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# Postoperative Analgesia with Continuous Epidural Sufentanil and Bupivacaine: A Prospective Study in 614 Patients

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To assess the efficacy and safety of postoperative analgesia with continuous epidural sufentanil and bupivacaine, we performed a prospective study in 614 patients undergoing major surgery. Before surgical incision, all patients received an initial dose of 50  $\mu$ g sufentanil in 6–10 mL bupivacaine 0.125% via a lumbar or thoracic catheter. After 1 h, a continuous infusion was started with 50  $\mu$ g sufentanil in 50 mL bupivacaine 0.125% at a rate of 6–10 mL/h. The infusion was continued postoperatively for 1–5 days or longer, depending on the type

of operation and the patient's analgesic need. In the majority of patients, adequate pain relief was obtained at rest and during movement. Late respiratory depression was observed in three patients; in most patients only minor side effects were seen. Technical complications during epidural puncture or insertion of the catheter were 4% and 3%, respectively. We conclude that continuous epidural sufentanil and bupivacaine is safe and effective.

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**M**orphine was the first opioid used epidurally for postoperative pain relief, but it soon became apparent that its hydrophilic properties could lead to severe side effects, especially respiratory depression (1). Thus, the application of continuous epidural analgesia on surgical wards has been controversial for a long time (2–4). Large studies showed an incidence of 0.1%–1% of respiratory depression (1–7). To reduce this incidence, more lipophilic opioids were studied, such as fentanyl (1) and sufentanil, sufentanil being the most lipophilic, with a fast onset and theoretically a lower risk of late respiratory depression (8).

An alternative is to add a local anesthetic at a low concentration. This has two advantages: First, the additive effect leads to a smaller dose of each drug and thus decreases dose-dependent side effects. Second, several studies indicate that a combination of an opioid and a local anesthetic at a low concentration provides better analgesia than either drug alone (9–12), especially in treating postoperative pain during coughing and mobilization (11,12).

Although early respiratory depression has been documented after a single dose of 50  $\mu$ g epidural sufentanil (8), data are lacking on efficacy and safety in patients treated with continuous epidural infusion of sufentanil and bupivacaine on the surgical ward.

Since 1987 we have used continuous epidural infusion with sufentanil and bupivacaine 0.125% for perioperative pain relief after major surgery. To assess the efficacy and safety of this pain regimen, a prospective study was performed in 614 patients during a period of 1–5 days or longer on the surgical ward.

## Methods

This study was conducted during a period of 2 yr and 3 mo (1991–1993) after the approval of institutional review board and after obtaining written, informed consent. Patients scheduled for elective major surgery were admitted to the study. Patients with coagulation disorders or patients who refused insertion of an epidural catheter were excluded. Concurrent administration of low-dose heparin subcutaneously or intraoperative use of intravenous heparin after catheter insertion were not considered as contraindications.

Patients were premedicated with midazolam, 0.1 mg/kg orally, 1 h before induction of anesthesia. Glucose 2.5%/NaCl 0.9%, 500 mL, was given and epidural puncture was performed with an 18-gauge Tuohy needle in the thoracic or the lumbar region, depending on the site of operation. For the thoracic puncture the paramedian approach was used and the hanging drop technique; in the lumbar region the midline approach with "loss of resistance" technique. A 20-gauge catheter was inserted cephalad 4–6 cm into the epidural space and tested with 3 mL lidocaine 2% and adrenaline 1:200,000 to exclude intravascular

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or intrathecal position of the catheter. Technical complications in relation to epidural puncture or insertion of the catheter were recorded.

General anesthesia was induced with thiopental 4–6 mg/kg, sufentanil 0.2–0.4  $\mu\text{g}/\text{kg}$  and vecuronium 0.1 mg/kg intravenously (IV). After intubation of the trachea, anesthesia was maintained with  $\text{N}_2\text{O}/\text{O}_2$  (fraction of inspired oxygen, 0.33%) and isoflurane at a 0.6%–1% inspiratory concentration. Sufentanil 50  $\mu\text{g}$  in 10 mL bupivacaine 0.125% was given epidurally. A urinary catheter was inserted to prevent urinary retention. About 15 min later surgical incision was begun. One hour after the epidural bolus injection, a continuous infusion was started, consisting of 50  $\mu\text{g}$  sufentanil in 50 mL bupivacaine 0.125% at a rate of 6–10 mL/h. At the end of surgery, the patients' tracheas were extubated if central temperature was higher than 36°C and if they were cardiovascularly stable.

In the recovery room, the epidural infusion was continued at the same infusion rate. If the patient indicated moderate or severe pain at rest or during movement, a bolus dose of the solution was given with the same amount as the infusion rate; the infusion rate was increased by 1–2 mL/h. If pain persisted, this procedure was repeated after 30 min and combined with a paracetamol suppository 1 g every 6 h. If pain recurred after 30–60 min, the epidural catheter was considered nonfunctioning and removed. Analgesia was then provided by intramuscular injection of opioids. On the ward, pain treatment was the same as in the recovery room and was performed by the surgeon in close cooperation with the anesthesiologist. Mental state, respiratory rate, blood pressure, and heart rate were evaluated every 3 h. If the anesthesiologist was in doubt about the position of the epidural catheter, a bolus dose with bupivacaine 0.25% was given. If a patient indicated severe pain at rest or during movement despite an infusion rate  $\geq 12$  mL/h, and responded well to a bolus dose of bupivacaine 0.25%, the concentration of bupivacaine in the solution was increased to 0.2% or 0.25%. The efficacy of pain relief was evaluated by a verbal rating scale (VRS; excellent pain relief = 4; good = 3; moderate = 2; poor = 1) during the next 5 postoperative days or longer, if the epidural catheter remained *in situ*. After having studied 190 patients, we added the visual analog scale (VAS; 0 = pain free and 10 = the worst pain imaginable) to assess pain. The efficacy of pain relief at rest and during movement, and side effects, such as drowsiness, itching, nausea, and vomiting, were assessed by a medical student who visited the patients every morning at the same time. Side effects were graded as mild, moderate, or severe. After 2 or 3 days, depending on the type of surgery and the analgesic

**Table 1.** Type of Surgery and Level of Catheter Insertion

	No. of patients
Type of surgery	
Upper abdominal	351
Midabdominal	66
Lower abdominal	70
Thoracoabdominal	30
Thoracotomy	10
Orthopedic surgery	34
Peripheral vascular surgery	33
Amputation	20
Level of catheter insertion	
Thoracic	420 (68%)
Lumbar	194 (32%)

needs of the individual patient, the epidural infusion rate was decreased by 1–2 mL  $\cdot$  h<sup>-1</sup>  $\cdot$  day<sup>-1</sup> and discontinued if the patient indicated no or mild pain at a low infusion rate ( $\leq 2$  mL/h).

Data are expressed as mean  $\pm$  SD. VRS and VAS scores for different types of surgery were analyzed with the  $\chi^2$  test. A *P* value less than 0.05 was considered statistically significant.

## Results

The mean age of the patients was 57  $\pm$  16 yr (range, 13–90 yr). Most patients belonged to ASA class II (304 patients) or III (166 patients). More male (57%) than female patients were involved in the study. Type of surgery and level of catheter insertion are shown in Table 1.

### Analgesia

Pain relief at rest was adequate (VRS good or excellent) in 92%–97% of the patients evaluated (Fig. 1). Pain relief during movement was adequate in 68% of the patients on the first postoperative day, increasing to 73%–80% on Days 2–5 (Fig. 2). The VAS scores were similar to the VRS scores: VAS was  $\leq 3$  at rest in 91%–94% of the patients and  $\leq 3$  during movement in 60%–70% of the patients (Fig. 3).

### Type of Surgery

We found no significant differences in VRS nor VAS scores after upper abdominal or lower abdominal surgery, after amputation of a lower limb, or after peripheral vascular or orthopedic surgery. There were no significant differences at rest or during movement at Days 1 through 5.

### Respiratory Depression

In three patients, respiratory depression occurred on the second, third, and fourth postoperative days, respectively (Table 2). One patient died for unknown

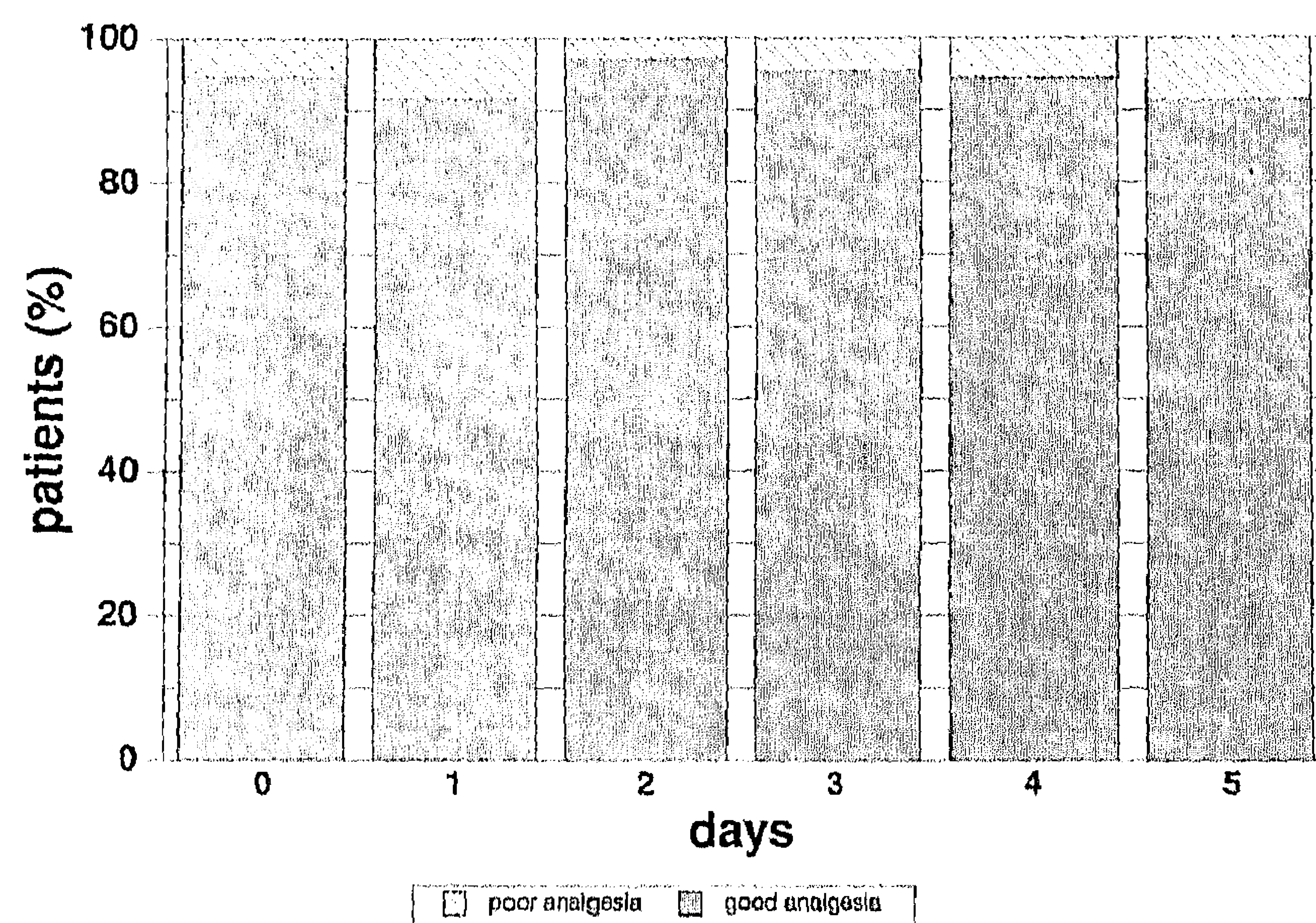


Figure 1. Verbal rating scale: patients with adequate pain relief at rest (% of patients).

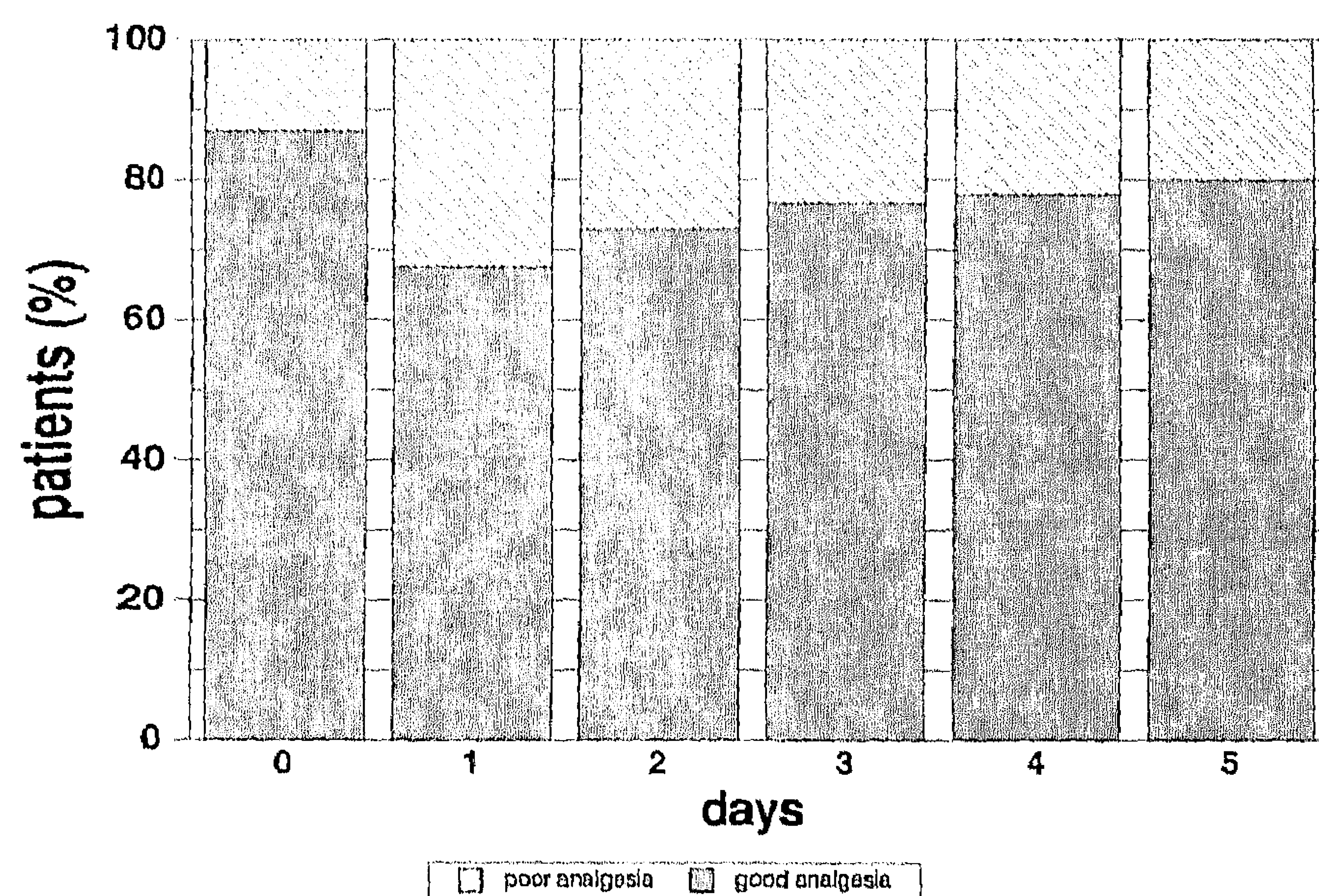


Figure 2. Verbal rating scale: patients with adequate pain relief during movement (% of patients).

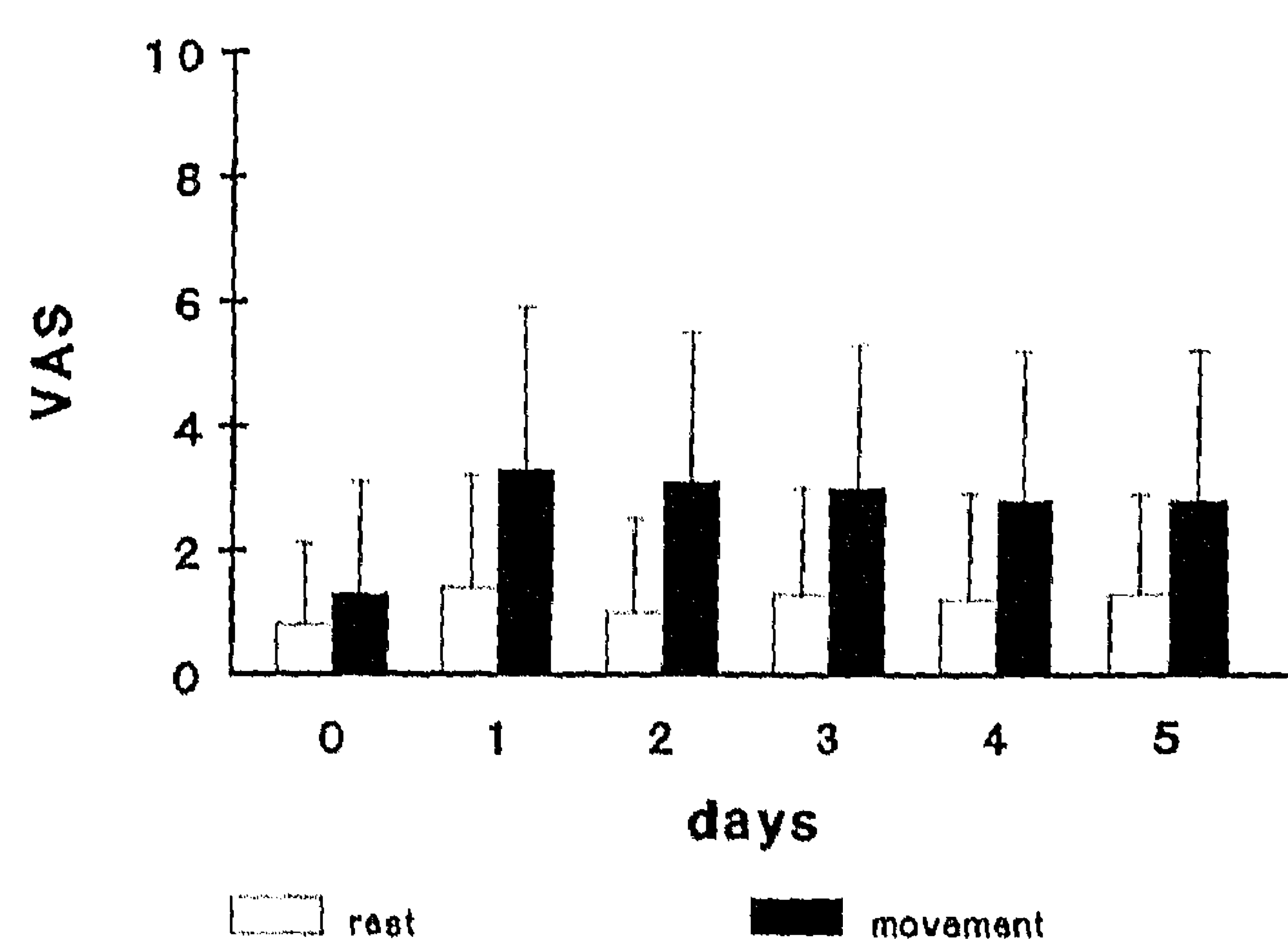


Figure 3. Visual analog scale (VAS): pain at rest and during movement (mean ± SD).

reasons on the second postoperative day. Retrospectively, we can neither prove nor refute the contribution of epidural treatment.

**Case 1.** Patient 362 had haloperidol as comedication. On the day of surgery he received three top-ups, twice with 5 mL bupivacaine 0.25% and once with 5 mL of the solution of the infusion, over a period of

11 h. The infusion rate was increased from 10 to 12 mL/h. The next day he was drowsy and therefore the dose was reduced to 10 mL/h. On the morning of Day 2 the patient was not arousable and gasping. His trachea was intubated and he was ventilated. Naloxone 0.16 mg IV was given and spontaneous respiration reoccurred. On the intensive care unit, another dose of naloxone was given and he was tracheally extubated 30 min after intubation. Further recovery was uneventful.

**Case 2.** Patient 376, who had chronic obstructive pulmonary disease, received 8 mL/h of the epidural solution and had excellent pain relief. On the third day she became drowsy with a respiratory rate of 10 breaths/min. She was transported to the recovery room and the epidural medication was discontinued. Further recovery was uneventful and the next day she returned to the surgical ward.

**Case 3.** Patient 579 had excellent analgesia with 8 mL/h during the first 3 postoperative days. The epidural medication was discontinued by the surgeon, but after a few hours he had severe pain. The visiting anesthesiologist restarted the epidural infusion with 8 mL/h after a bolus dose of 6 mL bupivacaine 0.25% with good result. During the night chlorpromazine was given for unknown reasons. Gradually the patient became drowsy. In the morning he was mobilized, but he became increasingly drowsy, had speech disturbances and had a slow respiratory rate (2-4 breaths/min). Naloxone 0.6 mg IV was administered. The patient was transported to the recovery room. Further recovery was uneventful and the patient was sent to the ward during the afternoon.

### Minor Side Effects

Itching occurred in a mild degree in 15% of the patients (Table 3). Motor block occurred only in patients with a lumbar epidural catheter. Numbness of the legs occurred in patients with a lumbar catheter or a catheter in the lower thoracic region, i.e., T9-12. One patient experienced speech and visual disturbances on the first postoperative day, suggesting central nervous system toxicity by bupivacaine. After the dose was reduced from 10 to 8 mL/h, the symptoms disappeared. The incidence of urinary retention could not be evaluated because all patients had an indwelling catheter during epidural treatment.

### Technical Complications

Complications due to epidural puncture were a bloody tap in 13 patients (2.0%) and inadvertent dural puncture in 12 patients (2.0%). Postdural puncture headache occurred in 2 patients.

Complications due to the insertion of the epidural catheter were the appearance of blood in the catheter

**Table 2.** Patients with Respiratory Depression: Characteristics and Outcome

	Patient No.		
	362	376	579
Age (yr)	60	71	72
ASA class	III	III	III
Surgery	Hemicolectomy	Abdominal aorta	Abdominal aorta
Postoperative ventilation		9 h	2.5 h
Puncture site	T8-9	T6-7	T7-8
Infusion rate	10 mL/h	8 mL/h	8 mL/h
Top-up doses			1
Comedication	Haloperidol 2.5 mg IM	Bronchodilators <sup>a</sup>	Chlorpromazine 25 mg IM
Onset (days after surgery)	2	3	4
Therapy	Naloxone 0.16 mg IV	Epidural discontinued	Naloxone 0.6 mg IV
Outcome	Fully recovered	Fully recovered	Fully recovered

IM = intramuscularly; IV = intravenously.

<sup>a</sup> Budesonide 1 mg, 2 times; salbutamol 400 µg, 4 times; ipratropium 500 µg, 4 times.**Table 3.** Side Effects of Continuous Epidural Infusion with Sufentanil and Bupivacaine

Side effects (% of patients)	Day					
	0 <sup>a</sup> (n = 435)	1 (n = 529)	2 (n = 456)	3 (n = 344)	4 (n = 244)	5 (n = 152)
Drowsiness	5.0	20.2	15.1	10.3	6.1	4.5
Respiratory depression	0	0	0.4	0.2	0.3	0
Itching	3.9	14.8	14.9	12.1	7.6	4.5
Nausea	3.9	7.8	5.9	4.2	3.5	3.3
Lower limb weakness	3.9	6.5	4.7	3.7	2.6	1.6
Numbness of the lower limbs	3.9	10.9	7.9	5.3	4.9	2.9
Hypotension <sup>b</sup>	2.0	1.0	0.4	0	0	0

n = No. of patients.

<sup>a</sup> One hundred fifty-four patients went to the intensive care unit for postoperative mechanical ventilation and, therefore, could not be evaluated on Day 0.<sup>b</sup> More than 20% decrease of the mean arterial pressure compared to the preoperative value or systolic blood pressure less than 100 mm Hg.

in 18 patients (2.8%). In 2 patients (0.3%) the catheter appeared to be in the subarachnoid space and the epidural technique was abandoned.

### Time Course of Epidural Treatment

The mean duration was  $4.2 \pm 3.2$  days. In 152 patients (25%) the epidural catheter remained in place for more than 5 days. The maximum duration of treatment was 46 days in a patient with cancer pain. There were no clinical signs of infection. The total of treatment days was 2591.

The number of patients decreased from 614 on the day of surgery to 152 on Day 5. Twenty-three patients had to be excluded on the day of surgery; in 12 patients inadvertent dural puncture occurred, in 2 patients the epidural catheter appeared to be in the subarachnoid space, in 6 patients the epidural catheter was removed a few hours after surgery because of inadequate analgesia, and three catheters migrated outward. In addition, 154 patients (25%) were ventilated on the intensive care unit postoperatively and could not be evaluated on that day. Most of these patients were tracheally extubated during the night

and went to the surgical ward on the following morning where they could be further evaluated. In 49 patients (8%) the epidural catheter was removed because of inadequate analgesia despite top-up doses and increasing the infusion rate. In 52 patients the epidural catheter migrated outward.

### Mean Dose

The mean infusion rate was  $7.5 \pm 2.8$  mL/h on the operating day, decreasing to  $1.3 \pm 2.6$  mL/h on Day 5. To 82 patients a top-up dose was administered—60 patients received one dose, 11 patients received two doses, and 11 patients received more than two top-up doses. Most top-up doses were administered on the day of surgery or the first or second postoperative day. In eight patients the concentration of bupivacaine had to be increased to 0.2% or 0.25% to obtain adequate pain relief. Five of these patients were treated for pain after amputation. Three patients underwent laparotomy.

### Discussion

In this study the regimen of a continuous epidural infusion of 50 µg sufentanil in 50 mL bupivacaine

0.125% at a rate of 6–10 mL/h during five consecutive postoperative days provided adequate pain relief in the majority of patients after major surgery.

In most studies, the efficacy of pain relief is only assessed in patients at rest. Recent studies have focused on pain relief during mobilization and coughing (11–15). Two studies (11,12) demonstrated that postoperative analgesia by an opioid-bupivacaine combination was significantly better during mobilization and coughing than by an epidural opioid alone.

Despite addition of bupivacaine, pain relief was moderate during movement in about 30% of the patients in this study; this finding accords with recent studies (16,17). This problem might be solved by increasing the dose of bupivacaine in the continuous infusion. Bupivacaine concentrations and infusion rates vary widely among different centers and no ideal mixture has been identified.

An unexpected finding was that the VAS scores were higher on Day 1 than on Day 0. This might be explained by the residual effects of general anesthesia. Patients were still drowsy during the first hours after surgery; this might have masked the perception of pain. Also, because of their drowsiness, patients did not move much. Thus, on Day 0 assessment of pain during movement was less adequate. On Day 1 the effects of general anesthesia had completely worn off and therefore, pain could be evaluated more adequately from this day on.

In our study the majority of patients underwent upper abdominal surgery. In 1961 Parkhouse et al. (18) found that the type of operation was by far the most important single factor determining the severity of postoperative pain. Operations in the upper abdomen appeared to be the most painful and distressing to the patients. In 1988 Stenseth et al. (6) found that, after prostatectomy, laparotomy, and especially thoracotomy, a higher dose of epidural morphine, i.e., 6 mg, was needed to achieve adequate analgesia than after major surgery of the lower limb, i.e., 4 mg. We found no relationship between the type of surgery and the efficacy of pain relief. This finding is apparently in contrast to previous results. We can only speculate on the explanation. A higher pain intensity after thoracic and upper abdominal surgery was expected than after lower abdominal surgery. Thus a higher infusion rate might be expected. However, for lower abdominal surgery, more segments have to be blocked after lumbar epidural analgesia (12 segments for a level of T-10) than in upper abdominal analgesia via a thoracic epidural (T4-12, nine segments). This may explain why the overall infusion rate did not differ between the different types of surgery. In contrast, we found that amputation of a lower limb was more painful compared with peripheral vascular and orthopedic surgery: in 5 of 20 patients the concentration of bupivacaine had to be increased.

Early respiratory depression, i.e., within five to 10 minutes after epidural administration of sufentanil, has been described after a bolus dose of 50  $\mu$ g (8). To our knowledge, no prospective study is available addressing the incidence of clinical symptoms of respiratory depression in a large number of patients after continuous infusion of sufentanil or sufentanil and a local anesthetic. Hasenbos et al. (13) compared continuous epidural sufentanil and bupivacaine with nicomorphine and bupivacaine for postoperative analgesia after thoracic surgery. They found an increase of the  $Paco_2$  on the day of surgery in two groups of 20 patients each, but there were no clinical symptoms of respiratory depression requiring the administration of naloxone. The mean plasma sufentanil concentrations gradually increased during the first three postoperative days. This might explain the late and insidious onset of the respiratory depression that we observed in three patients. Although we expected epidural sufentanil to be safer than epidural morphine, the incidence of respiratory depression appeared to be the same. Contributing risk factors are advanced age, high doses of opioids, concomitant use of systemic opioids or neuroleptic drugs, thoracic administration, impaired respiratory function, ASA class III and higher, major and prolonged surgery, and positive pressure ventilation (1,2,5). In our patients, four to six risk factors could be detected (Table 2).

Of the minor side effects, drowsiness occurred most frequently on the first postoperative day. Most patients did not find that bothersome. Itching, not spontaneously mentioned by most patients, was of a mild nature and diminished after two or three days. Itching is found in 11% of patients receiving epidural or spinal morphine (6); an incidence of even 40%–100% has been reported (8,19). In this study only one patient experienced severe itching, with no response to naloxone. Nausea occurred in 8% of the patients. Since most operations were in the abdominal region, this number is surprisingly low. Effective pain relief may possibly influence the incidence of nausea (6), since pain can cause nausea.

There is still controversy regarding the optimal epidural puncture site. Some studies show only marginal benefits of thoracic administration of fentanyl or sufentanil compared to lumbar injection (20,21). Others found more reliable analgesia (22) and better pulmonary function, lower incidence of nausea or sedation, shorter time to first bowel movement, and earlier discharge from the hospital (14) after thoracic administration. We believe that it is important to choose the epidural puncture site at a level appropriate to the innervation of the surgical incision, because the administration of sufentanil, which is highly lipophilic, results in segmental analgesia. Indeed, Boersma et al.

(23) have shown, in postmortem studies, that the largest concentration of sufentanil can be found near the tip of the epidural catheter.

With respect to the local anesthetic, it is equally important to choose the correct puncture site for optimal spread of the sensory blockade. We found, retrospectively, that in 15 of 49 patients with inadequate analgesia the insertion level of the catheter was incorrect: The catheters were inserted at the lumbar level for upper- and mid-abdominal surgery. In most of these patients the catheters were removed prematurely. Inadequate analgesia may result in a tendency to increase the infusion rate in an attempt to overcome this problem. As a result the incidence of side effects, notably respiratory depression, may increase. We recommend standardization of the epidural treatment according to a protocol. If the study solution is used, we advise limiting the epidural infusion rate to 10 mL/h in thoracic administration and to 15 mL/h in lumbar administration. In patients at risk for respiratory depression, we recommend reducing the total dose of the opioid by 50%.

Controversy remains regarding whether it is safe to administer continuous epidural opioid infusion on the ward (2-4). We believe, that with the above-mentioned precautions the utility of this technique will improve and lead to increased efficacy and safety.

In conclusion, postoperative analgesia for one to five consecutive days with continuous epidural infusion with sufentanil and bupivacaine was effective both at rest and during movement in the majority of patients after major surgery. Pain relief during movement was adequate in around 70% of the patients. Late respiratory depression occurred in three patients. Most patients experienced only minor side effects. Overall technical complications during epidural puncture or insertion of the catheter were 4% and 3%, respectively.

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