—**Original**—

Effect of Oral Tizanidine on Local-anesthetic Infiltration Pain during Epidural Catheterization

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Abstract

Purpose: Tizanidine is a clonidine derivative and has the same effects, such as sedation, anxiolysis and analgesic response. We evaluated the effect of tizanidine on infiltration pain during epidural catheterization.

Methods: Forty patients scheduled to undergo epidural anesthesia in elective surgery were randomly allocated into two groups. The control group received placebo 60 minutes before arrival in the operating room, and the tizanidine group received 3 mg of oral tizanidine as premedication 60 minutes before arrival in the operating room. Every patient was measured heart rate and blood pressure before receiving placebo or premedication and after arrival in the operating room. After an epidural catheter was indwelled, the patients were questioned about the infiltrating pain of local anesthetic, and the degree was assessed by means of visual analog scale score (VAS score, 0～100 mm).

Results: Blood pressure in the operating room was significantly attenuated in the tizanidine group compared to the control group (148±21 mmHg vs 130±15 mmHg). Heart rate was not significantly different between the two groups. Rate-pressure product was significantly lower in the tizanidine group (11282±2960 vs 9592±2632). VAS score in the tizanidine group was significantly lower than that in the control group ($P<0.001$).

Conclusion: It was possible to reduce the infiltration pain of local anesthetic during epidural catheterization by oral administration of 3 mg of tizanidine as premedication. Blood pressure and rate-pressure product in the operating room were also attenuated by receiving tizanidine. Therefore, we recommend premedication with tizanidine for patients undergoing epidural catheterization.

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Key words: Tizanidine, infiltration pain of local anesthetic, epidural catheterization

Introduction

Tizanidine, an orally active α_2-adrenoceptor agonist, is used mainly as a centrally acting muscular relaxant for patients with painful muscular spasms[1,2]. This drug is a clonidine derivative and has the same effects, such as sedation, anxiolysis, and

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Table 1 Demographic Data of the Patients

Variable	Control Group (n=20)	Tizanidine Group (n=20)
Age (yr)	54.1 ± 11.0	54.3 ± 12.3
Sex (M : F)	11 : 9	12 : 8
Height (cm)	161.0 ± 8.6	159.3 ± 8.1
Weight (kg)	61.5 ± 11.6	57.8 ± 7.3

Data are expressed as mean ± SD

analgesic response; however, side effects such as hypotension and bradycardia are less potent than with clonidine[3-8]. Both drugs reduce the need for volatile anesthetics, opioids, and benzodiazepines during and after anesthesia[9-16]. Moderate to severe pain associated with infiltration of local anesthetics during epidural catheterization is believed to sometimes induce tachycardia, hypertension, and myocardial ischemia. In this study, we administered 3 mg of tizanidine as premedication 60 minutes before patients' arrival in the operating room and evaluated the effect on infiltration pain.

Patients and Methods

Forty patients (ASA physical status 1～2; 23 men, 17 women; aged 24～68 years) scheduled to undergo elective surgery with epidural anesthesia were included in this study. No patients who received non-steroidal anti-inflammation drugs or other analgesics within a week of surgery or with a history of cerebrovascular disease, neuromuscular disease, cardiovascular disease, or alcohol abuse were included in the study. Patients diagnosed with hypertension were included, but patients receiving anti-hypertensive drugs were excluded from this study. Informed consent was obtained from each patient in this study.

Computer-generated numbers were used to randomly assign patients to either a control group (n＝20) or a tizanidine group (n＝20). The control group patients received a placebo 60 minutes before arrival in the operating room and the tizanidine group received 3 mg of oral tizanidine 60 minutes before arrival in the operating room.

The blood pressure and heart rate of each patient were measured on the ward before administration of the placebo or tizanidine. After arrival in the operating room, we started ECG monitoring and blood pressure measurement immediately, and each patient's sedation score, blood pressure, and heart rate were determined. Sedation levels were scored according to Kulka et al.'s four-level scale; 0, patient awake; 1, patient sedated, but awake; 2, patient asleep but reacts immediately to verbal commands; 3, patient asleep, and does not react to verbal commands[17]. The sedation score was estimated by an independent observer blinded to the premedication. Epidural catheterization by the paramedian approach was performed with the patient in the right lateral decubitus position. We used a long 23-gauge needle for superficial and deep infiltration of 1% lidocaine and to assist in defining the direction in which the epidural needle should be inserted at the skin puncture site. After insertion of the epidural catheter, patients were returned to the supine position. Patients were questioned regarding the degree of local anesthetic infiltration pain and responded by means of a visual analog scale (VAS, 0～100 mm).

Data are shown as mean±SD value unless otherwise indicated. Differences in VAS values between the control group and tizanidine group were analyzed by Mann-Whitney U test. Differences between the two groups in age, weight, height, and rate-pressure product were analyzed by unpaired t test, and differences between the two groups in sedation score and sex were analyzed by chi-square test. A P value of less than 0.05 was considered significant.

Results

There was no statistical difference in sex, age, height, or weight between the two study groups (**Table 1**). Blood pressure in the ward was 123±21

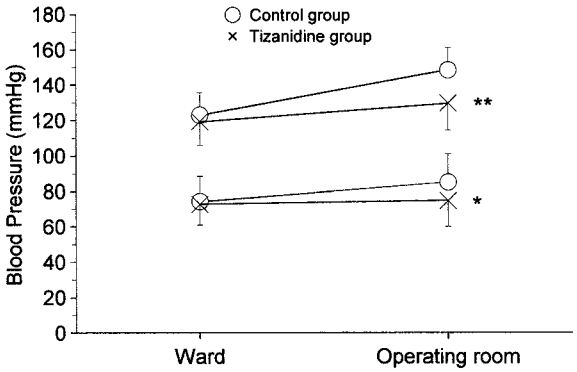

Fig. 1 The changes in blood pressure between ward and operating room
Data are mean ± SD.
*$P < 0.05$ versus control group.
**$P < 0.001$ versus control group.

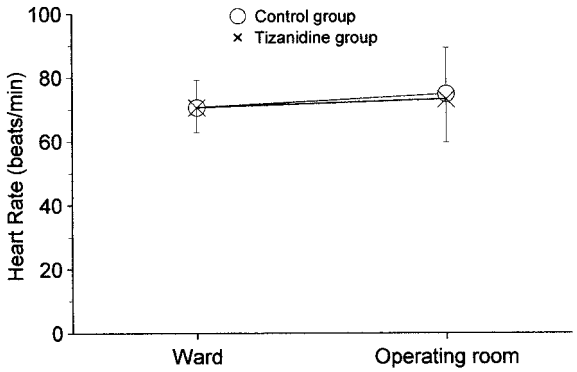

Fig. 2 The changes in heart rate between ward and operating room
Data are mean ± SD.

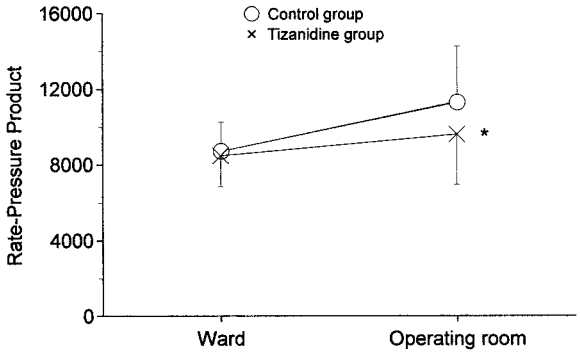

Fig. 3 Rate-pressure product between ward and operating room
Data are mean ± SD.
*$P < 0.05$ versus control group.

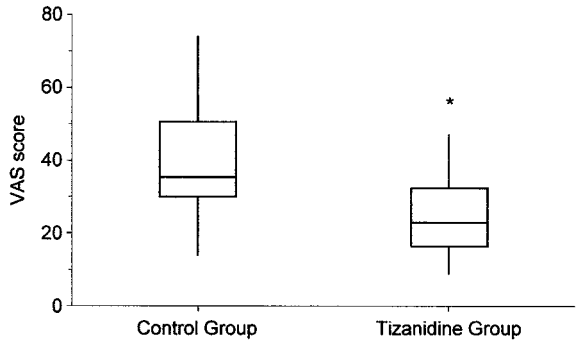

Fig. 4 Visual analog scale scores between control group and tizanidine group
The lower and upper borders of the box represent the 25th to 75th percentiles; The horizontal line within the box represents the median value; error bars represent the 10th to 90th percentiles.
*$P < 0.001$ versus control group.

mmHg in the control group and 119 ± 13 mmHg in the tizanidine group; however, in the operating room it was 148 ± 21 mmHg in the control group and 130 ± 15 mmHg in the tizanidine group (**Fig. 1**). There was no statistical difference in blood pressure as measured in the ward between the two groups, but the changes in blood pressure in the operating room were significantly lower in the tizanidine group than in the control group (systolic blood pressure, $P < 0.001$; diastolic blood pressure, $P < 0.05$) (**Fig. 1**). There was no statistical difference in heart rate between the two groups, either in the ward or in the operating room (**Fig. 2**).

Seventeen control group patients had a sedation score of 0 at the time of epidural catheterization, and three had a score of 1, whereas seven tizanidine group patients had a sedation score of 0, and thirteen had a score of 1. The difference in sedation score between the two groups was significant ($P < 0.01$). Rate-pressure product was significantly lower in the tizanidine group than in the control group in the operating room. ($P < 0.05$) (**Fig. 3**). VAS values were significantly lower in the tizanidine group than in the control group (**Fig. 4**).

Discussion

Sedation scores in the tizanidine group upon arrival in the operating room indicate that tizanidine

has a sedative effect like that of clonidine. The rate-pressure product, which correlates with myocardial oxygen consumption, was significantly lower in the tizanidine group than in the control group[18,19]. Therefore, we believe that premedication with tizanidine is advantageous for patients with ischemic heart disease.

The antinociceptive effect of tizanidine is reportedly weaker than that of clonidine; however, tizanidine produces fewer side effects than clonidine[5,20,21]. Timo et al. reported that patients who received 12 mg of tizanidine showed the same degree of analgesia as patients who received 150 μg of clonidine[22]. We used a much smaller (3 mg) dose of tizanidine, but it effectively suppressed infiltration pain. Tizanidine is rapidly absorbed after oral administration, reaching maximum plasma concentration within 0.75～2 hours in most studies; however, the duration of action is less than that of clonidine, so we administered tizanidine 1 hour before the patients' arrival in the operating room[21,23–27].

A dose-dependent antinociceptive effect of tizanidine has been observed in various animal models[28–30]. This effect seems to be mediated via α_2-adrenoceptors, rather than via opioids receptors, and it may involve inhibition of the release of aspartic and glutamic acids or substance P (a putative transmitter in primary afferent fibers that relays information about noxious stimuli to the central nervous system)[20,30–32]. It has been suggested that the spinal cord is the major site of analgesic action of α_2-adrenoceptor agonists, and recent evidence suggests that the antinociception produced by α_2-adrenoceptor agonists may be due in part to acetylcholine release in the spinal cord[33–35].

Reported side effects of α_2-adrenoceptor agonists are excessive bradycardia, hypotension, sinus arrest, profound sedation, and dry mouth[36]. However, in comparison to clonidine, tizanidine may induce fewer cardiovascular side effects. Omote et al. reported no significant change in systolic blood pressure and heart rate after premedication with tizanidine[37]. However, increase of systolic blood pressure in the operating room was significantly attenuated in our examination. This result may be due to the multiplier effect of sedative action and hypotensive action of tizanidine through α_2-adrenoceptor. Fryda-Kaurimsky et al. reported that a centrally mediated blood pressure lowering effect was observed in their diazepam group and tizanidine group[38].

The sedation score of patients was greater in the tizanidine group than in the control group in this study, and the sedative and anxiolytic action of tizanidine has a multiplier effect when it is administered with benzodiazepines[39]. Therefore, patients receiving both medications should be carefully monitored.

α_2-adrenoceptor agonists provide hemodynamic stability during anesthesia induction and tracheal intubation, and reduce the need for volatile anesthetics, opioids, and benzodiazepines during surgery. It is believed that α_2-adrenoceptor agonists also reduce pain associated with infiltration of local anesthetics and inhibit stress response to tracheal intubation and during surgery[40,41]. Injective tizanidine was not available to us, so it was impossible to compare the effects of orally administered tizanidine and injections of tizanidine.

In conclusion, it is possible to reduce the pain associated with infiltration of local anesthetics during epidural catheterization by oral administration of 3 mg of tizanidine 1 hour before the patient's arrival in the operating room. Blood pressure and rate-pressure product in the operating room are also reduced by premedication with tizanidine. None of our patients experienced excessive bradycardia or hypotension in this study. Therefore, we recommend premedication with tizanidine for patients undergoing epidural catheterization before induction of anesthesia.

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