a day-case or short-stay pathway, the difference between a patient who needs nothing after four hours and one who is still requesting analgesia at eight is the difference between a smooth discharge and a delayed one. The earlier ambulation we observed, though modest at 40 minutes, points the same way, and earlier mobilisation carries its own downstream benefits for respiratory and thromboembolic complications.

One result does not fit the narrative and should not be smoothed over. At 12 and 18 hours the direction of the VAS difference reversed, with scores modestly higher in the combination group before reverting to the combination's advantage at 24 hours. Several explanations are possible. The most benign is pharmacological: both study infusions stopped at extubation, and if the combination delivered denser early analgesia, the offset of that effect could produce a transient rebound in reported pain around the 12–18 hour mark — a pattern reported with other short-acting adjuncts. It is also relevant that no patient in either group received rescue analgesia after eight hours, so the higher scores at 12 and 18 hours went untreated in both arms. A less comfortable possibility is measurement or transcription error: the values recorded at 12 and 18 hours in the combination group were identical, as were those at 18 and 24 hours in the ketamine group, and such repetition warrants verification against the source records. We report the finding as observed rather than resolving it, and we would caution against claiming that the combination improves analgesia uniformly across 24 hours until this window has been re-examined prospectively.

The haemodynamic differences deserve brief comment. Intraoperative pressures were somewhat lower in the combination group during the middle of surgery, which is consistent with magnesium's known vasodilator and calcium-antagonist properties, and post-extubation diastolic pressure was higher in that group. None of these differences required treatment or produced any clinical consequence, and heart rate and oxygen saturation were unaffected throughout. In ASA I–II patients

this profile is reassuring; in patients with limited cardiac reserve or on calcium channel blockers, magnesium's cardiovascular effects would need closer attention, and our data cannot speak to that population.

Limitations

Several limitations bound these conclusions. This was a single-centre study of 60 patients, powered on rescue opioid consumption; the secondary outcomes, particularly time to ambulation with its narrow confidence interval barely excluding zero, should be regarded as exploratory. Although the observer recording outcomes was blinded and a placebo infusion was used, the study is best described as observer-blinded rather than fully double-blind, and the exact method of allocation concealment should be stated explicitly at submission. Duration of hospital stay was listed among the study objectives but no comparative data were generated, and it is therefore not reported here. Serum magnesium concentrations were not measured, so neither the achieved plasma level nor the possibility of subclinical hypermagnesaemia can be commented upon; neuromuscular monitoring was likewise not quantified, which matters because magnesium potentiates non-depolarising blockade. The 12–18 hour reversal in pain scores is unexplained and, as noted, may reflect a data-handling artefact. Follow-up ended at 24 hours, so nothing can be said about persistent post-surgical pain, which is one of the outcomes NMDA antagonists are theorised to influence. Finally, only a single dose regimen of each drug was studied in ASA I–II adults undergoing one operation, so extrapolation to other doses, other patients or other surgery is not warranted.

Implications

For elective laparoscopic cholecystectomy in fit adults, adding magnesium sulphate to a low-dose intraoperative ketamine infusion is a simple, inexpensive modification that meaningfully reduces early pain and rescue opioid requirement without sedating the patient. Larger multicentre trials with full double-blinding, serum magnesium monitoring, quantitative neuromuscular monitoring, longer follow-up and pre-specified analysis of the 12–24 hour window would settle the questions this study raises, as would a three-arm design including magnesium alone to determine how much of the benefit the combination actually contributes.

CONCLUSION

In adults undergoing elective laparoscopic cholecystectomy, combining intraoperative magnesium sulphate with a low-dose ketamine infusion gave better analgesia through the first eight postoperative hours, reduced 24-hour rescue fentanyl consumption from 35.8 to 14.3 µg, eliminated the need for rescue analgesia beyond four hours, and permitted earlier ambulation, with no increase in sedation and no clinically important haemodynamic disturbance. The combination is a practical opioid-sparing adjunct for this operation, although the transient reversal of pain scores at 12 and 18 hours should be verified before benefit across the full 24-hour period is assumed.

Abbreviations

ASA – American Society of Anesthesiologists; CI – confidence interval; DBP – diastolic blood pressure; MAC – minimum alveolar concentration; MAP – mean arterial pressure; NMDA – N-methyl-D-aspartate; PACU – post-anaesthesia care unit; SBP – systolic blood pressure; SD – standard deviation; SpO_2 – peripheral oxygen saturation; VAS – visual analogue scale.

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