

Pre-emptive intravenous ketamine analgesia in patients undergoing laparoscopic cholecystectomy: a prospective double blind randomised controlled trial

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ABSTRACT

Introduction: Pre-emptive analgesia is a technique that is initiated before noxious stimuli is experienced and has been shown to lower the pain intensity when compared to analgesics administered after the surgical incision. As previous studies were inconclusive in determining the optimal dose, this prospective double blind randomised controlled trial was carried out to evaluate if pain could be alleviated when comparing low doses of intravenous ketamine for pre-emptive analgesia. **Materials and Methods:** Seventy eight patients undergoing laparoscopic cholecystectomy were prospectively recruited and randomised into 3 groups after obtaining written consent: Group 1 (placebo); Group 2 (IV ketamine 0.25 mg/kg); and Group 3 (IV ketamine 0.5 mg/kg). All study drugs were given 5 minutes after endotracheal intubation prior to surgical incision. Blood pressure and heart rate were recorded before and after induction of anaesthesia and subsequently at 5 minute intervals for 30 minutes after the study drug was given. Post-operative pain control was evaluated through visual analogue scale (VAS) at 0, 3, 6, 12 and 24 hours post-operatively. Any adverse effects of ketamine were documented. **Results:** Group 3 patients had significantly lower VAS scores at 0, 3, 6 and 24 hours post-operatively compared to patients in Group 1. Groups 1 and 2 patients did not have significantly different VAS scores throughout the study period. Haemodynamic parameters including heart rate and mean arterial pressure were not significantly different among the three groups. Side effects documented were nausea, vomiting and blurring of vision. **Conclusion:** IV ketamine 0.5 mg/kg showed significant pre-emptive analgesic effects when compared to IV ketamine 0.25 mg/kg and placebo, in patients undergoing laparoscopic cholecystectomy.

Keywords: ketamine, analgesia, pain relief, laparoscopic cholecystectomy, adverse effects

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INTRODUCTION

Peripheral sensitisation begins with tissue injury which will incite the release of inflammatory mediators and nociceptive chemical

substances. This increases the sensitivity and responsiveness of high threshold nociceptive afferent neurons.¹⁻³ Persistent afferent inputs may lead to an increase in excitability of spinal cord neurons, widely termed as central sensitisation.¹⁻⁴ By decreasing the pain threshold and amplifying the noxious stimuli, both of these sensitisation processes can result in increased response to pain.

Various analgesic modes have been described to manage and minimise post-operative pain in order to decrease the pain score and improve early mobilisation. The approach ranges from skin infiltration with local analgesics to provision of strong opioids or non-opioid based analgesics. Several reviews have shown that opioids produce not only analgesia but are reported to be associated with the incidence of hyperalgesia.^{2-3, 5} Although opioids have a high efficacy for pain relief, unwanted side effects such as post-operative nausea and vomiting (PONV), drowsiness, respiratory depression, gastrointestinal and bladder dysfunction, have led to further research for alternative analgesia in the post-operative setting.²

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. It also acts on other nociceptive related sites including the muscarinic, monoaminergic and opioid receptors as well as voltage gated sodium and L-typed calcium channels. It prevents central sensitisation and assists in neural modulation by blocking the spinal cord neurons from hyper-excitability peripheral nociceptive stimulation.^{3-4, 6} Low-dose ketamine defined as either an intramuscular bolus of less than 2 mg/kg given via the intravenous (IV) or epidural route has been previously

reported to be effective for relieving post-operative pain.^{5, 7} The lower but effective ketamine dose serves as an opioid-sparing drug which plays an important role in the treatment of acute post-operative pain.⁵ Ketamine has been found to be effective for pre-emptive analgesia in patients undergoing various types of surgical procedures.⁴⁻⁵

Pre-emptive analgesia was first introduced into clinical practice by Crile in 1913 and was further developed by Wall and Woolf.^{2, 8} It is a technique that is initiated before noxious stimuli is experienced. It aims to reduce the physiological consequences of nociceptive transmission provoked by the operative procedure. It has been shown to lower the pain intensity when compared to analgesics administered after the surgical incision.⁹⁻¹⁰ Review of the literature has reported ketamine's role as an adjuvant therapy to be able to provide better anti-nociception by decreasing opioid consumption, prolonging the duration of analgesia while having fewer side effects.¹¹⁻¹⁴

We designed this prospective randomised controlled trial to evaluate the pre-emptive analgesic effects when comparing two low doses of IV ketamine, 0.25 mg/kg versus 0.5 mg/kg in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

Study Design: This prospective, double-blind, randomised controlled trial was carried out after obtaining institutional ethics approval from the Medical Research & Innovation Secretariat, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) (Project Code: FF-437-2012).

Study Population: Patients recruited were given an explanation on the study and written consents were obtained. Seventy eight American Society of Anaesthesiologist (ASA) physical status I or II patients, aged between 18 to 70 years, scheduled for laparoscopic cholecystectomy were recruited into the study. Patients with a history of seizures or pre-existing neurological illness, history of chronic pain, long-term use of analgesic medications, history of psychiatric illness, morbid obesity with body mass index (BMI) more than 35kg/m², history of ischaemic heart disease and those with known allergies or any contraindications to any of the study drugs were excluded from this study. During pre-operative assessment rounds, patients were instructed on the use of the visual analogue scale (VAS). Midazolam 7.5mg tablet was prescribed orally the night before surgery and when called to the operation theatre. Patients aged above 65 years received tablet midazolam 3.75mg instead.

Randomisation: Randomisation codes were generated using computer generated randomised numbers into three arms. Randomisation codes were then concealed into opaque non-translucent white envelopes in sequential numbers. Upon obtaining informed consent, each sequential numbered envelope were opened and patients were allocated based on the randomisation codes into 3 groups: Group 1 (placebo), Group 2 (IV racemic ketamine 0.25mg/kg) or Group 3 (IV racemic ketamine 0.5mg/kg). A 10ml syringe containing either placebo, 0.25mg/kg or 0.5mg/kg of ketamine diluted with isotonic sodium chloride solution was prepared by the primary investigator. These syringes were labelled according to the patient's study num-

ber. Recruited patients, attending anaesthetists, surgeons and nursing staff in the operation room were all blinded to the study drugs to ensure treatment blinding is maintained.

Study Interventions: In the operating room, peripheral IV access was obtained with an 18 Gauge cannula in all patients. Standard monitoring with continuous electrocardiography, non-invasive blood pressure, pulse oximetry and capnograph were used peri-operatively. Blood pressure (BP) and heart rate (HR) were recorded before induction, after intubation, and at every 5 minute intervals up to a maximum of 30 minutes following study drug administration. Patients were pre-oxygenated with 100% oxygen for 3 minutes. General anaesthesia was induced with IV fentanyl 1.5 mcg/kg, IV propofol 2-3mg/kg and IV rocuronium 0.6mg/kg. Patients were manually ventilated via face mask for 3 minutes with 100% oxygen and sevoflurane. They were then intubated with an appropriate sized endotracheal tube. Prophylactic IV dexamethasone 8 mg was given after induction of anaesthesia for post-operative nausea and vomiting (PONV). Anaesthesia was maintained with oxygen, air and sevoflurane mixture to achieve a MAC of 1.0-1.2. All patients received the assigned study drug according to their randomised grouping, delivered by the same investigator who prepared the drug. The study drug was given 5 minutes after endotracheal intubation and prior to surgical incision. The study drug was administered over 1 minute. Ten ml of local anaesthetic 0.5% plain levobupivacaine was infiltrated at the skin by the surgeon prior to the incision. Intravenous morphine 0.05 mg/kg was given 30 minutes after administration of the study drug. Both IV parecoxib 40 mg and IV grani-

setron 1mg were given 30 minutes before the end of the surgery. At the end of surgery and prior to skin closure, adequate decompression of surgical pneumo-peritoneum was performed. IV neostigmine 2.5mg and IV atropine 1.0mg was given for reversal of muscle relaxation and to facilitate extubation of the trachea.

After completion of surgery, patients were transferred to the post-anaesthesia recovery area. Patients' VAS score (ranging from 0 = no pain to 10 = worst pain imaginable) was assessed at 0, 3, 6, 12 and 24 hours post-operatively. Time zero (0 hour) was the time taken upon discharge from the recovery area. The pain scores from time zero onwards were recorded. The VAS score was assessed by trained nurses (who were blinded to the study drug given) in the recovery area and in the ward. If the VAS score exceeded 3, IV tramadol 50 mg was given as rescue analgesia. In the ward, patients were given tablet etoricoxib 120 mg as a single daily oral dose, 6 hours after being discharged from the recovery area. Adverse effects of ketamine such as nausea, vomiting, blurring of vision and hallucinations, if present, were managed accordingly and patients reassured that the effects would be transient. If patients experienced nausea or vomiting, IV metoclopramide 10 mg was administered.

Study outcomes: The primary outcome was to determine if pain can be alleviated through pre-emptive analgesic effects when comparing 2 low doses of IV ketamine, 0.25mg/kg versus 0.5mg/kg in patients undergoing laparoscopic cholecystectomy. Patients' VAS score for pain at 0, 3, 6, 12 and 24 hours post-operatively were assessed and recorded. As secondary outcomes, rescue analgesia with tramadol in the recovery area as well as in the wards and adverse effects related to the study drug were observed. Any interventions required were documented.

Sample size and Statistical Analysis: The sample size was estimated based on a previous study by Bilgin *et al.*⁸ Using a power and sample size calculator version 3.1.2 (2009) for continuous equivalence trials, 22 patients per group were required to detect a difference of at least 20% in VAS score. With the alpha (α) value of 0.05 and power of 80% while allowing for an additional dropout rate of 20%, a total of 78 patients were recruited.

Data analysis was performed with an intention to treat approach using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows version 20.0.0 Armonk, New York. Analysis of variance (ANOVA) and Chi-Square test were used where appropriate. A p value <0.05 was considered statistically significant.

Table 1: Demographic data and duration of surgeries

	Group 1 (n=26)	Group 2 (n=26)	Group 3 (n=26)
Age (years)	52.3 $\pm$ 13.2	47.1 $\pm$ 12.5	47.0 $\pm$ 12.0
BMI (kg/m ²)	26.5 $\pm$ 3.7	26.3 $\pm$ 3.7	26.2 $\pm$ 3.9
ASA status			
I	17 (65%)	15 (58%)	17 (65%)
II	9 (35%)	11 (42%)	9 (35%)
Gender			
Male	2 (8%)	6 (23%)	8 (31%)
Female	24 (92%)	20 (77%)	18 (69%)
Duration of surgery (minutes)	86.2 $\pm$ 30.9	89.0 $\pm$ 25.1	92.3 $\pm$ 33.1

RESULTS

Seventy eight patients were recruited into the study. None of the patients required conversion to open cholecystectomy. There were no significant differences in the demographic data and duration of surgery among the three groups as shown in Table 1.

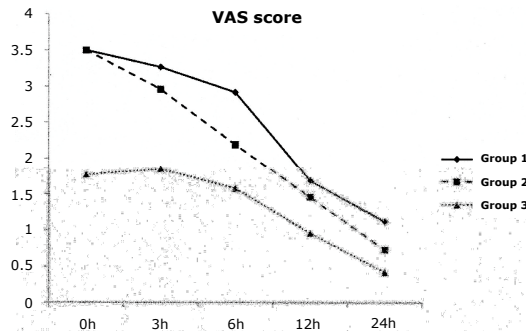


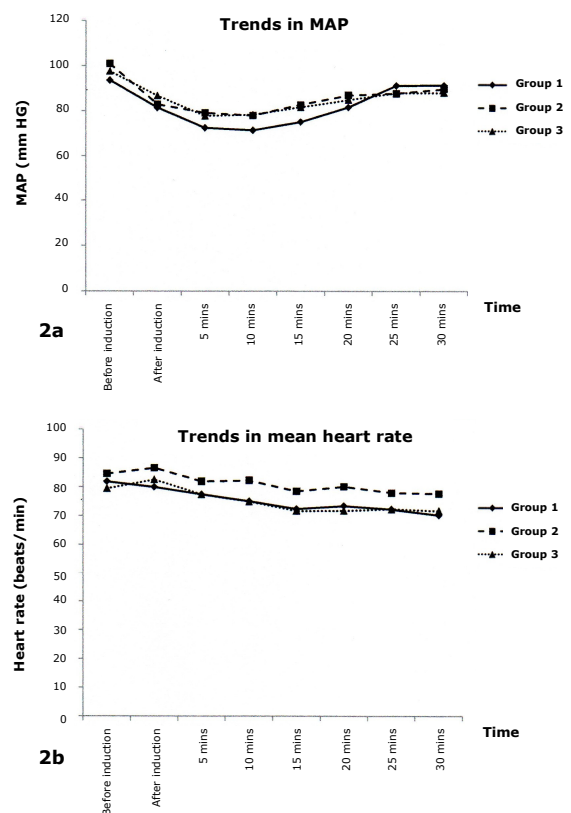
Fig. 1: Trends in VAS score over time among the three groups.

All recorded mean VAS scores were less than four as shown in Table 2. The trends in VAS scores over time among the three groups can be seen in Figure 1. No statistically significant differences were noted between Group 1 and 2 throughout the study period. Group 3 scored significantly lower VAS scores than Group 1 and Group 2 at 0 hour ($p=0.016$ and 0.016) and 3 hours ($p=0.002$ and 0.016) post-operatively respectively. At 6 and 24 hours after the surgery, patients in Group 3 also scored significantly lower VAS when compared with patients in Group 1 ($p=0.002$ and 0.023 respectively). However, no statistically significant differences were noted among three groups' VAS scores at 12 hours post-operatively ($p=0.056$).

Group 1 received significantly higher

IV tramadol dose at 73.1 ± 40.6 mg as rescue analgesia when compared to Group 2 and 3 patients who received 48.1 ± 41.2 mg and 13.5 ± 26.7 mg each ($p=0.043$ and <0.001 respectively). Group 2 also required higher doses of analgesics when compared to Group 3 and this was statistically significant ($p=0.003$) (Table 2).

There were no significant changes in



Figs. 2: a) MAP trends among the three groups, and b) Heart rates trends among the three groups.

TABLE 2: Mean VAS scores and total rescue analgesia among the 3 groups.

Time (hours)	Group 1 (n=26)	Group 2 (n=26)	Group 3 (n=26)	p value
0	3.5 ± 2.4	3.5 ± 2.5	1.8 ± 1.5	0.016* [§]
3	3.3 ± 1.8	3.0 ± 1.3	1.9 ± 1.0	0.002*; 0.016 [§]
6	2.9 ± 1.4	2.2 ± 0.9	1.6 ± 1.7	0.002*
12	1.7 ± 1.1	1.5 ± 1.1	1.0 ± 1.2	0.056
24	1.1 ± 1.2	0.7 ± 0.7	0.4 ± 0.8 *	0.023*
Total tramadol (mg)				
0	3 (10.0)	7 (23.3)	20 (66.7)	< 0.001
50	10 (33.3)	15 (50.0)	5 (16.7)	< 0.001 [§]
>100	13 (72.2)	4 (22.2)	1 (5.6)	< 0.001

Values expressed as mean ± SD, number (n) and percentage in parentheses where appropriate.

*Significant difference between Groups 1 and 3; and [§] Significant difference between Groups 2 and 3

the mean arterial pressure (MAP) and mean heart rate respectively among study groups (Figure 2b).

The incidences of PONV were 7.7%, 11.5% and 30.8% in Groups 1, 2 and 3 respectively and were comparable in all groups. One patient (3.8%) each in Group 2 and Group 3 reported transient blurring of vision post-operatively in the ward, which resolved spontaneously within a few hours. No patients complained of hallucinations in the post-operative period (Table 3).

DISCUSSION

Various analgesic drugs and modalities have been used to manage post-operative pain in laparoscopic surgery. The ideal analgesic modality used should be able to decrease pain scores, improve early mobilisation and rehabilitation with the least side effects.¹¹ Different doses of ketamine have been studied in the past. Most studies reported that low dose IV ketamine had no significant pre-emptive effects.¹⁶⁻²⁰ However, our study demonstrated that 0.5mg/kg of IV ketamine significantly reduced the VAS score when compared to placebo post-operatively. This low but effective ketamine dose at 0.5 mg/kg was similarly found by Singh *et al.* who demonstrated that this low dose exerted significant pre-emptive analgesic effect and consistently reduced VAS scores and rescue analgesic requirements.¹² Despite a mixed outcome from previous studies, the role of low dose ketamine warrants further evaluation to ensure that post-operative pain management is optimally achieved.

Ketamine exerts its analgesic effect when the plasma concentration reaches a lev-

Table 3: Side effects between the three groups.

Side effects	Group 1 (n=26)	Group 2 (n=26)	Group 3 (n=26)	p value
Nausea	1 (3.8)	3 (11.5)	6 (23.1)	0.113
Vomiting	1 (3.8)	0 (0)	2 (7.7)	0.353
Hallucination	0 (0)	0 (0)	0 (0)	-
Blurring of vision	0 (0)	1 (3.8)	1 (3.8)	0.599

el beyond 100 ng/ml.^{13, 20} Thus the dose of ketamine given must be high enough to reach and maintain this therapeutic plasma analgesic concentration level. At this plasma level, nociceptive input at the NMDA receptor is completely suppressed.²¹ There was no pre-emptive effect among patients who received IV ketamine 0.25 mg/kg in our study. We postulated that the therapeutic plasma ketamine levels in these patients were insufficient to exceed the required analgesic target of 100 ng/ml. However, we did not measure the serum concentration of ketamine in our study. In 2012, Adam *et al.* found that very low dose IV ketamine at 0.15 mg/kg had no significant pre-emptive effects among patients undergoing laparoscopic cholecystectomy.¹¹ The lack of efficacy in the ketamine-alone group could be due to under-dosing and the authors had suggested that a higher dose of ketamine could be more effective. Mathisen *et al.* used R(-)-ketamine in their study due to the lower tendency for neurological side effects but found no pre-emptive analgesic effect when used in doses up to 1.0 mg/kg.¹⁶ They concluded that the absence of pre-emptive effect was due to the difference in potency between the ketamine stereo-isomers in which S(+)-ketamine is two and four folds more potent

Than R(-)-ketamine and racemic ketamine respectively. There is a role for further research into using low dose S(+)-ketamine as an adjuvant for peri-operative analgesia.

Ketamine stimulates the sympathetic nervous system thus increasing circulating levels of catecholamines leading to transient tachycardia and a rise in blood pressure.¹⁵ Our patients did not have significant differences in their haemodynamic parameters. Most studies quoted no significant difference in the haemodynamic parameters between placebo and IV ketamine when doses of less than 1.0 mg/kg were used.^{12, 13, 19} Singh *et al.* found that the mean heart rate was significantly higher in the group who received 1 mg/kg of IV ketamine but the mean heart rate was low in the 0.75 mg/kg and 0.5 mg/kg groups as compared to the control group.¹²

Ketamine is proven as an effective adjunct to other analgesic drugs when used as part of multimodal analgesia.² Combining ketamine and opioids can decrease opioid consumption and prolong the duration of analgesia post-operatively.^{12, 22} A study by Lau-no *et al.* showed that intra-operative administration of 0.7 mg/kg IV ketamine reduced the average amount of rescue tramadol dose post-operatively.²² This finding was consistent with our study whereby significant reduction in post-operative rescue analgesic consumption was found in the ketamine groups when compared to the placebo group.

The perceived severity of nociception can be dissimilar due to the differences in stress response from different types of surgeries.²³ We standardised the degree of noci-

ception by studying only patients undergoing elective laparoscopic cholecystectomy. However, surgeries done in recruited patients were not performed by a single surgeon. Differing surgical skills including the surgeons' experience when operating under low or standard surgical pneumo-peritoneum can result in different pain perception among the patients.

Common ketamine side effects are nausea, vomiting, hallucinations, vivid dreams and blurring of vision. However, when higher ketamine doses exceeding 2mg/kg are given, the incidence of psychotomimetic side effects increases.^{7, 10} There is less tissue trauma with minimally invasive surgery leading to lesser peri-operative noxious input. Therefore, lower IV ketamine dose would be adequate for analgesia without causing significant psychotomimetic side effects.^{4, 7} Similarly, patients in our study did not have significant psychotomimetic effects at doses of 0.25 mg/kg and 0.5 mg/kg IV ketamine.

This study was not without limitations. We did not differentiate the VAS score according to different levels of pain during rest and ambulation. The VAS score was neither correlated to the timing of standard post-operative analgesic medications nor the rescue IV analgesic drugs. There was no documentation of before and after pain relief scores following the administration of the analgesic drugs.

In conclusion, patients undergoing laparoscopic cholecystectomy who received IV ketamine 0.5mg/kg had significant pre-emptive analgesic effect and required less post-operative analgesia when compared to

those who received IV ketamine 0.25mg/kg. The favourable haemodynamic and insignificant side effect profile of low dose ketamine also makes it a suitable choice as a pre-emptive analgesic.

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