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The Effect of Oral Clonidine Premedication on Lumbar Cerebrospinal Fluid Pressure in Humans

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Abstract

α-2 adrenergic agonists including clonidine decrease cerebral blood flow. The specific actions of clonidine on cerebrospinal fluid (CSF) pressure in humans remain to be elucidated. We evaluated the effect of oral clonidine premedication on lumbar CSF pressure in patients without intracranial disease. Seventy-four patients undergoing subarachnoidal block were divided randomly into either a clonidine or a control group. In the clonidine group, the patients were premedicated orally with 5 μg/kg clonidine 60 min before arrival in the operating room. Subarachnoidal puncture was performed via midline approach using a 23-gauge needle at the L 2-3 or L 3-4 intervertebral space with the patient in the lateral decubitus position. Before the injection of local anesthetic, lumbar CSF pressure was measured. Lumbar CSF pressure was 8.1 ± 2.4 mmHg in the clonidine group, which was significantly lower than that in the control group (9.4 ± 2.8 mmHg, $p<0.05$). The cerebral perfusion pressures were 76.2 ± 12.5 mmHg in the clonidine group and 91.7 ± 15.4 mmHg in the control group ($p<0.001$). In the clonidine group, preanesthetic mean blood pressure had a significant correlation with lumbar CSF pressure ($r=0.619$, $p=0.019$). We conclude that Lumbar CSF pressure was attenuated by oral premedication with 5 μg/kg clonidine. Clonidine also contributed to a significant correlation between preanesthetic mean blood pressure and CSF pressure. (J Nippon Med Sch 2000; 67: 429—433)

Key words: clonidine, lumbar cerebrospinal fluid pressure, cerebral perfusion pressure, cerebral blood flow

Introduction

As a premedicant in general anesthesia, α-2 agonist clonidine has been shown to be beneficial in several ways. Clonidine, which has been used mainly as an antihypertensive agent until now, has proven sedative and anxiolytic effects, it improves intraoperative hemodynamic stability, it potentiates the anesthetic actions of other agents, and it reduces the anesthesia requirement with a dose of 5 μg/kg orally[1-4]. Clonidine premedication is also effective in prolongation of subarachnoidal block[5]. Cerebral blood flow is maintained at nearly constant rates despite wide variations in mean blood pressure (BP) caused by adjustments in cerebral vascular resistance[6]. However, a reduction in cerebral blood flow by α-2 agonists has been reported in both humans and animals. Clonidine has been shown to decrease cerebral blood flow up to 36% in cats[7] and up to 28% in humans[8]. This reduced cerebral blood flow could effect a reduction in lumbar cerebrospinal fluid (CSF) pressure. However, the ef-

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fect of clonidine on intracranial pressure (ICP) or lumbar CSF pressure is still controversial[9-11]. In addition, the two human studies reported showed that α-2 agonists did not have any significant effects on ICP or CSF pressure[10,11]. These human studies were, however, conducted in patients who were undergoing intracranial surgery. To clarify exact actions of clonidine on CSF pressure, it is necessary to evaluate the change of lumbar CSF pressure in patients without intracranial disease. Therefore, we investigated whether oral clonidine premedication decreases lumbar CSF pressure in patients undergo subarachnoidal block.

Materials and Methods

This study was approved by the Committee on Human Subjects, and all patients gave informed consent. Seventy-four patients, ASA physical status I, undergoing lower abdominal or lower limb surgery were recruited and allocated randomly into two groups, a clonidine premedication group and a control group. Patients with known preoperative hypertension or current heart, hepatic, and/or renal disease were excluded. In addition, patients suffering from ascites and morbidly obese patients having a body mass index greater than 40 kg/m^2 were also excluded.

Patients in the clonidine group were premedicated orally with 5 μg/kg clonidine 60 min before arrival in the operating room, and patients in the control group received no premedication. BP and heart rate (HR) were also measured in each patient at 60 min before arrival in the operating room to obtain baseline values. An intravenous catheter was inserted into each patient the morning the day of surgery, and lactated Ringer's solution was infused at approximately 2 to 3 m*l*/kg/hr before arrival in the operating room. In the operating room, patients underwent lead II electrocardiogram monitoring, and BP was measured noninvasively several times before subarachnoidal puncture (Lifescope 14, Nihon Koden, Tokyo, Japan). The most frequently recorded preanesthesia BP and HR rates were taken as the preanesthesia values. If no stable rate could be determined during the period, the lowest rate recorded was taken.

The median approach was used for subarachnoidal puncture with a 23-gauge cutting needle at the L 2-3 or L 3-4 intervertebral space with the patient in the lateral decubitus position[12]. After a satisfactory return of CSF was observed, the stylet was reinserted into the needle, and the patient's neck and thighs were stretched carefully and relaxed to minimize the effect of posture on the lumbar CSF pressure. A sterile extension line was connected to the hub of the needle to position it vertically, and we obtained rhythmic oscillation of the CSF meniscus that reflected respiratory movement of the thorax. Lumbar CSF pressure was recorded as the fluid height from the puncture site to the bottom of the meniscus at the end of exhalation. Gentle manual compression of the internal jugular vein was done to prevent occlusion of the cerebrospinal fluid pathway. An increase in lumbar CSF pressure was confirmed after the measurement. Thereafter, local anesthetics were injected through the puncture needle. This course of treatment was followed according to the assessment specified by the anesthesiologist in charge of each surgery, who was unaware of which treatment the patient received.

To interpret pressure data, we converted the lumbar CSF pressure value (cmH_2O) to mmHg by dividing by 1.36, the specific gravity of mercury. Cerebral perfusion pressure was calculated as preanesthetic mean BP-lumbar CSF pressure. Data were expressed as mean ± SD. Demographic data, hemodynamic data, lumbar CSF pressure, and cerebral perfusion pressure were analyzed using Student's *t*-test or paired *t*-test. Differences between the sexes were analyzed by chi-square test with a contingency table. Pearson's correlation coefficient was used to determine the relationship between preanesthetic mean BP and lumbar CSF pressure. For all statistical analyses, $p<0.05$ was considered significant.

Results

There were no significant differences between the two groups in patient age, sex ratio, height, weight, preanesthetic infusion volume, or body mass index (**Table 1**). The clonidine group showed significantly lower preanesthetic mean BP and HR values than did the control group (**Table 2**). The clonidine group showed a significant decrease in mean BP compared to the baseline value (**Table 2**). In contrast, the con-

trol group showed a significantly high preanesthetic mean BP value compared to the baseline value (**Table 2**).

Lumbar CSF pressures were 8.1 ± 2.4 mmHg in the clonidine group and 9.4 ± 2.8 mmHg in the control group ($p<0.05$) (**Fig. 1**). The cerebral perfusion pressure of the clonidine group was also significantly lower than that of the control group (76.2 ± 12.5 mmHg vs 91.7 ± 15.4 mmHg, respectively, $p<0.001$) (**Fig. 1**). The lowest cerebral perfusion pressure values were 53.3 mmHg in the clonidine group and 66.4 mmHg in the control group. Correlation analysis of the two groups showed a significant relation only between preanesthetic mean BP and lumbar CSF pressure in the clonidine group ($r=0.619$, $p=0.019$) (**Fig. 2**).

Table 1 Patient characteristics according to group

	Clonidine group	Control group
Age (yr)	45 ± 17	47 ± 16
Male/Female	26/11	23/14
Height (cm)	165 ± 8	162 ± 8
Weight (kg)	64 ± 10	62 ± 12
Body mass index (kg/m^2)	23.4 ± 3.5	23.5 ± 4.2
Preanesthetic infusion volume (m*l*/kg)	7.2 ± 3.8	6.7 ± 5.3

Values are shown as mean ± SD, except sex ratio.

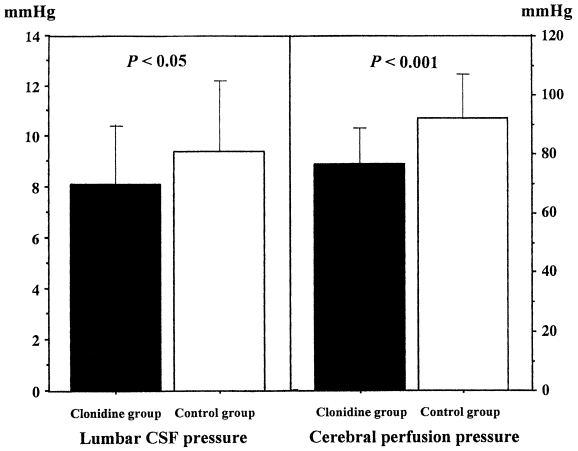

Fig. 1 Comparison of lumbar cerebrospinal fluid (CSF) pressure and cerebral perfusion pressure between the two groups. Both lumbar CSF pressure and cerebral perfusion pressure were significantly lower in the clonidine group than in the control group. Data are presented as mean ± SD.

Discussion

This is the first study demonstrating that oral clonidine premedication decreases lumbar CSF pressure and that it has a significant relationship with mean BP in patients without intracranial disease. Cerebral perfusion pressure also decreases significantly. No neurological signs indicating insufficient cerebral blood circulation were observed in the present study.

Several studies have shown that clonidine reduces cerebral blood flow[7,8,13]. Dexmedetomidine, more selective and potent α-2 agonist, also reduces cerebral blood flow up to 38% in halothane-anesthetized dogs[14] and up to 45% in isoflurane- anesthetized dogs[15]. These attenuating effects of α-2 agonists on cerebral blood flow suggest the possibility of decreased cerebral blood volume, which may reduce ICP. However, few studies have evaluated the effect of α-2 agonists on ICP and CSF pressure. Zornow et al.[9] showed that 20 μg/kg dexmedetomidine transiently decreased ICP by 31% in halothane-anesthetized healthy rabbits, despite having no effects on ICP at higher doses (80 and 320 μg/kg). However, human studies evaluating the effect of α-2 agonists on ICP or lumbar CSF pressure showed no changes in these pressures. In a study of patients who had undergone transsphenoidal pituitary tumor surgery, dexmedetomidine at an estimated plasma concentration of 600 pg/m*l* did not affect lumbar CSF pressure[10]. Another study in nor-

Table 2 Changes in mean blood pressure and heart tate (mean ± SD)

	Group	Baseline	Preanesthetic value
Mean blood pressure (mmHg)	Clonidine	88.2 ± 11.5	84.3 ± 13.2*†
	Control	92.1 ± 13.4	101.0 ± 14.6†
Heart rate (beats/min)	Clonidine	72.0 ± 11.7	69.4 ± 12.2*†
	Control	77.3 ± 11.7	78.9 ± 19.4

*$p<0.05$, compared with the control group. †$p<0.05$, compared with the baseline value within each group.

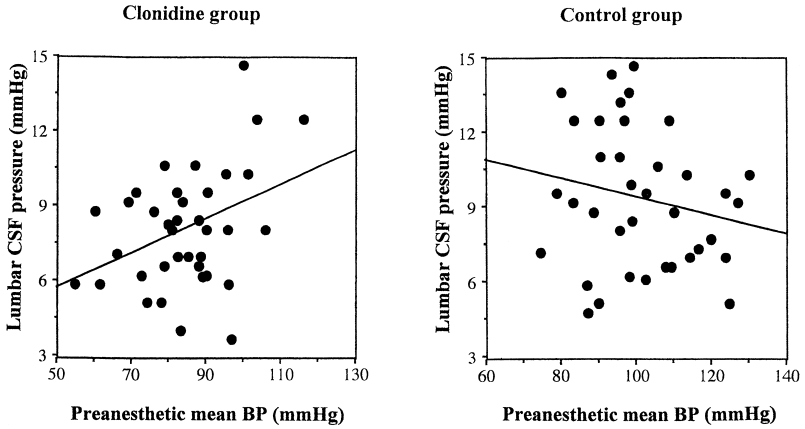

Fig. 2 Correlation between lumbar cerebrospinal fluid (CSF) pressure and preanesthetic mean blood pressure (BP) in the two groups. Lumbar CSF pressure correlated significantly with preanesthetic mean BP in the clonidine group ($r=0.619$, $p=0.019$) but not in the control group ($r=0.192$, $p=0.253$).

motensive patients with normal ICP undergoing elective cerebral tumor resection showed that 3 μg/kg clonidine did not change ICP[11]. However, these studies were conducted in patients with intracranial disease, although the pathologies were limited. Thus, the possibility of compromised intracranial compliance or modified of reactions of cerebral vessels to α-2 agonists may exist. We believe that our study is the first to show that clonidine reduces lumbar CSF pressure in humans without intracranial disease.

In the present study, a significant relationship between CSF pressure and pre-anesthetic mean BP was demonstrated in the clonidine group. In a laser-Doppler flowmetry study, Ganjoo et al[16]. showed that 20 μg/kg of dexmedetomidine reduced regional cerebral blood flow by 22% in halothane-anesthetized normocapnia rats with BP reduced by approximately 32 % decreased BP. However, the decreased regional cerebral blood flow improved to almost the control value when BP was restored to the control level by phenylephrine infusion. These results suggest, at least in part, that cerebral blood flow autoregulation is impaired by α-2 agonists, since BP-related alterations in cerebral blood flow occurred within reasonable BP limits. Also, it may lead to the progressive change of lumbar CSF pressure as mean BP rises due to an increase in cerebral blood volume. The impaired autoregulation of cerebral blood flow could explain why we observe a significant relationship between lumbar CSF pressure and preanesthetic mean BP when clonidine is administered.

Persistent CSF leakage at the puncture site may lead to intracranial hypotension during subarachnoidal block. Intracranial hypotension is the most likely cause of postdural puncture headaches[17]. Use of a small gauge needle is the most effective means of reducing the incidence of postdural puncture headaches. However, narrower needles increase the failure rate of subarachnoidal block[18]. The present data demonstrate that clonidine premedication decreases lumbar CSF pressure in patients who undergo subarachnoidal block. We hypothesize that decreased lumbar CSF pressure prior to subarachnoidal puncture might reduce leakage of CSF at the puncture site, which may prevent postdural puncture headaches.

The centrally mediated hypotensive and bradycardiac effects of clonidine are well recognized. In the present study, BP and HR were decreased significantly in the clonidine group. Cerebral perfusion pressure was also significantly reduced in the clonidine group, primarily due to reduction of BP. Reduction of cerebral perfusion pressure to less than 50 mmHg leads to insufficient cerebral blood flow and cerebral ischemia in normotensive patients[19]. No patient showed cerebral perfusion pressure of less than 50 mmHg in the present study. As in this study, lumbar CSF pressure can be measured easily by using a sterile tube connected to a subarachnoidal puncture needle. However, one possible limitation of the current technique is erroneous estimation of the pressure be-

cause of the low pressure in this system. Therefore, extreme care was taken to locate the correct baseline level, which was defined in the present study at the subarachnoidal puncture site by the midline approach. In addition, we substituted lumbar CSF pressure for intracranial pressure in our study because of the good correlation between lumbar CSF pressure and ICP when there is no pathological obstruction[20]. To confirm the CSF patency between the cranium and the puncture site, we verified an increase in lumbar CSF pressure caused by gentle compression of the internal jugular vein[21].

We conclude that oral premedication with 5 μg/kg clonidine decreases lumbar CSF pressure and cerebral perfusion pressure in patients without intracranial disease who undergo subarachnoidal block. Further studies are necessary to evaluate the effectiveness of clonidine in preventing postdural puncture headache. In addition, the reduction in CSF pressure is significantly correlated with preanesthetic mean BP in patients who take clonidine, which suggests that autoregulation of cerebral blood flow is impaired by clonidine.

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