Clinical Investigation

Comparison of ketorolac and low-dose ketamine in preventing tourniquet-induced increase in arterial pressure

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ABSTRACT

Background and Aims: Application of tourniquet during orthopaedic procedures causes pain and increase in blood pressure despite adequate anaesthesia and analgesia. In this study, we compared ketorolac with ketamine in patients undergoing elective lower limb surgery with tourniquet in order to discover if ketorolac was equally effective or better than ketamine in preventing tourniquet-induced hypertension. **Methods:** Approval was granted by the Institutional Ethics Review Committee and informed consent was obtained from all participants. A randomised double-blinded controlled trial with 38 patients each in the ketamine and ketorolac groups undergoing elective knee surgery for anterior cruciate ligament repair or reconstruction was conducted. Induction and maintenance of anaesthesia were standardised in all patients, and the minimum alveolar concentration of isoflurane was maintained at 1.2 throughout the study period. One group received ketamine in a dose of 0.25 mg/kg and the other group received 30 mg ketorolac 10 min before tourniquet inflation. Blood pressure was recorded before induction of anaesthesia (baseline) and at 0, 10, 20, 30, 40, 50, and 60 min after tourniquet inflation. **Results:** The demographic and anaesthetic characteristics were similar in the two groups. At 0 and 10 min, tourniquet-induced rise in blood pressure was not observed in both groups. From 20 min onward, both systolic and diastolic blood pressures were significantly higher in ketorolac group compared to ketamine group. **Conclusion:** We conclude that ketamine is superior to ketorolac in preventing tourniquet-induced increases in blood pressure.

Key words: Ketamine, ketorolac, tourniquet pain, tourniquet-induced hypertension

INTRODUCTION

Pneumatic tourniquets are used during orthopaedic procedures on limbs to minimise surgical bleeding and to provide a bloodless surgical field. Tourniquet inflation is associated with pain and an increase in arterial pressure observed 30–60 min after inflation of the tourniquet.[1] The increase in blood pressure is more marked under general anaesthesia and during lower limb surgeries and occurs despite adequate analgesia and depth of anaesthesia.[2,3] It could be deleterious in patients with cardiovascular disease.[4]

The mechanism for the rise in blood pressure seen with tourniquet inflation is not fully understood. A probable cause is the activation of C fibres leading to N-methyl-D-aspartic acid (NMDA) receptor activation which is involved in the process of central sensitisation.[3,5,6] Associated increase in blood pressure is due to sympathetic nervous system response to pain.[6,7] Studies have been performed using different analgesics and NMDA receptor antagonists to find an agent that would effectively attenuate tourniquet-induced increases in systemic arterial pressure.[1-4,7-10] Ketamine, an NMDA receptor antagonist, and a potent analgesic, has been found to be effective in this respect by many researchers.[3,8,9] Comparative analyses among the various agents studied have not been performed, except for comparison between magnesium sulphate and ketamine, both of which are NMDA receptor antagonists.[10] Ketamine can cause cardiovascular side effects, which could be

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deleterious in patients with ischaemic heart disease, although these effects are reduced when ketamine is used in low-doses.[3]

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) often used for perioperative analgesia. It has been shown to be effective in reducing tourniquet pain when used systemically.[11,12] Subarachnoid administration of ketorolac has been demonstrated to have a direct action by blocking hyperalgesia caused by substance P and NMDA receptor stimulation.[12,13] Keeping these actions of ketorolac in view, we compared it with ketamine to see if ketorolac was equally effective in blunting tourniquet-induced rise in blood pressure while avoiding the potential side effects related to ketamine.

METHODS

Ethical approval was obtained from the Institutional Ethics Review Committee (1369-ane-ERC-09) and informed consent was taken from each patient included in the study. A total of 76 patients were recruited and randomly assigned to ketamine group and ketorolac group using sealed opaque envelope technique. The inclusion criteria consisted of patients aged 18 years to 60 years belonging to American Society of Anaesthesiologists (ASA) physical status I and II undergoing elective knee surgery for anterior cruciate ligament repair or reconstruction under general anaesthesia with application of tourniquet for more than 60 min. The exclusion criteria included patients with known hypertension, ischaemic heart disease, diabetes mellitus, renal impairment, asthma, acid peptic disease, chronic obstructive pulmonary disease and patients weighing <50 kg. Patients in whom the tourniquet was deflated within 60 min, those who received epidural or spinal anaesthesia or required additional analgesics other than standardised analgesia provided to all patients were also excluded from the study. The primary investigator and patients were blinded to the identity of the study drug, which was prepared by a post-anaesthesia care unit (PACU) nurse in a volume of 5 ml according to sealed opaque envelope technique.

Uniform anaesthetic management was carried out in all participants. All patients were premedicated with tablet midazolam 7.5 mg 1 h prior to surgery. Monitoring included pulse oximetry, electrocardiogram, capnography, non-invasive blood pressure and inspiratory and expiratory analysis of gases and isoflurane. Induction of anaesthesia was achieved with intravenous (IV) propofol 2 mg/kg, atracurium 0.5 mg/kg and morphine 0.1 mg/kg and all patients were intubated after hand ventilation for 3 min with 40% oxygen in 60% nitrous oxide, and isoflurane delivered through TEC 5® (Datex Ohmeda, Finland) vaporiser. Anaesthesia was maintained with 40% oxygen in 60% nitrous oxide, and minimum alveolar concentration (MAC) of isoflurane was maintained at 1.2 throughout the study period. Volume controlled ventilation was started after endotracheal intubation and was adjusted to keep end-tidal carbon dioxide tension at 33–35 mmHg. IV paracetamol 1000 mg was started at the time of skin incision in all patients and administered over 20 min. Atracurium was administered in boluses of 10 mg at 30–40 min intervals, using a nerve stimulator to maintain a train-of-four count of 1–2 to ensure endotracheal tube tolerance and smooth ventilation. Study drug, either ketamine 0.25 mg/kg or ketorolac 30 mg, was given IV 10 min before tourniquet inflation. Each study drug was drawn in a 5 ml syringe and normal saline was added to achieve a volume of 5 ml by a senior nurse of PACU and the syringe was labelled as 'study drug'. The study drug was administered by the primary anaesthesiologist who was blinded to the grouping. In order to standardise the timing of tourniquet inflation in all patients and keeping in mind the onset of action of both drugs,[14,15] tourniquet was inflated 10 min after administration of the study drug. The tourniquet was applied on the thigh of the surgical side and was inflated to a pressure 100 mmHg above patient's baseline systolic blood pressure (SBP). Baseline SBPs and diastolic blood pressures (DBPs) were calculated as an average of two readings taken 5 min apart before induction of anaesthesia. Blood pressure was recorded at 0 (i.e., at the time of tourniquet inflation), 10, 20, 30, 40, 50 and 60 min after tourniquet inflation time. This marked the end of the study. To ensure patients' safety, authors had planned that if SBP rose to 200 mmHg or higher, fentanyl 100 μg IV would be administered and any further step required to manage hypertension would be left to the discretion of the primary anaesthesiologist. Such patients would be excluded from the study. The anaesthesiologist who charted the blood pressure did not have knowledge of the study protocol. After surgery, the anaesthetic agent was stopped, and the patient was extubated after reversal of neuromuscular blockade.

To estimate the sample size, findings of other researchers[3,8] on effect of ketamine in prevention of tourniquet-induced increases in blood pressure were

considered, according to which ketamine decreased the incidence by up to 60%. Assuming a 30% difference in preventing tourniquet-induced increases in blood pressure between the two groups, a Type I error $\alpha = 0.05$ and Type II error $\beta = 0.10$, an a priori power analysis suggested a sample size of 38 patients for each group.

Data were entered and analysed using Statistical Package for Social Sciences 19.0 (SPSS Inc., Chicago, IL, USA). The primary endpoint of the study was 30% or greater rise in blood pressure up to 60 min after inflation of tourniquet. Mean and standard deviations were estimated for continuous variables (age, blood pressure, weight, and height) and analysed by Student's *t*-test after the test of normality assumption by Kolmogorov–Smirnov. Frequency and percentage were computed for categorical variables (gender, ASA I and II, tourniquet-induced hypertension) and analysed by the Chi-square test and Fisher exact test. $P \leq 0.05$ was considered as statistically significant.

RESULTS

A total of 76 patients undergoing lower limb orthopaedic procedures were included in this study. The average age of the patients was 34.87 ± 11.72 years. 61 patients (80.3%) were male and 15 (19.7%) belonged to the female gender. The demographic and anaesthetic characteristics were not significantly different between groups as shown in Table 1.

No rise in blood pressure was observed in either of the groups at 0 and 10 min after tourniquet inflation and mean SBPs and DBPs were not significantly different between the groups. From 20 min onward, both SBP [Figure 1] and DBPs [Figure 2] were significantly higher in ketorolac group compared to ketamine group. Systolic pressure did not reach 200 mmHg or above in any patient, and therefore none of the recruited patients were excluded from the study.

Table 1: Demographic characteristics of patients

Variable	Ketorolac group (*n*=38)	Ketamine group (*n*=38)
Age (year)	33.50±11.17	36.24±12.24
Weight (kg)	72.39±9.38	71.42±8.72
Height (cm)	157.06±5.23	158.22±4.37
Gender (%)		
Male	30 (78.9)	31 (81.6)
Female	8 (21.1)	7 (18.4)
ASA physical status (%)		
I	29 (23.7)	25 (65.8)
II	9 (23.7)	13 (34.2)

ASA – American Society of Anaesthesiologists

Overall, during the study period, 30% or greater rise in blood pressure was observed in 39.5% (30/76) patients, being significantly higher in ketorolac group compared to ketamine group (65.8% vs. 13.2% $P < 0.001$) as shown in Table 2.

DISCUSSION

The results of this study showed that IV ketamine 0.25 mg/kg administered before inflation of tourniquet was significantly more effective in preventing tourniquet-induced rise in systemic arterial pressure compared to IV ketorolac 30 mg in patients undergoing knee surgery under general anaesthesia. In ketorolac group, both systolic and diastolic pressure trends were higher as compared to the ketamine group from 20 min onward, and the difference was significant from 40 to 60 min after tourniquet inflation.

Other researchers have demonstrated the prevention of tourniquet-induced arterial pressure increases with ketamine. Satsumae *et al*. found that pre-operative administration of 0.25 mg/kg or more IV ketamine to patients undergoing knee surgery significantly prevented tourniquet-induced increases in arterial pressure under general anaesthesia.[3] They compared this dose of ketamine with a higher dose of 1 mg/kg, which also prevented increase in arterial pressure with no psychological problems after anaesthesia. Park *et al*. obtained similar results in a placebo-controlled study with even a smaller dose of ketamine that is, 0.1 mg/kg given 10 min after induction of anaesthesia.[8] Takada *et al*.[9] found that low-dose ketamine attenuates tourniquet pain and arterial pressure increase during high-pressure tourniquet inflation in healthy

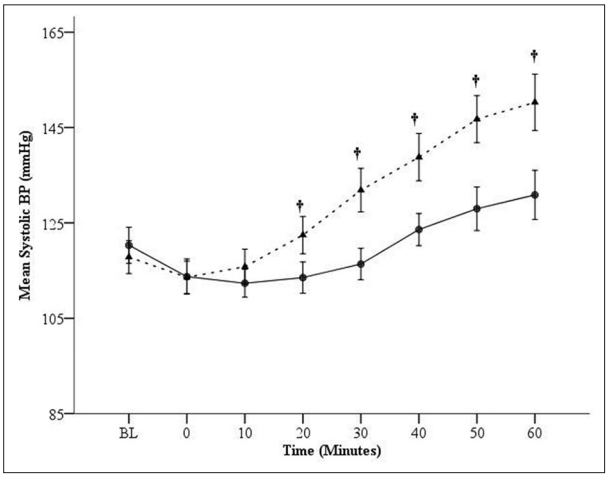

Figure 1: Comparison of mean systolic blood pressure between ketamine (●) and Ketorolac (▲). †Indicates significant difference between groups

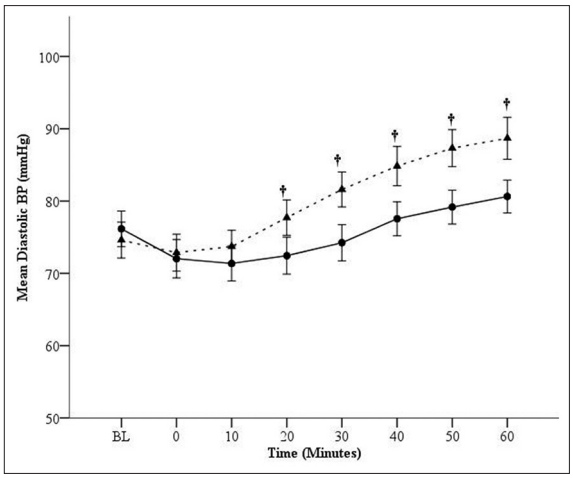

Figure 2: Comparison of mean diastolic blood pressure between ketamine (●) and Ketorolac (▲). †Indicates significant difference between groups

volunteers. Lee *et al.*[10] compared two NMDA antagonists, magnesium sulphate and ketamine, and found them to be equally effective in suppression of tourniquet-induced hypertension. They suggested that this suppression may be due to the reduced pain transmission associated with administration of magnesium and ketamine.

A rise in systolic or diastolic arterial pressure of more than 30% in patients with a tourniquet inflated for more than 30 min has been termed as tourniquet-induced hypertension.[16] We observed that tourniquet-induced hypertension occurred in 65.8% of patients in the ketorolac group compared to 13.2% of those in the ketamine group ($P < 0.001$). The exact mechanism for tourniquet-induced hypertension is not known. NMDA receptor activation due to repeated C fibre stimulation has been proposed as the cause of tourniquet pain and rise in arterial pressure.[3] The pain felt when tourniquet has been inflated for 30 min or more is believed to be related to firing of unmyelinated C-fibres.[10,17] This increase in C fibre activity leads to induction of central sensitisation and activation of NMDA receptors,that is part of the mechanism of central sensitisation.[5,6,18] Although ketamine is an NMDA receptor antagonist and has been shown to be effective in preventing tourniquet-induced hypertension,[3,8,9] there is a possibility that this effect could be due to relief in tourniquet-induced pain rather than antagonism of NMDA receptors, as ketamine has potent analgesic properties. Furthermore, ketamine is associated with side effects, such as, delirium, hallucinations, tachycardia, hypertension, etc.[19] Research has therefore been performed on other drugs to assess if they could effectively prevent tourniquet-induced

Table 2: Comparison of tourniquet-induced hypertension between ketorolac and ketamine groups

Tourniquet-induced hypertension	Ketorolac group (*n*=38) (%)	Ketamine group (*n*=38) (%)	*P*
Overall (during 10-60 min)	25 (65.8)	5 (13.2)	<0.0005*
10 min	0 (0)	0 (0)	NA
20 min	0 (0)	1 (2.6)	0.99
30 min	3 (7.9)	0 (0)	0.24
40 min	10 (26.3)	1 (2.6)	0.003*
50 min	19 (50)	3 (7.9)	0.0005*
60 min	21 (55.3)	3 (7.9)	0.0002*

Data are presented as *n* (%). *Significant difference observed between groups. NA – Not applicable

pain and hypertension and positive results have been obtained with remifentanil,[4] dexmedetomidine,[2] dextromethorphan,[1] etc., However, these agents have not been compared among themselves or with ketamine to see if a better drug could be identified in terms of prevention of tourniquet-induced hypertension, while avoiding potential side effects that could be harmful in patients with ischaemic heart disease.

We compared ketorolac with low-dose ketamine in patients undergoing elective lower limb surgery with tourniquet inflated for at least 1 h to see if it is equal to or more effective than ketamine in attenuating tourniquet-induced blood pressure increases. Ketorolac is a NSAID commonly used for post-operative pain management. In a study conducted by Chabel *et al.*,[20] it was suggested that tourniquet pain may arise from nerve fibre activation directly under the tourniquet, or from ischaemia of nociceptors distal to the tourniquet. It was further suggested that the tissue ischaemia under or distal to the tourniquet leads to release of inflammatory mediators that in turn may cause tourniquet pain. Ketorolac, being a NSAID, may have the potential to attenuate this inflammatory process.[12] Furthermore, ketorolac may have central analgesic effects as its subarachnoid administration has been demonstrated to have a direct action by blocking hyperalgesia caused by substance P and stimulation of NMDA receptors.[12,13] We hypothesised that these actions of ketorolac along with its analgesic effects might prove it to be an effective agent for prevention of tourniquet-induced blood pressure increases. Ketorolac has been used systemically as well as an adjuvant in IV regional anaesthesia to relieve tourniquet pain.[11] However, we found that ketamine was significantly more effective in attenuating tourniquet-induced increases in blood pressure when compared to ketorolac. This superior effect of ketamine further validates the theory that

NMDA receptor activation is the primary mechanism involved in the occurrence of tourniquet-induced hypertension.

A limitation of our study is that we did not use the bispectral index or electroencephalogram to ensure similar anaesthetic depth in all patients because of unavailability of equipment. However, to overcome this issue we closely monitored anaesthetic gases, including isoflurane and maintained a MAC value of 1.2 throughout the study period. Another limitation is that we did not assess the patients for post-operative psychological issues associated with ketamine. However, Satsumae *et al.*,[3] did not find any psychological adverse effects with similar doses of ketamine. Our research population consisted of patients belonging to ASA physical status I and II, while the risk related to tourniquet-induced hypertension would be potentially more harmful in patients with pre-existing cardiovascular disease, especially ischaemic heart disease. We, therefore, recommend that future research should include this patient population so as to assess the degree of attenuation of tourniquet-induced hypertension in patients who would truly benefit from this effect. Moreover, future research should compare the various drugs that have been shown to effectively suppress tourniquet-induced hypertension to discover the best drug for this purpose.

CONCLUSION

We conclude that low-dose ketamine, a potent NMDA receptor antagonist, is more effective in preventing tourniquet-induced rise in arterial pressure than an analgesic dose of ketorolac.

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