ORIGINAL ARTICLE

Comparative Study of Epidurally Administered Clonidine and Buprenorphine on Anesthetic Requirement and Electroencephalographic Activity

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Abstract. The author investigated the effects of epidurally administered buprenorphine (BPN) and clonidine (CLO) on the potentiation of halothane anesthesia in terms of the minimum alveolar concentration (MAC), hemodynamics, and electroencephalographic activity in the patients undergoing lower abdominal surgery. Thirty-four women (ASA-1) were studied after the epidural administration of either 10 ml saline (group A, n=8), 10 ml saline with 0.4 mg BPN (group B, n=13), or 10 ml saline with 150 µg CLO (group C, n=13). The MAC of halothane was reduced by 32% in group B (p<0.05), and by 23% in group C (p<0.05) compared with group A. The delta activity on the electroencephalogram (EEG) was more dominant in groups B and C 20 and 30 minutes after the administration of BPN and CLO compared with group A. The alpha activity in group A was significantly greater than that in the other groups. The delta activity in groups B and C was increased significantly compared with group A. The blood pressure was significantly lower after the epidural administration of CLO in group C, compared with groups A and B. The study concluded that epidurally administered CLO significantly reduce the MAC of halothane and also resulted in significant acceleration of delta activity on the EEG, as did BPN. The mechanisms by which the central nervous system (CNS) is depressed by epidural BPN and CLO are different, but this may have resulted from their direct action on the CNS via the systemic and spinal absorption of BPN and CLO.


Key words: clonidine, buprenorphine, epidural administration, minimum alveolar concentration, EEG

Introduction

The epidural administration of clonidine (CLO), an alpha2-adrenergic agonist, and buprenorphine (BPN), an opioid receptor agonist-antagonist, has been widely accepted and they are used as post-operative analgesics and for pain relief in cancer patients.1,2 Their effects on the central nervous system (CNS) have been studied intensively, and they induce sedation, analgesia, anxiety, and hemodynamic changes.3,4 But, BPN has some possible complications, such as delayed respiratory depression, nausea, and vomiting due to its distribution in the CNS via the cerebrospinal fluid (CSF), as morphine does.3,8 Whereas, CLO, an imidazoline with alpha2-adrenergic agonistic properties, has been shown to decrease both blood pressure and heart rate by sympathetic depression via its effect on presynaptic neurons.9 The high lipophilicity of CLO is responsible for the rapid onset of analgesia, as it is with BPN. CLO has been shown to be 10 and 60 times more potent than morphine at inducing analgesia.10 Nevertheless, its effect on the CNS during surgery is not well understood.

The purpose of this study was to clarify the effect of epidurally administered BPN and CLO on the CNS by means of electroencephalogram (EEG) and its interaction with the inhalation anesthetic, halothane, in terms of its minimum alveolar concentration (MAC).
Methods and Materials

Thirty-four adult women, who gave their informed consent, ASA physical status 1 undergoing elective gynecological surgery, were involved in this study. They received no premedication. Any patient, weighing over 70 kg, older than 60 yr old, or taking tricyclic antidepressants, alpha2-adrenergic agonists, opioids or any drugs known to sedate or modify MAC, were excluded from this study. The patients were divided into 3 groups at random according to the epidurally administered agents: group A (control, n = 8) received 10 ml saline, group B (n = 13) received 0.4 mg BPN in 10 ml saline, group C (n = 13) received 150 μg CLO in 10 ml saline. An epidural catheter was inserted in the lumbar 3-4 interspace, and each agent was injected via the epidural catheter before general anesthesia. Anesthesia was induced with halothane, and 66% nitrous oxide balanced with oxygen. After the patients were anesthetized deeply, an endotracheal tube was inserted with the aid of succinylcholine (1 mg/kg) intravenously, and then anesthesia was maintained with halothane in oxygen. Mechanical ventilation was adjusted to maintain an end-tidal CO₂ concentration within 35–45 mmHg. The end-tidal halothane concentration was monitored by infrared spectroscopy (CAPNOMAC, DATEX®, Helsinki, Finland) and kept constant for 15 minutes before the skin incision. The MAC of halothane was used as a measure of anesthetic potency. MAC was determined during surgery in 25 patients, i.e. in group A (n = 5) and groups B (n = 10) and C (n = 10). The EEG was adopted to assess the depth of anesthesia and was determined in 9 patients, from group A (n = 3) and from groups B (n = 3) and C (n = 3) anesthetized with 1 MAC of halothane (0.82% concentration) in oxygen during the first 60 minutes after the epidural administration of each agent. The MAC determination had been completed, all patients received a neuromuscular blocking agent, vecuronium bromide 0.08 mg/kg intravenously and then anesthesia was maintained with 66% nitrous oxide and 33% oxygen with the adjustable halothane concentration during surgery.

Electroencephalogram (EEG)

In each group, 3 patients anesthetized with 1 MAC of halothane concentration in oxygen were studied. All patients were injected intravenously with vecuronium bromide 0.08 mg/kg intravenously, and then additionally administered at a dose of 0.02 mg/kg intravenously. The end-tidal halothane concentration was maintained for 15 minutes prior to the epidural injection. EEG electrodes were placed at Fp1 and Fp2 with reference electrodes at A1 and A2, according to the International 10-20 system. EEG monitoring was started 10 minutes before the epidural injection. EEG signals were recorded every 10 minutes until 60 minutes after the administration of each agent. The raw EEG signals were digitized at 100 Hz by a computer system (acknowledge 3.0, BIOPAC systems, INC). Spectral analysis was performed by fast Fourier transformation (FFT) to obtain the spectral power of each band: 0.5–3.0 Hz (α-band), 3.0–8.0 Hz (β-band), 8.0–13.0 Hz (θ-band), and 13.0–30.0 Hz (δ-band), and the total power of the EEG was between 0.5 and 30.0 Hz. For the statistical analyses, the area under the power spectrum curve for each frequency band was computed.

Blood samples

To elucidate the pharmacokinetics of BPN and CLO and to measure the serum catecholamine concentrations (groups A and C), arterial blood was sampled 0, 5, 10, 20, 30, 60, 90, and 120 minutes after the injection of either agent. Blood samples were collected in an EDTA tube and immediately centrifuged (4°C) and the plasma was frozen at −10°C. Serum BPN and CLO concentrations were measured by gas chromatography and mass spectrometry, and catecholamine levels were measured by high performance liquid chromatography. The lower limit for the detection of epinephrine and norepinephrine...
was 5 pg/ml.

**Statistical analysis**

All values are expressed as the mean ± standard deviation. Statistical analysis was performed by analysis of variance with repeated measures, followed by the paired t-test. For the analysis of EEG activity, the two-tailed t-test was used, where appropriate. A probability of less than 5% was considered statistically significant.

**Results**

The demographic data of patients who participated in this study are summarized in Table 1. There was no significant difference among the groups with respect to age, body weight, body temperature, end-tidal CO2, and the time from the epidural injection to incision.

To determine the MAC of the 3 groups, the percent response to surgical skin incision was plotted against the alveolar halothane concentration by using Eger's method. An upward deflection indicates the patient’s movement in response to surgical skin incision. A downward deflection indicates that the patient did not move at the surgical skin incision (Fig 1). The percentage of patients who had positive response to surgical skin incision were plotted on the vertical axis against the end-tidal concentration of halothane (Fig 2). The plots of both groups B and C were shifted to the left in comparison with group A. MAC is the point on the sigmoid curve where a line connecting the individual points which passes through the 50% point (Fig 2). The MAC for halothane was 0.79% in group A, 0.52% in group B and 0.61% in group C. The MAC of halothane in groups B and C were reduced by 32% and 23%, respectively (p<0.05), when compared with that of group A.

The hemodynamics results are shown in Table 2. Systolic/diastolic blood pressures were 129.5 ± 8.0 mmHg/69.6 ± 8.2 mmHg in group A, 134.4 ± 19.1 mmHg/82.2 ± 6.5 mmHg in group B, and 131.2 ± 18.9 mmHg/78.8 ± 12.7 mmHg in group C respectively before the epidural injection. There were no significant differences among these groups. Five minutes after the epidural injection of each agent, there were no significant differences in the systolic/diastolic blood pressures among the groups. The systolic blood pressure in group C decreased significantly before the skin incision compared with group A (p<0.05), but the diastolic blood pressure in group C did not change significantly, compared with group A (p<0.05). Five minutes after the skin incision, the systolic/diastolic blood pressure in group C was significantly lower than groups A and B (p<0.05). In group C, the heart rate increased after the epidural injection, before and after the skin incision, but there were no significant differences among the groups.
Table 2  Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Pre-injection (5 minutes before the skin incision)</th>
<th>Post-injection (5 minutes after the skin incision)</th>
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<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
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<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
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<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>110.2 ± 23.7</td>
<td>107.0 ± 6.5</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>56.6 ± 4.8</td>
<td>75.0 ± 6.4</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>69.7 ± 10.1</td>
<td>73.4 ± 18.5</td>
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Group A (halothane in oxygen, n=5); Group B (halothane in oxygen with epidural BPN, n=10); Group C (halothane in oxygen with epidural CLO, n=10)

*: compared to group A (p<0.05). #: compared to group B (p<0.05). Mean±SD.

The plasma norepinephrine level in group C was lower significantly between 5–120 minutes after the injection, despite surgical stress, compared with group A (p<0.05) (Fig 4–2). The plasma norepinephrine levels in group A increased gradually in the initial 30 minutes, and then these high levels were not suppressed until after 120 minutes.

In group A, the alpha activity was dominant on the EEG compared with the other groups. A decrease in voltage and the number of alpha waves was observed after 20 minutes up until 60 minutes in group B, and after 30 minutes up until 60 minutes in group C (Table 3–1,2). The increasing delta activity in group B appeared earlier than in group C. This increase was observed 20 minutes after the administration of the respective agent in group B, and 30 minutes after this in group C. The percentage of delta activity was 18.0 ± 2.1% in group A, 27.9 ± 2.0% in group B, and 20.4 ± 0.8% in group C after 20 minutes. The percentage of delta activity was 19.5 ± 3.3% in group A, 23.5 ± 2.8% in group B, and 33.1 ± 10.3% in group C after 30 minutes. Delta activity appeared more prominent in group B (between 20–60 minutes) and group C (between 30–60 minutes) compared with group A. In group C, delta activity was more dominant after 50–60 minutes following the administration of each agent compared with group B (p<0.05).

Discussion

Epidural administration of narcotics and related agents has been widely accepted and used in clinical practice as the post-operative analgesics with minimal side effects.\(^\text{12}\)
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Fig 4-1 Plasma epinephrine concentration. The mean ± SD of the plasma epinephrine concentrations before and after epidural injection of saline and 150μg clonidine, * p < 0.05 vs group C.

Fig 4-2 Plasma norepinephrine concentration. The mean ± SD of the plasma norepinephrine concentration before and after epidural injection of saline and 150μg clonidine, * p < 0.05 vs group A.

Recently, preoperative regional blockade of wound pain by epidural and other neural blockade has been shown to lead to the desensitization of the CNS which is responsible for the diminished post-operative pain, called preemptive analgesia. 13-16 However, the interaction of preemptively administered epidural analgesics with inhaled anesthetics, especially their effects on perioperative analgesia and the CNS activity need to be elucidated for optimal patient care. CLO is used clinically as an anti-hypertensive agent. Recently, it has been shown that an alpha2-adrenergic agonist, which is given as premedication to patients with preoperative hypertension, could provide with analgesia and sedation. 17 It has been shown to be 10 and 60 times more potent than morphine. 10

The possibility of epidural administration of CLO for the potentiation of general anesthetics still needs to be extensively studied to elucidate the mechanism involved in its analgesic and sedative effects. This study clearly demonstrates that the epidural administration of analgesics, BPN, and an alpha2-adrenergic agonist, CLO, resulted in the potentiation of halothane anesthesia and depressed EEG activity during general anesthesia with halothane. Similar analgesic and sedative effects were obtained with these agents, even though their agonistic actions are different.

The author used a dose of 0.4mg BPN and 150μg CLO for several reasons. Firstly, 0.4-0.6mg BPN is within the optimal dose range used epidurally for human preoperative anesthesia. 2,4,5 Secondly, Eisenach et al reported that 100-300μg epidural CLO improved efficacy and safety for postoperative analgesia after surgery. 18

<table>
<thead>
<tr>
<th>Table 3</th>
<th>The Percentage of Alpha Wave Activity (1) and the Percentage of Delta Wave Activity (2) in All the EEGs after Epidural Injection</th>
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<tbody>
<tr>
<td>(1)</td>
<td>Alpha Wave (%)</td>
</tr>
<tr>
<td>0 min.</td>
<td>24.1 ± 4.2</td>
</tr>
<tr>
<td>10 min.</td>
<td>19.6 ± 2.0</td>
</tr>
<tr>
<td>20 min.</td>
<td>28.7 ± 3.4</td>
</tr>
<tr>
<td>30 min.</td>
<td>30.3 ± 1.8</td>
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<tr>
<td>40 min.</td>
<td>31.3 ± 2.2</td>
</tr>
<tr>
<td>50 min.</td>
<td>29.1 ± 2.1</td>
</tr>
<tr>
<td>60 min.</td>
<td>26.7 ± 2.0</td>
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* : compared to group A at same time. (p < 0.05)  unit: %

(2) Delta Wave (%)  Group A  Group B  Group C
0 min.  22.3 ± 4.4  19.6 ± 0.8  22.2 ± 5.9
10 min.  28.8 ± 3.6  25.7 ± 1.5  19.2 ± 0.7
20 min.  18.0 ± 2.1  27.9 ± 2.0*  20.4 ± 0.8
30 min.  19.5 ± 3.3  23.5 ± 2.8*  33.1 ± 10.3* #
40 min.  17.0 ± 1.6  24.3 ± 2.5*  28.2 ± 2.0* #
50 min.  16.6 ± 3.7  25.5 ± 2.2*  35.6 ± 0.4* #
60 min.  14.1 ± 2.0  20.2 ± 0.7*  30.1 ± 3.0* #

* : compared to group A at same time. (p < 0.05)  unit: %
# : compared to group B at same time (p < 0.05)

Group A (halothane in oxygen, n = 3); Group B (halothane in oxygen with BPN, n = 3); Group C (halothane in oxygen with CLO, n = 5).
The epidural space is rich in vasculature, such as the epidural plexus and the spinal radicular arteries, and thus the agent could be absorbed into systemic circulation. The absorbed agent might affect various organs throughout the body, including the CNS.

The penetration of the epidurally administered agents through the dura is dependent on several factors, such as lipophilicity, molecular weight, pKa, intracellular pH, and the molecules radius. The lipophilicity, which is not the principal determinant of meningeal permeability, is usually determined by the octanol-water partition coefficient, where that of BPN and CLO is 61 and 114, respectively. Both of them are high lipid solubility. This property promotes rapid onset of action that could be available to migrate to brain. The molecular weight of the agent is another factor, and that of BPN and CLO is 504 and 230 daltons, respectively. High molecular weight drugs across the dura with less ease than drugs of low molecular weight. Since the onset of action and its duration is dependent on the lipophilicity and molecular weight, the patients that received epidural CLO reduced their systolic blood pressure more rapidly than those given epidural BPN before skin incision in this study. However, BPN could have a more rapid onset than CLO as shown by their EEG activities in this study. This feature suggests that consists of several different components. First, the reduction in blood pressure is probably due to a reduction in the sympathetic out flow by epidural CLO. Ghignone et al suggested that the activation of alpha2-adrenoceptors causes both a reduction in peripheral sympathetic tone and increases the vagally induced reflex. Second, it seemed that CLO had more anxiolytic properties than BPN during the induction of halothane anesthesia. In general, it is difficult to separate the sedative effect from the anxiolytic effect. Bloor et al suggested that alpha2 agonists do induce anxiolysis independently of sedation. However, the anxiolytic effect could not be evaluated by processed EEG in this study. Another reason was that 0.4 mg BPN administered epidurally was not as equipotent as 150 μg CLO. The heart rate increased during hypotension in this study. Kirno et al reported that heart rate would have increased during hypotension due to baroreceptor reflex mechanisms. This finding might be also due to the same mechanism in this study.

The lipophilicity of the epidurally administered agents is also responsible for the affinity for receptors in the spinal cord. This study has revealed the potentiation of halothane anesthesia, which was confirmed by a reduction in MAC by epidural BPN and CLO. Suppression of neurotransmission at the spinal level might be one of possibilities which have reduced the anesthetic requirement of halothane. In this study, BPN and CLO reduced the MAC of halothane by 32% and 23%, respectively, compared with epidural saline injection. A reduction in the MAC of halothane was caused by CLO, which suppressed catecholaminergic activity. The effect of the systemic administration of CLO on the anesthetic requirement has been studied in several reports. Ghignone reported that treatment with oral CLO (5 μg/kg) reduced the MAC of isoflurane by 40%. Bloor also reported that intravenous treatment with CLO (5 μg/kg) reduced the MAC of halothane by 42% in mongolian dogs by decreasing central catecholaminergic activity. Although BPN and CLO act at the different receptor sites, i.e. μ receptor and alpha2 receptor, their resultant analgesic and sedative effects are quite similar. Bloor suggested that both μ-opioid agonist and alpha2 agonist could activate membrane-associated G-proteins. The activation of those G-proteins results in the opening of K+ channels, leading to hyperpolarization of membrane and thus inhibition of excitatory neurons in the CNS. Both μ receptors and alpha2 receptors exist in the locus coeruleus and the rostral ventrolateral medulla. Activation of either receptor may result in the inhibition of those neurons, especially the inhibition of transmitter release. Peripherally, the stimulation of alpha2 receptor, which have been identified in the spinal dorsal horn, could inhibit the transmission of nociceptive impulses from Aδ and C fibers. Therefore, CLO might be as potently analgesic as BPN is at the central site and the spinal level as shown by the reduced MAC of halothane.

Systemic absorption from the epidural space might be responsible for various changes in cardiovascular and respiratory functions as well as in the adrenal gland. It has been reported that systemic administration of CLO can inhibit the norepinephrine release from sympathetic nerve endings. Bloor found that anesthetic requirement is dependent on the central sympathetic activity. The reduction of the MAC of halothane seen in this study could be explained by the decreased plasma norepinephrine concentrations, as well as the inhibition of sympathetic nerve endings by CLO, since plasma catecholamine levels were lower than in the control before skin incision, and at least equal to the control level even under surgical stress. Adrenal function can be affected not only by systemic CLO, but also by the level of regional blockade. Bonica reported that the adrenal medulla, which is innervated by Th6–12 spinal segments, could be blocked by thoracic epidural blockade. Pflug also suggested that the adrenal response to surgical stress was suppressed by the spinal blockade at the Th9 level or lower. These findings support that there were no significant changes in plasma catecholamine concentrations during surgery in this study, and this might be due to adrenal suppression by spinal blockade as well as the systemic inhibitory effect of CLO.

Other epidurally administered agents which penetrate...
the dura migrate in the CSF to the CNS. The high lipophilicity of both of these agents enables them to easily penetrate the dura and explains their rapid and short lived effects, however it may also limit cephalad spread in the CSF. Another highly ionized and hydrophilic drug, such as morphine, has a slow onset and its blocking effects last a long time, it also induces delayed respiratory depression. The effects of BPN and CLO on the CNS were evaluated by processed EEG, and the deceleration of alpha activity was found after the epidural injection of both agents. Generally, a rapid wave of 20–25 Hz was established after 2 minutes, and then the 10 Hz wave was prominent after 20 minutes in those that inhaled 4% halothane with oxygen to induce anesthesia.

In this study, the significant deceleration of alpha activity was demonstrated 20 minutes and 30 minutes after the injection of BPN and CLO, respectively. The shift of the processed EEG signal toward the delta range is thought to represent the deeping of anesthesia with the opioid. Kock reported that delta activity increased in a biphasic fashion, i.e. peaks 12 and 30 minutes after the epidural injection of CLO. It seemed that the first peak might be caused by systemic vascular absorption, and the second one could be due to its distribution from the epidural space to the subarachnoid space. In this study, while plasma epinephrine and norepinephrine concentration were decreased 10 minutes after the administration of epidural CLO, the decreasing catecholamine level was not reflected by the EEG activity. The peak acceleration of delta activity was observed only 20 and 30 minutes after the epidural BPN and CLO injections, and was not biphasic. Although the mechanisms which provided monophasic changes in EEG activity are not clear in this study, the significant increase in delta activity might be due to the migration of the agents in the CSF to the CNS.

This study has revealed that epidural CLO enhances the analgesic effects of other anesthetics without inducing any serious hemodynamics and adrenergic changes and reduces the anesthetic requirement, as BPN does, during surgery. These agents may reduce the MAC of halothane and increase the delta activity on the EEG of both the peripheral and central effects. This is mediated through peripherally and centrally alpha2-adrenergic mechanisms. In the future, the modifying effects of CLO and other alpha2-adrenergic agonist, such as dexmedetomidine, on anesthesia need to be investigated.

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