—Original—

Oral Clonidine Premedication Exacerbates Hypotension Following Tourniquet Deflation by Inhibiting Noradrenaline Release

Koichi Maruyama, Shinhiro Takeda, Takashi Hongo,
Noriyuki Kobayashi, Chol Kim and Ryo Ogawa

Department of Anesthesiology and Intensive Care, Nippon Medical School

Abstract

Clonidine premedication prevents tourniquet pain and reduces sympathetic nerve activity. We evaluated hemodynamic changes and catecholamine release following tourniquet deflation during spinal anesthesia in patients who received oral clonidine premedication. The final analysis included 24 otherwise healthy patients undergoing lower-limb surgery randomly assigned to two groups: those receiving approximately 5 μg/kg of oral clonidine 1 hr before anesthesia (clonidine group, n=12), and those receiving no premedication (control group, n=12). After lumbar anesthesia, a tourniquet was applied for approximately 60 minutes to each patient. Electrocardiogram, arterial blood pressure, and consumption of butorphanol for tourniquet pain were monitored. Blood samples were obtained at different times to measure serum concentration of catecholamine. In the clonidine group, mean blood pressure decreased from 87±7 mmHg at baseline to 65±10 mmHg after tourniquet deflation ($P<0.05$). This peak reduction of mean blood pressure in the clonidine group was significantly lower than in the control group. After receiving clonidine premedication, the plasma noradrenaline concentrations in the clonidine group were significantly lower than those in the control group. Noradrenaline concentration increased in the control group from 162.3±89.2 pg/mL before tourniquet deflation to 199.3±95.7 pg/mL afterward ($P<0.01$), but there was no significant change in noradrenaline concentration after tourniquet deflation in the clonidine group. We conclude that oral clonidine premedication exacerbated the reduction in mean blood pressure following tourniquet deflation by inhibiting noradrenaline release.
(J Nippon Med Sch 2004; 71: 44–50)

Key words: catecholamine, clonidine, hypotension, premedication, tourniquet pain

Introduction

Inflation of the tourniquet applied to the extremities provides a bloodless operative field by avascularization. However, application of the tourniquet is frequently associated with tourniquet pain, which is described as a severe, dull, aching sensation at the site of the tourniquet or in the distal extremities. It can develop even in patients who have received adequate anesthesia during surgery[1]. Clonidine, an α-2 agonist, provides sedation and anxiolysis and reduces the need for anesthesia[2,3]. Moreover, premedication with clonidine has been shown to prevent

Correspondence to Shinhiro Takeda, MD, Ph D, Department of Intensive Care Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: shinhiro@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

tourniquet pain[4,5]. The centrally mediated hypotensive and bradycardiac effects of clonidine may help prevent hypertension or tachycardia caused by tourniquet pain.

Tourniquet deflation can trigger acute hypotension and, in rare instances, fatal circulatory collapse[6]. Clinicians must bear in mind the possible adverse effects of clonidine premedication during surgery involving use of a tourniquet. Under normal circumstances, any rapid changes in blood pressure are detected by the baroreceptor, leading to a change in sympathetic nerve activity to maintain hemodynamic stability. Some evidence suggests that clonidine may alter baroreflex activity, thereby upsetting the hemodynamic balance[7–9]. However, data on this subject are contradictory. The effects of clonidine on tourniquet deflation-induced hypotension have not yet been established. We hypothesized that clonidine premedication exacerbates this hypotension. The purpose of the present study was to prospectively evaluate the effect of premedication with oral clonidine on hemodynamics and catecholamine release following tourniquet deflation in patients during spinal anesthesia.

Materials and Methods

After obtaining institutional approval and informed consent for our study, we enrolled 27 patients undergoing lower-limb surgery; the patients had no preoperative hypertension or current heart, hepatic, or renal disease. Patients were randomly assigned to two groups: a clonidine group (14 patients who were premedicated orally with approximately 5 μg/kg of clonidine 60 min before the operation) and a control group (13 patients who received no premedication). Randomization was achieved as follows: the patients undergoing surgery on even number days were assigned to the control group, and those undergoing surgery on odd number days were assigned to the clonidine group.

On the day of the operation, an intravenous catheter was inserted approximately 1 hr before anesthesia, and lactated Ringer's solution was infused at 1～2 m*l*/kg/hr. An arterial catheter was inserted in the radial artery under local anesthesia for blood pressure monitoring and blood sampling. During the study period, arterial blood pressure, heart rate, and oxygen saturation were monitored continuously (Lifescope 14, Nihon Koden, Tokyo, Japan). Spinal anesthesia was achieved with 2.0～2.3 m*l* of 0.5% tetracaine dissolved in 10% glucose administered via a 23-gauge spinal needle inserted at the L 2/3 or L 3/4 interspace. Analgesia was evaluated by pinprick 10 min after tetracaine injection and again after tourniquet deflation to determine whether the entire area involved in the surgical procedure was covered.

A tourniquet was placed on the affected lower extremity and inflated approximately 20 min after induction of spinal anesthesia. After tourniquet inflation, the operation was begun. Rescue analgesia for tourniquet pain was provided by a patient-controlled balloon infuser with 3-m*l* reservoir (DIB International Co. Ltd., Tokyo, Japan). The infusion balloon contained butorphanol dissolved with normal saline to a concentration of 100 μg/m*l*, and filling period was set at approximately 18 minutes. A single manual squeeze elicited the maximal 300-μg dose of butorphanol. All patients were informed about the characteristics of tourniquet pain and encouraged to use the balloon infuser whenever they felt tourniquet pain during inflation. We regarded use of this device during tourniquet inflation as incidence of tourniquet pain, and we interpreted total butorphanol consumption as the measure of pain intensity in the patients who suffered from tourniquet pain. Approximately 1 hr after tourniquet inflation, the lower extremities was straightened on the horizontal operating table and the tourniquet was deflated.

Blood pressure and heart rate were recorded continuously and evaluated at six time points: in the patient ward on the day before the operation (baseline), in the operating room after arterial catheter placement and before anesthesia induction (induction), after tourniquet inflation (inflation), immediately before tourniquet deflation (predeflation), and 10 min after tourniquet deflation (postdeflation). In addition, arterial blood pressure and heart rate were carefully observed for 10 min after tourniquet deflation to determine the maximum change in each value (maximal change); we also evaluated the amount of time that elapsed before the minimum

Table 1 Patient characteristics

	Clonidine group	Control group
Number of patients	12	12
Age (yr)	44 ± 15	40 ± 16
Sex (male/female)	6/6	6/6
Height (cm)	161 ± 8	165 ± 8
Weight (kg)	63 ± 10	64 ± 11
Perioperative infusion (mL)	1,146 ± 297	986 ± 341
Duration of tourniquet inflation (min)	58 ± 11	55 ± 6
Analgesic levels		
Preoperative	Th 5.6 ± 0.8 (range: 4 ～ 7)	Th 5.5 ± 0.9 (range: 4 ～ 6)
Postoperative	Th 6.6 ± 2.0 (range: 3 ～ 10)	Th 6.4 ± 1.5 (range: 4 ～ 9)
Incidence of tourniquet pain		
Number of patients (%)	4 (33%) *	9 (75%)
Dose of butorphanol for tourniquet pain (μg)	450 ± 268 (range: 250 ～ 750)	586 ± 306 (range: 150 ～ 950)

Values are mean ± SD.
Differences from control group, * $P < 0.05$.

value of blood pressure and maximal value of heart rate were reached and started to recover. Critical hypotension was defined as systolic blood pressure less than 80 mmHg, and critical bradycardia was defined as less than 45 beats/min. When critical hypotension or bradycardia occurred, the patient was given ephedrine or atropine and excluded from this study.

Blood samples were taken for baseline, induction, predeflation, and postdeflation analysis of catecholamine concentrations. Samples were collected into polypropylene tubes prepared with the anticoagulant EDTA-2Na, kept on ice, and then centrifuged at 4℃. Separated plasma samples were stored immediately at −80℃ until analysis. Adrenaline and noradrenaline were separated by high-performance liquid chromatography and concentrations were determined with a fluorescence detector.

For statistical analysis, repeated-measures analysis of variance and Bonferroni multiple comparisons procedure were performed to distinguish within-group differences over time. The Mann-Whitney test was used to evaluate between-group differences patient characteristics and in blood pressure and heart rate at the various time points. Mean blood pressure and heart rate at maximal change were also compared with predeflation values in each group using Mann-Whitney test. The chi-square test was used to analyze differences in patient characteristics. All values are reported as mean ± SD, and all P values less than 0.05 were considered significant.

Results

Two patients in the clonidine group and one patient in the control group were excluded from the final analysis because of hypotension requiring ephedrine administration after tourniquet deflation; thus, 24 patients completed the study. There was no significant difference between the groups with regard to patient characteristics, however, the incidence of tourniquet pain was significantly lower in the clonidine group than in the control group (**Table 1**).

In the both groups, mean blood pressure changed significantly after tourniquet deflation in comparison to the point of predeflation (**Table 2**). Mean blood pressure at the point of maximal change was significantly lower in the clonidine group than in the control group (**Table 2**). The mean time elapsing before the maximal change in blood pressure was 140 ± 57 sec in the clonidine group and 53 ± 43 sec in the control group ($P < 0.01$). Heart rate was significantly increased after tourniquet deflation in both groups in comparison to the point of predeflation. However, there were no differences between the two groups at the point of maximal change. The mean time elapsing before the maximal change in heart rate was 103 ± 50 sec in the clonidine group and 84 ± 52

Table 2 Changes of mean blood pressure and heart rate

	Baseline	Induction	Inflation	Predeflation	At maximal change	Postdeflation
Mean blood pressure (mmHg)						
Clonidine group	87 ± 7	82 ± 12 †	83 ± 13	85 ± 10	65 ± 10 * # †	77 ± 11
Control group	86 ± 12	92 ± 15	82 ± 7	88 ± 7	76 ± 7 #	83 ± 10
Heart rate (beats/min)						
Clonidine group	70 ± 8	68 ± 11	58 ± 10 * †	58 ± 9 * †	67 ± 10 #	60 ± 9 *
Control group	72 ± 10	78 ± 14	68 ± 14	68 ± 15	75 ± 12 #	67 ± 11

Values are mean ± SD.
Differences from baseline, * $P < 0.05$. Differences from predeflation, # $P < 0.05$. Differences from control group, † $P < 0.05$.

Table 3 Changes of plasma concentrations of adrenaline and noradrenaline

	Baseline	Induction	Predeflation	Postdeflation
Adrenaline (pg/mL)				
Clonidine group	31.2 ± 17.5	50.3 ± 37.1	46.7 ± 60.3 †	43.8 ± 45.4
Control group	39.8 ± 20.4	77.7 ± 43.3	83.8 ± 67.3 *	76.8 ± 52.4
Noradrenaline (pg/mL)				
Clonidine group	287.2 ± 108.0	131.8 ± 72.0 * †	83.0 ± 60.0 * †	81.3 ± 47.7 * ‡
Control group	325.2 ± 196.6	218.8 ± 101.0 *	162.3 ± 89.2 *	199.3 ± 95.7 * #

Values are mean ± SD.
Differences from baseline, * $P < 0.05$. Differences from pre-deflation, # $P < 0.01$, Differences from control group, † $P < 0.05$, ‡ $P < 0.01$.

sec in the control group. This also did not differ between the two groups.

Predeflation plasma adrenaline concentration was significantly lower in the clonidine group than in the control group (**Table 3**). Induction, predeflation, and postdeflation plasma noradrenaline concentrations were also significantly lower in the clonidine group than in the control group (**Table 3**). The control group showed a statistically significant increase in the postdeflation noradrenaline concentration from the predeflation concentration. In the clonidine group, however, there was no significant change in noradrenaline concentration after tourniquet deflation.

Discussion

Our results show that oral clonidine exacerbates the reduction in mean blood pressure and that the delay in blood pressure recovery following tourniquet deflation involves the inhibition of noradrenaline.

Acute hypotension after tourniquet deflation is commonly observed in clinical settings, and a fatal case of circulatory collapse has been reported[6]. Tourniquet deflation leads to a rapid decrease in peripheral vascular resistance and an increase in venous pooling in the affected limb. These changes contribute to a reduction in venous return to the right atrium, thereby lowering cardiac output[10]. Moreover, influx of metabolites from the ischemic limb to the systemic circulation occurs after tourniquet release[11,12]. These metabolites, which include adenosine and lactic acid, may directly cause vasodilation and deterioration in cardiac function. Under normal circumstances, rapid fluctuations in blood pressure cause the baroreflex to induce changes in sympathetic nervous system activity. The baroreflex response to hypertensive stress mainly involves vagal activity, whereas the response to hypotension is predominantly sympathetic[13]. Clonidine is known to reduce both central sympathetic outflow and release of

noradrenaline from peripheral presynaptic terminals[7,14–16], but the effect of clonidine on baroreflex sensitivity is controversial. Harron et al. reported that clonidine enhanced baroreflex sensitivity in awake humans[8], whereas other investigators saw no effect of clonidine on baroreflex sensitivity[7]. Watanabe et al. found that clonidine attenuated baroreflex sensitivity with hypotensive stress but not with hypertensive stress[9]. These authors proposed that clonidine modifies baroreflex sensitivity by suppressing noradrenaline release from peripheral presynaptic terminals. However, they did not evaluate changes in plasma catecholamines. In our study, mean blood pressure decreased significantly and heart rate increased significantly after tourniquet deflation in both groups. This suggests that hypotension and reactive tachycardia induced by tourniquet deflation occurred via the baroreflex system in both groups. Our study also showed that clonidine premedication exacerbated hypotension and prevented the increase of plasma noradrenaline that would otherwise follow tourniquet release. These findings suggest strongly that clonidine exerted a suppressive effect on peripheral presynaptic terminals, thus contributing to the profound mean blood pressure reduction following tourniquet deflation.

In fact, an increase in heart rate was also observed immediately after tourniquet deflation without any increase in serum noradrenaline concentration in the clonidine group. Maximal increases of heart rate in both groups were recorded within 2 min of tourniquet deflation. However, blood samples were taken to evaluate catecholamine 10 min after tourniquet deflation. We supposed that noradrenaline release from the peripheral presynaptic terminal might occur immediately after tourniquet deflation in both groups, but that the amount of noradrenaline might not be abundant in the clonidine group due to suppression by clonidine, which would lead to earlier elimination of noradrenaline before sampling.

Kahn et al. reported that mean blood pressure decreased maximally within 1 minute of tourniquet release and recovered immediately in patients receiving epidural anesthesia[10]. In our study, the maximum decrease in mean blood pressure after tourniquet deflation was significantly delayed in the clonidine group; i.e. the delay prolonged the postdeflation hypotensive period in this group. Nishikawa et al. found that the pressor responses to ephedrine[17,18] and phenylephrine[19] were enhanced in patients who received oral clonidine premedication. Therefore, hypotension following tourniquet release may be treatable by a pressor agent. However, it is important to recognize that the effects of clonidine premedication on mean blood pressure may increase the risk of cardiovascular collapse after tourniquet release.

The centrally mediated hypotensive effect of clonidine is well known, and hypotension is frequently observed after spinal anesthesia. Ota et al. evaluated the effect of clonidine premedication on hemodynamic change after spinal anesthesia, in addition to optimum premedication administration time for the prolongation of spinal anesthesia[20]. In their study, hemodynamic changes were compared during spinal anesthesia between patients given 150 μg of oral clonidine premedication 1 hr before induction and those given 0.25 mg of triazolam. There was no statistical difference between the two groups in arterial blood pressure or heart rate during spinal anesthesia. Patients whose systolic blood pressure decreased 30% below preanesthetic values or was less than 90 mmHg were considered hypotensive and treated with ephedrine; patients with a heart rate less than 45 beats/min were considered bradycardic and treated with atropine. The authors evaluated the frequency of bradycardia and hypotension, and found no difference between groups. This showed that clonidine premedication did not exacerbate hypotension and bradycardia after spinal anesthesia, and the finding is consistent with ours. We observed no remarkable decrease in blood pressure in either the clonidine or control group after induction of spinal anesthesia. We conclude that in patients receiving clonidine premedication, blood pressure change is of greater concern at the time of tourniquet deflation than it is during spinal anesthesia.

Chabel et al. noted that afferent nerve activity of C-fibers might be the neurophysiologic basis of tourniquet pain[21]. In their study, tourniquet-induced ischemia caused spontaneous afferent nerve activity with a slow firing rate and slowed conduction velocities in C-fibers. This activity was unaffected by

mechanical stimulation, local anesthetic, or cold block distal to the tourniquet; however, it was suppressed by nerve blockade just proximal to the tourniquet and by tourniquet deflation. Clonidine has been reported to cause presynaptic inhibition of C-fiber afferent activity in the spinal cord of cats[22]. Two studies suggest that this clonidine effect may explain its prevention of tourniquet pain[4,5]. Our study showed that clonidine premedication successfully prevents tourniquet pain, a finding consistent with those of the previous studies. However, the dose of butorphanol for tourniquet pain in the clonidine group was smaller than that in the control group, but, the difference between the two groups was not statistically significant in the present study. We compared the dose of butorphanol between the two groups only in the patients who complained of tourniquet pain: 4 patients in the clonidine group and 9 patients in the control group. Therefore, the number of cases in the present study might not to be large enough to evaluate the effect of clonidine premedication on tourniquet pain intensity.

Premedication with approximately 5 μg/kg of oral clonidine attenuated tourniquet pain. However, clonidine exacerbated the reduction in mean blood pressure and delayed blood pressure recovery following tourniquet deflation. These effects are associated with clonidine-induced inhibition of noradrenaline release. These findings also suggest that premedication with clonidine increases the risk of circulatory collapse in surgery patients who require a tourniquet. Clinicians should be alert to avoid hemodynamic deterioration following tourniquet deflation, especially in patients who have being given clonidine. In these patients, close observation of blood pressure is essential and prophylactic administration of vasopressor may be needed before tourniquet deflation.

References

1. Hagenouw RR, Bridenbaugh PO, Van Egmond J, Stuebing R: Tourniquet pain: A volunteer study. Anesth Analg 1986; 65: 1175–1180.
2. Wright PMC, Carabine UA, Mcclune S, Orr DA, Moore J: Preanaesthetic medication with clonidine. Br J Anaesth 1990; 65: 628–632.
3. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O: Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 1986; 64: 36–42.
4. Bonnet F, Diallo A, Saada M, Belon M, Guilbaud M, Bioco O: Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine. Br J Anaesth 1989; 63: 93–96.
5. Jaakola M-L: Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. J Clin Anesth 1994; 6 : 204–211.
6. 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: 279–283.
7. Muzi M, Goff DR, Kampine JP, Roerig DL, Ebert TJ: Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology 1992; 77: 864–871.
8. Harron DW, Riddell JG, Shanks RG: Effects of azepexole and clonidine on baroreceptor mediate reflex bradycardia and physiological tremor in man. Br J Clin Pharmacol 1985; 20: 431–436.
9. Watanabe Y, Iida H, Tanabe K, Ohata H, Dohi S: Clonidine premedication modifies responses to adrenoceptor agonists and baroreflex sensitivity. Can J Anaesth 1998; 45: 1084–1090.
10. Karn RL, Marino V, Urquhart B, Sharrock NE: Hemodynamic changes associated with tourniquet use under epidural anesthesia for total knee arthroplasty. Reg Anesth 1992; 17: 228–232.
11. Collis MG: The vasodilator role of adenosine. Pharmac Ther 1989; 41: 143–162.
12. Benzon HT, Toleikis JR, Meagher LL, Shapiro BA, Ts'ao C-h, Avram MJ: Changes in venous blood lactate, venous blood gases, and somatosensory evoked potentials after tourniquet application. Anesthesiology 1988; 69: 677–682.
13. Dohi S, Tsuchida H, Mayumi T: Baroreflex control of heart rate during cardiac sympathectomy by epidural anesthesia in lightly anesthetized humans. Anesth Analg 1983; 62: 815–820.
14. Bloor BC, Flacke WE: Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 1982; 61: 741–745.
15. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: defending the role in clinical anesthesia. Anesthesiology 1991; 74: 581–605.
16. Constantine JW, McShane WK: Analysis of the cardiovascular effects of 2-(2, 6-dichlorophenylamino)-2-imidazoline hydrochloride (Catapres) . Eur J Pharmachol 1968; 4 : 109–123.
17. Nishikawa T, Kimura T, Taguchi N, Dohi S: Oral clonidine preanesthetic medication augments the pressor responses to intravenous ephedrine in awake or anesthetized patients. Anesthesiology 1991; 74: 705–710.
18. Tanaka M, Nishikawa T: Effects of clonidine premedication on the pressor response to alpha-adrenergic agonists. Br J Anaesth 1995; 75: 593–597.

19. Inomata S, Nishikawa T, Kihara S, Akiyoshi T: Enhancement of pressor response to intravenous phenylephrine following oral clonidine medication in awake and anaesthetized patients. Can J Anaesth 1995; 42: 119–125.
20. Ota K, Namiki A, Iwasaki H, Takahashi I: Dosing interval for prolongation of tetracaine spinal Anesthesia by oral clonidine in humans. Anesth Analg 1994; 79: 1117–1120.
21. Chabel C, Russell LC, Lee R: Tourniquet-induced limb ischemia: A neurophysiologic animal model. Anesthesiology 1990; 72: 1038–1044.
22. Calvillo O, Ghignone M: Presynaptic effect of clonidine on unmyelinated afferent fibers in the spinal cord of the cat. Neurosci Lett 1986; 64: 335–339.

(Received, August 7, 2003)
(Accepted, September 18, 2003)