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Short communication

Preadministration of low-dose ketamine reduces tourniquet pain in healthy volunteers

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Abstract
We evaluated whether preadministration of low-dose ketamine could attenuate tourniquet pain and arterial pressure increase using high tourniquet pressure in ten healthy awake volunteers. Ketamine, 0.1 mg·kg^{-1}, or normal saline was given intravenously in a double-blind fashion before tourniquet inflation with a pressure of 400 mmHg at the thigh. Visual analog scale (VAS) scores and systolic blood pressure (SBP) were measured at 5-min intervals. Ketamine significantly reduced VAS scores compared to saline just after tourniquet inflation [90 (64–100) mm, median (range), with saline versus 66 (50–81) mm with ketamine, $P < 0.01$] and at 30 min [92 (61–100) mm with saline versus 70 (50–100) mm with ketamine, $P < 0.03$), and significantly prolonged tourniquet time (28 ± 6 min with saline, mean ± SD, versus 37 ± 7 min with ketamine, $P < 0.01$). SBP (120 ± 9 mmHg) significantly increased before tourniquet deflation (133 ± 16 mmHg) in the saline trial, but not in the ketamine trial. The results show that preadministration of low-dose ketamine attenuates tourniquet pain and arterial pressure increase during high-pressure tourniquet application and prolongs tourniquet time in healthy volunteers.

Key words Tourniquet · Pain · *N*-Methyl-D-aspartate

Pneumatic tourniquets are widely used to minimize surgical bleeding during limb surgery. However, tourniquets are sometimes associated with severe tourniquet pain characterized by a gradual onset and dull aching sensation at the site of the tourniquet or distal extremity [1]. Tourniquet inflation often causes a progressive increase in systemic arterial pressure, and it has been reported that an increase in plasma concentration of norepinephrine was related to the tourniquet-induced arterial pressure increase in an experimental study [2]. Segardahl et al. [3] reported that 0.1 mg·kg^{-1} of intravenous ketamine reduced upper limbtourniquet pain induced by a pressure exceeding the systolic blood pressure by 100 mmHg or a minimum of 250 mmHg in healthy awake volunteers. Satsumae et al. [4] showed that preoperative low-dose (0.25 mg·kg^{-1}) intravenous ketamine prevented tourniquet-induced arterial pressure increase under general anesthesia, and suggested that the increase in arterial pressure might have been related to *N*-methyl-D-aspartic acid (NMDA) receptor activation by nociceptive input from the affected limb and that ketamine, an NMDA receptor antagonist, might attenuate tourniquet-induced arterial pressure increase. However, in their reports, the relationship between ketamine dose and tourniquet pressure remains unclear because a ketamine dose of 0.25 mg·kg^{-1} may cause a general anesthetic effect and the lower tourniquet pressure may weaken NMDA receptor activation. This study was designed to evaluate the effect of preadministration of low-dose ketamine (0.1 mg·kg^{-1}) and a tourniquet pressure of 400 mmHg on tourniquet pain in healthy awake volunteers.

With approval of the Institutional Human Committee and written informed consent from the subjects, ten healthy volunteers who were receiving no medication were included in the study (all were men, age 22–50 years, weight 62–85 kg). It was stressed that the subjects could terminate the trial at any time and that participation was voluntary. Subjects were continuously monitored with pulse oximetry, three-lead electrocardiography, and noninvasive blood pressure measurement during the trial. A cubital vein was cannulated for intravenous injection and for obtaining blood samples.

All trials were performed using an 11-cm wide standard orthopedic tourniquet (Zimmer, Dover, OH, USA) for the lower extremities. Tourniquet inflation was performed at the thigh with a pressure of 400 mmHg. Pain was assessed using a visual analog scale (VAS) until maximum pain was reached or until the maximum time of 60 min had expired. A 100-mm hori-

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zontal VAS with end descriptors of "no pain" and "pain as bad as it could be" was used. If the subjects recorded a VAS score of 100 before the end of the 60-min period, they were assigned the maximum value for the rest of the time.

A solution containing ketamine (Ketalar; Parke-Davis, Morris Plains, NJ, USA) 0.1 mg·kg^{-1} or a solution containing only normal saline was given i.v. 5 min before tourniquet inflation (T_0). Each subject received both test substances in a random order. The period between the two trials was more than 1 week. This was a placebo-controlled, double-blinded study.

Measurements included VAS score, tourniquet time (from inflation to deflation), systolic blood pressure (SBP), heart rate (HR), and plasma concentrations of catecholamines (CAs). VAS, SBP, and HR were measured 5 min before tourniquet inflation (T_0) and at 5-min intervals thereafter ($T_{1–13}$). Plasma concentrations of CAs [epinephrine (E) and norepinephrine (NE)] were measured before tourniquet inflation (before the injection of test substance) and just before tourniquet deflation using a fully automated high-performance liquid chromatography–fluorometric system (model HLC-8030 Catecholamine Analyzer, Tosoh, Tokyo, Japan). The interassay and intraassay variations were less than 3%. SBP and HR after inflation and before deflation were compared with baseline values.

Interval variables were expressed as mean ± SD and analyzed using Student's *t* test. Ordinal variables (VAS scores) are presented as median (range). The Kruskal–Wallis test was used for evaluation of differences between the groups, followed by Wilcoxon's rank sum test where necessary. Wilcoxon's signed rank test was applied to paired data. $P < 0.05$ was regarded as significant.

No subject could tolerate tourniquet pain for more than 45 min. All subjects receiving ketamine experienced moderate sedation and six subjects receiving saline experienced slight sedation lasting for about 5 min. VAS scores showed a parallel and biphasic change in both the saline and ketamine trials. However, ketamine adminstration significantly reduced the VAS score compared to saline at T_1 [90 (64–100) mm, median (range) in saline versus 66 (50–81) mm in ketamine, $P < 0.01$], at T_6 [86 (61–100) mm in saline versus 57 (12–90) mm in ketamine, $P < 0.02$], and at T_7 [92 (61–100) mm in saline versus 70 (50–100) mm in ketamine, $P < 0.03$] (Fig. 1) and significantly prolonged average tourniquet time (28 ± 6 min in saline, mean ± SD, versus 37 ± 7 min in ketamine, $P < 0.01$).

SBP with saline showed a similar change to VAS score, and significantly increased before deflation (133 ± 16 mmHg) compared to baseline (120 ± 9 mmHg). SBP with ketamine showed no change throughout the time course (Table 1). There were no significant differ-

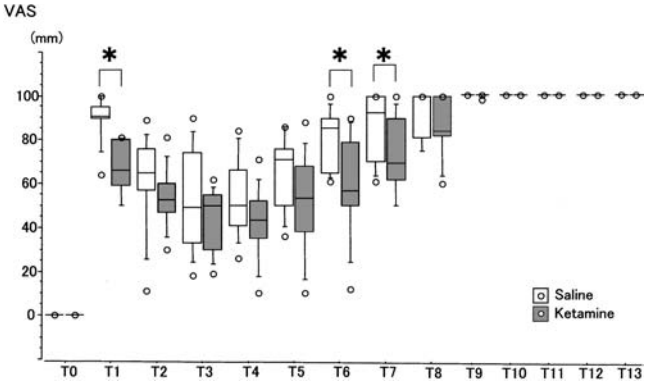

Fig. 1. Boxplots of visual analog scale (VAS) score (median ± upper and lower quartiles) during tourniquet with 400 mmHg. Lines in the center of boxes represent medians, the lower border of the box represents the lower quartile, and the upper border of box (if present) represents the upper quartile. Whiskers represent minimum and maximum values, and circles represent outliers. Preadministration of low-dose ketamine significantly reduced VAS at T_1, T_6 and T_7 compared to saline. T_0, 5-min before tourniquet inflation; T_1, just after tourniquet inflation; T_{2-13}, following 5-min intervals. Asterisks indicate $P < 0.03$

Table 1. Hemodynamic and catecholamine responses during tourniquet application

Parameter	Agent	Baseline	After inflation	Before deflation
SBP (mmHg)	Saline	120 ± 9	124 ± 12	133 ± 16*
	Ketamine	124 ± 12	129 ± 21	129 ± 13
HR (beat·min^{-1})	Saline	69 ± 8	73 ± 9	72 ± 9
	Ketamine	75 ± 12	76 ± 10	73 ± 11
NE (ng·ml^{-1})	Saline	0.21 ± 0.08	—	0.20 ± 0.08
	Ketamine	0.26 ± 0.11	—	0.26 ± 0.12
E (ng·ml^{-1})	Saline	0.05 ± 0.02	—	0.05 ± 0.03
	Ketamine	0.04 ± 0.02	—	0.08 ± 0.06

The data are means ± SD
SBP, systolic blood pressure; HR, heart rate; NE, norepinephrine; E, epinephrine
*SBP significantly increased before tourniquet deflation compared to baseline in the saline trial, but not in the ketamine trial, $P < 0.05$

ences in SBP between the two trials. HR and the concentrations of CAs showed no change in either trial. No subject had nightmares, psychological problems, or adverse effects as a result of tourniquet use.

The present results show that the preadministration of low-dose ketamine ($0.1\,mg{\cdot}kg^{-1}$) attenuates tourniquet pain and arterial pressure increase using a hightourniquet pressure of 400 mmHg and prolongs tourniquet time in healthy awake volunteers. In the present study, VAS scores showed first and the second peaks during tourniquet inflation. The time course of VAS scores was similar to the curve reported by Hagenouw et al. [1]. Tourniquet inflation produced immediate pain at the site of the tourniquet that subsided to a tolerable level within a few minutes. Ten to fifteen minutes after inflation, numbness or paresthesia occurred, which gradually changed to intolerable pain. This biphasic change might represent nociceptive pain and so-called tourniquet pain.

It is known that the impulses from unmyelinated C-fibers are inhibited by the earlier-arriving impulses from myelinated A-δ fibers. However, tourniquet limb compression causes loss of conduction in the large nerves, i.e., the myelinated A-δ fibers, before it is lost in the small C-fibers [5]. At 30 min after tourniquet inflation, the A-δ fibers but not the C-fibers are blocked, resulting in the disinhibition of pain conducted by the C-fibers [5,6].

Accordingly, the first VAS score peak indicates nociceptive pain conducted by both myelinated A-δ fibers and small C-fibers, whereas the second VAS score peak indicates the tourniquet pain conducted by C-fibers alone. Tourniquet ischemia produces an increase in C-fiber action potential frequency resulting in induction of central sensitization [7]. NMDA receptor activation is involved in the mechanism of central sensitization induced by repeated nociceptive afferent input [8]. Ketamine, an NMDA-receptor antagonist, can prevent or reverse central sensitization [9]. Satsumae et al. [4] showed that preoperative low-dose ketamine ($0.25\,mg{\cdot}kg^{-1}$) prevented tourniquet-induced arterial pressure increase in lower limb surgery under general anesthesia, and suggested that tourniquet–induced arterial pressure increase might be caused by NMDA receptor activation.

In the present study, $0.1\,mg{\cdot}kg^{-1}$ was adopted as the low dose of ketamine according to the report of Segerdahl et al. [3]. This level of low-dose ketamine also suppressed arterial pressure increase as well as tourniquet-induced pain following application of a high tourniquet pressure of 400 mmHg.

Some reports showed that prolonged tourniquet inflation correlated with activation of the sympathetic nervous system [2,10]. Crews and Sehlhorst [2] reported that an increase in plasma norepinephrine level was related to tourniquet-induced hypertension in anesthetized monkeys. However, in the present study, the plasma concentrations of CAs showed no change in either trial. The sympathetic nervous system was not activated because the tourniquet time might not have been adequate to activate the sympathetic nervous system in this study.

We conclude that preadministration of low-dose ketamine ($0.1\,mg{\cdot}kg^{-1}$) attenuates tourniquet pain produced by a tourniquet pressure of 400 mmHg and prolongs tourniquet time in healthy awake volunteers.

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