Preemptive low-dose intravenous ketamine in the management of acute and chronic postoperative pain following laparoscopic cholecystectomy: a prospective randomized control study

Shruti Jain¹⁻, Nazia Nazir², Saurav Mitra Mustafi¹
1 Department of Anesthesiology, Vardhaman Mahavir Medical College & Safdarjung Hospital, Delhi, India
2 Department of Anesthesiology, Government Institute of Medical Sciences, Greater Noida, India

*Correspondence to: Shruti Jain, MD, shruti.anaesth@gmail.com.
orcid: 0000-0002-9340-8800 (Shruti Jain)

Abstract
Preemptive analgesia with intravenous ketamine has been utilized as a part of multi-modal analgesia for acute postoperative pain following laparoscopic cholecystectomy with mixed outcomes. We tested the effectiveness of low-dose ketamine for acute and chronic postoperative pain after laparoscopic cholecystectomy in a randomized controlled experiment. The study involved 50 individuals who had a laparoscopic cholecystectomy under general anesthesia. All the patients were separated into two equal groups. The ketamine and control groups were given 0.5 mg/kg ketamine and 2 mL of normal saline, respectively, at 15 minutes before incision. Patients in the ketamine group had a significantly lower numeric pain rating scale score at 0 minutes than those in the control group. The numeric pain rating scale score of the ketamine group was considerably greater than the control group after a half-hour interval. At other time periods, there was no significant difference in numeric pain rating scale scores between the two groups. The ketamine group had a greater duration of analgesia and sedation score than the control group. The cumulative tramadol demand at 24 hours and the incidence of chronic pain did not differ significantly across the groups. Substantial analgesic effect of intravenous ketamine lasted only up to 30 min postoperatively. There was no discernible effect in terms of chronic pain prevention.

Key words: acute pain; analgesia; cholecystectomy; chronic pain; ketamine; laparoscopic; N-methyl-D-aspartate receptor; pre-emptive analgesia; numeric pain rating scale; postoperative pain

doi: 10.4103/2045-9912.337995
How to cite this article: Jain S, Nazir N, Mustafi SM. Preemptive low-dose intravenous ketamine in the management of acute and chronic postoperative pain following laparoscopic cholecystectomy: a prospective randomized control study. Med Gas Res. 2022;12(4):141-145.

Introduction

Despite the fact that laparoscopic cholecystectomy (LC) is associated with decreased discomfort and impairment, 17–41% of patients experience significant pain in the postoperative period,¹ and 3.4–7% of patients have persistent pain.² As an adjuvant to multimodal analgesia, preemptive analgesia has been proven to improve analgesic efficacy and reduce the overall analgesic requirement.³ It has a protective impact on the nociceptive system, which means it not only relieves surgical pain but also prevents chronic pain from developing.⁴ Preemptive analgesia is usually achieved with ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist. It operates by affecting central sensitization and neural modulation. Although it is routinely used in a variety of procedures, there is no conclusive evidence that it is useful in LC.⁵,⁶ Its dosage and administration technique are also not well defined. Traditionally, ketamine has been used as a single low-dose bolus or as a bolus followed by infusion. The adverse effects generally associated with ketamine infusion have been observed to be absent in a single bolus dose.⁷

The current research seeks to explore the preemptive analgesic efficacy of intravenous (IV) ketamine in a single bolus dosage of 0.5 mg/kg and its role in the prevention of acute and chronic pain in LC which is a brief and minimally invasive operation.

Subjects and Methods

This was a prospective, randomized, triple-blind study undertaken in a tertiary care hospital’s anesthesia department. On June 24, 2016, the Institutional Ethics Committee of the School of Medical Sciences & Research and Sharda Hospital, Sharda University, Greater Noida (approval No. IEC/2016/76-A/04) granted ethical approval for the study (Additional file 1), and it was registered with the Clinical Trial Registry – India (No. REF/2021/10/037604). For protocol reporting, this study followed the CONsolidated Standards Of Reporting Trials (CONSORT) declaration (Additional file 2).

Study Population

The study included 50 patients undergoing elective LC under general anesthesia of Grade I or II (American Society of Anesthesiologists).⁸ Patients ranged in age from 20 to 60 years old and were of either sex. All of the patients gave written informed consent (Additional file 3) after counselling. Numeric pain rating scale (NRS), was used for pain assessment postoperatively.⁹ Patients were instructed about the NRS, with 0 representing no pain and 10 being the most severe pain imaginable before surgery. Choledocholithiasis, acute pancreatitis, current opiate usage, pregnancy, difficulty to interpret NRS, and conversion of LC to open cholecystectomy were all criteria for exclusion.
The lead investigator used a computer-generated random number technique to randomize the patients. The patients were divided into two groups (n = 25 per group): control and ketamine groups. Allocation sequence concealment was done by putting the group allocated in a sealed envelope. After a patient was transferred to the operating room, the envelope was opened by an anesthesiologist who did not participate in the study and the medication solution was prepared accordingly. The patient, attending anesthesiologist, and the nurse who recorded the postoperative data were all blinded to the grouping information in the study.

**Anesthetic protocol**

Patients were given standardized premedication with IV injections of midazolam (0.025 mg/kg; Celon Labs Pvt. Ltd., Telangana, India), fentanyl (2 g/kg; Verve Healthcare Ltd., Dehradun, India), and ondansetron (0.1 mg/kg; Cipla Ltd., Hyderabad, India) after fasting for eight hours. Patients in the control group received 2 mL of normal saline, while those in the ketamine group received 0.5 mg/kg ketamine (Baxter Pharmaceuticals India Pvt. Ltd., Ahmedabad, India) diluted to 2 mL intravenously 15 minutes before surgery.

2 mg/kg IV propofol (Neon Labs Ltd., Mumbai, India) was used to induce general anesthesia, and 0.1 mg/kg IV vecuronium bromide was used to establish muscular relaxation (Celon labs Pvt. Ltd.). The patient was intubated and anesthesia was maintained with 0.8–1% isoflurane in a mixture of oxygen and nitrous oxide (Triokaa Pharmaceuticals Ltd., Ahmedabad, India). During surgery, the minimum alveolar concentrations of isoflurane and propofol were monitored.

During operation, the intraabdominal pressure was kept below 1.176 kPa. Non-invasive monitoring was used to record hemodynamic data (mean arterial pressure and heart rate) every 5 minutes. During surgery, all patients received 1.5 mg/kg IV diclofenac sodium (Daffodils Pharma Centinal Ltd., Jawahar Nagar, India) as an analgesic. It was repeated at 8 and 16 hours after surgery.

Isoflurane and nitrous oxide were terminated at the end of surgery, and neuromuscular blockade was reversed with a mixture of neostigmine (0.04 mg/kg; Neon Labs Ltd.) and glycopyrrolate (0.01 mg/kg; Neon Labs Ltd.) before the patient was extubated. The patients were then moved to the recovery area. For data recording purposes, 0 minutes was taken as the time when the patient was received by nursing staff in postoperative recovery area.

**Data collection**

The nursing staff used NRS to record pain scores at 0, 10 minutes, 1, 2, 4, 6, 8, 12, and 24 hours after surgery, or whenever the patient complained of pain. Sedation scores (1 = alert, 2 = asleep, alert after arousal, 3 = sleeping, sleepy after arousal, 4 = asleep, difficult to arouse, and 5 = unarousable) were also recorded at the same interval.18 When the patient’s pain was equal to or greater than NRS 4, an IV injection of tramadol (2 mg/kg; Magnet Labs Pvt Ltd., New Delhi, India) was given as a rescue analgesic. The time interval between 0 and the first need for a rescue analgesic was recorded and referred to as the duration of analgesia (DOA). Ketamine side effects such as hallucination, nausea, and vomiting were identified and noted. Chronic pain was defined as the pain which developed after LC, lasted at least for 2 months and other possible causes of pain such as chronic infection and malignancy were excluded.11 Patients were contacted on phone every 15 days for any residual pain, up to 6 months after surgery, to document chronic discomfort.

The primary goal was to see if 0.5 mg/kg ketamine had a preemptive analgesic effect in individuals undergoing LC. As secondary outcomes, sedation score, DOA, cumulative requirement of rescue analgesic (tramadol), incidence of side effects in 24 hours postoperatively and occurrence of chronic pain in both the groups were assessed and recorded.

**Sample size calculation**

We conducted a pilot study in 7 patients and calculated that 23 cases in each group were required for the study with a significance of 0.05 and a power of 90% (AI-Therapy Statistics BETA, https://www.ai-therapy.com/psychology-statistics). To account for any dropouts, each group was given a total of 25 patients.

**Statistical analysis**

The Statistical Package for the Social Sciences (SPSS) for Windows version 20.0 was used to analyze the data (IBM, Armonk, NY, USA). The number of patients or the mean standard deviation (SD) was used to record the data. Student’s t-test was used to compare demographic data, surgery duration, NRS score, DOA, and cumulative rescue analgesic demand between groups. To investigate disparities in categorical data, the Chi-square test was used. P values of ≤ 0.05 were considered significant. The biostatistician from Vardhman Mahavir Medical College, Safdarjung Hospital reviewed the statistical methodologies used in this work.

**RESULTS**

From July 14, 2016 to September 9, 2017, 50 patients were enrolled in the trial. In all the cases LC was successfully completed and no patient was lost to follow-up (Figure 1).

---

**Figure 1** Consor flow diagram.
Patient characteristics
Both groups had similar demographic profiles in terms of age, weight, and sex distribution, as well as operation length (Table 1). The intraoperative hemodynamic characteristics (mean arterial pressure and heart rate) were also comparable between groups (Figure 2). In both groups, propofol during induction and the minimal alveolar concentration of isoflurane throughout operation were comparable (Table 1). Both groups of patients were given the same intraoperative analgesics (fentanyl 2 g/kg and diclofenac sodium 1.5 mg/kg).

| Table 1: Demographic and operative characteristics of the patients after laparoscopic cholecystectomy |
|-----------------------------------------------------------------------------------------------------|
| Control (n=25) | Ketamine (n=25) | P-value |
| Age (yr) | 37.64±15.22 | 33.44±10.84 | 0.737 |
| Sex (male/female) | 10/15 | 11/14 | – |
| Weight (kg) | 55.16±8.92 | 56.04±9.49 | 0.798 |
| Duration of surgery (min) | 57.96±7.46 | 52.96±15.62 | 0.155 |
| Propofol requirement (mg) | 108.73±14.52 | 107.73±16.65 | 0.76 |
| Minimum alveolar concentration of isoflurane | 0.90±0.07 | 0.93±0.07 | 0.7 |

Note: Data are expressed as mean ± SD (n = 25) and were analyzed by Student’s t-test, except sex.

Comparison of analgesia
Patients in the ketamine group had a significantly lower NRS score at extubation than those in the control group (P = 0.000; Table 2). Patients in the control group received rescue analgesia as soon as they arrived in the recovery area. As a result, the NRS score of the ketamine group was considerably greater than the control group at the half-hour interval. Also, about 30 minutes after surgery, the majority of the patients in the ketamine group complained of pain with NRS ≥ 4, necessitating the use of a rescue analgesic. At all other time periods, there was no significant difference in NRS score between the two groups.

The patients in the ketamine group had a longer DOA than the patients in the control group (P = 0.000). There was a significant difference in the sedation scores between both groups at 0 minutes (P = 0.000). Sedation scores were comparable in both groups at 30 minutes onwards. Cumulative requirement of tramadol in 24 hours postoperatively was comparable in both groups (Table 2).

Table 2: Duration of analgesia, tramadol requirement and NRS at different time intervals in patients after laparoscopic cholecystectomy

| | Control (n=25) | Ketamine (n=25) | P-value |
|--------------------------------------------------|
| Duration of analgesia | 1.76±2.047 | 16.58±6.57 | 0 |
| NRS | | | |
| 0 min | 3.76±0.97 | 1.68±0.69 | 0 |
| 30 min | 1.48±0.65 | 3.96±0.79 | 0.056 |
| 1 h | 1.04±0.68 | 1.44±0.77 | 0.13 |
| 2 h | 1.08±0.70 | 1.40±0.76 | 0.29 |
| 4 h | 1.20±0.76 | 1.44±0.82 | 0.29 |
| 6 h | 1.60±1.19 | 1.76±1.09 | 0.623 |
| 8 h | 1.76±1.36 | 2.28±1.34 | 0.18 |
| 12 h | 1.60±1.26 | 2.04±1.17 | 0.207 |
| 24 h | 1.12±0.67 | 1.44±0.82 | 0.137 |
| Cumulative requirement of tramadol in 24 h (mg) | 150.00±51.08 | 132.00±7.61 | 0.208 |
| Sedation score | Extubation | 1.08±0.28 | 3.04±0.61 | 0 |
| | 30 min | 1.00±0.00 | 1.12±0.33 | 0.07 |
| | 1 h | 1.00±0.00 | 1.00±0.00 | – |
| Chronic pain | 15 d | 1.44±1.38 | 1.44±1.73 | 1 |
| | 30 d | 0.72±1.46 | 0.52±1.05 | 0.58 |
| | 45 d | 0.12±0.44 | 0.12±0.60 | 1 |
| | 60 d | 0.00±0.00 | 0.00±0.00 | – |

Note: Data are expressed as mean ± SD and were analyzed by Student’s t-test.

Comparison of side effects
None of the patients reported hallucinations in any of the groups. Incidences of nausea and vomiting were also comparable in both groups (Table 3). There were no complications or unintended side effects of ketamine in the study.

Table 3: Incidence of hallucination and nausea/vomiting in patients after laparoscopic cholecystectomy

| | Control (n=25) | Ketamine (n=25) | P-value |
|--------------------------------------------------|
| Hallucination | 0 | 0 | – |
| Nausea/vomiting | 5 | 5 | 0.905 |

Note: Data are expressed as number and were analyzed by Chi-square test.

Comparison of chronic pain
Number of patients reporting pain 15, 30 and 45 days postoperatively was comparable in both groups. None of the patients complained of pain 60 days postoperatively till the last follow-up at 6 months. There were no dropouts (Table 4).
patients in the ketamine group required rescue analgesia on acute and chronic pain following LC. We investigated the effects of the same dose of 0.5 mg/kg ketamine based on the findings of Singh et al. 0.7 mg/kg ketamine had positive effects, but also reported a DOA of nearly one hour with substantial side effects. Singh et al. on the other hand, reported a DOA of 1.98 hours with 0.5 mg/kg ketamine, with no significant difference in DOA between 1, 0.75 and 0.5 mg/kg ketamine.

It is also likely that, for ketamine to be effective as a preemptive analgesic, even for minimally invasive procedures like LC, it needs to be given throughout the surgical procedure and for a period of time after surgery, to prevent central and peripheral pain pathways from being sensitized. In a meta-analysis, Zhu et al. found that IV ketamine infusion combined with a pre-operative bolus dose significantly lowers post-operative pain scores and opioid usage in LC patients. Patients in the control group got alert at zero minutes, while those in the ketamine group became alert after 30 minutes. No other study has evaluated the level of sedation. Despite the fact that Singh et al. and Wang et al. observed a considerable reduction in opioid demand in just 24 hours, we discovered no significant change in opioid requirement in both groups, even when the dosages were the same.

At different time intervals, there was no significant difference in the incidence of chronic pain in both groups. Both groups of patients were pain-free two months after surgery, with no recurrence until the final follow-up at six months. Following LC, Bisgard et al. found chronic pain in 18 of 150 patients, concluding that the incidence of chronic pain is highly related to the intensity of acute pain. Low levels of acute pain were found to be associated with a lower incidence of chronic pain in our study. In this context, no previous research has looked into the influence of low-dose ketamine on the occurrence of chronic pain.

The limitation of our study was that we did not explore the analgesic effect on dynamic pain. To assess the adequate analgesic efficacy of IV ketamine and its side effects, future investigations using high-quality randomized control trials with large sample sizes comparing different doses and administration strategies (bolus versus infusion) are required.

In conclusion, IV ketamine in single bolus dose of 0.5 mg/kg showed significant analgesic effect lasting only up to half an hour postoperatively. There was no significant chronic pain after LC.

### Author contributions
SJ conceived and conducted the study, interpreted the results and wrote the manuscript. NN conducted the study and interpreted the results. SMM supervised the study, helped in data collection, writing and revising manuscript. All authors have read and approved the manuscript provided.

### Conflicts of interest
None.

### Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

### Open access statement
This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-

### Table 4: Incidence of chronic pain in patients after laparoscopic cholecystectomy

| Time point | Control (n=25) | Ketamine (n=25) | P-value |
|------------|---------------|----------------|---------|
| 15 d       | 8(32)         | 7(28)          | 0.757   |
| 30 d       | 6(24)         | 6(24)          | 1.000   |
| 45 d       | 4(16)         | 3(12)          | 0.683   |
| 60 d       | 0             | 0              | –       |

Note: Data are expressed as number (percentage) and were analyzed by Chi-square test.

### Discussion
Postoperative pain management is critical for surgery patients to have a better recovery. Free nerve endings in peripheral nerves called nociceptors detect pain signals from injured tissues. Myelinated A delta nociceptors cause a sudden sharp pain response known as “first pain,” whereas unmyelinated C nociceptors cause a longer delayed reaction known as “second pain.” Excessive firing of C fibers before and after surgery produces the production of excitatory amino acids such as aspartate, glutamate, and substance P. These chemicals bind to the NMDA and 2-amino-3 hydroxyl-5-methyl-4 isoxazole propionic acid receptors. Inflammatory and neuropathic pains are exacerbated by NMDA receptor activation, which leads to secondary hyperalgesia. The activation of NMDA receptors causes translational alterations in second order neurons, which may be the cause of chronic pain. Preemptive analgesia is a treatment that begins before painful stimuli and continues during the surgical procedure to minimize the physiological effects of noiceptation. As a result, immediate postoperative pain may be decreased, and chronic pain development may be avoided.

Opioids, NMDA receptor antagonists, nonsteroidal anti-inflammatory medications, local anesthetics, and gabapentin are now used for preemptive analgesia. Ketamine is the best studied NMDA receptor antagonist among them. Ketamine has been used as a preemptive analgesic in LC as a single low-dose bolus or as an infusion along with the bolus dosage. When given as a bolus, low dosage IV ketamine is defined as a dose of no more than 1 mg/kg. Because of its high affinity for NMDA receptors, even at low dosages, ketamine is thought to reduce central sensitization. Because LC is a relatively brief, minimally invasive procedure, a single low-dose bolus of ketamine was employed to alleviate postoperative pain in the current study. In LC, Morro et al. and Kotsovolis et al. utilized 0.4 mg/kg and 0.3 mg/kg ketamine bolus, respectively, and observed no benefit in postoperative analgesia. Launo et al. and Singh et al. found that 0.7 mg/kg ketamine had positive effects, but also reported a significant increase in unfavorable effects. We utilized 0.5 mg/kg IV ketamine based on the findings of Singh et al. and Wang et al. who exhibited a strong preemptive analgesic benefit with no side effects at a similar dosage for acute pain following LC. We investigated the effects of the same dose on acute and chronic pain following LC.

Although the NRS score in the ketamine group was much lower than that in the control group at extubation, all of the patients in the ketamine group required rescue analgesia within 30 minutes postoperatively. This brief DOA could be the result of a single tiny bolus of ketamine. To demonstrate postoperative analgesic effects of ketamine, a higher dose may be required, but the risk of side effects may limit its use.

With an IV ketamine dose of 0.7 mg/kg, Launo et al. found a DOA of 1.98 hours with 0.5 mg/kg ketamine, with no significant difference in DOA between 1, 0.75 and 0.5 mg/kg ketamine.

In a meta-analysis, Zhu et al. found that IV ketamine infusion combined with a pre-operative bolus dose significantly lowers post-operative pain scores and opioid usage in LC patients. Patients in the control group got alert at zero minutes, while those in the ketamine group became alert after 30 minutes. No other study has evaluated the level of sedation. Despite the fact that Singh et al. and Wang et al. observed a considerable reduction in opioid demand in just 24 hours, we discovered no significant change in opioid requirement in both groups, even when the dosages were the same.

At different time intervals, there was no significant difference in the incidence of chronic pain in both groups. Both groups of patients were pain-free two months after surgery, with no recurrence until the final follow-up at six months. Following LC, Bisgard et al. found chronic pain in 18 of 150 patients, concluding that the incidence of chronic pain is highly related to the intensity of acute pain. Low levels of acute pain were found to be associated with a lower incidence of chronic pain in our study. In this context, no previous research has looked into the influence of low-dose ketamine on the occurrence of chronic pain.

The limitation of our study was that we did not explore the analgesic effect on dynamic pain. To assess the adequate analgesic efficacy of IV ketamine and its side effects, future investigations using high-quality randomized control trials with large sample sizes comparing different doses and administration strategies (bolus versus infusion) are required.

In conclusion, IV ketamine in single bolus dose of 0.5 mg/kg showed significant analgesic effect lasting only up to half an hour postoperatively. There was no significant chronic pain after LC.
Additional files

Additional file 1: Hospital ethics approval.
Additional file 2: CONSORT checklist.
Additional file 3: Informed consent form.

REFERENCES

1. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain.* 2001;90:261-269.
2. Stiff G, Rhodes M, Kelly A, Telford K, Armstrong CP, Rees BI. Long-term pain: less common after laparoscopic than open cholecystectomy. *Br J Surg.* 1994;81:1368-1370.
3. Nicolau AE, Merlan V, Grecu I, Nicolau M, Micu B. Multimodal analgesia in elective laparoscopic cholecystectomy. A double-blind randomized controlled trial. *Chirurgia (Bucur).* 2008;103:547-551.
4. Woolf CJ, Chong MS. Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg.* 1993;77:362-379.
5. Ithnin FB, Tan DJA, Xu XL, Tan CH, Sng BL. Low-dose S+ ketamine in target-controlled intravenous anaesthesia with remifentanil and propofol for open gynaecological surgery: A randomised controlled trial. *Indian J Anaesth.* 2019;63:126-133.
6. Toleska M, Dimitrovski A. Is an opioid-free anaesthesia possible without using alpha-2 agonists? *Indian J Anaesth.* 2020;64:428-431.
7. Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Pre-emptive analgesia with ketamine for laparoscopic cholecystectomy. *J Anaesthesiol Clin Pharmacol.* 2013;29:478-484.
8. Abouleish AE, Leib ML, Cohen NH. ASA provides examples to each ASA Physical Status Class. *ASA Newsol.* 2015;79:38-49.
9. de Williams AC, Davies HTO, Chadury Y. Simple pain rating scales hide complex idiosyncratic meanings. *Pain.* 2000;85:457-463.
10. Dahl JB, Mainiche S. Pre-emptive analgesia. *Br Med Bull.* 2004;71:13-27.
11. Schug SA, Williams WA. Chronic postsurgical pain (CPSP). In: Gebhart GF, Schmidt RF, eds. *Encyclopedia of pain.* Berlin, Heidelberg: Springer Berlin Heidelberg; 2013:662-663.
12. Voscopoulos C, Lena M. When does acute pain become chronic? *Br J Anaesth.* 2010;105 Suppl 1:i69-85.
13. Wang SS, Yahya N, Ping S, et al. Pre-emptive intravenous ketamine analgesia in patients undergoing laparoscopic cholecystectomy: A prospective double blind randomised controlled trial. *Brunei Int Med J.* 2015;11:288-296.
14. Mishra A, Aftal M, Mookerjee S, Bandyopadhyay K, Paul A. Pre-emptive analgesia: Recent trends and evidences. *Indian J Pain.* 2013;27:114-120.
15. Launo C, Bassi C, Spagnolo L, et al. Preemptive ketamine during general anaesthesia for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. *Minerva Anestesiol.* 2004;70:727-734; 734-728.
16. Kotsovolis G, Karakoulas K, Grosomanidis V, Tziris N. Comparison between the combination of gabapentin, ketamine, lornoxicam, and local ropivacaine and each of these drugs alone for pain after laparoscopic cholecystectomy: a randomized trial. *Pain Pract.* 2015;15:355-363.
17. Moro ET, Feitosa I, de Oliveira RG, et al. Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: a randomized controlled trial. *Acta Anaesthesiol Scand.* 2017;61:740-748.
18. Lee MH, Chung MH, Han CS, et al. Comparison of effects of intraoperative esmolol and ketamine infusion on acute postoperative pain after remifentanil-based anesthesia in patients undergoing laparoscopic cholecystectomy. *Korean J Anesthesiol.* 2014;66:222-229.
19. Choi SK, Yoon MH, Choi JI, et al. Comparison of effects of intraoperative nefopam and ketamine infusion on managing postoperative pain after laparoscopic cholecystectomy administered remifentanil. *Korean J Anesthesiol.* 2016;69:480-486.
20. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain.* 1999;82:111-125.
21. Guignard B, Coste C, Costes H, et al. Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. *Anesth Analg.* 2002;95:103-108; table of contents.
22. Zhu J, Xie H, Zhang L, Chang L, Chen P. Efficiency and safety of ketamine for pain relief after laparoscopic cholecystectomy: A meta-analysis from randomized controlled trials. *Int J Surg.* 2018;49:1-9.
23. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. *Scand J Gastroenterol.* 2005;40:1358-1364.

Date of submission: March 15, 2021
Date of decision: April 14, 2021
Date of acceptance: May 27, 2021
Date of web publication: April 17, 2022
## CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic       | Item No | Checklist item                                                                 | Reported on page No |
|---------------------|---------|---------------------------------------------------------------------------------|---------------------|
| **Title and abstract** |         |                                                                                |                     |
|                     | 1a      | Identification as a randomised trial in the title                              | 1                   |
|                     | 1b      | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 1                   |
| **Introduction**    |         |                                                                                |                     |
| Background and objectives | 2a  | Scientific background and explanation of rationale                             | 2                   |
|                     | 2b      | Specific objectives or hypotheses                                              | 2                   |
| **Methods**         |         |                                                                                |                     |
| Trial design        | 3a      | Description of trial design (such as parallel, factorial) including allocation ratio | 2                   |
|                     | 3b      | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | NA                 |
| Participants        | 4a      | Eligibility criteria for participants                                          | 2                   |
|                     | 4b      | Settings and locations where the data were collected                           | 2                   |
| Interventions       | 5       | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 3                   |
| Outcomes            | 6a      | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 4                   |
|                     | 6b      | Any changes to trial outcomes after the trial commenced, with reasons         | NA                 |
| Sample size         | 7a      | How sample size was determined                                                 | 4                   |
|                     | 7b      | When applicable, explanation of any interim analyses and stopping guidelines   | NA                 |
| **Randomisation:**  |         |                                                                                |                     |
| Sequence generation | 8a      | Method used to generate the random allocation sequence                         | 2                   |
|                     | 8b      | Type of randomisation; details of any restriction (such as blocking and block size) | 2                   |
| Allocation concealment mechanism | 9   | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 2                   |
| Implementation      | 10      | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 2                   |
| Blinding            | 11a     | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 3                   |
| Item | Description | Page |
|------|-------------|------|
| 11a  | If relevant, description of the similarity of interventions | NA   |
| 12a  | Statistical methods used to compare groups for primary and secondary outcomes | 4    |
| 12b  | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 4    |
| **Results** | | |
| 13a  | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 4    |
| 13b  | For each group, losses and exclusions after randomisation, together with reasons | 4    |
| 14a  | Dates defining the periods of recruitment and follow-up | 4    |
| 14b  | Why the trial ended or was stopped | NA   |
| 15   | A table showing baseline demographic and clinical characteristics for each group | 5    |
| 16   | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | 5,6,7|
| 17a  | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | 5,6,7|
| 17b  | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | -    |
| 18   | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | NA   |
| 19   | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 7    |
| **Discussion** | | |
| 20   | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 9    |
| 21   | Generalisability (external validity, applicability) of the trial findings | 9    |
| 22   | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 8,9  |
| **Other information** | | |
| 23   | Registration number and name of trial registry | 2    |
| 24   | Where the full trial protocol can be accessed, if available | 10   |
| 25   | Sources of funding and other support (such as supply of drugs), role of funders | 9    |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).*