

Magnesium sulfate attenuates tourniquet pain in healthy volunteers

Tsuyoshi Satsumae · Hiroshi Yamaguchi ·
Shinichi Inomata · Makoto Tanaka

Received: 23 July 2011 / Accepted: 13 September 2012 / Published online: 7 October 2012
© Japanese Society of Anesthesiologists 2012

Abstract

Purpose Preoperative administration of an *N*-methyl-D-aspartate (NMDA) receptor antagonist has been shown to attenuate tourniquet-induced blood pressure increase under general anesthesia, suggesting that the mechanism of this blood pressure increase includes NMDA receptor activation. The attenuation of this increase may be associated with the pain relief induced by NMDA receptor antagonism. We tested the hypothesis that magnesium sulfate, an NMDA receptor antagonist, attenuates tourniquet pain.

Methods Twenty-four healthy volunteers were randomly assigned to four groups ($n = 6$ each): control (normal saline), M1 (magnesium, 1 g), M2 (magnesium, 2 g), and M4 (magnesium, 4 g). Normal saline or magnesium solution was given intravenously over a 15-min period, in a double-blind fashion, before tourniquet inflation, which was continued for 60 min or until the “pain score” (0 = no pain, 100 = highest tolerable pain) reached 100. Pain scores were recorded before and every 5 min during tourniquet inflation. If subjects reported a pain score of 100 before the end of the 60-min period, we adopted a pain score of 100 for the remaining period.

Results The duration of tourniquet inflation in the M4 group was significantly longer than that in the control group (54.3 ± 8.3 vs. 42.9 ± 9.9 min, $P = 0.03$). Pain scores in the M4 group were significantly lower than those in the control group from 10 through 50 min after the start

of tourniquet inflation. The area under the curve for pain scores in the M4 group was significantly smaller than the areas in the other groups.

Conclusion Magnesium sulfate, 4 g, significantly attenuated tourniquet pain in healthy awake volunteers, suggesting that NMDA receptor activation is involved in tourniquet pain.

Keywords Tourniquet pain · Magnesium sulfate · NMDA receptor antagonist

Introduction

Tourniquets are widely used to minimize bleeding and keep the surgical field dry during orthopedic surgery involving the upper or lower limbs. However, this modality is sometimes accompanied by so-called tourniquet pain and tourniquet-induced arterial blood pressure (BP) increase. Tourniquet pain is characterized by a gradual onset of dull aching at the site of the tourniquet or the distal extremity despite otherwise adequate regional anesthesia, occasionally necessitating supplemental general anesthesia [1]. Tourniquet-induced BP increases may develop after the start of tourniquet inflation and these changes follow the same time course as the tourniquet pain [1, 2].

Ketamine, dextromethorphan, and magnesium are antagonists of the *N*-methyl-D-aspartate (NMDA) receptor [3]. We have previously reported that low-dose intravenous ketamine attenuates the tourniquet-induced BP increase under general anesthesia [4]. Dextromethorphan [5] and magnesium [6] have also been reported to have this effect. These results suggest that the mechanism of tourniquet-induced BP increase includes NMDA receptor activation.

T. Satsumae (✉) · S. Inomata · M. Tanaka
Department of Anesthesiology, University of Tsukuba,
Tsukuba, Ibaraki 305-8575, Japan
e-mail: tsuu@md.tsukuba.ac.jp

H. Yamaguchi
Department of Anesthesiology, Tsukuba Medical Center
Hospital, Tsukuba, Ibaraki, Japan

The attenuation of the tourniquet-induced BP increase may be associated with pain relief induced by NMDA receptor antagonism. However, few data are available that directly link tourniquet pain to NMDA receptor activation. We therefore tested the hypothesis that magnesium sulfate, which, in contrast with ketamine [7], does not have a direct analgesic effect, would attenuate tourniquet pain in healthy awake volunteers.

Subjects, materials, and methods

The study protocol was approved by our ethics committee and the study was performed in a randomized, double-blind, prospective fashion. We explained to the volunteers that they could ask to have the tourniquet deflated when they felt the pain to be intolerable. Written informed consent was obtained from each volunteer. Twenty-four healthy male volunteers, American Society of Anesthesiologists (ASA) physical status class I, aged 22–23 years, were recruited to the study. Exclusion criteria were hypertension, ischemic heart disease, deep vein thrombosis, and a past history of chronic pain, mental disorder, or substance misuse. Subjects were randomly assigned, using computerized random number generation, to one of four groups (described below) with six volunteers in each group. A staff member not involved in the study prepared identical bags containing each test solution. One of the authors, who was blinded to the test solution, collected data from all the volunteers.

During the experiment, BP (measured noninvasively), heart rate (HR), electrocardiography, and oxygen saturation were monitored. The following test solutions were used in the four groups, to give a total volume of 100 ml in each: control group ($n = 6$), normal saline; M1 group ($n = 6$), 10 ml of 10 % magnesium sulfate (1 g) diluted with saline; M2 group ($n = 6$), 20 ml of 10 % magnesium sulfate (2 g) diluted with saline; and M4 group ($n = 6$), 40 ml of 10 % magnesium sulfate (4 g) diluted with saline. The saline and magnesium sulfate solutions were similar in appearance. After venous access was secured from the dorsal venous network of the hand or the cephalic vein, the test solution was given over a 15-min period before tourniquet inflation. Pain intensity was evaluated using a 100-mm visual analogue scale (“pain score”: 0 = no pain, 100 = highest tolerable pain). An 11-cm-wide standard orthopedic tourniquet was inflated at the thigh level to 400 mmHg, and inflation at this level was continued for 60 min or until the volunteers stated that they could not tolerate the pain any more (“pain score” = 100). Venous blood was sampled to measure the serum magnesium concentration before and after the experiment.

The pain score, BP, and HR were recorded every 5 min during tourniquet inflation. If the subjects reported a pain score of 100 before the end of the 60-min period, we adopted a pain score of 100 for the remaining time. We also recorded the duration of tourniquet inflation (tourniquet time). Side effects attributed to magnesium toxicity (nausea, sedation, cardiac conduction disorder, and hypoventilation) were also recorded during the study period. The volunteers were instructed to report any symptoms, such as nausea, drowsiness, muscle weakness, or dyspnea. Furthermore, at the end of experiment a blinded observer asked the volunteers whether they had experienced these symptoms. During the experiment, the blinded observer assessed cardiac conductive function using ECG and monitored respiration using pulse oximetry.

Demographic data, tourniquet time, and serum magnesium concentration were expressed as means \pm SD and compared among the four groups using one-way analysis of variance (ANOVA) with Bonferroni’s correction. Hemodynamic data were analyzed by repeated-measures ANOVA. In addition, BP and HR were statistically compared with their baseline values using Student’s *t*-test. Changes of pain scores were compared among the four groups using repeated-measures ANOVA. When statistical significance was found, post-hoc comparisons were made by Bonferroni’s method. The area under the curve (AUC) for pain scores was determined and the values in the four groups were compared using one-way ANOVA with Bonferroni’s correction. *P* values of less than 0.05 were considered statistically significant. The sample size was determined assuming that the AUC for pain scores would be 2400 in the M4 group and 4000 in the control group. The required numbers for each group in this study were calculated using power analysis to find a significant difference of $P < 0.05$ ($\alpha = 0.05$) with a power of 90 % (β error = 0.1). This analysis determined 6 volunteers per group as sufficient. The primary outcome measure of this study was the effect of magnesium sulfate in attenuating tourniquet pain.

Results

The four groups were similar in terms of age, height, and weight (Table 1). Tourniquet time in the M4 group (54.3 ± 8.3 min) was significantly longer than that in the control group (42.9 ± 9.9 min) ($P = 0.03$) (Table 1). Serum magnesium concentrations before the experiment were similar in the four groups. At the end of the study, volunteers in the M1, M2, and M4 groups had significantly increased serum magnesium concentrations compared with those before the experiment (Table 1). There was no significant difference in baseline BP between the groups. No

Table 1 Volunteers’ demographic data, the duration of tourniquet inflation, and serum magnesium concentrations

Group	Control group	M1 group	M2 group	M4 group
Number of volunteers	6	6	6	6
Age (years)	22.2 ± 0.4	22.2 ± 0.4	22.3 ± 0.5	22.5 ± 0.5
Height (cm)	171.0 ± 2.8	171.0 ± 4.6	174.3 ± 2.8	172.5 ± 5.5
Weight (kg)	66.0 ± 6.0	65.0 ± 4.1	66.7 ± 3.9	62.3 ± 5.5
Tourniquet time (min)	42.9 ± 9.9	44.7 ± 4.3	42.5 ± 10.1	54.3 ± 8.3*
Mg concentration (mg/dl): PRE	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1
Mg concentration (mg/dl): POST	2.2 ± 0.1	2.8 ± 0.3*	3.3 ± 0.2*	3.8 ± 0.3*

Values are presented as means ± SD. *Tourniquet time* the duration of tourniquet inflation, *PRE* before the experiment, *POST* after the experiment

* $P < 0.05$ compared with the control group

Table 2 Volunteers’ hemodynamic data

Variable	Group	Baseline	30 min	After deflation
Systolic AP (mmHg)	Control	128.2 ± 13.7	139.5 ± 14.7*	132.8 ± 19.3
	M1	117.0 ± 8.1	130.0 ± 9.6*	129.8 ± 6.2*
	M2	125.2 ± 15.0	139.7 ± 16.1*	140.2 ± 14.7
	M4	115.7 ± 6.5	125.5 ± 13.9	118.0 ± 13.7
Diastolic AP (mmHg)	Control	71.8 ± 8.9	85.5 ± 14.1*	73.5 ± 8.5
	M1	74.0 ± 8.2	87.5 ± 6.5*	79.2 ± 9.7
	M2	69.5 ± 7.5	85.3 ± 6.0*	73.2 ± 18.7
	M4	62.8 ± 5.6	77.3 ± 6.6*	57.3 ± 15.9
HR (bpm)	Control	73.7 ± 14.2	76.3 ± 12.6	72.8 ± 14.8
	M1	70.7 ± 7.4	69.5 ± 7.0	76.3 ± 9.0
	M2	67.7 ± 3.9	71.0 ± 7.3	72.8 ± 7.7
	M4	71.7 ± 9.6	74.7 ± 12.4	69.3 ± 14.7

Values are expressed as means ± SD. *30 min* = 30 min after the start of tourniquet inflation

AP arterial blood pressure, HR heart rate

* $P < 0.05$ compared with baseline

significant hemodynamic differences among the four groups were observed over time. However, there was a significant systolic BP increase 30 min after tourniquet inflation in the control ($P = 0.03$), M1 ($P = 0.03$), and M2 ($P = 0.01$) groups, and this increase was not seen in the M4 group ($P = 0.22$) (Table 2).

The pain scores showed significantly less change over time in the M4 group than those in the other three groups (Fig. 1). Pain scores in the M4 group were significantly lower than those in the control group from 10 to 50 min after tourniquet inflation (Fig. 1). In the M4 group, the AUC for pain scores (2400 ± 939) was also significantly smaller than the areas in the other three groups (control: 3952 ± 291 , M1: 3438 ± 440 , M2: 3740 ± 745).

During the study period, no change was observed on electrocardiography and oxygen saturation was kept at more than 97 %. No symptoms of magnesium toxicity were reported.

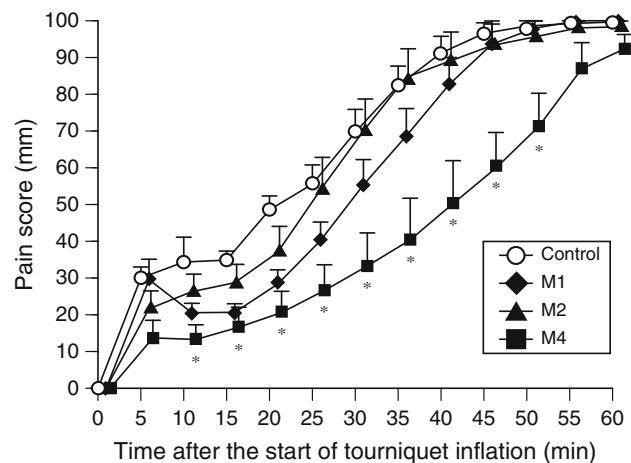


Fig. 1 Intensity of pain after the start of tourniquet inflation, determined using a 100-mm visual analogue scale (pain score: 0 = no pain, 100 = highest tolerable pain). Pain scores in the M4 group were significantly lower than those in the control group (* $P < 0.05$ vs. control group). Data are presented as means, and error bars represent the standard deviations

Discussion

We found that magnesium sulfate, at a dose of 4 g, significantly delayed the subjects reaching a pain score of 100, attenuated tourniquet pain, and prevented systemic BP increase during tourniquet inflation in healthy awake volunteers.

The etiological factors and neural pathways involved in tourniquet pain remain controversial [8]. In the present study, magnesium attenuated tourniquet pain despite not having a direct analgesic action. Magnesium is a physiological antagonist of calcium channels [9] and NMDA receptors [10], and these actions are considered important in its antinociceptive effect [11, 12]. Tourniquet inflation activates C fibers [13, 14], and the prolonged firing of C fiber nociceptors activates NMDA receptors in the spinal cord, initiating a series of central sensitization changes

such as the wind-up phenomenon and long-term potentiation [15]. Such central neuronal plasticity has an important role in pathological pain perception, and its induction and maintenance depends on the NMDA receptor [12]. It is possible that tourniquet pain is caused by acute-onset temporary hyperesthesia via central neuronal plasticity. Voltage-dependent and noncompetitive block of the NMDA receptor by magnesium ions probably attenuates persistent pain by inhibiting calcium influx into the cell [10] and suppressing the central sensitization resulting from persistent inputs of noxious stimuli. However, further confirmation of this mechanism is required. In fact, magnesium is reported to reduce neuropathic pain probably by blocking NMDA receptors [16].

Other mechanisms are possible. Intra-articular magnesium has been found to be effective for postoperative analgesia in arthroscopic knee surgery [17, 18], suggesting that the antagonism of peripheral NMDA receptors prevents peripheral sensitization [19, 20]. This action might, accordingly, be associated with the reduction of tourniquet pain observed in the present study. Moreover, magnesium protects the central nervous system from ischemic damage [21], such as that caused by tourniquet inflation.

The effective magnesium concentration in serum and cerebrospinal fluid (CSF) necessary for the antagonism of central NMDA receptors remains unclear. It has been shown that magnesium suppresses neuropathic pain responses via a spinal site of action in rats [22]. Although intravenous magnesium administration leads to a significant and long-term increase in CSF magnesium concentration, the magnitude of this increase is small [23], indicating that a high dose of systemic magnesium is needed for spinal analgesia. A high dose of magnesium, 4 g, was also necessary to reduce tourniquet pain in our study. We, accordingly, agree with Hwang et al. [24] that adequate doses of magnesium sulfate are important for effective analgesia.

In general, symptoms of magnesium toxicity develop at serum magnesium concentrations above 2 mmol/l [24]. In the present study, the serum magnesium concentration after the experiment in the M4 group (1.54 ± 0.10 mmol/l) was below this level, and no symptoms of magnesium toxicity were observed. A higher dose of magnesium sulfate is used for the treatment of pre-eclampsia [21]. In addition, intravenous bolus of magnesium sulfate 80 mg/kg followed by an infusion of 2 g/h did not produce sedation or reduce muscle strength in healthy volunteers [25]. Thus, 4 g of magnesium sulfate seems to be a reasonable dose; however, special regard should be paid when administering this drug to patients with renal dysfunction.

The present study has some limitations. Firstly, although NMDA receptor activation is suggested to be involved in the mechanism of tourniquet pain, we could not obtain

conclusive evidence of this. Further basic animal experiments are needed to clarify the more precise mechanism of tourniquet pain. Secondly, the dose of magnesium was not adequate to prevent tourniquet pain. The maximum magnesium dose was set at 4 g for ethical reasons. While larger doses of magnesium sulfate might be more effective in attenuating tourniquet pain, the risk of side effects or toxic symptoms would be heightened. Thirdly, we recruited only male participants because the menstrual cycle influences the experience of pain [26]; we believed that limiting the study to men would allow us to gather data under more uniform conditions and evaluate the effect of magnesium more precisely. Finally, the similar ages and body weights of the volunteers and the risk of magnesium toxicity prevented us from determining the optimal dose of magnesium.

In conclusion, magnesium sulfate, at a dose of 4 g, significantly reduced tourniquet pain. Our findings suggest that NMDA receptor activation is involved in the mechanism of tourniquet pain.

References

- Hagenouw RR, Bridenbaugh PO, van Egmond J, Stuebing R. Tourniquet pain: a volunteer study. *Anesth Analg*. 1986;65: 1175–80.
- Valli H, Rosenberg PH, Kytta J, Nurminen M. Arterial hypertension associated with the use of a tourniquet with either general or regional anaesthesia. *Acta Anaesthesiol Scand*. 1987;31: 279–83.
- McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of *N*-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg*. 2004;98:1385–400.
- Satsumae T, Yamaguchi H, Sakaguchi M, Yasunaga T, Yamashita S, Yamamoto S, Kida H. Preoperative small-dose ketamine prevented tourniquet-induced arterial pressure increase in orthopedic patients under general anesthesia. *Anesth Analg*. 2001;92:1286–9.
- Yamashita S, Yamaguchi H, Hisajima Y, Ijima K, Saito K, Chiba A, Yasunaga T. Preoperative oral dextromethorphan attenuated tourniquet-induced arterial blood pressure and heart rate increases in knee cruciate ligament reconstruction patients under general anesthesia. *Anesth Analg*. 2004;98:994–8.
- Lee DH, Jee DL, Kim SY, Kim JM, Lee HM. Magnesium sulfate attenuates tourniquet-induced hypertension and spinal c-fos mRNA expression: a comparison with ketamine. *J Int Med Res*. 2006;34:573–84.
- Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth*. 1981;53:27–30.
- Estebe JP, Le Naoures A, Chemaly L, Ecoffey C. Tourniquet pain in a volunteer study: effect of changes in cuff width and pressure. *Anaesthesia*. 2000;55:21–6.
- Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J*. 1984;108:188–93.
- Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurons. *Nature*. 1984;307:462–5.
- Omote K, Kawamata M, Satoh O, Iwasaki H, Namiki A. Spinal antinociceptive action of an N-type voltage-dependent calcium

- channel blocker and the synergistic interaction with morphine. *Anesthesiology*. 1996;84:636–43.
12. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain*. 1991;44:293–9.
 13. Chabel C, Russell LC, Lee R. Tourniquet-induced limb ischemia: a neurophysiologic animal model. *Anesthesiology*. 1990;72:1038–44.
 14. MacIver MB, Tanelian DL. Activation of C fibers by metabolic perturbations associated with tourniquet ischemia. *Anesthesiology*. 1992;76:617–23.
 - 15.Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain*. 1993;52:259–85.
 16. Brill S, Sedqwick PM, Hammann W, Di Vadi PP. Efficacy of intravenous magnesium in neuropathic pain. *Br J Anaesth*. 2002;89:711–4.
 17. Bondok RS, Abd El-Hady AM. Intra-articular magnesium is effective for postoperative analgesia in arthroscopic knee surgery. *Br J Anaesth*. 2006;97:389–92.
 18. Elsharnouby NM, Eid HE. Abou Elezz NF, Moharram AN. Intraarticular injection of magnesium sulphate and/or bupivacaine for postoperative analgesia after arthroscopic knee surgery. *Anesth Analg*. 2008;106:1548–52.
 19. Cairns BE, Svensson P, Wang K, Hupfeld S, Graven-Nielsen T, Sessle BJ, Berde CB, Arendt-Nielsen L. Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. *J Neurophysiol*. 2003;90:2098–105.
 20. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of *N*-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg*. 2003;97:1108–16.
 21. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth*. 1999;83:302–20.
 22. Xiao WH, Bennett GJ. Magnesium suppresses neuropathic pain responses in rats via a spinal site of action. *Brain Res*. 1994;666:168–72.
 23. Fuchs-Buder T, Tramèr MR, Tassonyi E. Cerebrospinal fluid passage of intravenous magnesium sulphate in neurosurgical patients. *J Neurosurg Anesthesiol*. 1997;9:324–8.
 24. Hwang JY, Na HS, Jeon YT, Ro YJ, Kim CS, Do SH. I.V. infusion of magnesium sulphate during spinal anaesthesia improves post-operative analgesia. *Br J Anaesth*. 2010;104:89–93.
 25. Wadhwa A, Sengupta P, Durrani J, Akça O, Lenhardt R, Sessler DI, Doufas AG. Magnesium sulphate only slightly reduces the shivering threshold in humans. *Br J Anaesth*. 2005;94:756–62.
 26. Ring C, Veldhuijzen van Zanten JJ, Kavussanu M. Effects of sex, phase of the menstrual cycle and gonadal hormones on pain in healthy humans. *Biol Psychol*. 2009;81:189–91.