

# Influence of Epinephrine as an Adjuvant to Epidural Morphine

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The effects of epinephrine 1/200,000 as an adjuvant to epidural morphine were investigated in three healthy male volunteers, during 26-h observation sessions. Peak blood concentrations of morphine were  $44 \pm 12.9$  ng/ml after plain morphine and  $13.7 \pm 6.7$  ng/ml after epinephrine-morphine. Cutaneous hypalgesia was more intense, faster in onset, and longer in duration after epinephrine-morphine than after plain morphine, and analgesia to ice-water immersion of extremities lasted longer. Adverse side effects of pruritus, nausea, vomiting, and difficulty of micturition were also more intense after epinephrine-morphine, and respiratory sensitivity to CO<sub>2</sub> was depressed more severely between 6 and 16 h. The results indicated that epinephrine 1/200,000 reduces vascular absorption of epidural morphine and intensifies all the manifestations of cord and brainstem uptake. (Key words: Analgesics: morphine. Anesthetic techniques: epidural narcotic. Spinal cord. Sympathetic nervous system: catecholamines, epinephrine. Ventilation: carbon dioxide response.)

EPINEPHRINE IS COMMONLY USED as an adjuvant to prolong and intensify the clinical effects of local and regional anesthesia. In the epidural space, epinephrine 1/200,000 (5 µg/ml) reduces local anesthetic uptake into the azygos vein by about 60%.<sup>1</sup> This reduction of vascular absorption is thought to enhance the quality and duration of blockade by leaving proportionally more local anesthetic available for uptake into the cerebrospinal fluid and the neuraxis.<sup>2</sup> We were interested to see if epinephrine would have a similar enhancing influence upon the action of epidural morphine. An earlier clinical study had revealed no obvious difference between plain and epinephrine-containing narcotic solutions.<sup>3</sup> However, this question is difficult to answer with any degree of precision in a clinical situation because uncontrolled variables arising from the effects of pain and postoperative alterations of blood flow may alter the pharmacokinetics of uptake from the epidural space. Accordingly, we investigated the influence of epinephrine 1/200,000 added to 10 mg of epidural morphine in three healthy volunteers. The study was de-

signed to see if epinephrine reduced vascular uptake of morphine from the epidural space, and if a reduction of vascular absorption bore any relation to the subsequent intensity and duration of spinal cord effects. Because these effects are very prolonged, subjects were observed throughout experimental sessions lasting for 26 h.

## Methods

Three healthy male volunteers aged 19, 20, and 33 years were studied. Informed consent and institutional approval were obtained. Each volunteer had been the subject of an earlier comparison of sensory and respiratory changes after intravenous and epidural morphine carried out over two similar 26-h sessions in our laboratory,<sup>4</sup> and data from this earlier study were used for comparative purposes. An interval of 4-7 months was allowed to elapse between the plain epidural morphine study and the present epinephrine-morphine investigation.

Subjects were studied reclining in a 20° head-up position. Following a period of control measurements, an epidural catheter was inserted at the second lumbar interspace, and catheter placement was validated by a preliminary dose of 10 ml of 2% chloroprocaine. Thirty minutes after complete regression of the chloroprocaine block, 10 mg preservative-free morphine in 10 ml normal saline were injected through the epidural catheter at the second lumbar interspace, and the catheter was flushed with 1.5 ml saline. Plain morphine was injected at one session and morphine with freshly added epinephrine in a concentration of 5 µg/ml at the other. A horizontal, supine posture was maintained for the next 10-15 min and then the subjects stood up and emptied their bladders into a measured container. One subject returned for an additional session, when epinephrine 1/200,000 without morphine was injected epidurally in 10 ml saline.

Segmental levels of cutaneous hyposensitivity to ice and pin-scratch were sought under control conditions before morphine injection, and then at 10, 30, and 45 min, and 1, 3, 6, 10, 16, and 22 h or more frequently after morphine injection, as described previously.<sup>4</sup> Segmental levels of hypalgesia were recorded on dermatome charts.

Seventh nerve acuity for taste was examined as a possible indication of depression of brainstem nuclei from rostral spread of morphine. Taste discrimination was tested by asking the subjects to distinguish salt and sweet

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Received from the Departments of Anesthesiology, Duke University Medical Center, Durham, North Carolina, and the University of Colorado Medical School, Denver, Colorado. Accepted for publication August 26, 1982. Supported by a grant from A. H. Robins.

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TABLE 1. Influence of Epinephrine 1/200,000 on Vascular Uptake of Epidural Morphine Serum Concentrations of Unchanged Morphine (ng/ml) after Epidural Injection of 10 mg in Three Volunteers

Volunteer	Plain Morphine (Hours)						Morphine + Epinephrine (Hours)					
	Control	0.5	1	3	6	10	Control	0.5	1	3	6	10
1	BDC	33.5	11.2	4.7	BDC	BDC	BDC	6.4	10.4	4.7	3.7	BDC
2	BDC	58.4	18.4	8.9	BDC	BDC	BDC	19.6	15.1	10.4	3.2	BDC
3	BDC	40.0	18.3	8.0	BDC	BDC	BDC	15.2	8.9	3.6	BDC	1.5
MEAN	BDC	44.0*	16.0	7.2			BDC	13.7*	11.5	6.2	2.3	0.5
SD	—	12.9	4.1	2.2			—	6.7	3.2	3.7	2.0	

BDC = below detectable concentration (&lt;1 ng/ml).

\* Significance of differences of means:  $P < 0.05$ .

solutions in concentrations at, or slightly above, normal threshold for taste. Glucose (taste threshold = 0.08 M) was used in concentrations of 0.05, 0.1, 0.15, and 0.2 M, and sodium chloride (threshold = 0.01 M) in concentrations of 0.01, 0.015, and 0.02 M. Four drops of the test solution or tap water were placed on the anterior tongue in random sequence, with mouth rinses between tests. Subjects were scored for correct identification of the test solutions before morphine administration and at 4 h and 8 h after morphine.

Serial cold pressor response tests (CPRT) by ice-water immersion of an extremity were used as a powerful noxious stimulus and as an objective index of hypalgesia in hands and feet, as described previously.<sup>5</sup> The test was applied before morphine administration and at 1.5, 4, 7, 11, 16, and 22 h after injection of morphine. Results for each limb were expressed as percentage changes from the blood pressure response prior to morphine administration.

The time of onset and duration and intensity of pruritus, nausea, and vomiting were noted. Retention of urine was estimated from urinary volumes and the interval between voiding at time of morphine administration and subsequent micturition. Respiratory depression was observed by measurements of end-tidal CO<sub>2</sub> and by CO<sub>2</sub>-response curves using a rebreathing technique. End-tidal CO<sub>2</sub> (PET<sub>CO<sub>2</sub></sub>) was measured by a Godart® capnograph calibrated against two chemically verified concentrations, accurate within 1%, of 4.7% and 8.3% carbon dioxide in oxygen and plotted on a Grass® 4-channel recorder. Respiratory rates and volumes were measured with a nine-liter Collins recording spirometer. CO<sub>2</sub> responses were compared from the slopes of the CO<sub>2</sub>-response curves ( $\Delta\dot{V}_E/\Delta P_{CO_2}$ ) and from the minute volume at a PET<sub>CO<sub>2</sub></sub> of 55 mmHg ( $\dot{V}_{55}$ ). These observations were made under control resting conditions before insertion of the epidural catheter, and then at 1, 3, 6, 10, 16, and 22 h after injection of epidural morphine.

Ten milliliters of blood were drawn from a forearm vein for serum morphine assay at the following times:

control, before injection of test morphine solution, and then at 0.5, 1, 3, 6, 10, 16, and 22 h after injection. Blood was drawn by a 20-gauge needle into all-glass syringes and centrifuged in glass Vacutainers®. The serum was transferred to Teflon® tubes and frozen until analyzed. Unchanged morphine was assayed by high pressure liquid chromatography, using electrochemical detection, and with nalorphine as an internal standard.<sup>6</sup> The method had an accuracy of  $\pm 2.25$  ng/ml at 40 ng/ml concentration, and a lower limit of detection of about 1 ng/ml.

Statistical comparison of results for plain and epinephrine-containing morphine were made by parametric and non-parametric methods. Differences of slope for the speed of spread of segmental hypalgesia and for the time of regression of analgesia (CPRT) were compared by analysis of covariance. Paired and unpaired *t* tests were used for comparison of respiratory effects and for comparison of serum morphine concentrations. The Wilcoxon rank sum test was used to compare the frequency of adverse side effects.

## Results

### SERUM CONCENTRATION OF MORPHINE

Vascular uptake of morphine was reduced by the addition of 1/200,000 epinephrine, as shown in table 1. Peak plasma concentrations of morphine measured at 30 min were lowered by 69%, from a peak of  $44 \pm 12.9$  ng/ml to  $13.7 \pm 6.7$  ng/ml, and this difference is significant ( $P < 0.05$ ).

All three volunteers remarked that the subjective effects of morphine with epinephrine were more intense than after plain epidural morphine. Objective measurements confirmed these subjective impressions.

### TRIAL CHLOROPROCAINE BLOCK

In each subject the extent and duration of the trial chloroprocaine block were similar at both sessions. The extent of segmental spread was identical in one subject

Epidural Morphine: Influence of Epinephrine  $1/200,000$  on Rostral Spread of Hypalgesia

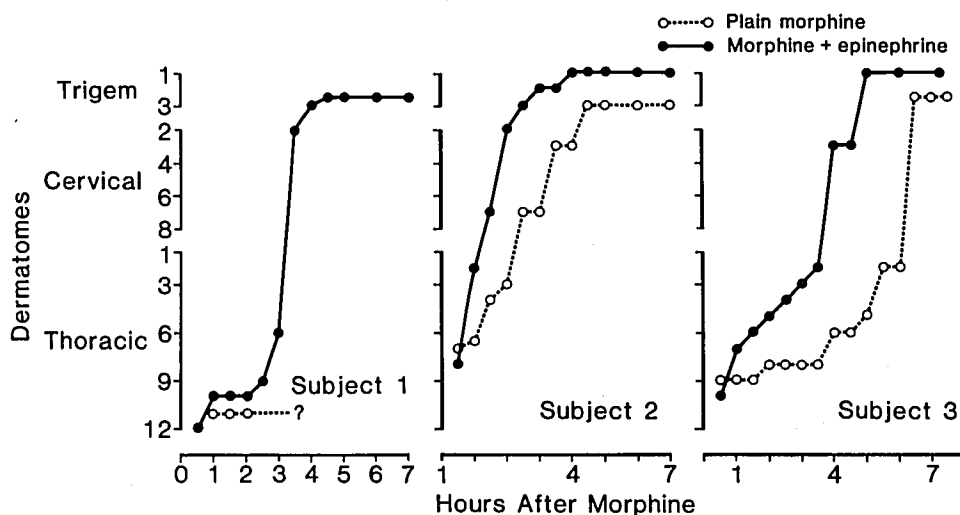


FIG. 1. Influence of epinephrine on rostral spread of hypalgesia after 10 mg epidural morphine (at second lumbar interspace) in three volunteers.  $\circ$ — $\circ$  = plain morphine;  $\bullet$ — $\bullet$  = morphine +  $1/200,000$  epinephrine.

(to T9), and differed by one segment in the other two subjects. The mean duration from initial onset to complete regression was 47 min for both epidural sessions, although individual differences of 5 to 10 min existed between subjects.

SENSORY CHANGES

*Rostral Spread of Hypalgesia.* Cutaneous hypalgesia was better-defined and spread faster and further in a rostral direction after epinephrine-morphine than after plain epidural morphine. Figure 1 shows the rate of rostral spread with epinephrine in the three subjects compared to the slower ascent after plain epidural morphine. Subject 1 had vague and transient hypalgesia after plain morphine, but after epinephrine-morphine the dermatome levels were easily discernible. Note that hypalgesia never spread to the ophthalmic division of the fifth cranial nerve after plain morphine, whereas two of the three subjects had hypalgesia of the forehead after the epinephrine solution. In spite of quite large individual variations, the mean rostral spread after epinephrine-morphine was significantly greater than after plain morphine between the second and sixth hours ( $P < 0.05$ ) and duration of cutaneous hypalgesia was prolonged. After plain morphine, the upper level of hypalgesia became indistinct and disappeared between 6 and 17 h, but after epinephrine-morphine the upper level remained consistent for longer, and then regressed caudally in a detectable fashion until 18 to 22 h.

*CPRT: Hand and Foot.* Intensity of analgesia, as measured by the pressor response to ice-water immersion, was not appreciably different during the early stages of the plain and epinephrine sessions (see fig. 2). At both

sessions, marked attenuation of the CPR occurred in the foot by 1.5 h, while the hand lagged behind. By the fourth hour the mean depression of CPRT was profound and indistinguishable in both upper and lower limbs, with and without epinephrine. From the fourth hour onwards, until about the eleventh hour, both groups remained depressed to a similar degree in the range of 70–100% below control pre-morphine responses. However, from 16 to 22 h the CPRT in the hand and foot remained significantly more depressed during the epinephrine session ( $P < 0.05$ ) indicating a more prolonged analgesia.

ADVERSE EFFECTS

The times of onset of side effects were unaltered by the addition of epinephrine, but all the adverse effects were more frequent, more severe, and more prolonged after epinephrine-morphine than after plain morphine, as shown in figure 3. Respiratory depression was markedly worse after epinephrine-morphine, and apneic spells lasting 10 to 50 s gave rise to some concern in two of the three subjects between 6 and 16 h of the epinephrine-morphine session. Resting end-tidal  $CO_2$  increased from a mean control level of 37 mmHg to 40 mmHg by the sixth hour, and 41 mmHg at the tenth hour after plain morphine. After epinephrine-morphine end-tidal  $CO_2$  rose from  $36 \pm 1$  mmHg to  $45 \pm 1$  mmHg by the sixth hour, and in one subject it rose to 52 mmHg at the tenth hour. At the tenth hour,  $\dot{V}_{55}$  was reduced  $26.3 \pm 8.7\%$  below control after plain morphine and  $68.2 \pm 7.7\%$  below control after epineph-

Plain vs Epinephrine Morphine (Lumbar Epidural 10 mg)

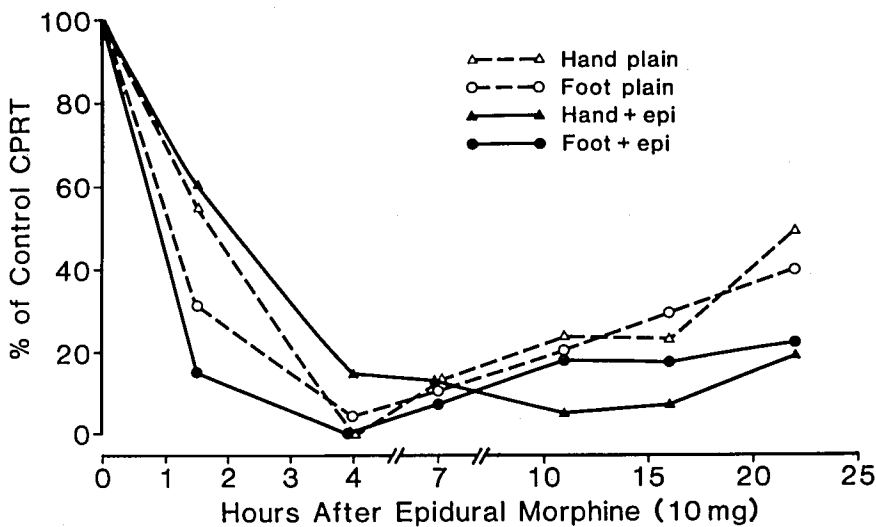


FIG. 2. Change of cold pressor response test (CPRT) in the hand and foot as an index of hypalgesia after 10 mg lumbar epidural morphine, and influence of epinephrine 1/200,000 in three volunteers. Plain morphine: hand,  $\Delta$  ---  $\Delta$ ; and foot,  $\circ$  ---  $\circ$ . Morphine + 1/200,000 epinephrine: hand,  $\blacktriangle$  —  $\blacktriangle$ ; and foot,  $\bullet$  —  $\bullet$ .

rine-morphine. These differences between groups are all highly significant ( $P < 0.01$ ).

Pruritus occurred in two of the three subjects after plain morphine, but in all three after epinephrine-morphine. The time of onset was approximately the same but epinephrine had the effect of increasing the inten-

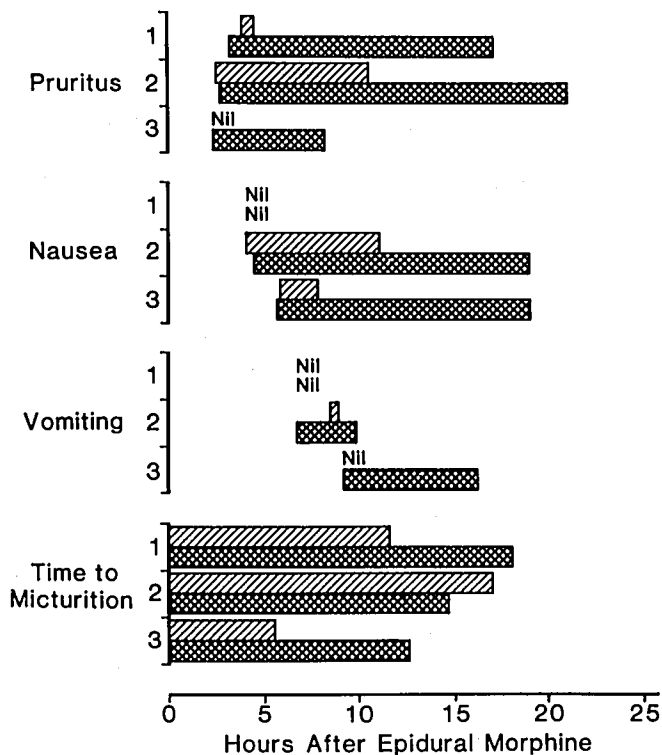


FIG. 3. Influence of 1/200,000 epinephrine on incidence, onset, and duration of non-respiratory side effects of 10 mg epidural morphine in three volunteers.  $\square$  = plain morphine (10 mg);  $\blacksquare$  = 10 mg morphine + 1/200,000 epinephrine.

sity of itch and doubling the duration. Itching appeared to play an interesting arousal role during the apneic spells that occurred between 6 and 16 h after epinephrine-morphine, when the subjects roused to scratch themselves and to recommence regular respiration. To the watchers it seemed as if the itching was supplying vitally needed internal afferent input to replace what was missing from blunted normal sources. Nausea and vomiting were also markedly intensified and prolonged, and all three subjects remarked on the comparative severity of nausea after epinephrine-morphine.

All three subjects experienced difficulty and delay with micturition. None had to be catheterized, but all three required pharmacologic assistance at one or the other session before they were able to void. The effects of epinephrine were inconsistent in this small group. Subjects 1 and 3 voided spontaneously, but with some difficulty after plain morphine, at the times shown in figure 3. Both of these subjects experienced greater difficulty after epinephrine-morphine and required 0.4 mg naloxone iv, before they were able to void. On the other hand, Subject 2 required naloxone after plain morphine, but he was able to micturate intermittently without assistance after epinephrine-morphine.

No diminution of acuity of taste to sweet and salt was found in any of the subjects at any time. Resting blood pressure did not change significantly throughout the period of investigation.

EPIDURAL EPINEPHRINE ALONE

Surprisingly, objective signs of limited segmental hypalgesia developed 20 min after injecting 50  $\mu$ g epidural epinephrine in 10 ml saline, and lasted about six hours. An easily detectable band of hypalgesia to ice and pin-

scratch extended from T10 to L2, and piloerection was clearly visible within the same segmental area, and then faded after the sixth hour. However, hypalgesia to CPRT did not develop in the hands or feet. Also, the CO<sub>2</sub>-response curves did not change from control and there were no adverse effects such as nausea, pruritus, or retention of urine.

### Discussion

In an earlier study of narcotics for postoperative pain relief, we were unable to detect gross differences of analgesia or side effects between plain and epinephrine-morphine.<sup>3</sup> However, a volunteer model such as we used during 26-h study periods has certain advantages over observations in a clinical setting. The background physiologic state is stable and undisturbed by the shifting events associated with surgical pain. Experimental pain by the cold-pressor response test is standardized and has objective and easily quantifiable reactions, free of any possible modulations from ongoing clinical pain. Segmental spread of cutaneous hypalgesia is more readily and accurately discernible in a volunteer than in a patient distracted by background pain, and CO<sub>2</sub> rebreathing is tolerated more easily. Also, CO<sub>2</sub>-response curves reflect the sensitivity of respiratory control centers more faithfully than under stimulation by painful sensory input, for respiratory drive has been shown to be increased by both acute and chronic pain.<sup>7-9</sup> The greater precision of respiratory observations in volunteers is borne out in this study, where respiratory depression was similar to that found by Knill *et al.* using 7.0 mg epidural morphine in volunteers<sup>10</sup> and greater than reported by Dobljar *et al.* using the same dose of epidural morphine (10 mg) for postoperative pain.<sup>11</sup>

Ten milligrams of epidural morphine were chosen as the experimental dose because this is the amount that we had found necessary to provide effective analgesia after major upper abdominal surgery.<sup>3</sup> Epinephrine added in a dose of 50 µg in 10 ml saline intensified and prolonged all the effects of morphine that we observed, as if a larger amount of morphine had been given. Segmental spread of hypalgesia was enhanced and prolonged, and the analgesia of hands and feet also was prolonged. Respiratory depression and all other side effects were worse in intensity and duration. These results of epinephrine as an adjuvant cannot be ascribed to enhanced systemic action of morphine at peripheral opiate receptor sites, since epinephrine reduced peak blood concentrations by two-thirds. This reduction of vascular clearance from the epidural space suggests that the enhanced effects of epinephrine-morphine could be due to a correspondingly increased passage of morphine into the CSF and neuraxis, in a similar manner to the

effects of epinephrine on epidural local anesthetics.<sup>1,12</sup> The strikingly different times of remission of adverse side effects after plain and epinephrine-morphine were related to the different time courses for decay of dermatomal hypalgesia and analgesia to ice-water immersion, suggesting that both phenomena are associated with neuraxial events.<sup>13</sup>

Tests of taste acuity did not provide any positive evidence to support the idea of rostral spread through the ventricular system rather than over the outer pial surface of the brainstem. However, the markedly exaggerated respiratory and visceral complications suggest that morphine may have penetrated to shallow nuclei, such as the nucleus of tractus solitarius, in the floor of the fourth ventricle.

The direct effects of epinephrine on  $\alpha$ -adrenergic systems within the spinal cord also must be considered as a possible mechanism for the enhanced effects that were seen in these subjects. There is good evidence that  $\alpha$ -adrenergic agents cause hypalgesia when applied to the cord and brainstem, and 35 years ago animal and human experiments led to epinephrine being proposed as a spinal anesthetic.<sup>14,15</sup> Recently, intrathecal norepinephrine, epinephrine, and clonidine have been shown to produce hypalgesia by themselves and to augment the analgesic action of spinal morphine.<sup>16-19</sup> The effects of clonidine are prolonged over several hours,<sup>19</sup> but the action of norepinephrine is very transient, and in cats, all analgesic effects disappear within 60-90 min.<sup>17</sup> Thus, it seems unlikely that activation of  $\alpha$ -adrenergic systems within the cord could have been the cause of the very prolonged enhancement lasting 20 h or so that we observed after epinephrine-morphine. This is supported by the relatively brief and insignificant sensory effects of epinephrine alone after epidural injection of 50 µg epinephrine in saline in Subject 3. While epinephrine by itself may produce a relatively short-lived, tenuous, and limited segmental hypalgesia, duration is short compared to morphine, and apart from piloerection, free of side effects.

Thus, we conclude that all the enhanced effects observed in our volunteers were mainly due to the actions of epinephrine outside the spinal cord and to reduced vascular clearance of morphine from the epidural space. Direct action of epinephrine on  $\alpha$ -adrenergic systems within the cord may have contributed to the overall effect, but we suggest that the  $\alpha$ -agonist component was probably of minor importance compared to the local vascular effects of epinephrine.

It is not the purpose of this paper to approve or condemn the use of epinephrine with epidural narcotics. Nevertheless, the side effects were markedly intensified when epinephrine was added to our large dose of 10 mg epidural morphine, and thus we cannot recommend

epinephrine as an adjuvant at that dose level. However, this does not imply that epinephrine is contraindicated when smaller doses of morphine are used. Moreover, our adverse data with morphine and epinephrine should not be extrapolated to more lipid-soluble narcotics, such as meperidine or dilaudid, since their different physicochemical characteristics may give rise to more favorable clinical effects. While the sample size of this small series has not allowed the enhancing effects of epinephrine to be quantified precisely, we suggest that it would be prudent for practitioners to reduce their customary dose of epidural morphine if epinephrine is used as an adjuvant.

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