Comparison of Anesthetic Effects of Epidural and Intravenous Administration of Buprenorphine during Operation

Eiji YONEMURA and Kazuaki FUKUSHIMA

Thirty six patients were received epidural anesthesia with or without buprenorphine (BPN) during upper abdominal surgery. They were divided into three groups of 12 patients as follows; G-I received 20 ml of 1% lidocaine epidurally, G-II received 20 ml of 1% lidocaine epidurally and 0.6 mg BPN intravenously, G-III received 20 ml of 1% lidocaine with 0.6 mg BPN epidurally. Additional 5 ml of 1% lidocaine was given to any patient if systolic blood pressure or heart rate increased 10% compared to control value. Trachea was intubated following anesthetic induction with thiopental. The lungs were ventilated with a mixture of N_2O/O_2 (33%) and pancuronium was used for muscle relaxation. The total required doses of lidocaine in G-II and G-III were decreased 60% compared to control group (G-I) ($P < 0.05$). The mean period of time until the first administration of pentazocine for postoperative pain was 13 ± 10 hr (mean ± SD) in G-II and 19 ± 24 hr in G-III compared to 5 ± 4 hr in G-I ($P < 0.001$). The dose of the administration of pentazocine that was required for pain relief during the first 48 postoperative hr in G-III was 54 ± 10 mg (mean ± SD) compared to 150 ± 21 mg in G-I ($P < 0.02$) and 106 ± 28 mg in G-II ($P < 0.05$). Recovery from anesthesia in G-III was more rapid than that in G-I ($P < 0.05$). The Pa_{CO_2} values in G-II and G-III increased 15% compared to control group at about 4 hr and 8 hr after administration of BPN, but any clinical treatment was not needed for them. Nonrespiratory side effects, e.g., nausea, vomiting, fatigue and headache, were comparably common in all groups. Mild hematuria associated with acute hypotension occurred in two patients in G-II (17%) immediately after the intravenous injection of 0.6 mg of BPN. The results showed that 0.6 mg of BPN given epidurally demonstrated better anesthetic and more potent postoperative analgesic effects and lesser side effects than 0.6 mg of BPN given intravenously in patients undergoing upper abdominal surgery. (Key words: epidural buprenorphine, intravenous, opiate receptor, postoperative)

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The effects of the combination of an opioid with a local anesthetic in epidural blockade during operation have been investigated[1–3]. Rucci[3] reported that longer analgesic effect and fewer instances of acute hypotension were obtained without any obvious respiratory depression following the epidural administration of 0.5% bupivacaine 20 ml containing fentanyl 200 μg. Buprenorphine (BPN) is an opiate of high potency with agonist-antagonist effect at the morphine receptor and a long duration of ac-

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tion. Several studies have shown that BPN is an effective analgesic agent perioperatively when administered intravenously or epidurally[4,5]. Recently we reported the usefulness of BPN and lidocaine mixture for epidural blockade[6–8,11].

The present study was undertaken to compare the perioperative pain relieving effect of epidural and intravenous administration of BPN.

Methods

Thirty six patients belonging to ASA I or II underwent upper abdominal surgery. The patients were from 32 to 72 years of age and 56 kg (mean) in weight. Informed consent was obtained from each patient prior to the study. The premedication was with atropine sulphate (0.5 mg) and hydroxyzine chloride (50 mg) given intramusculary 30 min prior to induction of anesthesia. Epidural puncture was performed at interspace between Th 7 and Th 8. The tip of a continuous epidural catheter was advanced 5 cm cephalad into the epidural space. All patients were divided into three studying groups at random, and each group was of twelve patients as the following;

Group I (control) received 20 ml of 1% lidocaine epidurally;

Group II received 20 ml of 1% lidocaine epidurally, and 0.6 mg BPN intravenously;

Group III received a mixture of 20 ml of 1% lidocaine and 0.6 mg BPN epidurally.

Anesthesia was induced with thiopental (5 $mg \cdot kg^{-1}$) and the trachea was intubated with the aid of succinylcholine chloride (1 $mg \cdot kg^{-1}$). Patients in group II and III were ventilated with oxygen 33% in nitrous oxide (N_2O-O_2) and patient in group I was ventilated with N_2O-O_2-halothane 0.2%. Ventilation was controlled with pancuronium bromide (0.1 $mg \cdot kg^{-1}$) with maintaining a Pa_{CO_2} of 30–35 mmHg. In group I halothane 0.2% was continued until 10 min before antagonism of the neuromuscular blocking drug.

In this study we observed arterial pressure, respiratory rate, minute volume, arterial blood gas, ECG and heart rate at 0 hr (control), 1 hr, 2 hr, extubation and 8 hr after the epidural or intravenous injection of each drug. Minute volume was measured by the spirometer of Right and Pa_{O_2} and Pa_{CO_2} were measured using a Radiometer ABL3 blood-gas analysis system. An additional 5 ml of 1% lidocaine was administered when arterial pressure or heart rate was increased 10% compared to control value. If arterial pressure was decreased 20% compared to control value, 5 mg increments of ephedrine were given intravenously. During operation fluid replacement was with 10 $ml \cdot kg^{-1} \cdot hr^{-1}$ of Hartman's solution followed by blood depending on blood loss and preoperative haemoglobin concentration. Recovery time from anesthesia, postoperative analgesic effects of BPN and nonrespiratory side effects, e.g., nausea, vomiting and pruritus, were also assessed. Pentazocine was administered intramuscularly on demand for analgesia by patient. If patient complained of both postoperative pain and insomnia, a mixture of 30 mg of pentazocine and 50 mg of hydroxyzine was administered intramuscularly for the treatment of them. Serum and cerebro-spinal fluid (CSF) BPN concentrations after epidural BPN 0.2 mg and 0.4 mg, CSF BPN concentrations after intrathecal BPN 0.05 mg and plasma BPN concentrations after intravenous administration of 0.3 mg BPN were measured in one patient respectively (n=1) at the following times: 0.5, 1, 2, 3, 4 or 6 hr after each injection. Measurements of serum and CSF BPN concentrations were performed by the method of Hand and colleagues[9]. The results were analysed with Student's t-test.

Results

1. Clinical background (table 1)

Age, weight, operation time and urine volume were not different in all groups. Required doses of lidocaine for obtaining of analgesic effect were 2.3 ± 1.0 $mg \cdot kg^{-1} \cdot hr^{-1}$ (mean ± SD) in group II and 2.0 ± 0.4 $mg \cdot kg^{-1} \cdot hr^{-1}$ in group III. Those doses were decreased significantly 60% compared to con-

Table 1. Clinical background
Background of patients

(Mean ± SD, n=12)

	age (yrs)	weight (kg)	operation time (min)	urine volume ($ml \cdot kg^{-1} \cdot h^{-1}$)	lidocaine dosis ($mg \cdot kg^{-1} \cdot h^{-1}$)
G-I	53 ± 17	56 ± 4	280 ± 172	0.86 ± 0.57	5.0 ± 2.6
G-II	53 ± 11	56 ± 3	211 ± 103	0.85 ± 0.52	2.3 ± 1.0*
G-III	54 ± 10	58 ± 5	217 ± 64	1.02 ± 0.65	2.0 ± 0.4*

*$P < 0.05$ significantly different from G-I

Required doses of lidocaine for obtaining of analgesic effect decreased significantly in G-II and G-III compared with that in G-I ($P < 0.05$).

Table 2. Respiratory function
Respiratory rate, minute volume, blood gas

(Mean ± SD, n=12)

		pre-anesth	1 hr	extubation	8 hr
RR ($rate \cdot m^{-1}$)	G-I	17 ± 3	11 ± 2	18 ± 4	18 ± 4
	G-II	16 ± 3	12 ± 2	15 ± 3	18 ± 4
	G-III	16 ± 2	11 ± 1	17 ± 4	15 ± 4
MV ($l \cdot m^{-1}$)	G-I	5.8 ± 1.3	5.6 ± 0.6	5.3 ± 2.4	5.9 ± 1.8
	G-II	6.0 ± 1.5	5.8 ± 0.8	4.7 ± 1.8	6.3 ± 1.9
	G-III	5.3 ± 1.2	5.8 ± 0.6	6.6 ± 3.5	4.9 ± 1.3
Pa_{CO_2} (mmHg)	G-I	40 ± 3	30 ± 5	40 ± 4	40 ± 5
	G-II	41 ± 4	30 ± 3	47 ± 3*	44 ± 3*
	G-III	40 ± 2	32 ± 4	45 ± 3*	45 ± 4*
Pa_{O_2} (mmHg)	G-I	90 ± 6	152 ± 28	78 ± 11	82 ± 2
	G-II	88 ± 12	165 ± 30	73 ± 10	80 ± 6
	G-III	90 ± 4	149 ± 33	75 ± 9	80 ± 7
F_2O_2		0.21†	0.33‡	0.21†	0.21†

†spontaneous respiration, ‡controlled ventilation

*$P < 0.05$ significantly different from G-I

RR: respiratory rate MV: minute volume

The Pa_{CO_2} values in G-II and G-III increased mildly at 4 hr (extubation) and 8 hr after administration of BPN compared with each pre-anesthetic value ($P < 0.05$).

trol group ($P < 0.05$).

2. *Arterial pressure and heart rate*

Mean arterial pressure during operation was not different significantly between group I and group III. Hypotension (< 80 mmHg systolic arterial pressure) occurred in five patients in group II (42%) 5 min after the injection of BPN, and the intravenous injection of ephedrine (range 5–20 mg) was administered for the treatment. Arterial pressure in group III was increased by 10% of control value immediately after operation. Heart rate in group II and group III tended to be decreased by 10% of each preoperative value, but in group I it was unchanged during operation.

3. *Respiratory function* (table 2)

Respiratory rate (RR), minute volume and Pa_{O_2} were not different in all groups, but the Pa_{CO_2} values in group II and group III were increased significantly by 10 to 16% of control value at about 4 hr (extubation)

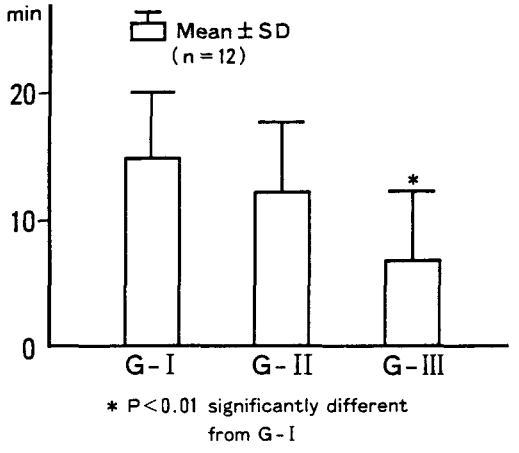

Fig. 1. Recovery Time

Recovery from anesthesia was rapid in G-III compared with that in G-I ($P < 0.01$). There was no difference in recovery time between G-II and G-III.

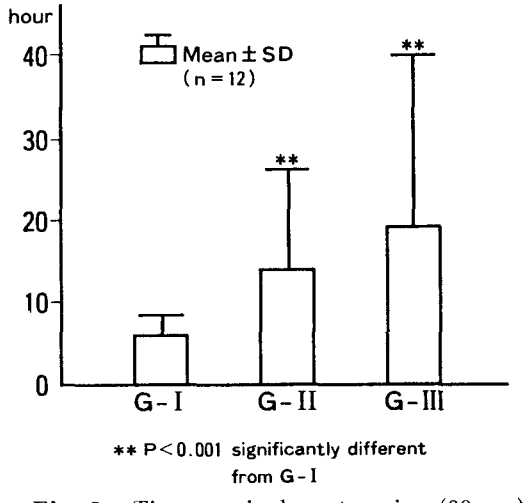

Fig. 2. Time required pentazocine (30 mg) for initial postoperative pain

Mean time required the administration of pentazocine (30 mg) for initial postoperative pain prolonged remarkably in G-II and G-III compared with that in G-I ($P < 0.001$), but there was no difference in the time between G-II and G-III.

and 8 hr after the administration of BPN ($P < 0.05$). Moderate bradypnoea (RR was 8 breath·min^{-1}) was observed tempolarily in three patients in group III about 30 min after a mixture of 30 mg of pentazocine and 50 mg of hydroxyzine was injected intramus-

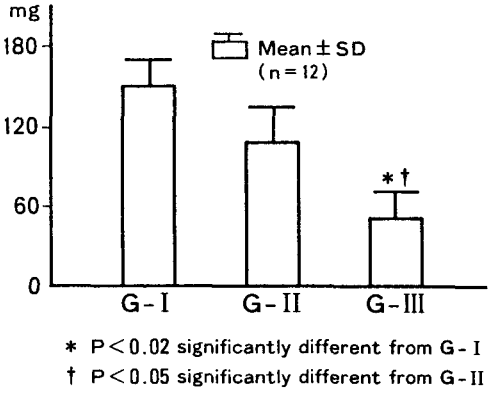

Fig. 3. Doses of pentazocine required for postoperative pain (over 48 postoperative hr)

Total dose of pentazocine required for postoperative pain (over the 48 postoperative hrs) decreased significantly in G-III compared with that in G-I ($P < 0.02$) and that in G-II ($P < 0.05$).

culary for postoperative pain relief and the treatment of insomnia, but no instance was required ventilatory support.

4. *Recovery time* (fig. 1)

Recovery time was 7 ± 7 min (mean ± SD) in group III and 12 ± 7 min in group II compared to 15 ± 7 min in group I. Recovery from anesthesia in group III was more rapid than that in group I ($P < 0.05$), but there was no difference in recovery time between group II and group III.

5. *Assessment of postoperative analgesia* (figs. 2,3)

a) The first dose of pentazocine

It was given immediately after patient complained of postoperative pain. Mean time required the administration of pentazocine for initial postoperative pain was 5 ± 4 hr (mean ± SD) in group I, 13 ± 10 hr in group II and 19 ± 24 hr in group III. The each time in group II and group III was longer than the value in group I ($P < 0.001$), but there was no difference in the time between group II and group III.

b) Total dose of pentazocine

Additional doses of pentazocine were administered on demand for analgesia by patients. The total mean doses given over the 48 postoperative hours of assessment period were 150 ± 21 mg in group I (mean ± SD),

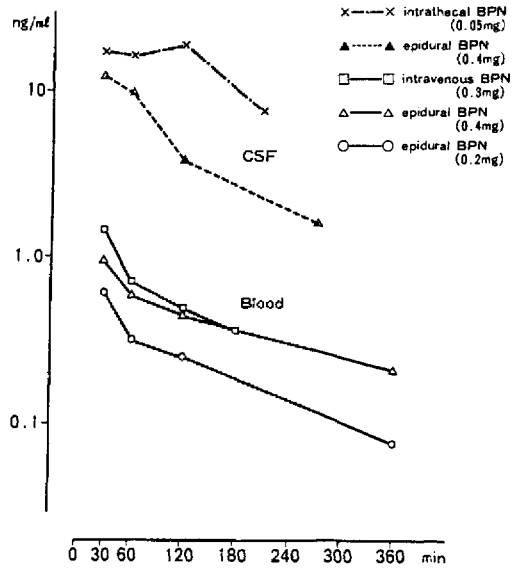

Fig. 4. Blood and CSF concentrations after injection of buprenorphine (BPN)

Blood and CSF concentrations after administration of buprenorphine (n = 5: intravenous BPN, n = 1: intrathecal and epidural BPN) CSF: cerebro-spinal fluid, BPN: buprenorphine

106 ± 28 mg in group II, and 54 ± 10 mg in group III. The dose of pentazocine in group III was less than the value in group I ($P < 0.02$) and the value in group II ($P < 0.05$).

6. Blood and CSF BPN concentrations (fig. 4)

Serum concentrations (n=1) 1 hr after epidural BPN were 0.32 ($ng \cdot ml^{-1}$) and 0.61 for the 0.2- and 0.4- mg groups, respectively. The CSF concentration (n=1) 1 hr after 0.4 mg of epidural BPN was 9.73 $ng \cdot ml^{-1}$, but it tended to be lower than that of 0.05 mg of intrathecal BPN (16.21 $ng \cdot ml^{-1}$). The mean plasma concentration 1 hr after 0.3 mg of intravenous BPN (n=5) was 0.85 $ng \cdot ml^{-1}$ and it tended to be higher than that of 0.4 mg of epidural BPN.

7. Other side effects

Nonrespiratory side effects e.g. nausea, vomiting, fatigue, sweating, shivering were seen commonly in all groups, but none of them were serious. Pruritus did not occurred in all groups. Mild hematuria associated with acute hypotension was observed in two patients in group II (17%) immediately after intravenous injection of BPN.

Discussion

In this study we assessed the anesthetic and postoperative analgesic effect after epidural administration of 0.6 mg of buprenorphine (BPN) compared with that after intravenous administration of 0.6 mg of BPN. The results indicated that BPN was useful as the supplement of anesthetic agent without so serious respiratory depression, and that it also demonstrated longer analgesic effect and fewer cases of hypotension when it was administered epidurally compared with those when administered intravenously (table 1, figs. 2, 3, results 2). Lanz et al.[10] found a dose-related analgesic duration following epidural BPN, 0.15 mg or 0.3 mg. In our previous study[11] epidural BPN 6 $\mu g \cdot kg^{-1}$ (range 0.3–0.4 mg) for anesthesia and postoperative relief of pain had an too weak effect for lower abdominal gynecological surgery. Rucci et al.[3] demonstrated that the time to regression of analgesic blockade was significantly prolonged only with epidural fentanyl 200 μg or more administered intraoperatively.

The plasma concentrations and clinical effects of a single intravenous dose of BPN 0.3 mg or 0.6 mg were studied by Watson et al.[12] in patients over the age 80 years recovering from surgery. The mean plasma concentration 120 min after intravenous dose of BPN 0.3 mg and 0.6 mg was about 0.55 $ng \cdot ml^{-1}$ and 1.0 $ng \cdot ml^{-1}$, respectively. Duration of analgesia after intravenous BPN 0.6 mg was 492 min (it was 13 hr in our study) and longer significantly than 250 min after intravenous BPN 0.3 mg. Respiratory depression was moderate and the mean Pa_{CO_2} values increased to 56 mmHg and 52 mmHg at 240 min after the intravenous administration of BPN 0.6 mg and 0.3 mg, respectively. The higher Pa_{CO_2} values compared with those of our study might be caused by the aged studing population. From their results, they showed that BPN produced significantly increased analgesia at the greater dose without an equivalent

increase in respiratory depression. However, several workers reported prolonged respiratory depression following the use of benzodiazepines and BPN[13–15]. In our study, moderate bradypnoea (8 bpm) was observed tempolarily in three patients in group III 30 min after the intramuscular injection of pentazocine 30 mg and hydroxyzine 50 mg for the relief of postoperative pain and the treatment of insomnia, but no instance was required ventilatory suport.

The postoperative analgesic effect of epidural BPN 0.6 mg lasted for about 19 hr in our study. The slow dissociation constant of the BPN drug-receptor complex[16] provides one explanation of prolonged analgesia because receptor occupancy will remain high for a long time. Its side effects were mild and there seemed to be little risk of late respiratory depression – advantages over epidural morphine. Our results gave good agreement with the values which were obtained by Watson et al., except for the Pa_{CO_2} values. Mean plasma concentrations after intravenous administration of BPN were lower than those of morphine but increased in a dose dependent manner[12,17]. However, BPN is pharmacologically effective at low plasma concentrations. This is shown by the sublingual use of the drug, which works well at plasma concentrations of 1 $ng \cdot ml^{-1}$ or less[18].

On the other hand, the pharmacokinetics of BPN given epidurally is complicated. As BPN is highly lipid soluble drug, it may be easily transferred across the dura into CSF and may rapidly bind with spinal cord. It is also possible that BPN is mostly uptaked into epidural adipose tissue and removed by the epidural venous blood flow. Serum and CSF concentrations following the epidural administration of BPN were much lower than those of morphine and meperidine[12,17,19]. Analgesic effect after epidural meperidine which is more lipid soluble than morphine, correlated very well with blood meperidine concentration[19]. But six hr after epidural injection, analgesia was still present despite very low serum concentration of morphine[20]. It suggests that epidural morphine travels cephalad in the cerebrospinal fluid to reach the brain stem and fourth ventricle by the sixth hour. In our study long analgesic effects with the administration of epidural BPN may also be related CSF concentration. BPN has a higher partition coefficient. The higher lipophilicity of BPN allows more rapid penetration into brain than for other hydrophilic opioids. BPN with a slow receptor dissociation constant might result in low CSF concentrations of BPN[16,21]. Analgesia produced by epidural BPN may originate at least in part at μ-opiate receptor sites in the spinal cord, but the minute amounts of BPN that may reach the brain through CSF after epidural administration of BPN may amplify the spinal action[22]. These features suggested that BPN might have a rapid onset and a suitable duration of action. Our previous study demonstrated that analgesic effect after administration of epidural BPN 0.4 mg was equipotent to that after injection of intrathecal BPN 0.05 mg in patients undergoing lower abdominal gynecological surgery[8,23]. In conclusion 0.6 mg of epidural BPN was more useful than 0.6 mg of intravenous BPN for control of surgical pain during and after upper abdominal surgery. But further study will be necessary for the determination of optimal dose of epidural administration of BPN (it may be in a range of 0.4 mg to 0.6 mg) during upper abdominal surgery in the future.

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