Continuous Epidural Infusion for Postoperative Mechanical Ventilation

Shinichi SAKURA, Mariko SUMI, Yoji SAITO, Jyunken KOH, Makoto ASANO, Akio TANAKA* and Yoshihiro KOSAKA

We evaluated in analgesic and sedative effects of continuous epidural infusion of two analgesic regimens in ventilated patients following esophagectomy. Forty-six patients, divided into two treatment groups, received postoperative continuous epidural infusion of morphine, or that of a combination of bupivacaine and morphine. Assessments were made with the following indices: pain relief score, somnolence score, patient ventilator coordination score, and the number of supplemental administrations of analgesics and sedatives. No significant differences occurred in somnolence scores or patient ventilator coordination scores between the two groups, which revealed satisfactory sedation for mechanical ventilation. Patients receiving the combination of bupivacaine and morphine had significantly less pain postoperatively, requiring a smaller number of supplemental administrations of analgesics and sedatives ($P < 0.05$). It is concluded that: 1) continuous epidural infusion of analgesics gives potent analgesia and sedation of ventilated patients following esophagectomy; 2) the combination of bupivacaine and morphine gives pain relief superior to morphine alone. (Key words: mechanical ventilation, postoperative, epidural, morphine, bupivacaine)

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The wide variation in the drugs and techniques used to sedate patients receiving mechanical ventilation is an indication that the ideal drug or drug combination has not yet been found[1,2]. Although the most common methods are intermittent i.v. injections of opioids and benzodiazepines, in spite of very large doses of analgesics and sedatives many patients are restless, agitated and inadequately sedated for mechanical ventilation. Neuromuscular blocking drugs are therefore commonly used to avoid struggling and facilitate patient ventilator coordination. Recently continuous i.v. infusions have also been used, especially after major surgery[3–5].

At our intensive care unit (ICU), continuous epidural infusion of analgesics for postoperative pain relief has been in use for several years[6]. In addition, our practice has evolved to apply this method to the patients receiving postoperative mechanical ventilation. Although this appears to be useful for ventilated patients, we are not aware of a controlled study which demonstrates its effectiveness. The purpose of this study is to demonstrate the usefulness of continuous epidural infusion for pain relief and sedation of ventilated patients following esophagec-

*Department of Anesthesiology, *Surgical Operation Center, Shimane Medical University, Shimane, Japan*

Address reprint requests to Dr. Sakura: Department of Anesthesiology, Shimane Medical University, 89-1 Enya-cho, Izumo, 693 Japan

tomy. We also compare the efficacy of a continuous epidural infusion of morphine and a combination of morphine and bupivacaine in terms of their ability to produce postoperative analgesia, sedation, and patient ventilator coordination.

Methods

Subjects

Forty-six patients, ASA physical status I and II, aged 50–77 yr, and undergoing esophageal cancer surgery were investigated. Every patient was interviewed the night before surgery by one of the investigators to explain the study and to obtain consent.

Premedication comprised 25–100 mg of hydroxyzine and 0.4–0.5 mg of atropine given intramuscularly 1 hr before arrival in the operating room, where an i.v. infusion of lactated Ringer's solution was commenced. Before induction of general anesthesia, with the patient in the lateral decubitus position, an epidural catheter (Portex) was introduced into the Th1–Th10 intervertebral space. The epidural space was identified by the hanging drop technique. General anesthesia comprised induction with 4 $mg \cdot kg^{-1}$ of thiamylal followed by 1 $mg \cdot kg^{-1}$ of succinylcholin to facilitate tracheal intubation, and maintenance with nitrous oxide, oxygen, halothane or enflurane, and small doses of narcotics. Some of the patients also received several intermittent injections of plain mepivacaine in the epidural catheter. Nondepolarizing muscle relaxants were frequently used for control of ventilation. After the completion of surgical procedures, without reversal of neuromuscular block, the patients were transferred to ICU, where they firstly received intermittent positive-pressure ventilation (IPPV) by a time-cycled constant minute volume ventilator (Servo 900B or C, Siemens Elema, Solna, Sweden) with a positive end-expiratory pressure of 3–10 cmH_2O. When the patients' condition had improved such that weaning from IPPV was appropriate, intermittent mandatory ventilation (IMV) and/or spontaneous respiration with continuous positive airway pressure (CPAP) followed by extubation were performed to maintain Pa_{CO_2} at 40 ± 5 torr.

Table 1. Scales for measurement of the degree of pain relief, somnolence, or patient ventilator coordination

I. Pain Relief Scale
- 1 = No pain on coughing
- 2 = Pain on coughing but not on deep breathing
- 3 = Pain on deep breathing but not at rest
- 4 = Pain at rest, slight
- 5 = Pain at rest, severe

II. Somnolence Scale
- 1 = Oriented and initiates conversation
- 2 = Responds to all forms of stimulation, is well oriented but feels sleepy and does not initiate conversation
- 3 = Responds to verbal command and painful stimulation but is disoriented and does not initiate conversation
- 4 = Responds to painful stimulation but not to verbal command
- 5 = Unresponsive to verbal command or painful stimulation

III. Patient Ventilator Coordination Scale
- 1 = Excellent coordination
- 2 = Uncomfortable with the ventilator
- 3 = Fights the ventilator several times
- 4 = Fights the ventilator frequently
- 5 = Poor coordination

Postoperative analgesia

A continuous epidural infusion was started immediately after the operation with a volumetric infusion pump. All patients were randomly assigned to one of two groups to receive postoperative pain treatment. Patients in group A received continuous epidural infusion of 0.01% morphine in normal saline at a rate of 1–2 $ml \cdot hr^{-1}$. Patients in group B received continuous epidural infusion of a combination of 0.25% bupivacaine and 0.005% morphine at a rate of 2–4 $ml \cdot hr^{-1}$ until the solution amounted to 40 ml. Then the concentration of bupivacaine was decreased to 0.125%, while that of morphine was kept unchanged. The use of narcotics being regulated in Japan, the study was not double-blinded, but patients did not know which solutions were being used. In both groups if pain relief was in-

Table 2. Patient characteristics

	Group A (n=18)	Group B (n=28)
Sex F/M	0/18	1/27
Age (yr)	65.9 ± 6.6 (58–79)	64.5 ± 8.1 (50–77)
Height (cm)	161.7 ± 3.6	159.3 ± 7.0
Weight (kg)	54.1 ± 5.1	52.3 ± 8.8
Epidural site	Th 7.6 ± 1.8	Th 6.9 ± 1.8
Duration of operation (min)*	485.6 ± 91.8	397.1 ± 63.4
ICU stay (days)	13.8 ± 10.5 (5–43)	10.1 ± 8.4 (4–47)
Duration of mechanical ventilation (hr)	126.5 ± 144.2 (17–607)	65.0 ± 55.1 (17–233)

Ranges are given in parentheses.

*Significantly different between the two groups, $P < 0.01$.

sufficient, bolus injection of 4 ml of the solution was allowed only twice in succession. In addition, when the patients of both groups asked for more analgesics and complained of anxiety, supplemental analgesics (buprenorphine 0.2 mg) and benzodiazepines (flunitrazepam 1 mg or diazepam 5 mg) were intravenously administered, respectively. Indomethacin was allowed to alleviate fever. The patients received the infusion until one of the investigators felt that they could do without analgesics.

Methods of evaluation

The degree of pain relief and somnolence of the ventilated patients were assessed using respective modifications of previously determined scales[7,8], both of which used five point rating systems (table 1). Assessments were made at 16 and 40 hr following completion of the operation. However, those for whom mechanical ventilation had been discontinued before 40 postoperative hours were discharged from subsequent assessment. A 2 hr interval was observed between the assessments and parenteral analgesic and sedative injections. The degree of patient ventilator coordination was evaluated with regard to the entire period of mechanical ventilation by using a scoring scale with five levels also (table 1). The number of supplemental analgesics and sedatives each patient required was recorded.

Postoperative monitoring of electrocardiogram, rectal temperature, urinary volume, and respiratory frequency followed the routines of the ICU. Arterial pressure was measured throughout this study, and blood gas samples were taken at intervals of 6 hr.

Of possible side effects, noted were hypotension and respiratory depression, which was respectively defined as the need for volume and pressors and as the appearance of Pa_{CO_2} higher than 55 torr during IMV or CPAP. Urinary retention could not be evaluated due to the presence of urethral catheters.

Statistics

Data are expressed as mean ± SD. Data were analyzed for statistical significance using the χ^2 analysis, Wilcoxon's test and Student's t-test. $P < 0.05$ was considered statistically significant.

Results

Demographic data from the 46 patients studied are summarized in table 2. There were no significant differences between group A (N = 18) and group B (N = 28) with respect to sex, age, height, weight, epidural site, ICU stay, or duration of mechanical ventilation, which was defined as the time from the end of the surgical procedure until the first weaning from the ventilator. However, the duration of surgery in group A was significantly longer than that of group B ($P < 0.01$). Those who received mechanical ventilation for more than 40 hr were 13 in group A and 17 in group B. In the course of the treatment, in group A, 5 of 18 patients developed postoperative pulmonary complications such as atelectasis, pneumonia, lung edema, and or adult respiratory syndrome, being comparable with 6 of 28 in group B. Of the patients who developed postoperative pulmonary complications, there was one death in group A and two in group B.

Postoperative analgesia

In group A, the mean morphine consumption and the rate of morphine infusion over 48 hr was 8.4 ± 1.8 mg and 3.3 ±

Table 3. Scores with three scales

	Group A (n=18)	Group B (n=28)
Pain Relief Score		
16 hr*	3.3 ± 0.9	2.5 ± 0.7
40 hr**	3.3 ± 0.9	2.5 ± 0.7
Somnolence Score		
16 hr	3.3 ± 1.3	3.1 ± 0.8
40 hr	3.1 ± 1.2	2.9 ± 0.6
Patient Ventilator Coordination Score		
	2.2 ± 1.2	1.6 ± 0.6

The number of patients at 40 hr was 13 in group A and 17 in group B.

* Significantly different between the two groups, $P < 0.01$.

** Significantly different between the two groups, $P < 0.05$.

Table 4. Number of patients receiving supplemental analgesics or sedatives

	Group A (n=18)	Group B (n=28)
First 24-hr period	10 (55.6%)	17 (60.7%)
Second 24-hr period	12 (66.7%)*	11 (39.3%)**
During mechanical ventilation	16 (88.9%)	21 (75.0%)
For night sedation	5 (27.8%)	5 (17.9%)
For other reasons	11 (61.1%)	16 (57.1%)

No significant difference between the two groups.

* Including 2 spontaneously breathing patients.

** Including 1 spontaneously breathing patient.

0.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, respectively. Every patient except one frequently required additional bolus injections of the morphine solution. The duration of the infusion ranged from 35 to 168 hr (mean 90.0, SD 42.1). Three out of 18 patients enrolled in this group were withdrawn from this treatment in spite of the need for it: two were withdrawn because of bleeding at the site of insertion or accidental dislodgment, and one was removed due to inadequate effect.

In group B, the mean morphine consumption and the rate of morphine infusion over 48 hr was, respectively, 9.1 ± 1.5 mg and 3.7 ± 0.8 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, which were not significantly different from group A. The mean bupivacaine infusion rate over 48 hr was 0.11 ± 0.02 $mg \cdot kg^{-1} \cdot hr^{-1}$. Additional bolus injections of the combined solution were required by 14 out of 28 patients, which was approximately half as many as those in group A. The duration of the infusion ranged from 13 to 168 hr (mean 103.1, SD 51.3), which was not significantly different from group A. However, No patients were removed from this treatment with complaint of pain. One patient from whom this infusion was discontinued at only 13 postoperative hours had severe hypotension.

Assessments of the effects

Assessments using three scales, namely, pain relief score, somnolence score and patient ventilator coordination score, are listed in table 3. As for the two patients from whom the continuous epidural infusion was discontinued at only 13 and 35 postoperative hours, scores at the time of discontinuation were regarded as those at 16 and 40 hr, respectively. Group B had significantly better pain relief at 16 hr ($P < 0.01$) and at 40 hr ($P < 0.05$). On the other hand, there were no significant differences in somnolence and patient· ventilator coordination scores between the two groups. Satisfactory sedation for mechanical ventilation was achieved in the majority of patients. In group A, however, two patients had a patient ventilator coordination score of 4, and another patient had that of 5. Excessive sedation was not a problem in any of the groups during the study.

There were no significant differences between the two groups in the number of patients receiving supplemental analgesics or sedatives (table 4). The number of administrations of supplemental analgesics and sedatives varied greatly among individuals, averaging that group A required it more than three times and group B about one and a half times during mechanical ventilation (table 5).

Complications

One patient in group A (6%) and ten pa-

Table 5. Number of administrations of supplemental analgesics and sedatives

Reason	Group A (n=18)	Group B (n=28)
First 24-hr period		
Pain	0.2±0.4	0.2±0.4
Excitement or struggle	0.3±0.5	0.3±0.5
Insomnia	0.6±0.6	0.4±0.6
Total	1.1±1.1	0.9±0.9
Second 24-hr period		
Pain	0.3±0.6+	0
Excitement or struggle	0.2±0.5	0.1±0.4
Insomnia	0.7±0.8++	0.3±0.5+
Total**	1.2±1.4++	0.4±0.6+
During mechanical ventilation		
Pain	0.7±0.8	0.3±0.4
Excitement or struggle**	1.1±1.0	0.6±0.7
Insomnia	1.3±0.9	0.8±0.8
Total*	3.1±2.1	1.7±1.5

* Significantly different between the two groups, $P < 0.01$.

** Significantly different between the two groups, $P < 0.05$.

+ Including 2 spontaneously breathing patients.

++ Including 4 spontaneously breathing patients.

tients in group B (36%) developed severe hypotension. In four out of the ten patients in group B, hypotension was transient, associated with night sedation. The remaining six patients in group B and another patient in group A did develop long-term hypotension treated with continuous infusion of dopamine and/or dobutamine. On the other hand, one patient in each group required treatment for hypertension. There was no evidence of respiratory depression during IMV and CPAP in either group.

Discussion

A number of investigations[9–11] have indicated the efficacy of continuous administration of epidural analgesics in the relief of postoperative pain. Most of their cases were limited, however, to non-ventilated patients. There is only one report showing the analgesic effect of this method in ventilated patients. Rawal et al.[12] showed that epidural morphine gave excellent analgesia in ICU patients requiring controlled ventilation especially for those who are restless and inadequately sedated in spite of large doses of parenteral analgesic sedative combinations, but have not shown the effect on postoperative ventilated patients.

The present study was designed to determine if continuous administration of epidural analgesics following surgery could provide not only good postoperative pain relief but also good sedation for mechanical ventilation with an acceptably low level of associated side effects. Although we did not compare this method with the other parenteral ones, this appears to be true for either the continuous epidural infusion of morphine or that of the combination of morphine and bupivacaine, as judged by the scores of three scales and the number of the administration of supplemental analgesics and sedatives.

The postoperative course of esophageal cancer surgery involving simultaneous thoracic and abdominal procedures is well known to be extremely painful. In the present study, we did not adopt a continuous epidural infusion of local anesthetics solely. Satisfactory analgesia would have required large volumes of local anesthetics, and hence excessive blood concentration of them might have occurred.

A wide variety of reasons for mechanical ventilation leads to controversy over the ideal depth of sedation and degree of detachment from the environment[1,13]. With regard to patients following esophagectomy, considering the need for weaning from IPPV, we regarded score 3 of the somnolence scale as optimal.

Some significant differences between the epidural morphine and the combined regimen have emerged from this investigation. With regard to postoperative pain relief, the patients receiving the combined regimen tended to have more complete relief than with the morphine alone. This is in accordance with several previous studies[14–16] which have shown the synergetic effects of

combinations of epidural opioids and local anesthetics. Although no significant differences occurred in somnolence scores or patient ventilator coordination scores between the two groups, some of the patients receiving the morphine alone complained of severe anxiety and discomfort. This appears to be in accordance with our previous report[6] that revealed the increased likelihood of drowsiness associated with the combined regimen. Furthermore, this result suggests that inadequate sedation causing restlessness, agitation and patient ventilator incoordination is intimately involved with pain.

Prolonged ventilation requires a drug regimen that is non-cumulative. The method of delivery of drug to the epidural space has shown to be important in reducing the amount needed. Rawel et al.[12] demonstrated that the analgesic requirement can be reduced about ten times by the use of epidural morphine. A larger dose of morphine would create a problem of the risk of accumulation, especially when drugs are not rapidly metabolised because of hepatic or renal dysfunction which may occur in patients following major surgery such as esophagectomy. Furthermore, a small number of supplemental administrations of analgesics and sedatives is another advantage of the epidural morphine. The increased interval between administrations should result in fewer periods of pain and restlessness, particularly in a situation where a doctor is busy with other patients and hence is not immediately available to administer supplemental drugs.

Epidural morphine has been documented to depress the ventilatory response to CO_2[17]. Respiratory depression, if it occurs, may be advantageous in patients requiring controlled ventilation, but may necessitate alteration of the analgesic regimen at the beginning of ventilator weaning. In our study none of the patients, however, showed any clinical evidence of respiratory depression during IMV or CPAP.

In the present study, some patients were induced into severe hypotension that necessitated immediate treatment. Suffering from dehydration and depletion of body fluids before surgery because of dysphagia[18], patients with esophageal cancer are prone to hypotension, especially after esophagectomy, considered to be one of the most invasive surgeries. Epidural analgesia has been shown to relieve postoperative pain by blocking afferent nociceptive stimuli[19]. Considering that stimulation of pain is reflected in an increased sympathetic discharge, preventing hypotension, it is presumed that good analgesic technique results in hypotension.

In conclusion, the study shows that the continuous epidural infusion of analgesics, either morphine alone or the combination of morphine and bupivacaine, offers not only good postoperative pain relief but also smooth and reliable sedation for mechanical ventilation following esophagectomy. Of the two regimens, the combination technique can provide better analgesia and sedation, suggesting that pain is a main cause of restlessness and agitation leading to patient ventilator incoordination.

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