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Pain management after lumbar spinal fusion surgery using continuous subcutaneous infusion of buprenorphine

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Abstract
Purpose. The continuous subcutaneous infusion (CSI) technique is a simple, inexpensive method for managing postoperative pain. We examined the analgesic effects of CSI of buprenorphine in patients undergoing lumbar spinal fusion surgery.
Methods. The patients were randomly assigned to one of three groups for postoperative pain management: control group ($n = 17$), high-dose buprenorphine group (BH group, $n = 17$), and low-dose buprenorphine group (BL group, $n = 16$). Infusion solutions containing buprenorphine at concentrations of 25.0 and 16.7 $\mu g \cdot ml^{-1}$ combined with droperidol at a concentration of 52.0 $\mu g \cdot ml^{-1}$ were used in the BH and BL groups, respectively; and an infusion solution containing droperidol at a concentration 52.0 $\mu g \cdot ml^{-1}$ was used in the control group. CSI of each solution was started at a rate of 1 $ml \cdot h^{-1}$ and was continued for 48 h.
Results. The BH and BL groups showed significantly lower scores than the control group on the Visual Analogue Scale. There were significantly fewer administrations of flurbiprofen as a supplemental analgesic in the BL and BH groups than in the control group. The incidences of sedation and nausea were comparable in the three groups. The median number of administrations of flurbiprofen was significantly less in the BH group than in the control group on the day of the operation and on the first postoperative day, whereas the number in the BL group was less than that in the C group only on the day of the operation.
Conclusion. CSI of buprenorphine effectively reduces pain after lumbar spinal fusion surgery without apparent side effects. This technique is simple and useful for postoperative pain management.

Key words Buprenorphine · Continuous subcutaneous · Postoperative pain

Introduction

It is well known that conventional intermittent administration of an analgesic for postoperative pain management has several disadvantages [1]. Although patient-controlled analgesia (PCA) has been widely accepted, it is more expensive than conventional methods [2,3] and requires sufficient understanding of the technique by the patient [4,5]. The continuous subcutaneous infusion technique is an old but simple and inexpensive method for postoperative pain management, and has been reported that continuous subcutaneous infusion of morphine is useful postoperatively [6–8]. Buprenorphine is a mu-opioid receptor partial agonist and is similar in structure to morphine but approximately 33 times more potent [9]. Buprenorphine has several pharmacological characteristics that are different from those of morphine. The metabolites of buprenorphine, buprenorphine-3-glucuronide and norbuprenorphine, are less potent and have lower affinities for the mu receptor. Therefore, it is unlikely that their accumulation in patients with renal failure would exert unexpected pharmacological activity [10]. In addition, buprenorphine does not increase pressure in the biliary and pancreatic ducts [11], and it slows intestinal transit but probably less so than does morphine [12]. Therefore, continuous subcutaneous infusion of buprenorphine may be useful for postoperative pain management. However, there is little information about the analgesic effects and safety of continuous subcutaneous infusion of buprenorphine for postoperative pain management. This study was designed to examine the analgesic effects and side effects of continuous subcutaneous infusion of buprenorphine in patients undergoing lumbar spinal fusion surgery.

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Methods

The protocol of our study was approved by our institution's ethics committee, and informed consent was obtained from each patient. Patients with a medical history of cardiovascular, pulmonary, hepatic, renal, neurological, psychiatric, or metabolic disease were excluded from the study. Fifty patients [American Society of Anesthesiologists (ASA) I–II] who were scheduled to undergo lumbar spinal fusion surgery were enrolled in this study. Exclusion criteria included coexisting disease that could affect the reliability of clinical assessments, known or suspected drug abuse, and pregnancy.

Each patient was premedicated with 3.0 mg intramuscular midazolam 30 min before arriving at the operating room. Anesthesia was induced with propofol 2.0 mg·kg^{-1} i.v. Muscle relaxation was achieved with vecuronium 0.1–0.2 mg·kg^{-1}, and the trachea was intubated. After intubation, 1.25 mg droperidol was intravenously administered. Anesthesia was maintained with 1.5%–2.5% sevoflurane and 60% nitrous oxide in oxygen and with intravenous fentanyl.

On completion of surgery, a 27-gauge butterfly needle was subcutaneously placed 1–2 cm below the midline of the left clavicle and was secured on the skin with sterile tape. The butterfly needle was connected to a disposable pump (Coordech Syringector; Daiken-iki, Osaka, Japan). The patients were randomly assigned to one of three groups for postoperative pain management: control group (C group, n = 17), high-dose buprenorphine group (BH group, n = 17), and low-dose buprenorphine group (BL group, n = 16). Infusion solutions containing buprenorphine at concentrations of 25.0 μg·ml^{-1} (1.2 mg · 48 ml^{-1} total volume) and 16.7 μg·ml^{-1} (0.6 mg · 48 ml^{-1} total volume) combined with droperidol at a concentration of 52.0 μg·ml^{-1} (1.0 mg · 48 ml^{-1} total volume) were used in the BH and BL groups, respectively; and the infusion solution containing droperidol at a concentration of 52.0 μg·ml^{-1} was used in the control group. The volume of each solution to be infused was adjusted to 48 ml by diluting with saline. After extubation, all patients initially received 200 μg of intravenous buprenorphine, and then a continuous subcutaneous infusion was started at the rate of 1 ml·h^{-1}. For postoperative pain relief, 50 mg of intravenous flurbiprofen was given as a supplemental analgesic on patient demand. In addition, 10 mg of metoclopramide was administered intravenously, if the nausea score (described below) was 2 or the patients required it.

For the collection of postoperative data, the investigator and patients were blinded to the patient group assignment. The intensity of postoperative pain was evaluated using the Visual Analogue Scale (VAS). The VAS consisted of a 100-mm horizontal line without graduation and with endpoints marked as "no pain" and "worst possible pain." The patients were told to indicate how they felt at that moment at rest by placing a mark perpendicular to the line. In addition, the number of administrations of flurbiprofen was recorded. Nausea was assessed using a 3-point score of 0 to 2 (0, none; 1, moderate; 2, severe). The Observer Assessment of Alertness/Sedation Scale (OAA/S) [13] was used to determine the level of sedation (Table 1). Assessments were made 2 and 4 h after starting the continuous subcutaneous infusion and at 8:00 a.m. and 6:00 p.m. on the first and second postoperative days. VAS scores of six patients in each group were also assessed 8 h after starting the continuous subcutaneous infusion. Because VAS scores 8 h after administration were similar to those 4 h after administration, assessments were made 2 and 4 h after administration on the day of operation to reduce the patients' burden associated with postoperative data recording. Respiratory depression was defined as a respiratory rate of ≤8 breaths per minute. The respiratory rate was recorded at intervals of 2 h from the end of surgery to 8:00 a.m. on the first postoperative day. Thereafter, the respiratory rate was monitored only if necessary.

Demographic data of the patients are presented as means ± SD. There were no data available in the litera-

Table 1. Observer assessment of alertness/sedation (OAA/S) scale [10]

Responsiveness	Speech	Facial expression	Eyes	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild prodding or shaking	—	—	—	1

Table 2. Patient characteristics

Group	No. of patients	Sex (M:F)	Age (years)	Weight (kg)	Fentanyl dose (μg)
C	17	8:9	58 ± 8	58 ± 12	300 ± 130
BL	17	7:10	56 ± 7	60 ± 7	270 ± 190
BH	16	9:7	57 ± 13	58 ± 10	370 ± 200

C group, controls; BL group, low-dose buprenorphine; BH, high-dose buprenorphine

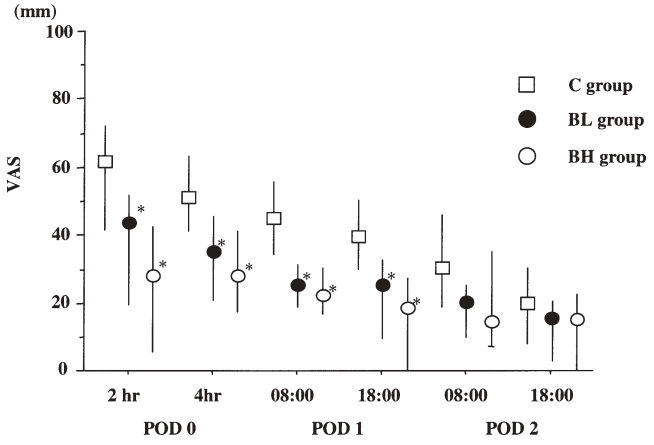

Fig. 1. Visual Analogue Scale (*VAS*). Values are presented as medians (25th–75th percentiles). *C group*, control group; *BL group*, low-dose buprenorphine group; *BH group*, high-dose buprenorphine group; *POD*, postoperative day. *$P < 0.05$ compared to C group

ture on the VAS under circumstances similar to those in the current study, and sample size could therefore not be calculated in advance with respect to statistical power. The data for the sedation score, nausea score, VAS score, and number of administrations of flurbiprofen are presented as medians. Demographic data were analyzed using one-way analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD). VAS scores and number of administrations of flurbiprofen were analyzed using the Kruskal-Wallis test followed by Bonferoni's test. $P < 0.05$ was considered statistically significant.

Results

There were no differences in sex, age, weight, or administered dose of fentanyl during surgery among the three groups (Table 2). Figure 1 shows the time courses of the VAS scores. The BH and BL groups showed significantly lower VAS scores than the C group from the day of the operation to 6:00 p.m. on the first postoperative day. There was no significant difference between the VAS scores in the BH and BL groups during the study period. The median number of administrations of flurbiprofen was significantly less in the BH group than in the C group on the day of the operation and on the first postoperative day, whereas the number in the BL group was less than that in the C group only on the day of the operation (Table 3). One patient in the C group had a 4 on the OAA/S scale on the day of the operation. Three patients in the BL and BH groups had a 4 on the OAA/S scale 2 and 4 h after administration, but they showed 5 on the OAA/S scale 8 h after administration. The remaining patients in the three groups had a 5 on the OAA/S scale on the day of the operation. All patients in the three groups had 5 on the OAA/S scale on the first and second postoperative days. Two patients in each group complained of nausea (nausea score of 1) during the observation period. Two patients in the C group, one patient in the BL group, and two patients in the BH group received intravenous metoproclamide once or twice during the observation period, and their nausea was diminished. Pain on injection or local toxicity at the site of the subcutaneous infusion was not seen in any patients. There was no respiratory depression, and there were no complications requiring treatment in any patients.

Table 3. Administration of flurbiprofen

Group	No. of doses			
	POD 0	POD 1	POD 2	Total
C	2 (2–4)	1 (0–2)	0 (0–2)	4 (2–7)
BL	0 (0–1)*	1 (0–2)	0 (0–1)	1 (0–4)*
BH	0 (0–1)*	0 (0–1)*	0 (0–1)	1 (0–3)*

POD, postoperative day
* $P < 0.05$ compared to C group

Discussion

In the current study, continuous subcutaneous infusion of buprenorphine alleviated postoperative pain after lumbar spinal fusion surgery compared to that in the control group without increasing the incidence of side effects. We expected that continuous subcutaneous in-

fusion of buprenorphine 25.0 μg·ml^{-1} would have a more potent analgesic effect than that of continuous subcutaneous infusion of buprenorphine 16.7 μg·ml^{-1}. However, although the VAS score in the BH group tended to be lower than that in the BL group 2 h after starting the continuous infusion, we did not find any significant differences between VAS scores in the BH and BL groups throughout the observation period. On the other hand, the median number of administrations of flurbiprofen was significantly less in the BH group, but not the BL group, than that in the control group on both the day of the operation and the first postoperative day. With regard to the number of administrations of a rescue analgesic, the analgesic effect of continuous subcutaneous infusion of buprenorphine 25.0 μg·ml^{-1} was more potent than that of continuous subcutaneous infusion of buprenorphine 16.7 μg·ml^{-1}. In addition, the median VAS scores in the patients receiving buprenorphine 25.0 μg·ml^{-1} were less than 30, which is commonly considered satisfactory pain relief, throughout the observation period.

The most common side effect of buprenorphine is thought to be nausea and vomiting. In our preliminary study, administration of buprenorphine alone often induced nausea and vomiting. Therefore, droperidol was administered intravenously during surgery and was added to the buprenorphine solution to prevent buprenorphine-induced nausea and vomiting. Droperidol at doses ≥2.5 mg has been reported to induce excessive sedation, hypotension, extrapyramidal symptoms [14], and delayed recovery from anesthesia [15]. It has been reported that droperidol induced the prolongation of QT in an electrocardiogram [16]. However, based on a review of the cases, Habib and Gan concluded that in none of the cases in which arrhythmias occurred after administration of ≤1.25 mg of droperidol was there evidence of a cause-and-effect relation [17]. Droperidol was administered as a 1.25-mg bolus followed by continuous subcutaneous infusion at 1.25 mg/day in our study, and we did not observe any side effects associated with the droperidol. Another noted side effect of buprenorphine is respiratory depression, although it has not been a major problem in clinical trials [9]. The doses used in our study did not produce apparent respiratory depression. Thus, because the incidence of side effects in the BH and BL groups was comparable to that in the control group, we did not examine the effects of lower doses of buprenorphine than the dose administered in the current study.

When compared with continuous subcutaneous infusion with intravenous infusion, continuous intravenous infusion has several disadvantages: (1) an extra demand on venous access, which may be important in a patient with few available veins; (2) drug interactions may occur in the intravenous line if it is used to administer other drugs; and (3) the intravenous cannula may become displaced and a doctor required to resite the cannula [18]. Continuous subcutaneous infusion is one means of overcoming all these disadvantages. However, because absorption of buprenorphine from subcutaneous tissue depends on skin perfusion, it is possible that the blood concentration of burenorphine with subcutaneous infusion is not as stable as that with intravenous infusion. Therefore, attention should be paid to the local skin temperature, which affects skin perfusion.

Ono et al. examined the effects of continuous subcutaneous infusion of morphine (12 or 24 mg per day) for pain management after spinal surgery [19]. The patients treated with continuous subcutaneous of morphine showed significantly lower VAS scores but had an increased incidence of nausea, vertigo, and respiratory depression compared to the other patients. Because droperidol was added to buprenorphine in our study, we could not compare the effects of continuous subcutaneous infusion of morphine with those of buprenorphine. However, in our study, continuous subcutaneous infusion of buprenorphine did not produce vertigo or respiratory depression and did not increase the incidence of nausea. Thus, continuous subcutaneous infusion of buprenorphine with droperidol allows postoperative pain management with a lower incidence of side effects than are seen with morphine alone.

Patient-controlled analgesis has been widely used for postoperative pain management, and many studies have shown its efficacy. A meta-analysis by Ballantyne et al. [20] indicated that PCA has significantly greater analgesic efficacy than intermittent administration of analgesics, but the magnitude of the difference was small. Some recent studies have reported that PCA does not offer clinical advantages over regular administration of morphine [2,21,22]. PCA requires sufficient instruction on use for patients to obtain satisfactory analgesic effects [4]. PCA requires special devices and is more costly than conventional methods, so it is not available in all hospitals. Stamer et al. [23] reported that PCA was performed in 93.8%, 74.1%, and 69.8% of departments providing acute pain service (APS) with basic quality criteria (QC), APS without QC, and no APS, respectively, in Germany. A survey by Rawal and Allvin [24] revealed that many anesthesiologists were unable to introduce PCA in wards in Europe because of the high equipment costs. Similarly, PCA is not widely used in Japan [25]. Continuous subcutaneous infusion of buprenorphine would be a simple, effective method for alleviating/avoiding postoperative pain after spinal surgery in departments in which PCA is not available. However, we did not compare results obtained using PCA with those obtained using the continuous subcutaneous infusion technique. Further study is thus necessary regarding this point.

Conclusion

The results of our study have shown that continuous subcutaneous infusion of buprenorphine 25 μg·ml^{-1} at a rate of 1 ml·h^{-1} is effective for pain relief after lumbar spinal fusion surgery without apparent side effects.

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