

## Continuous-plus-on-demand Epidural Infusion of Morphine for Postoperative Pain Relief by Means of a Small, Externally Worn Infusion Device

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In this study, 50 patients received an initial bolus epidural injection of 2 mg morphine-hydrochloride followed by a continuous-plus-on-demand epidural infusion of a 0.25% morphine-hydrochloride solution by means of a small, externally worn infusion device, for constant pain relief after abdominal operations. Mean morphine consumption on the operation day (until 8:00 AM on the first postoperative day) was  $4.8 \pm 0.2$  mg, on the first postoperative day (until 8:00 AM on the second postoperative day)  $1.9 \pm 0.2$  mg, and on a second postoperative day until 8:00 PM,  $0.6 \pm 0.1$  mg. The mean morphine consumption over 50 h was  $7.1 \pm 0.3$  mg; in the first 25 h and in the following 25 h after the operation,  $5.44 \pm 0.3$  mg and the significantly lower amount of  $1.64 \pm 0.2$  mg morphine, respectively, were consumed ( $P < 0.001$ ). There were no serious side effects. Serum levels of free, unmetabolized morphine immunoreactivity decreased during the treatment. The described method is recommended for treating postoperative pain, as it offers constant analgesia and the possibility of individualized treatment. (Key words: Analgesics: morphine-HCl. Anesthetic technique: epidural, on-demand infusion. Pain: postoperative.)

SINCE COOMBS first described continuous epidural morphine infusion for chronic pain relief,<sup>1</sup> other favorable reports have been published.<sup>2-4</sup> In order to determine whether continuous epidural morphine infusion also is effective in treating acute pain, we recently investigated patients after abdominal operations.<sup>5</sup> Surprisingly, only low doses of morphine were needed to maintain analgesia of constant quality. Moreover, an initial bolus epidural injection prior to the morphine epidural infusion reduced total morphine consumption in the early postoperative period.<sup>6</sup> The aim of the present study was to evaluate the method in a greater number of patients.

### Methods

Fifty patients (30 men, 20 women, age range 25-82 yr), who were to undergo abdominal operations, were

investigated. The subjects were fully informed, and the protocol received institutional approval by the Department of Anesthesiology of the University of Freiburg. All patients were given 0.5 mg atropine, 50 mg demerol, and 20 mg triflupromazine for premedication. The clinical details of the patients are summarized in table 1. Immediately preceding the operation, an epidural catheter was placed between the TH 10 and L-3 interspace, according to the operation. A test dose of 3 ml mepivacaine was administered to confirm the correct catheter position. All patients received thiopental, N<sub>2</sub>O and halothane; in addition, 46 patients received mepivacaine via the epidural catheter. Pain scores were assessed on a modified visual pain analogue scale (no pain = 0, worst pain = 10).<sup>7</sup> In order to guarantee an individualized pain treatment, patients were asked to indicate their pain score frequently, as well as at the predetermined intervals of our project protocol: at the beginning of the treatment, after 1 h, at 8:00 PM on the operation day, and subsequently every 12 h until 8:00 PM on the second postoperative day. Furthermore, the patients were told that if they experienced any discomfort or pain, they were to press a button on the bed to summon the nurse, who would react to their individual pain according to their scores on the analogue scale.

Postoperatively, 2 mg of preservative-free morphine-hydrochloride in 1 ml were administered by syringe through the epidural catheter, which was already in place. Following this bolus epidural injection, a 0.25% morphine-HCl solution was infused by means of a small, externally worn infusion device (Promedos E1, Siemens, Erlangen; see fig. 1), at a basal rate of 0.06 ml/h (=0.16 mg morphine/h). If after 60 min from the beginning of the treatment the pain score remained above 5, a second bolus epidural injection of 2 mg morphine-HCl was administered by syringe. If in the course of the treatment, the pain score exceeded 3 on the pain analogue scale, extra epidural infusions of 0.25 ml over 60 min, supplementary to the basal rate, were provided by the staff on demand. The basal dose rate was reduced stepwise (0.04 ml/h; 0.03 ml/h; 0.01 ml/h) at the predetermined intervals of 12 h, starting at 8:00 PM on

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TABLE 1. Operations and Clinical Data of the Patients

|   |              |
|---|--------------|
| Proctocolectomy                           | 8            |
| Proctopexy                                | 1            |
| Colectomy                                 | 7            |
| Gastrectomy                               | 7            |
| Cholecystectomy + choledochotomy          | 5            |
| Cholecystojejunostomy                     | 2            |
| Cholecystectomy + hepaticojejunostomy     | 1            |
| Cystectomy                                | 1            |
| Palliative abdominal operation            | 6            |
| Nephrectomy                               | 1            |
| Fascioplasty                              | 2            |
| Herniotomy                                | 1            |
| Lymphadenectomy                           | 3            |
| Exploratory laparotomy in cancer patients | 3            |
| Aortoplasty                               | 2            |
| Age                                       | 25-82 yr     |
| Weight                                    | 68 ± 14 kg   |
| Size                                      | 167 ± 8 cm   |
| Male:female                               | 30:20        |
| Length of operation                       | 137 ± 65 min |
| Length of anesthesia                      | 223 ± 73 min |
| Intraoperative mepivacaine (n = 46)       | 342 ± 120 mg |

the operation day, but only after the pain score had remained at 0 for at least 3 h.

In accordance with Zenz *et al.*, morphine consumption on the operation day (until 8:00 AM on the first postoperative day), on the first postoperative day (until 8:00 AM on the second postoperative day), and on the second postoperative day until 8:00 PM was recorded.<sup>8</sup> In addition to the regular supervision, blood pressure, pulse, and respiratory rate were measured twice daily until the second postoperative day; the arterial blood gases were measured daily until the third postoperative day. Blood samples were taken prior to the operation, at 8:00 PM on the operation day, and subsequently

every 12 h to determine free morphine immunoreactivity by radioimmunoassay (RIA Diagnostic Products Corporation, Los Angeles, California), whose antibody is specific for pharmacologically active, unmetabolized morphine. Cross-reactivity to morphine-3-glucuronide is 0.22%. For statistical calculations, the *t* test for paired and unpaired data were used.

## Results

Mean morphine consumption ( $\pm$ SEM) on the operation day was  $4.8 \pm 0.2$  mg (range: 3.8-8.1 mg), on the first postoperative day,  $1.9 \pm 0.2$  mg (range: 1.3-4.5 mg), and on the second postoperative day,  $0.6 \pm 0.14$  mg (range: 0.0-1.9 mg) (fig. 2). Because the operations ended at various times of the day between 11:00 AM and 6:00 PM, the minimum period of treatment was at least 50 h. The mean morphine consumption over 50 h was  $7.1 \pm 0.3$  mg; in the first 25 h and in the following 25 h after the operation,  $5.44 \pm 0.3$  and the significantly lower amount of  $1.64 \pm 0.2$  mg morphine, respectively, were consumed ( $P < 0.001$ ). Individual patterns of infusion rates of five patients are presented as examples in figure 3.

Analgesia was attained in 40 patients within 1 h after the beginning of the treatment. After 1 h of treatment, four patients required a second 2-mg bolus epidural injection of morphine, and six patients required an extra epidural infusion. Mean subjective pain while immobile remained continuously under 1, and pain under physical stress (coughing, moving, *etc.*), below 2 on the visual analogue scale (table 2). In order to maintain analgesia throughout the treatment, it was necessary to give 18 patients extra epidural infusions, supplementary to the basal epidural infusion. In individual cases, patients received up to four extra epidural infusions of 0.25 ml over 60 min.

During the treatment, blood pressure, heart rate, respiratory rate, arterial carbon dioxide tension, and the pH of the blood, measured at the predetermined intervals and during regular supervision, showed no change necessitating treatment. Arterial blood oxygen tension increased from  $82 \pm 1$  to  $100 \pm 5$  mmHg as a consequence of postoperative oxygen therapy but subsequently returned to a normal level. Nine patients (five men, four women, age range: 25-82 yr) complained of urinary retention, but none required a bladder catheter. These patients, who were all among the 46 who had received mepivacaine intraoperatively via the epidural catheter, consumed a total of  $6.6 \pm 0.9$  mg morphine.

Four patients suffered briefly from nausea and vomiting before administration of the morphine; three patients suffered the same following the bolus epidural injection. None of the patients required antiemetic

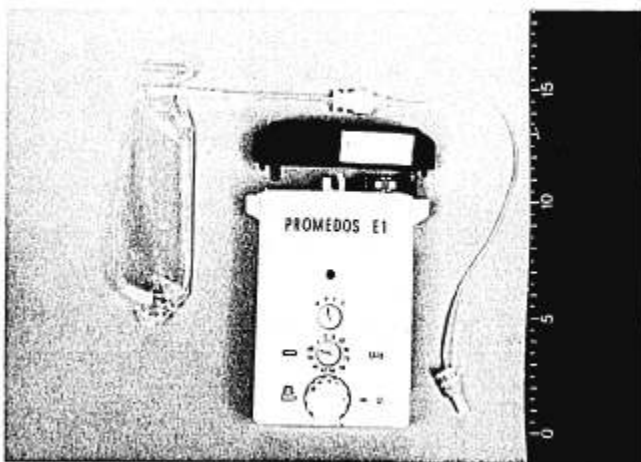


FIG. 1. The externally portable infusion device, worn around the patient's neck, for example (size: 11.4 × 6.6 × 2.7 cm, weight: 260 g with the reservoir empty), is connected to the epidural catheter, which is fixed on the patient's back by a special plaster.

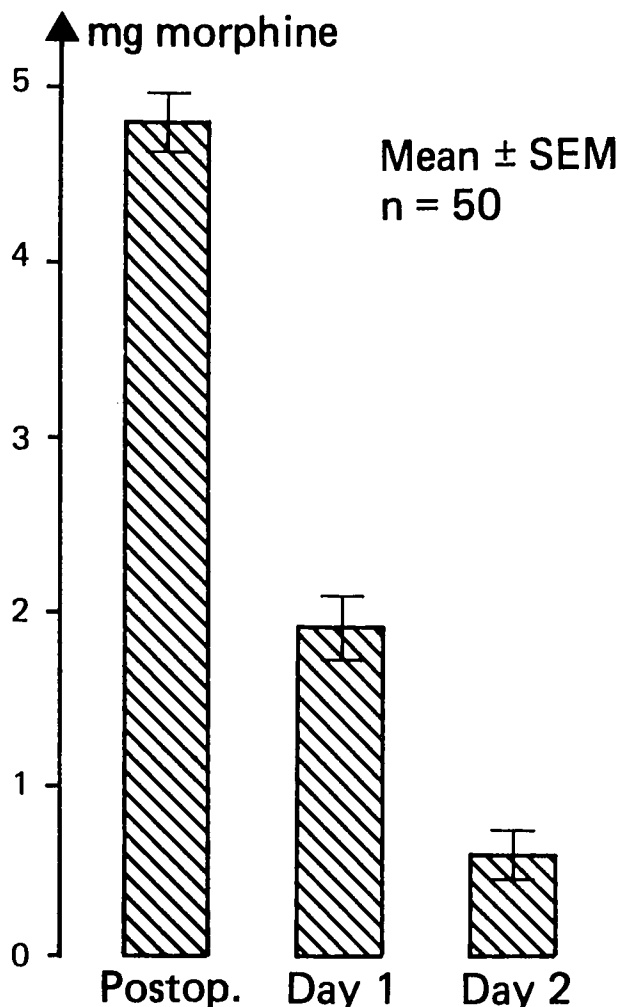


FIG. 2. Mean morphine consumption (mg) on the day of the operation, the first and second postoperative day during continuous-plus-on-demand epidural infusion of morphine. Total morphine consumption =  $7.3 \pm 0.4$  mg (range: 5.1–12.6 mg).

drugs. Other side effects did not occur, and there were no complications with the catheters.

Sixteen patients required a total of 132.4 mg triflu-promazine and 55 mg diazepam, particularly during the night, in order to sleep. The total morphine consumption of these patients until 8:00 PM on the second postoperative day was  $8.8 \pm 0.6$  mg. The 34 patients who did

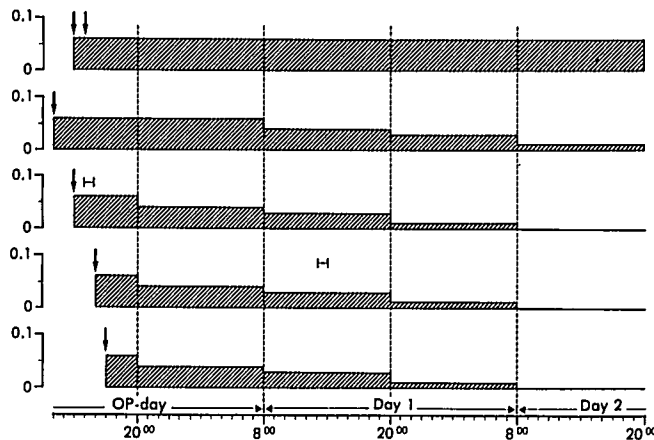


FIG. 3. Individual infusion patterns of 5 (of 50) patients who were treated by continuous-plus-on-demand epidural infusion of morphine for constant pain relief after abdominal operations. The maximum basal rate of the 0.25% morphine solution was 0.06 ml/h. ↓ = Bolus injection of 2 mg morphine; ▬ = extra infusion of 0.25% morphine solution.

not need sedatives consumed the significantly lower amount of  $7.3 \pm 0.4$  mg ( $P < 0.001$ ).

During continuous-plus-on-demand, low-dose morphine epidural infusion, free, unmetabolized morphine immunoreactivity decreased from  $6.7 \pm 0.9$  ng/ml at 8:00 PM on the operation day to  $1.3 \pm 0.4$  ng/ml at 8:00 PM on the second postoperative day ( $P < 0.001$ ) (fig. 4).

### Discussion

The above results confirm that continuous-plus-on-demand, low-dose epidural infusion of morphine is an excellent analgesic treatment following abdominal operations. The method offers constant analgesia and the possibility of individualized treatment. Subjective pain, which varies greatly among patients undergoing the same operation, is the variable on which morphine supply is based. Higher morphine requirements can be satisfied by infusions supplementary to the basal rate of morphine, administered on the patient's demand. The maximum basal rate of 3.75 mg morphine per day following the initial bolus epidural injection of 2 mg

TABLE 2. Subjective Pain Score on the Modified Visual Pain Analogue Scale (No Pain = 0, Worst Pain = 10) during Continuous-plus-on-demand Epidural Infusion of Morphine on the Operation Day, the First and the Second Postoperative Days (Day 1 and Day 2), (n = 50, mean  $\pm$  SEM)

|  | After the Operation | Operation Day |               | Day 1         |               | Day 2         |               |
|--|---------------------|---------------|---------------|---------------|---------------|---------------|---------------|
|  |                     | at 60 min     | 8:00 PM       | 8:00 AM       | 8:00 PM       | 8:00 AM       | 8:00 PM       |
| While immobile                                       | $7 \pm 0.6$         | $1.8 \pm 0.2$ | $0.7 \pm 0.2$ | $0.6 \pm 0.2$ | $0.2 \pm 0.1$ | $0.1 \pm 0$   | $0 \pm 0$     |
| While under physical stress (coughing, moving, etc.) | $8 \pm 0.5$         | $2.6 \pm 0.3$ | $1.7 \pm 0.3$ | $1.3 \pm 0.2$ | $1.2 \pm 0.2$ | $0.6 \pm 0.2$ | $0.2 \pm 0.1$ |

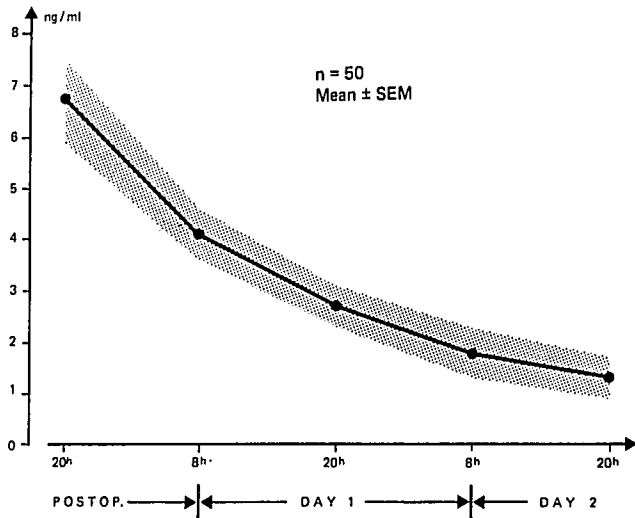


FIG. 4. Serum concentrations of free, unmetabolized morphine immunoreactivity during continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief.

was chosen empirically, because bolus epidural injections of less than 5 mg morphine are generally insufficient for pain relief after abdominal operations.<sup>8-11</sup> With this dosage, constant analgesia could be maintained in more than 60% of the patients. Less than 40% of the patients needed supplementary epidural infusions of morphine and less than 10% additional bolus epidural injections of 2 mg morphine to keep the subjective pain score below 2.

As we have demonstrated recently, there is no loss of analgesic effectiveness when epidural morphine is injected in low volumes.<sup>12,13</sup> Therefore, it is of no surprise that total morphine consumption for constant pain relief is at approximately the same level with postoperative, continuous-plus-on-demand epidural infusion of morphine as with epidural treatment by intermittent bolus injections of morphine.<sup>8</sup> Yet periods of pain inevitable with intermittent treatment are eliminated, presumably because with low-dose morphine epidural infusion, constant analgesia is maintained by the continuous replacement of morphine that diffuses from the opiate receptors of the spinal cord. The speed of the morphine that actually penetrates the dura, its distribution in the cerebrospinal fluid, and the extent of its binding on receptors determine the onset time of the analgesic effect of epidural morphine. Epidural morphine takes full analgesic effect generally up to 1 h after bolus epidural injections of morphine.<sup>9,14-16</sup> Our results confirm this. To minimize the onset of time of analgesia, the epidural catheter should be placed into the epidural interspace area with maximum nociceptive input.<sup>17</sup>

We already have shown that a 2-mg bolus epidural injection of morphine prior to the epidural infusion

reduces total morphine consumption postoperatively.<sup>18</sup> In epidural pain treatment by bolus injections, the optimal dosage for the first bolus epidural injection seems to be 2 mg,<sup>14</sup> because higher amounts of morphine do not speed up onset of analgesic efficacy.

The risk of respiratory depression has been a major point of contention for opponents of administration of epidural morphine in the postoperative period.<sup>9,19,20</sup> Until now, however, there has been no indication that respiratory depression results from continuous infusion of morphine, even with those increasing basal rates that are necessary for long-term treatment of cancer patients.<sup>2,3</sup> Hug *et al.* have shown that there is a relation between the morphine concentration in the cerebello-medullary cistern and the end-tidal CO<sub>2</sub>, following intravenous morphine administration.<sup>21</sup> It seems evident that morphine concentrations in the cerebellomedullary cistern should be kept as low as possible. Our investigations in dogs proved that the morphine concentrations near the respiratory center are significantly lower under epidural infusion of morphine than with bolus epidural injections of morphine.<sup>22</sup> Therefore, we conclude that the risk of respiratory depression also will be lower under treatment by continuous-plus-on-demand epidural infusion of morphine following an initial, low-volume bolus epidural injection than by treatment with bolus epidural injections.

While tachyphylaxis and accumulation of local anesthetics in the blood occur under postoperative continuous-plus-on-demand infusion of local anesthetics,<sup>23,24</sup> our results show that no tachyphylaxis occurred during postoperative short-term treatment with epidural infusion of morphine (fig. 2), and that under the treatment, serum morphine concentrations decreased (fig. 4).

Continuous epidural low-dose treatment with morphine does not appear to sedate the sensorium to a great extent.<sup>25</sup> Therefore, some patients required the administration of sedatives to be able to sleep at night. The amounts of morphine consumed by patients who had received sedatives were not reduced by the concomitantly administered drugs.

Urinary retention, seen in less than 20% of the patients, can be attributed partly to morphine and partly to mepivacaine. Morphine affects the tone of the bladder muscle irrespective of the dosage administered<sup>26</sup>; and approximately 20% of patients who receive local anesthetics intraoperatively suffer from bladder disorders in the early postoperative period.<sup>27</sup> At any rate, none of the cases was so severe that a bladder catheter was required.

In summary, continuous-plus-on-demand, epidural infusion of morphine for treatment of postoperative pain has the following advantages: low morphine consumption, constant analgesia, individualized treatment, no

incidence of respiratory depression, the practicality of the device, and the convenience of the method. The only disadvantages are occasional urinary retention and nausea or vomiting. The described method therefore can be recommended for treating postoperative pain, especially when epidural anesthesia is indicated.

### References

1. Coombs DW, Saunders L, Gaylor MS, Pageau MG, Leith MG, Schaiberger C: Continuous epidural analgesia via implanted morphine reservoir. *Lancet* ii:425-426, 1981
2. Coombs DW, Saunders RL, Gaylor M, Pageau MG: Epidural narcotic infusion reservoir: implantation technique and efficacy. *ANESTHESIOLOGY* 56:469-473, 1982
3. Harbaugh RE, Coombs DW, Saunders RL, Gaylor M, Pageau M: Implanted continuous epidural morphine infusion system. Preliminary report. *J Neurosurg* 56:803-806, 1982
4. Müller H, Vogelsberger W, Aigner K, Herget HF, Hempelmann G: Kontinuierliche peridurale Opiatapplikation mit einer implantierten Pumpe. *Reg Anaesth* 6:47-51, 1983
5. Chrubasik J: Programmierte Medikamentendosierung zur postoperativen Schmerzbehandlung. *Dtsch Med Wochenschr* 108:1297, 1983
6. Chrubasik J: Individuelle postoperative Schmerzbehandlung durch kleine, extern tragbare, programmierbare Morphinpumpe. *Anaesthesist (Suppl)* 32:209-210, 1983
7. Scott J, Huskisson EC: Graphic representation of pain. *Pain* 2:175-184, 1976
8. Zenz M, Piepenbrock S, Otten B, Otten G, Neuhaus R: Peridurale Morphin-Analgesie. I. Postoperative Phase. *Anaesthesist* 30:77-82, 1981
9. Weddel SJ, Ritter RR: Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. *ANESTHESIOLOGY* 54:210-214, 1981
10. Steppe J, Camu F: Epidural morphine for postoperative analgesia following abdominal surgery in elderly patients. *Acta Anaesthesiol Belg* 33:43-51, 1982
11. Bromage PR, Camporesi E, Chestnut D: Epidural narcotics for postoperative analgesia. *Anesth Analg* 59:473-480, 1980
12. Chrubasik J: Low-dose epidural morphine by infusion pump. *Lancet* i:738-739, 1984
13. Chrubasik J, Wiemers K: Kein analgetischer Wirkverlust durch peridurale "Low-volume"-Morphingabe. *Anästhesist (Suppl)* 33:451, 1984
14. Martin R, Salbaing J, Blaise G, Tétreault JP, Tétreault L: Epidural morphine for postoperative pain relief: A dose-response curve. *ANESTHESIOLOGY* 56:423-426, 1982
15. Reiz S, Ahlin J, Ahrenfeldt B, Andersson M, Andersson S: Epidural morphine for postoperative pain relief. *Acta Anaesthesiol Scand* 25:111-114, 1981
16. Rutter DV, Skewes DG, Morgan M: Extradural opioids for postoperative analgesia. *Br J Anaesth* 53:915-920, 1981
17. Gessler M, Rust M, Egbert R, Zieglganzberger W, Struppler A: Segmentale Analgesie bei epiduraler Opiatmedikation. *Anaesthesist (Suppl)* 32:257-258, 1983
18. Chrubasik J: Individuelle postoperative Schmerzbehandlung durch kleine, extern tragbare, programmierbare Morphinpumpe. *Anaesth Intensivther Notfallmed* 19:30-33, 1984
19. Reiz S, Westberg M: Side-effects of epidural morphine. *Lancet* ii:203-204, 1980
20. Nordberg G, Hedner T, Mellstrand T, Dahlström B: Pharmacokinetic aspects of epidural morphine analgesia. *ANESTHESIOLOGY* 58:545-551, 1983
21. Hug CC, Murphy MR, Rigel EP, Olson WA: Pharmacokinetics of morphine injected intravenously into the anesthetized dog. *ANESTHESIOLOGY* 54:38-47, 1981
22. Chrubasik J, Scholler KL, Wiemers K, Weigel K, Friedrich G: Low-dose infusion of morphine prevents respiratory depression. *Lancet* i:793, 1984
23. Renck H, Edström 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* 20:47-97, 1976
24. Ross RA, Clarke JE, Armitage EN: Postoperative pain prevention by continuous epidural infusion. *Anaesthesia* 35:663-668, 1980
25. Rawal N, Sjöstrand U, Dahlström B: Postoperative pain relief by epidural morphine. *Anesth Analg* 60:726-731, 1981
26. Rawal N, Möllefors K, Axelsson K, Lingardh G, Widman B: An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. *Anesth Analg* 62:641-647, 1983
27. Lanz E, Theiss D, Riess W, Sommer U: Epidural morphine for postoperative analgesia: A double-blind study. *Anesth Analg* 61:236-240, 1982