Continuous Epidural Infusion for Postoperative Pain Relief: A Comparison of Three Regimens

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We evaluated the postoperative pain relief and side-effects of continuous epidural infusion of three analgesic regimens following major thoracic and/or abdominal surgery. One hundred and twenty patients were randomly divided into three treatment groups: (1) 0.25% or 0.5% bupivacaine at a rate of 3–7 $ml \cdot hr^{-1}$, (2) 0.01% morphine at a rate of 1–2 $ml \cdot hr^{-1}$, (3) a combination of 0.125% or 0.25% bupivacaine and 0.0025% or 0.005% morphine at a rate of 2–4 $ml \cdot hr^{-1}$. The study continued for the first 48 postoperative hours. The effect of pain relief was evaluated by assessment of the further requirement for parenteral analgesics. Sixty-four percent of the patients given bupivacaine, 56% of the patients given morphine and 80% of the patients given the combination required no supplemental analgesics. Continuous epidural infusion of bupivacaine was associated with hypotension (21%) and with numbness and weakness of hands or legs (18%). Continuous epidural infusion of morphine was associated with pruritus (18%) and with peristaltic depression (12%). The combination regimen was associated with pruritus (17%) and with drowsiness (14%). We conclude that the combination of bupivacaine and morphine significantly provides superior analgesia with less deleterious complications compared with either bupivacaine or morphine alone. (Key words: postoperative pain, epidural, morphine, bupivacaine)

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Postoperative pain relief can be achieved more efficaciously by means of continuous infusion techniques than by intermittent injections of analgesics which are invariably given after pain has developed. Postoperative analgesia provided by epidural infusion of local anesthetics or opioids has been described after abdominal and thoracic surgery[1–4]. Although it is obvious that these methods can be effective, there has been no published work comparing various epidural infusion regimens in Japan.

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At our hospital, continuous postoperative epidural infusions of both bupivacaine and morphine have been in use for several years[5,6]. In addition, our practice has evolved to combine morphine with dilute solution of bupivacaine. The purpose of this study is to compare the efficacy of three epidural infusion regimens in terms of their effects to produce postoperative analgesia and the side-effects following various major surgeries. The solutions used contained either bupivacaine or morphine alone, or a mixture of the two.

Methods

Subjects

Every patient was interviewed the night

before surgery by one of the investigators to explain the purpose of the study and to obtain consent. Patients who met all the following criteria were considered eligible for entry into this study: (1) not contraindicated for the insertion of an epidural catheter (localized infection, septicemia, preoperative coagulopathy); (2) scheduled for thoracic and/or abdominal surgery and; (3) scheduled preoperatively by surgical staff to receive postoperative care in an intensive care unit (ICU) due either to the severity of pre-existing disease(s), the magnitude of the anticipated surgical procedure, or both. All the patients were premedicated with hydroxyzine (25–100 mg) and atropine (0.3–0.5 mg) intramuscularly 1 hr before arrival in an operating room, where an i.v. infusion of lactated Ringer's solution was commenced. Before induction of general anesthesia an epidural catheter was inserted at the level corresponding to the middle dermatome crossed by the surgical incision. The epidural space was identified by the hanging drop technique. General anesthesia was induced with thiamylal (4 $mg \cdot kg^{-1}$) followed by succinylcholin (1 $mg \cdot kg^{-1}$) to facilitate tracheal intubation. Anesthesia was maintained with nitrous oxide, oxygen, halothane, and a low dose of narcotics, and the patients received intermittent injections of plain mepivacaine via the epidural catheter. Non-depolarizing muscle relaxants were used for the control of ventilation, particularly during surgery of the upper abdomen or thorax. On completion of surgery, the patients were transferred to ICU.

Postoperative analgesia

A continuous epidural infusion was started immediately after the operation. All the patients were randomly divided into three groups to receive postoperative pain treatment for a 48 hr period as follows: group A – continuous epidural infusion of 0.25% or 0.5% of plain bupivacaine at a rate of 3–7 $ml \cdot hr^{-1}$; group B – continuous epidural infusion of 0.01% morphine in normal saline at a rate of 1–2 $ml \cdot hr^{-1}$; group C – continuous epidural infusion of a combination of 0.125% or 0.25% bupivacaine and 0.0025% or 0.005% morphine at a rate of 2–4 $ml \cdot hr^{-1}$. The use of narcotics being regulated in Japan, the study was not double-blinded, but the patients did not know which drugs were being used. In groups B and C, if pain relief was insufficient, bolus injection of 4 ml of the solution was allowed only twice in succession. In addition, when the patients of all the groups asked for more analgesics or complained of restricted breathing because of pain, supplemental analgesics (usually buprenorphine) were administered intravenously.

Indomethacin was allowed to alleviate fever and benzodiazepines (usually flunitrazepam or diazepam) were used for night sedation.

Methods of evaluation

The degree of pain relief was measured by scoring based on the requirement by patients for supplemental analgesics during the first 48 postoperative hours as follows: no analgesics = 0; no analgesics but antifebriles = 1; analgesics only once = 2; analgesics more than once = 3.

Postoperative monitoring of the electrocardiogram, rectal temperature, urinary volume, and respiratory frequency was carried out in accordance with the routines of the ICU. The arterial pressure was measured throughout this study, and blood gas samples were taken at intervals of 6 hr.

All the side-effects related to epidural analgesia were recorded by nurses, and were reported immediately to anesthesiologists for consultation. The incidence of each side-effect in each group was compared. The bladder was catheterized in every case, and so urinary retention could not be assessed.

Statistics

The data are expressed as mean ± SD. They were analyzed for statistical significance using one-way analysis of variance, χ^2 test, and Student's t-test. $P < 0.05$ was considered statistically significant.

Results

A total of 120 patients was used in this study, 28 in group A, 34 in group B, and 58 in group C. The profiles of pa-

Table 1. Profiles of patients in three study groups

	Group A (n=28)	Group B (n=34)	Group C (n=58)
Age (yr)	64 ± 14	64 ± 11	62 ± 8
Weight (kg)	48 ± 9	50 ± 6	51 ± 8
Sex (F/M)	13/15	7/27*	13/45*
ASA physical status classification	2.3 ± 0.5	2.2 ± 0.4	2.1 ± 0.4
Goldman Index	7.4 ± 4.8	6.7 ± 4.4	6.8 ± 4.9

Group A: continuous epidural infusion of bupivacaine.
Group B: continuous epidural infusion of morphine.
Group C: continuous epidural infusion of a combination.
Values indicate mean ± SD.
*Significantly different from group A, $P < 0.05$.

Table 2. Surgical procedures in three study groups

Procedure	Number Group A (n=28)	Group B (n=34)	Group C (n=58)
Thoracic procedure*			
Esophagectomy+	1	10	20
Pneumonectomy	1	3	7
Others	0	1	2
Upper abdominal procedure*			
Gastrectomy	15	11	18
Pancreato-duodenostomy	4	3	8
Cholecystectomy	2	1	0
Liver resection	0	3	0
Lower abdominal procedure			
Rectosigmoid resection	2	0	0
Others	3	2	3

+Reconstruction was performed simultaneously in all cases.
*Significantly different between group A and others, $P < 0.01$.

tient groups are summarized in table 1. The three study groups were comparable with respect to age, weight and the preoperative assessment (American Society of Anesthesiologists' Physical Status, Goldman Index). Males dominated in all the groups, and the female/male ratios in group B and C were similar, while that in group A was considerably higher ($P < 0.05$).

The surgical procedures in the three groups are listed in table 2. These were distributed equally between group B and C, while in group A the number of thoracic procedures was considerably smaller ($P < 0.01$). Every patient who underwent esophagectomy received postoperative controlled ventilation.

Postoperative analgesia

In group A, 16 patients received 0.25% bupivacaine solution at a rate of 4–7 $ml \cdot hr^{-1}$, while the remaining 12 patients 0.5% at a rate of 3–5 $ml \cdot hr^{-1}$. The mean total bupivacaine consumption in this group was 0.35 ± 0.10 $mg \cdot kg^{-1} \cdot hr^{-1}$. Eighteen patients (64%) in this group did not request supplemental analgesics, while the number of patients who required analgesics more than once was only 2 (7%) (fig. 1). The mean pain relief score based on the scale of analgesic

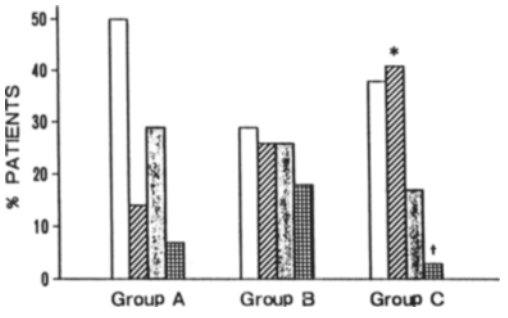

Fig. 1. Frequency of analgesic usage

The degree of pain relief was evaluated in terms of the frequency of analgesics prescribed during the first 48 postoperative hours. White columns = no analgesics; oblique-lined columns = no analgesics but antifebriles; black columns = analgesics only once; crossed-lined columns = analgesics more than once.

* Significantly different from group A, $P < 0.05$.

$^{+}$ Significantly different from group B, $P < 0.05$.

usage was 0.9 ± 1.1.

In group B, 20, 7, and 7 patients received 0.01% morphine solution at a rate of 1 $ml \cdot hr^{-1}$, 2 $ml \cdot hr^{-1}$, and 2 $ml \cdot hr^{-1}$ followed by 1 $ml \cdot hr^{-1}$ after 24 hr, respectively. The mean total morphine consumption was 3.1 ± 1.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Patients in group B also had good postoperative analgesia, the mean pain relief score being 1.3 ± 1.1, which was not significantly different from that in group A. The numbers of patients who did not request supplemental analgesics and required analgesics more than once were 19 (56%) and 6 (18%), respectively, both of which were also not significantly different from those in group A. All the patients in this group, however, required additional bolus injections of morphine especially at the beginning of the postoperative period, and the frequency of the injections was 2.1 ± 1.7 injections/48 hr period.

In group C, the patients firstly received 0.25% bupivacaine solution with 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 (45 patients) or decreased to 0.0025% (13 patients). The mean total bupivacaine consumption in this group was 0.11 ± 0.02 $mg \cdot kg^{-1} \cdot hr^{-1}$, which was considerably smaller than in group A ($P < 0.01$), while that of morphine was 3.5

Table 3. Complications in three study groups

Complication	Number Group A (n = 28)	Group B (n = 34)	Group C (n = 58)
Headache	0	0	0
Nausea/Vomiting	0	1 (3%)	2 (3%)
Pruritus	0	6 (18%)*	10 (17%)*
Numbness	5 (18%)	0*	2 (3%)*
Motor loss	5 (18%)	0*	0**
Drowsiness	0	2 (6%)	8 (14%)*
Respiratory depression#	0	1 (3%)	0
Hypotension requiring volume, pressors	6 (21%)	1 (3%)*	9 (16%)
Peristaltic depression	0	4 (12%)	0+

#Respiratory depression was defined as the appearance of a respiratory rate lower than 10 breaths per minute and/or Pa_{CO_2} higher than 55 mmHg.

*Significantly different from group A, $P < 0.05$.

**Significantly different from group A, $P < 0.01$.

+Significantly different between groups B and C, $P < 0.05$.

$\pm$ 1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, which was not significantly different from that in group B. The mean pain relief score was 0.9 $\pm$ 0.8 and the number of patients who did not request supplemental analgesics was 46 (80%), both of which were significantly larger than in group B. And the number of patients who required analgesics more than once was only 2 (3%), which was considerably smaller ($P < 0.05$). In addition, the number of patients whose pain relief score was 1 was significantly larger than in group A. Eighteen patients in this group required additional bolus injections of the combination, and the frequency of the injections was 0.7 $\pm$ 1.2 injections/48 hr period, which was significantly smaller than in group B ($P < 0.01$).

Complications

The complications in the three study groups are summarized in table 3. Six patients (18%) in group B and 10 patients (17%) in group C had pruritis, while no patients in group A did ($P < 0.05$). Six patients (21%) in group A ($P < 0.05$) and 9 patients (16%) in group C (no statistical significance) developed severe hypotension, which was immediately and successfully controlled by the anesthesiologists, while no patients did in group B. The incidence of weakness and numbness of hand(s) or leg(s) in group A was significantly higher than in the two other groups ($P < 0.05$). Peristaltic depression occurred only in group B. A significantly larger number of patients in group C complained of drowsiness than in group A ($P < 0.05$). Only one patient in group B developed respiratory depression.

Discussion

Previous studies have demonstrated that epidural administration of local anesthetics effectively relieves postoperative pain[1,2], improves postoperative pulmonary function[2,7,8], and minimizes endocrine-metabolic and stress responses[9] associated with surgery and postoperative pain. This study likewise demonstrated that the continuous postoperative epidural infusion of bupivacaine provided excellent analgesia. There were, however, some unavoidable complications in these regimens. First, weakness and numbness of hands and legs often occurred, which aroused severe anxiety in many patients. Second, severe hypotension took place due to sympathetic nerve blockade in the upper thoracic region[10]. Furthermore, excessive blood concentration of local anesthetics is a potential problem associated with continuous epidural infusion of bupivacaine. There was, however, no evidence of systemic toxicity in this study. Satisfactory analgesia would have required larger volumes of local anesthetics after major surgery involving simultaneous thoracic and abdominal procedures such as esophagectomy. And it has been reported that tachyphylaxis is also associated with maintenance of analgesia by continuous epidural blockade with local anesthetics[11].

Our data demonstrated that postoperative analgesia provided by the continuous epidural infusion of morphine was also excellent. More than half of the patients in this regimen did not request supplemental analgesics, which was not significantly different from that of bupivacaine. Several researchers[3,4] also have recognized its efficacy. El-Baz et al.[3], for example, reported that the continuous epidural infusion of morphine at 0.1 $mg \cdot hr^{-1}$ with intravenous morphine (2 mg) supplementation achieved effective pain relief after thoracic operations. However, several problems are associated with this regimen. First, inadequate pain relief at the beginning of the infusion often required additional bolus injections of the solution. Second, peristaltic depression occurred in a large number of patients. Parenteral and epidural opioids are known to induce gastrointestinal stasis[12] and therefore it would appear that this method of pain relief should be avoided following abdominal surgery which inhibits gastrointestinal motility. Third, we encountered one case of delayed respiratory depression. Therefore, patients, particularly elderly and high risk patients, should be monitored carefully[13]. Finally, it has been shown that the respiratory dysfunction observed after major surgery, such as upper abdominal surgery, was not modified by selective spinal analgesia achieved by epidural injection of

opiates. Simmoneau et al.[14] demonstrated that the dysfunction was not modified after epidural opioids.

This study was designed to determine if postoperative analgesia provided by the continuous epidural infusion of the combination of bupivacaine and morphine could be superior to the analgesia provided by the single regimens. As shown in our results, this appears to be true, and this regimen also circumvents to some extent the foregoing problems of the other regimens. Furthermore, considering that some analgesics administered in this study group were used for sedation of ventilated patients and if surgical procedures had been equally distributed between this group and group A, there would have been more striking difference in pain relief scores between these groups. This is in agreement with several previous studies[15–17] which have shown synergetic effects of combinations of epidural opioids and local anesthetics, while reducing the incidence and severity of side-effects. Although Logas et al.[18] reported contradictory results which showed no significant difference between the continuous infusion of morphine alone and the combination of morphine and bupivacaine following thoracotomy, it may presumably be the result of their larger doses of morphine than ours.

Besides its excellent analgesia, the use of the combination regimen had some other advantages. First, we found that patients who received this regimen had a reduced incidence of peristaltic depression, which suggested that concomitant bupivacaine might attenuate the depressive effect on gastrointestinal motility by epidural morphine. It has been shown that in such a situation with considerable sympathetic discharge as occurs after abdominal operations, epidural analgesia normalizes the electric activity of the stomach and intestine[19]. Second, because of an increased likelihood of drowsiness, which is presumed to be due to a central effect secondary to vascular absorption of morphine, we found this regimen to be of great value in sedating critically ill patients, especially ventilated patients. Many patients could do without an administration of sedatives, also during the night.

On the other hand, some patients were induced into severe hypotention that necessitated immediate treatment by the anesthesiologists. Considering that 5 out of these 9 patients underwent esophagectomy which was one of the most invasive operations and had a tendency to postoperative hypovolemia, it may be concluded that lower doses of epidural bupivacaine than in group A were necessary and successful.

In summary, this study shows that the continuous epidural infusion of bupivacaine or morphine alone, or the combination of bupivacaine and morphine produces a stable level of analgesia, and proves to be a practical method after major surgery. Out of the three regimens, the combination technique can provide most excellent postoperative analgesia with an acceptable level of complications irrespective of surgical procedures performed.

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References

1. Ross RA, Clarke JE, Armitage EN: Postoperative pain prevention by continuous epidural infusion. Anaesthesia 35:663–668, 1980
2. Pflug AE, Murphy TM, Butler SH, Tucker GT: The effects of postoperative peridural analgesia on pulmonary therapy and pulmonary complications. Anesthesiology 41:8–17, 1974
3. El-Baz NM, Faber LP, Jensik RJ: Continuous epidural infusion of morphine for treatment of pain after thoracic surgery: a new technique. Anesth Analg 63:757–764, 1984
4. Chrubasik J, Wiemers K: Continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief by means of a small, externally worn infusion device. Anesthesiology 62:263–267, 1985
5. Takasaki M, Hatano M, Saitoh Y, Nishio Y, Kawasaki H, Kosaka Y: Continuous epidural infusion of bupivacaine for postoperative pain relief. Masui (Jap J Anesth) 35:1550–1555, 1986
6. Saitoh, Y, Takasaki M, Kosaka Y: Contin-

uous epidural infusion of 0.01% morphine for postoperative pain relief. Masui (Jap J Anesth) 37:47–52, 1988
7. Wahba WM, Don HF, Craig DB: Postoperative epidural analgesia: effects on lung volumes. Can Anaesth Soc J 22:519–527, 1975
8. Mankikian B, Cantineau JP, Bertrand M, Kieffer E, Sartene R, Viars P: Improvement of diaphragmatic function by a thoracic extradural block after upper abdominal surgery. Anesthesiology 68:379–386, 1988
9. Kehlet H: The modifying effect of general and regional anesthesia on the endocrine-metabolic response to surgery. Reg Anesth 7:S38–48, 1982
10. Bromage PR: Physiology and pharmacology of epidural analgesia. Anesthesiology 28:592–622, 1967
11. Renck H, Edstrom H, Kinnberger B, Brandt G: Thoracic epidural analgesia- II: prolongation in the early postoperative period by continuous injection of 1.0% bupivacaine. Acta Anaesthesiol Scand 20:47–56, 1976
12. Thoren T, Wattwil M: Effects on gastric emptying of thoracic epidural analgesia with morphine of bupivacaine. Anesth Analg 67:687–694, 1988
13. Rawal N, Wattwil M: Respiratory depression after epidural morphine – an experimental and clinical study. Anesth Analg 63:8–14, 1984
14. Simmoneau G, Vivien A, Sartene R, Kunstlinger F, Samii K, Noviant Y, Duroux P: Diaphragm dysfunction induced by upper abdominal surgery: role of postoperative pain. Am Rev Respir Dis 128:899–903, 1983
15. Hjortso NC, Lund C, Mogensen T, Bigler D, Kehlet H: Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. Anesth Analg 65:1033–1036, 1986
16. Fischer RL, Lubenow TR, Liceaga A, McCarthy RJ, Ivankovich AD: Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. Anesth Analg 67:559–563, 1988
17. Cullen ML, Staren ED, El-Ganzouri A, Logas WG, Ivankovich AD, Economou SG: Continuous epidural infusion for analgesia after major abdominal operations: a randomized, prospective, double-blind study. Surgery 98:718–728, 1985
18. Logas WG, El-Baz NM, El-Ganzouri A, Cullen M, Staren E, Faber LP, Ivankovich AD: Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. Anesthesiology 67:787–791, 1987
19. Gelman S, Feigenberg Z, Dintzman M, Levy E: Electroenterography after cholecystectomy: the role of high epidural analgesia. Arch Surg 112:580–583, 1977