J Anesth (1994) 8:410–414

Journal of
Anesthesia

Lumbar epidural buprenorphine for postoperative pain relief following hepatectomy

TAKEKAZU TERAI, HIDEKAZU YUKIOKA, OSAMU MORIMOTO, and MITSUGU FUJIMORI

Department of Anesthesiology and Intensive Care Medicine, Osaka City University Medical School, 1-5-7 Asahi, Abeno-ku, Osaka, 545 Japan

Abstract: The induction of postoperative pain relief with lumbar epidural or intramuscular buprenorphine was studied in 30 patients undergoing hepatectomy. When patients first complained of pain after surgery, 0.06 mg or 0.12 mg of buprenorphine in 10 ml or 20 ml of saline was administered through an epidural catheter inserted at the L3–4 interspace, or 0.12 mg was administered intramuscularly. Two of seven patients receiving epidural buprenorphine 0.12 mg in 10 ml saline were completely pain-free, and the other five patients in this group had only slight pain. Four of eight patients receiving epidural buprenorphine 0.12 mg in 20 ml saline were completely pain-free, and the other four patients in this group had only slight pain. Epidural buprenorphine 0.06 mg in 20 ml saline and intramuscular buprenorphine 0.12 mg each yielded only incomplete analgesia. The duration of analgesia of epidural buprenorphine 0.12 mg administered at the lumbar level was about 8 h. There were no significant changes over time in circulatory or respiratory variables induced by buprenorphine. No patient had serious adverse effects. Lumbar epidural administration of buprenorphine 0.12 mg diluted to 10 or 20 ml (20 ml might be preferable) with saline is recommended for induction of postoperative analgesia following hepatectomy.

Key words: Epidural analgesia—Buprenorphine—Hepatectomy—Postoperative pain

Introduction

In a previous study [1], lumbar epidural administration of morphine 2 mg following hepatectomy was found to produce excellent analgesia without any adverse effects; lumbar epidural buprenorphine 0.06 mg produced unsatisfactory pain relief, while thoracic epidural buprenorphine 0.06 mg provided effective analgesia. The difference in analgesic effect between lumbar epidural morphine 2 mg and buprenorphine 0.06 mg seemed to be related to the difference in lipid solubility of the two drugs, suggesting that epidural buprenorphine has a more sharply segmental analgesic effect than does morphine. Therefore, for the purpose of obtaining a maximum analgesic effect with the minimum dose, thoracic epidural buprenorphine may be preferable for postoperative pain relief following hepatectomy [1]. However, epidural catheter placement at the thoracic level is sometimes difficult and is associated with a greater risk of dural puncture and spinal cord damage, and catheter placement in the lumbar region has been found to be just as satisfactory as the thoracic region for the relief of thoracic pain if a higher dose of opioid and greater diluent volumes are used [2].

The aim of this study was to determine whether use of a higher dose of buprenorphine and of greater diluent volume administered into the lumbar epidural space would yield a satisfactory analgesic effect in terms of magnitude, onset, and duration compared with intramuscular buprenorphine, and also to evaluate the effect of buprenorphine on respiration and circulation and the incidence of adverse effects associated with its use.

Materials and methods

Institutional ethics committee approval and patient informed consent were obtained for this study. Thirty Japanese patients scheduled for partial resection of the liver for hepatoma, cholangioma or intrahepatic cholangiolithiasis participated in the study. No patient had any clinical evidence of a bleeding or clotting abnormality, nor any severe respiratory, cardiac, or renal disease. Liver function test results did, however, demonstrate mild or moderate liver dysfunction in every patient in the study. Following the intramuscular administrations

Address correspondence to: T. Terai
Received for publication on July 14, 1993; accepted on March 4, 1994

of atropine 0.5 mg and of either secobarbital 100 mg or diazepam 10 mg as premedication, an epidural catheter to be used for postoperative pain relief was inserted using a Tuohy needle and advanced 3–5 cm cephalad into the epidural space following epidural puncture at the L3–4 interspace. The epidural space was identified by the "loss of resistance" technique using saline. Anesthesia was induced with thiopental and either succinylcholine or vecuronium, and maintained with N_2O-O_2-enflurane and either pancuronium or vecuronium. No supplemental analgesics were administered during surgery.

Following reversal of neuromuscular blockade at the end of surgery, the patients were extubated and taken to the intensive care unit (ICU). Patients were assigned to one of four groups. When the patients first complained of pain after surgery, buprenorphine was administered epidurally or intramuscularly in each group:

Group A: patients were given 0.12 mg of buprenorphine in 10 ml of saline epidurally at L3–4.
Group B: patients were given 0.06 mg of buprenorphine in 20 ml of saline epidurally at L3–4.
Group C: patients were given 0.12 mg of buprenorphine in 20 ml of saline epidurally at L3–4.
Group D: patients were given 0.12 mg of buprenorphine intramuscularly.

The patients in group A, B, and C were blind to the contents of the injected solution. The effectiveness of analgesia was assessed by the ICU staff or an anesthesiologist who directly questioned the patient but who was unaware of the nature and administration route of the injectate used. Pain relief was graded as excellent when the patient was completely pain-free following an injection, adequate when the patient had only slight pain, and poor when the patient had moderate or severe pain. Sleep periods were considered to be pain-free. The time required for onset was defined as the time from drug injection to initial pain relief. Complete time required for onset was defined as the time from drug injection to maximum pain relief. The duration of analgesia was considered to be the time between the onset of adequate analgesia and the first request for additional pain medication. When pain relief was graded as poor 1 h after the injection, 2 mg of morphine in 10 ml of saline were administered epidurally, and patients receiving this medication were excluded from further study. The onset time, complete onset time, and the duration of analgesia for patients with poor pain relief were therefore not assessed.

All patients were monitored continuously in the ICU for electrocardiogram and for blood pressure with indwelling arterial cannulas for a period of at least 18 h. Respiratory rate was assessed every 10 min for the first 90 min, then every 30 min until 12 h from the time of the buprenorphine injection. Thereafter the respiratory rate was recorded hourly. All patients received 3–5 $l \cdot min^{-1}$ of oxygen through a face mask to prevent hypoxia. Arterial blood samples were drawn at 0, 0.5, 1, and 2 h after the drug injection and at the time of the first top-up administration for blood gas tension measurement. All patients were observed for at least 18 h after drug injection for the appearance of adverse effects such as pruritus, nausea, vomiting, headache, or other similar symptoms. No attempt was made to assess disturbances of micturition, since all patients had catheterization of the bladder during the study period.

The measured values were expressed as the mean ± SD. Differences in age, body weight, height, onset time, and duration of analgesia between groups were assessed using factorial analysis of variance (ANOVA). The chi-square test was used to compare sex ratio distributions. Differences in grade of pain relief between groups were assessed using the Mann-Whitney U-test. Repeated-measure ANOVA and Scheffé's F-test for post hoc analysis as indicated were used for comparisons of respiratory rate, $Paco_2$, arterial blood pressure, and heart rate before and after administration of buprenorphine. Differences between groups were considered significant when $P < 0.05$.

Results

The four groups of patients were almost identical in male/female ratio, age, body weight, and height (Table 1).

Table 1. Patient characteristics

	Group A	Group B	Group C	Group D
Number of patients	7	9	8	6
Gender (M/F)	5/2	8/1	6/2	6/0
Age (years)	61 ± 7	63 ± 7	58 ± 8	64 ± 4
Weight (kg)	56 ± 5	55 ± 7	55 ± 9	62 ± 6
Height (cm)	160 ± 8	160 ± 3	159 ± 7	163 ± 9

Data are expressed as mean ± SD. No significant differences were noted between groups in any of these characteristics.

Pain relief

In none of the groups did patients require any additional intravenous administration of analgesics for severe pain within the 1-h period following the first buprenorphine injection (Table 2). All patients receiving 0.12 mg of buprenorphine epidurally (groups A and C) were evaluated as having excellent or adequate analgesia. Of the patients receiving 0.06 mg of buprenorphine in 20 ml of saline epidurally (group B), four (44%) had poor pain relief. Of the patients receiving buprenorphine 0.12 mg intramuscularly (group D), five (83%) had poor pain relief. The nine patients who had poor pain relief in groups B and D were completely pain-free following the epidural administration of 2 mg morphine. Groups A and C had better analgesia than did group D ($P < 0.01$), and group C had better analgesia than group B ($P < 0.05$). There was no significant difference in analgesic effect between groups A and C.

For groups B and D, the means ± SD of onset time, complete onset time, and duration of analgesia were not calculated, since only five of the nine patients in group B and one of the six patients in group D had excellent or adequate pain relief. There were no statistically significant differences in onset time, complete onset time, or duration of analgesia between groups A and C.

Respiratory changes

In all patients, Pao_2 was above 90 mmHg throughout the study period. For groups A and C, changes in respiratory rate and $Paco_2$ were assessed during the study, but no significant changes were observed over time for either of these groups (Table 3). None of the patients in the study required ventilatory assistance.

Circulatory changes

For groups A and C, changes in arterial blood pressure and heart rate were assessed (Table 3). There were no significant changes over time in arterial blood

Table 2. Grade, onset time and duration of pain relief in each group

	Grade of pain relief			Pain relief		
Group	Excellent (no pain)	Adequate (slight pain)	Poor (no pain relief)	Onset time (min)	Complete onset time (min)	Duration (h)
A	2	5	0	25 ± 16	56 ± 30	8.1 ± 3.7
B	1	4	4	—	—	—
C	4	4	0	23 ± 8	70 ± 22	7.9 ± 4.3
D	0	1	5	—	—	—

Data are expressed as mean ± SD. Significant differences in grade of pain relief were found between groups A and D ($P < 0.01$), groups B and C ($P < 0.05$), and groups C and D ($P < 0.01$). No significant differences in onset time, complete onset time or duration were found between groups A and C.

Table 3. Effects of 0.12 mg lumbar epidural buprenorphine in 10 ml or 20 ml saline on respiration and circulation

	Time after injection				
Group	0	0.5 h	1 h	2 h	before top-up[a]
Respiratory rate (beats·min^{-1})					
A	22 ± 4	22 ± 3	21 ± 2	20 ± 2	20 ± 3
C	26 ± 6	22 ± 4	22 ± 4	20 ± 4	19 ± 4
$Paco_2$ (mmHg)					
A	40 ± 2	40 ± 2	41 ± 8	42 ± 3	41 ± 3
C	42 ± 2	43 ± 2	44 ± 3	44 ± 2	43 ± 2
Arterial blood pressure (systolic/diastolic, mmHg)					
A	138 ± 20/76 ± 10	151 ± 18/79 ± 9	144 ± 14/73 ± 7	153 ± 21/74 ± 8	152 ± 27/73 ± 10
C	125 ± 20/70 ± 16	135 ± 23/66 ± 12	139 ± 23/67 ± 11	135 ± 20/67 ± 11	136 ± 20/70 ± 11
Heart rate (beats·min^{-1})					
A	88 ± 11	94 ± 12	95 ± 15	97 ± 19	94 ± 24
C	90 ± 14	90 ± 14	95 ± 17	100 ± 19	98 ± 18

[a] The time of top-up epidural injection was 8.1 ± 3.7 h after drug injection in group A and 7.9 ± 4.3 h after drug injection in group B. Findings are expressed as means ± SD. No significant differences were noted between the two groups in any of these variables.

pressure or heart rate observed for either of these groups.

Adverse effects

No patient had any adverse effect such as pruritus, nausea, vomiting, or headache. None of the patients developed serious respiratory or cardiovascular depression.

Discussion

Buprenorphine, which has a high lipid solubility, a high affinity for opiate receptors, and a long duration of action, produces segmental analgesia and, less frequently, respiratory depression when administered epidurally. Cahill et al. [3] recommended the use of thoracic epidural buprenorphine 0.06 mg for pain relief following upper abdominal surgery since it provided excellent analgesia in low dosage with fewer adverse effects than morphine similarly administered. Lanz et al. [4] administered 0.3 mg of high-dose buprenorphine epidurally without evidence of late respiratory depression. Since epidural buprenorphine has a more sharply segmental analgesic effect than does morphine, it should be administered at the thoracic level in patients undergoing hepatectomy in order to obtain maximum analgesic effect with minimum dosage. Yukioka and Fujimori [1] reported that 0.06 mg of epidural buprenorphine diluted with 10 ml of saline injected at the thoracic level produced good and long-lasting (22.6 ± 9.9 h) pain relief, although the same dose of buprenorphine injected at the lumbar level resulted in incomplete analgesia. However, epidural catheter placement at the thoracic level is more difficult than at the lumbar level, and may be associated with serious complications such as spinal cord injury. Determination of optimal dose, optimal diluent volume, and adverse effects of lumbar epidural buprenorphine for postoperative analgesia in patients following hepatectomy is therefore important, since use of the lumbar epidural route necessitates the use of a higher dose of opioid and a greater diluent volume to mechanically push the opioid into a wider space of distribution [2].

In the present study, lumbar epidural buprenorphine was administered at higher dosage (0.12 mg in groups A and C) and/or greater diluent volume (20 ml of saline in groups B and C) than those (0.06 mg in 10 ml of saline) administered at the thoracic level in the previous study [1]. Birnbach et al. [5] reported that use of epidural fentanyl, a highly lipid soluble narcotic agonist, as is buprenorphine, resulted in more rapid onset and longer duration of analgesia when the volume of diluent was increased. However, in the present study, the analgesic effect of lumbar epidural buprenorphine 0.06 mg diluted to 20 ml with saline was poor. On the other hand, 0.12 mg of lumbar epidural buprenorphine diluted to either 10 ml or 20 ml with saline yielded good pain relief, whereas buprenorphine 0.12 mg im yielded only poor pain relief. The analgesic effect of lumbar epidural buprenorphine 0.12 mg was not due to systemic absorption of the drug, although Matsunaga et al. [6] have reported that they found no differences in analgesic effects between epidural and intravenous buprenorphine. It is possible that buprenorphine diffuses more widely throughout the epidural space with the use of incremental doses.

In contrast to findings for epidural fentany [5], there were no significant differences in onset time or duration of analgesia between buprenorphine 0.12 mg diluted with 10 ml and that diluted with 20 ml of saline. In the quality of analgesia, pain relief was graded excellent for four of eight (50%) patients in group C, but for only two of seven (29%) patients in group A. The number of patients graded excellent in group C was greater than in group A, although all patients in both groups had excellent or adequate analgesia and there were no significant differences. The quality of analgesia in group C, which received 20 ml of saline, might have been better than that in group A, which received 10 ml.

In the present study, no evidence was obtained of adverse effects such as respiratory and circulatory depression, pruritus, nausea, headache, or vomiting. However, since early and late respiratory depression following epidural administration of buprenorphine have been reported [7, 8], respiration should be continuously monitored following the use of buprenorphine.

In conclusion, administration of 0.12 mg of epidural buprenorphine diluted to 10 or 20 ml (20 ml might be preferable) with saline at the lumbar level is both effective and safe for postoperative pain relief following hepatectomy, although the duration of analgesia achieved with it is rather short.

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