

KETAMINE INFUSION VERSUS SINGLE BOLUS FOR PREVENTION OF TOURNIQUET-INDUCED HYPERTENSION: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: The prolonged use of a tourniquet can cause tourniquet-induced hypertension (TIH). Low dose ketamine has been shown to prevent the incidence of TIH. This prospective double blind study was carried out to compare the effectiveness of ketamine infusion versus single bolus in preventing TIH.

Method: Patients were randomized into two groups: Group B (ketamine bolus 0.2 mg/kg followed by saline infusion) and Group I (ketamine bolus 0.2 mg/kg followed by 2 µg/kg/min infusion). A study drug bolus was given prior to tourniquet inflation and infusion was started at time of tourniquet inflation. Systolic/diastolic blood pressure and heart rate relative to tourniquet inflation and deflation were recorded at 10 minute intervals. Incidence of TIH and ketamine related side effects at 30 minutes and 24 hours post-surgery were recorded.

Results: Fifty two patients were analyzed up to 110 minutes of tourniquet inflation. The changes in hemodynamics between Groups B and I were comparable to each other. TIH occurred in Group B only (15.4%) but this was not statistically significant ($p = 0.114$). Two patients in Group I developed ketamine related side effects at 30 minutes post surgery.

Conclusion: Ketamine bolus followed by ketamine infusion was found to be comparable to a single bolus ketamine bolus given prior to tourniquet inflation in reducing the incidence of TIH among patients undergoing lower limb surgery under general anesthesia.

Keywords: Ketamine; tourniquet; hypertension; general anesthesia; tourniquet-induced hypertension

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Introduction

Usage of a pneumatic tourniquet is common in limb surgery¹⁻⁴. However, it can cause a variety of complications⁴. Tourniquet inflation causes an increase in systemic vascular resistance. This shifts blood volume into the central circulation resulting in an increase in systolic arterial pressure which is normally transient and seen at the beginning of inflation^{4,5}. The initial transient increase in systolic pressure averages only 18 mmHg in pressure⁶. A second gradual increase in arterial pressure is subsequently seen 30-60 minutes after inflation of the tourniquet. Prolonged tourniquet inflation results in pain and an increase in heart rate and blood pressure^{4,5,6}.

Kaufman *et al* demonstrated that the overall incidence of tourniquet-induced hypertension in surgery was 11%⁶. This did not take into consideration the anesthetic technique used. Tourniquet-induced hypertension (TIH) is defined as more than 30% increase in arterial blood pressure above baseline, after tourniquet inflation exceeding 30 minutes^{1,7}. This phenomenon develops despite giving adequate general anesthesia and can also occur despite adequate regional anesthesia⁸. In order to counteract the resultant increase in heart rate and blood pressure, depth of anesthesia is usually increased. This opens up the possibility of exposing patients to unwanted side effects from the anesthetics as well as prolongs time for patients to fully recover⁹.

Various intravenous agents such as dexmedetomidine, remifentanyl, magnesium sulphate, propofol or ketamine have been studied to reduce the development of TIH^{1,2,10-13}. Ketamine is a non-competitive N-methyl-D aspartate (NMDA) receptor antagonist. It is used as an anesthetic agent and can also be used as a supplement in regional and local anesthesia¹⁴. Clinical use of ketamine is limited however due to psychomimetic adverse effects such as hallucinations, bad dreams, dizziness, blurred vision, nausea and vomiting. At low doses of 0.1-0.5 mg/kg, it has an analgesic action especially when given preemptively^{15,16}.

Park *et al* and Satsumae *et al* demonstrated TIH during prolonged tourniquet inflation in orthopedic lower limb surgery under general anesthesia^{1,10}. Both

studies were conducted with a tourniquet inflation time of up to one hour. To our knowledge, no studies have looked at the effectiveness of ketamine bolus when tourniquet inflation time exceeds more than one hour. There are also no known studies investigating the effectiveness of ketamine infusion on TIH.

We designed this study to evaluate two different methods of ketamine administration in the prevention of TIH.

Methods

This prospective, double-blind, randomized controlled trial was conducted after obtaining our institution's ethics committee approval, from the Medical Research & Innovation Secretariat, Universiti Kebangsaan Malaysia Medical Centre (UKMMC).

Patients aged between 18 to 60 years old with American Society of Anesthesiologists (ASA) physical status I or II undergoing lower limb surgery under general anesthesia were recruited into the study after obtaining their written informed consents. Patients with known allergy to the study drug, hypertensive or on regular analgesics with/without chronic pain and those with a Body Mass Index (BMI) of more than 35 kg/m² were excluded.

Randomization codes were generated using computerized generated randomized numbers into two arms and were then concealed into opaque non-translucent white envelopes in sequential numbers. Upon obtaining informed consent, each sequential numbered envelope was opened and patients were allocated using the codes into two groups: Group B (ketamine bolus 0.2 mg/kg, followed by saline infusion as placebo) and Group I (ketamine infusion-0.2 mg/kg bolus followed by 2 µg/kg/min ketamine infusion).

The study drugs were prepared and labelled by the primary investigator according to the patients study number. Intravenous (IV) bolus preparation was done in a 10 ml syringe containing 0.2 mg/kg of ketamine diluted in an isotonic sodium chloride solution. A 20 ml syringe was used for IV infusion preparation, containing either 50 mg ketamine in isotonic sodium chloride or plain isotonic sodium chloride solution as

placebo. The attending anesthetists who collected the data were blinded to the content of these syringes.

Preoperatively, oral midazolam 7.5 mg was given as premedication to all patients prior to being sent to the operating theater. In the operating room, intravenous access using an IV cannula (20 Gauge) was established and standard monitoring applied with continuous electrocardiography, non-invasive blood pressure, and pulse oximetry. Before induction of anesthesia, a baseline blood pressure and heart rate was recorded. Anesthesia was induced with 2 mg/kg of propofol and 1 µg/kg of fentanyl. IV morphine of 0.1 mg/kg was given as analgesia. An appropriately sized Proseal Laryngeal Mask airway (PLMA) was used to secure the patient's airway and capnography was monitored continuously. Anesthesia was maintained with sevoflurane in oxygen, and its end-tidal concentration was adjusted to attain a Minimum Alveolar Concentration of 1.1-1.3 in 50:50 oxygen mixed with air.

Both groups received the IV bolus of the study drug just prior to tourniquet inflation. A pneumatic tourniquet, Automated Tourniquet System (A.T.S. 2000), was applied to the relevant limb and inflated at 100 mmHg above the systolic blood pressure. A tourniquet cuff size of 15 cm for the lower limb was used. At the time of tourniquet inflation, infusion of the respective study drugs was then commenced at a rate of 2 µg/kg/min.

The time of tourniquet inflation was denoted as time at 0 minute. Systolic and diastolic blood pressure and heart rate (HR) were documented at 10 minute intervals. During the study period, we defined a patient developing TIH when the systolic blood pressure (SBP) increased to more than 30% of baseline value after 30 minutes of tourniquet inflation time. If the SBP or DBP remained raised above 30% from baseline values following three rescue boluses of IV fentanyl 0.5 µg/kg, then IV labetalol 2.5 mg boluses were given.

The infusion of the study drug or placebo was stopped after tourniquet deflation. At the end of surgery, anesthesia was discontinued and PLMA was removed. The BP immediately after tourniquet deflation was documented. Post-surgery patients were screened twice for possible ketamine-related side effects such

as hallucinations, nightmares, agitation and delirium. These were managed accordingly and patients reassured that the effects would be transient. This was done at 30 minutes post-surgery in the recovery area and at 24-hours post-surgery in the ward by anesthetic trainees on duty who were blinded to the allocation of the drug regime given.

Statistical Analysis

The sample size estimation was derived using the mean maximum systolic blood pressure and standard deviation, based on a previous study done by Elmawgood *et al.*¹² Using a power and sample size calculator program version 3.1.2 (2009), 23 patients per group were calculated using Student's t-test. With the alpha (α) value of 0.05 and power of 80% while allowing for an additional dropout rate of 10%, our study required 52 patients in total.

Data analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Macintosh version 23 Armonk, New York. Numerical data were analyzed using Student's t-test. Categorical data were analyzed using Chi-square test. A *p* value of <0.05 was considered statistically significant.

Results

Fifty-two patients were recruited into the study. There were no significant differences in the demographic data between the two groups as shown in Table 1.

There was no significant difference in baseline mean SBP between the two groups before induction of anesthesia. There was a significant reduction in SBP from baseline in Group I at 30 minutes and 40 minutes of tourniquet inflation. In Group B, the SBP was significantly higher at 80, 90, 100 and 110 minutes of tourniquet inflation compared to baseline. There was no significant difference in SBP between both groups throughout the study period.

There was no significant difference in baseline mean DBP between the two groups before induction of

Table 1

Demographic data and duration of tourniquet are expressed as mean (SD) or number (percentage)

| | Group B (n = 26) | Group I (n = 26) |
|----------------------------------|---------------------|---------------------|
| Age (years) | 45.0 ± 11.6 | 44.7 ± 12.5 |
| Gender | Male | 16 (61.5%) |
| | Female | 10 (38.5%) |
| ASA | I | 15 (57.7%) |
| | II | 11 (42.3%) |
| BMI (kg/m ²) | 24.9 ± 3.0 | 25.3 ± 4.1 |
| Duration of tourniquet (minutes) | 98 ± 8 | 103 ± 13 |

anesthesia. A significant difference in DBP compared to baseline at 100 minutes was seen in Group B. The DBP in Group B was significantly higher at 80 and 90 minutes when compared to Group I.

There was no significant difference in baseline HR between the two groups before induction of anesthesia. HR in Group B was significantly increased compared to baseline from 10 minutes to 110 minutes tourniquet inflation time. No significant heart rate changes were seen in Group I when compared to their baseline. A significant difference was seen between the two groups at the 110 minute tourniquet inflation time.

Four out of 26 patients in Group B showed TIH (15.4%). In Group I, none of the patients developed TIH. However, there was no significant difference between the two groups ($p = 0.114$). None of the patients required any boluses of IV labetalol to treat TIH (Table 2).

Two patients from the Group I exhibited ketamine-related side effects (hallucinations and nightmares) at 30 minutes post-surgery and none at 24 hours post-surgery. None of the patients in Group B had ketamine-related side effects. There was no significant difference in ketamine related side effects between the two groups ($p = 0.205$).

Table 2

Incidence of Tourniquet-induced hypertension between Group B and Group I at each 10 minute intervals of tourniquet inflation, expressed as number and percentage in parentheses where appropriate

| Duration of tourniquet inflation (minutes) | Group B (n = 26) | Group I (n = 26) |
|--|---------------------|---------------------|
| 30 | 1 (3.8%) | 0 (0.0%) |
| 40 | 0 (0.0%) | 0 (0.0%) |
| 50 | 0 (0.0%) | 0 (0.0%) |
| 60 | 0 (0.0%) | 0 (0.0%) |
| 70 | 0 (0.0%) | 0 (0.0%) |
| 80 | 2 (7.6%) | 0 (0.0%) |
| 90 | 3 (11.5%) | 0 (0.0%) |
| 100 | 1 (10%) | 0 (0.0%) |
| 110 | 0 (0.0%) | 0 (0.0%) |

Discussion

Our study showed interesting patterns of cardiovascular (CVS) parameter changes in both groups. The SBP rise seen in Group B are similar to some previous studies^{1,2}. Takada *et al* studied awake volunteers while Park *et al* investigated patients undergoing lower limb surgery under general anesthesia, where both administered 0.1 mg/kg bolus dose of IV ketamine prior to tourniquet inflation in their studies^{1,2}. The maximum tourniquet inflation duration of about 45 minutes was taken in the study by Takada *et al* and 60 minutes in the study by Park *et al*^{1,2}. Similarly, both studies observed significant SBP rise in the control arms (saline only) and insignificant SBP changes in the ketamine groups from baseline during tourniquet inflation. When the ketamine groups were compared to control groups up to 60 minutes, they were not statistically different. In contrast to both studies which limited the duration of tourniquet inflation time up to one hour, we administered a higher bolus dose of 0.2 mg/kg IV ketamine and did not limit the duration of tourniquet inflation time

taken. We were able to demonstrate insignificant SBP changes from baseline up to 80 minutes of tourniquet inflation duration in the bolus group. Therefore, we postulate that the larger bolus dose used in our study allowed us the extension of the duration of tourniquet inflation without causing significant SBP changes. This duration was further extended up to 110 minutes as shown in our study when the bolus administration was followed by an infusion of IV ketamine during tourniquet inflation.

When IV ketamine was administered as such in our study with an infusion, we observed better CVS parameter profiles when compared to their baseline readings. Satsumae *et al* postulated that the activation of NMDA receptors may contribute to the cause of arterial blood pressure increase during tourniquet inflation^{10,13}. These findings suggest that a bolus dose followed by an infusion of IV ketamine during tourniquet inflation may delay the first peak effects of tourniquet inflation and delay the onset of any significant SBP changes from baseline as ketamine infusion results in continued deactivation of the NMDA receptors.

Intravenous bolus of low dose ketamine when given prior to the inflation of the tourniquet variably affects the heart rate following tourniquet inflation. Park *et al* showed that heart rates increased from the baseline similar to our study¹. However, Takada *et al* using the same bolus dose as Park *et al* did not detect any significant changes in the heart rate from the baseline^{1,2} and neither did Satsumae *et al* who used an even higher IV ketamine bolus of 0.25 mg/kg¹⁰. In our study, the heart rates did not change significantly from baseline in Group I even when ketamine was infused at 2 µg/kg/min.

Few studies had shown that low dose IV ketamine bolus prior to tourniquet inflation resulted in a lesser percentage of patients developing TIH^{1,10,17}. Park *et al* in their study were not able to detect a significant difference of TIH incidence when compared to the control group¹. Whereas, Satsumae *et al* using a larger bolus dose of IV ketamine 0.25 mg/kg were able to demonstrate a statistically significant reduction in incidence of TIH when compared to their control group¹⁰. While these studies looked at how low dose bolus of IV ketamine affects the incidence of TIH, our study instead compared the incidence of TIH between

low dose bolus of IV ketamine with and without an infusion of IV ketamine during tourniquet inflation. To date, no similar study has been done. In our study, although TIH was only seen in Group B (15.4%), this difference between groups was statistically insignificant. This finding would perhaps be stronger if we were able to compare it to a control group of placebo only.

As there are no earlier studies done using ketamine infusion during tourniquet inflation, we did not have any reference to base our infusion rate used in our study. Thus, we decided on a ketamine infusion rate to administer after reviewing the proposed infusion regimen by Himmelseher *et al*¹⁸. An increase in ketamine-related side effects were not seen in his review postoperatively. As a result, we chose an infusion rate of 2 µg/kg/min during tourniquet inflation. In contrast, we detected ketamine-related side effects 30 minutes post-surgery however it was not significant. Previous studies reported the safety of infusing IV ketamine for a prolonged duration without causing significant side effects. Guignard *et al* studied the use of ketamine infusion for approximately four hours to reduce perioperative analgesic requirements in abdominal surgery while Yeom *et al* used ketamine infusion intraoperatively and continued it postoperatively for a total of 48 hours in reducing postoperative pain for spinal fusion. No ketamine-related side effects were seen in both studies^{19,20}.

This study was not without limitations. Clinically, ketamine bolus followed by ketamine infusion was better at reducing the incidence of TIH when compared to a ketamine bolus alone especially when the tourniquet inflation time extended beyond one hour. However, this was not shown to be statistically significant. The inclusion of a control/placebo only group which would have strengthened the study was considered at the initial phase of designing our study but was later omitted due to ethical reasons. The other limitation of our study was the lack of standardization of the type of lower limb surgery the patients would be undergoing. Nociception stimulation would vary according to the type of surgery. The amount of fluids used, as well as total blood loss intraoperatively were not quantified. These factors could possibly affect the CVS parameters. However, we would assume that

blood loss during surgery would be minimized due to tourniquet usage.

better cardiovascular parameter profiles.

Summary

The administration of IV ketamine bolus followed by IV ketamine infusion was found to be comparable to IV ketamine bolus alone in reducing TIH among patients undergoing lower limb surgery. Nevertheless, the infusion of IV ketamine following ketamine bolus during tourniquet inflation showed

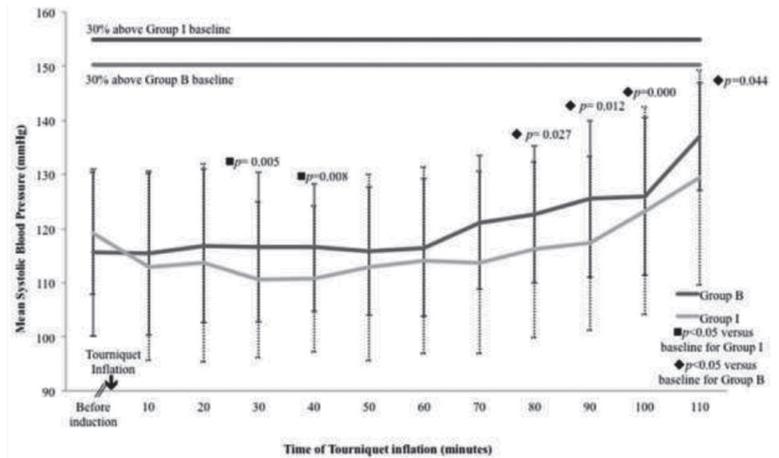
Declaration

The authors received no funding for this study.

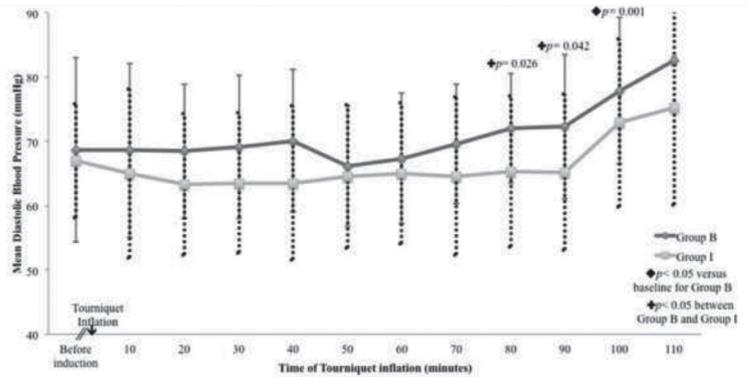
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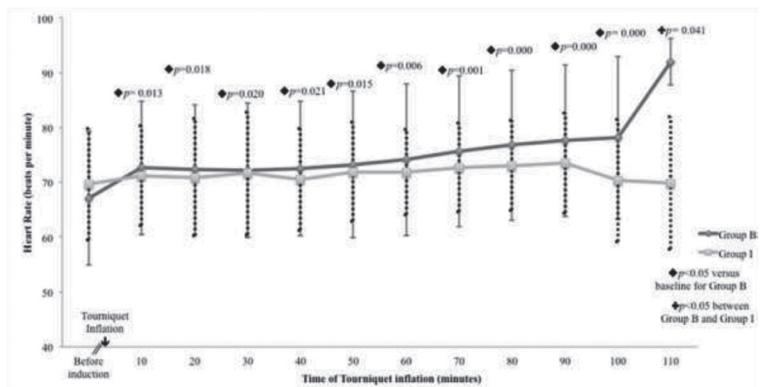
*Fig. 1
Mean systolic blood pressure ± SD over time between Group B and Group I*



*Fig. 2
Mean diastolic blood pressure ± SD over time between Group B and Group I*



*Fig. 3
Mean heart rate ± SD over time between Group B and Group I*



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