

Tramadol Infusion for Postthoracotomy Pain Relief: A Placebo-Controlled Comparison with Epidural Morphine

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We compared continuous IV tramadol as an alternative to neuraxial or systemic opioids for the management of postthoracotomy pain in a prospective, randomized, double-blinded, controlled study. General anesthesia was supplemented by thoracic epidural analgesia with 0.25% bupivacaine. At rib approximation, patients received one of the following: IV tramadol (150-mg bolus followed by infusion, total 450 mg/24 h, $n = 29$), epidural morphine (2 mg, then 0.2 mg/h, $n = 30$), or patient-controlled analgesia (PCA) morphine only ($n = 30$). All patients received PCA morphine and rescue morphine as necessary postoperatively. For the first 24 h, pain and sedation scores and respiratory, cardiovascular, and side effect measures were monitored. There was no significant difference in pain

scores and PCA morphine use between tramadol and epidural morphine. Pain scores at rest and on coughing were lower in the Tramadol and Epidural Morphine groups than in the PCA Morphine group at various time points over the first 12 h. The Tramadol and Epidural Morphine groups used significantly less hourly PCA morphine than the PCA Morphine group at specific time points in the first 10 h. Vital capacities in the Tramadol group were significantly closer to baseline values at the 20-h point than in the PCA Morphine group. We conclude that an intraoperative bolus of tramadol followed by an infusion was as effective as epidural morphine and avoided the necessity of placing a thoracic epidural catheter.

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Tramadol hydrochloride is a synthetic opioid agonist analgesic acting at the μ receptor (OP_3) (1). Its analgesic potency has been described as 5-10 times less than that of morphine, equal to that of meperidine (2) and to 0.001 that of fentanyl (3). Its analgesic efficacy lies between that of codeine and morphine. Tramadol is a racemic mixture of two enantiomers with a structure similar to that of other opioid analgesics (4). However, only 30% of its effect can be antagonized by naloxone (2), and a significant portion of its action is mediated through non-opioid mechanisms, including monoamine modulation and synergy with opioid agonism (3,5). The opioid affinity, the inhibition of the uptake of norepinephrine and serotonin, and the further presynaptic release of serotonin (6) are dependent on the enantiomers, which have a complementary and synergistic antinociceptive effect (7).

A previous trial comparing the analgesic efficacy and respiratory effects of different treatment regimens showed that a single tramadol bolus given at the end of surgery provided postoperative analgesia equivalent to that of continuous epidural morphine for the initial postoperative period (8). Arterial oxygen and carbon dioxide tensions were significantly better in the Tramadol group for the first 4 h postoperatively. Continued use of tramadol might extend these observed benefits further into the postoperative period. To investigate this possibility, we compared the analgesic efficacy produced by an IV tramadol infusion with that obtained with the use of an epidural morphine infusion, our current postoperative standard for thoracotomy patients, by using patient-controlled analgesia (PCA) with IV morphine as a concomitant control.

Methods

Patients undergoing posterolateral thoracotomy for lung resection were recruited for this prospective, randomized, double-blinded study. Appropriate informed consent was obtained according to the Treaty of Helsinki.

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Exclusion criteria were contraindications to the placement of an epidural catheter or to the use of any of the study medications, deviation from the protocol anesthetic technique, anticipation of postoperative ventilation, or the use of any analgesic medication during the 36 h before surgery. Patients were randomized by the hospital pharmacy to receive tramadol, epidural morphine, or IV PCA morphine, by using tables of random numbers.

Before the induction of anesthesia, a thoracic epidural catheter was inserted at the T5-6, T6-7, or T7-8 interspace, and 5-10 mL of 0.25% bupivacaine was administered for intraoperative analgesia. Adequate analgesia covering the proposed surgical field (T3 to T10) was established, as assessed by cold insensitivity, before the induction of general anesthesia. Failure to establish a satisfactory block was a *post hoc* reason for exclusion.

Anesthesia was induced with IV thiopental. Muscle relaxation, assessed by a peripheral nerve stimulator, was achieved with pancuronium. No IV analgesics were administered. After double-lumen endobronchial intubation, anesthesia was maintained with isoflurane at 1% to 1.5% in oxygen-enriched air, sufficient to maintain arterial oxygen saturation not <90%. Intraoperative analgesia obtained from the thoracic epidural was supplemented with further doses of 0.25% bupivacaine if indicated by a sustained increase in heart rate and blood pressure >20%. The last dose of bupivacaine (2-3 mL) was given at least 45 min before skin closure.

At the time of rib approximation, all patients received a slow 5-mL IV bolus from a syringe labeled with the words "IV drug" and the patient study number. At the same time, all patients also received a 10-mL epidural bolus from a syringe labeled with the words "epidural drug" and the patient study number. In the Tramadol group, the IV drug syringe contained 150 mg of tramadol; in the Epidural Morphine and PCA Morphine groups, the syringe contained an equivalent volume of saline. The epidural syringe contained 10 mL of saline in the Tramadol and PCA Morphine groups, whereas in the Epidural Morphine group the syringe contained 2 mg of morphine in 10 mL of saline. Thereafter an epidural infusion was set up by using identical infusion bags prepared and labeled by the pharmacy which contained either saline (Tramadol and PCA Morphine groups) or morphine in saline (Epidural Morphine group). The epidural infusion delivered 0.2 mg morphine per hour (Epidural Morphine group) or an equivalent volume of saline (Tramadol and PCA Morphine groups). All patients also received an IV infusion from identical bags containing either saline (Epidural Morphine and PCA Morphine groups) or tramadol (Tramadol group). The IV infusion in the Tramadol group delivered tramadol at 20 mg/h for 6 h and thereafter 10 mg/h, for a total

of 450 mg/24 h, or an equivalent volume of saline (Epidural Morphine and PCA Morphine groups). At all times, all participants were blinded as to the nature of the drugs administered.

After surgery all patients were transferred to the cardiothoracic intensive care unit. Patient response was assessed with sedation and pain scores, PCA requirements, and plasma catecholamine (epinephrine and norepinephrine) concentrations. Scoring was both objective, using observer scores, and subjective, using a 10-cm visual analog scale (VAS). Respiratory measurements included respiratory rate, vital capacity (which was compared with the preoperative measurement), arterial oxygen saturation, and blood gas analysis. Cardiovascular data were collected every 2 h and between-group comparisons made, but these were not the principal efficacy response criteria.

Epidural conduction blockade was monitored by cold sensation every hour postoperatively until it had regressed to a point at which fewer than two dermatomes were blocked, at which point it was said that the sensory block had receded. Pain intensity was assessed by a blinded observer using a four-point pain scale (0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain) at hourly intervals for 4 h and thereafter at 4-h intervals for 20 h. The patient was also asked to assess his or her own pain by using a VAS along a 10-cm line marked from "no pain" to "most severe pain imaginable." Objective and subjective pain scores were assessed at rest and on coughing. The level of sedation was recorded at the same time intervals by using a five-point score (0 = natural sleep; 1 = awake and alert; 2 = restless or agitated; 3 = drowsy, 4 = unrousable or unconscious). All patients were maintained on a 40% oxygen face mask overnight. Vital capacity estimations were performed at 4-h intervals.

All patients were supplied with a PCA machine set to deliver IV morphine boluses in 1.5-mg increments with a lockout period of 8 min. Patients assessed as being in pain, on the basis of either an observer score of Grade 3 or a VAS score >6, were offered rescue medication of morphine 0.04 mg/kg IV, repeated as necessary until adequate analgesia was obtained. The amount of rescue morphine required was included in the total morphine (PCA plus rescue) required up to that time point. Arterial oxygen saturation was continuously monitored by a pulse oximeter. Blood gases were measured at 2-h intervals, and the period of the study was for 24 h postoperatively. Arterial blood was sampled at 1, 6, and 18 h postoperatively for catecholamine concentrations. Nausea and vomiting were treated with metoclopramide 10 mg IV, followed by droperidol 0.5 mg if the problem persisted. Pruritus was treated with 12.5 mg of promethazine IV. All patients had urinary catheters for the first 24 h.

Between-group comparisons for scoring data were conducted with nonparametric statistics (Kruskal-Wallis analysis of variance [ANOVA]). ANOVA for repeated measures was used to identify differences between groups in which the data were parametric and normally distributed. Within-group changes were analyzed with ANOVA for repeated measures. Individual/group differences were identified *post hoc* by using 95% confidence intervals. Distributive data were tested with the χ^2 analysis. Power analysis was performed on the basis of data from our previous study (8). With an α level of 0.05 and a β level of 0.1, power analysis indicated that 30 observations would be needed to detect clinically relevant differences in morphine consumption, a difference of 3% in oxygen saturation with an assumed *sd* of 5, and a pain score difference of 1 U; 27 comparisons would be necessary to detect a P_{aO_2} difference of 30 mm Hg between groups with an assumed *sd* of 7. There were insufficient data available on which to base a reasonable estimate of *sd* of vital capacity, because this is highly variable; however, by using inpatient variation (pre- versus postsurgery) it was attempted to minimize the variability in these data. A study group size of 90 (30 subjects per group) was therefore deemed to be sufficient to answer the principal objectives of the study.

Results

Ninety patients were entered, of whom one patient from the Tramadol group was withdrawn after returning to surgery for hemorrhage; there were no other patient withdrawals. Thus there were 29 patients in the Tramadol group and 30 patients in each of the Epidural Morphine and PCA Morphine groups. Results are given as means (*sd*).

The groups were comparable in terms of demographic data and preoperative pulmonary function. The procedures performed within each group were similar (Table 1).

Cold sensation had returned in all but two patients by the end of the first postoperative hour and in all patients by 2 h postoperatively. Pain scores were highest at 1 h, with subjective pain scores at rest more than 6 in the PCA Morphine group only. The median VAS pain score was in an acceptable range (2-4) by the first 2 h postoperatively in the Tramadol group only; pain scores at rest were not significantly different from those in the Epidural Morphine group for the first 12 h. Pain scores at rest were significantly lower in the Tramadol group than in the PCA Morphine group at 2, 3, 4, and 8 h postoperatively. Pain scores at rest were significantly lower in the Epidural Morphine group than in the PCA Morphine group at 3 and 4 h. The subsequent disappearance of these differences was not

due to worsening pain control by tramadol or epidural morphine, but to diminished pain scores in the PCA Morphine group (Fig. 1).

Pain on coughing was less well controlled (Fig. 2). There were no statistically significant differences between the Tramadol and Epidural Morphine groups. Statistically significant differences were found between the Tramadol and PCA Morphine groups at 2, 3, and 4 h and between the Epidural Morphine and PCA Morphine groups at 4 h.

Hourly PCA morphine consumption in the three groups is shown in Figure 3. There were no significant differences in morphine consumption between the Tramadol and Epidural Morphine groups. There were significant differences between the Tramadol and PCA Morphine groups at 2, 5, 6, 7, and 8 h and between the Epidural Morphine and PCA Morphine groups at 4, 5, 6, 7, and 10 h. At 20 h, Tramadol subjects had a significantly larger PCA morphine consumption than either of the other two groups. Total PCA morphine consumption over the 24-h period was significantly more in the PCA Morphine group (48.8 [21.9] mg) than in the Tramadol (34.2 [20.6] mg) and Epidural Morphine groups (35.6 [15.4] mg). The need for rescue medication in the three groups was different, with significantly more Epidural Morphine patients (nine) requiring rescue medication than in the Tramadol group (two). All rescue medication in the Epidural Morphine group was given in the first 6 h postoperatively. There was no statistically significant difference between the Tramadol and PCA Morphine groups or between the Epidural Morphine and PCA Morphine groups in the need for rescue medication. There were also few adverse effects requiring treatment, with one patient in the Tramadol group with pruritus and two in the Epidural Morphine group with nausea. Sedation scores were similar for all three groups for the first 3 h, after which they were lowest in the Epidural Morphine group, but this difference did not achieve statistical significance. From 12 h onward, they were again similar for the Epidural Morphine and the Tramadol groups.

Vital capacities in the Tramadol group were significantly closer to preoperative baseline values at the 20-h point than those in the PCA Morphine group. The differences between the Epidural Morphine and PCA Morphine groups did not reach statistical significance (Fig. 4).

There were some differences in respiratory rate that achieved statistical significance; these were, however, not at the same time points at which significant differences were noted in the blood gases (Fig. 5). Arterial oxygen tension was significantly higher in the Tramadol group than in the Epidural Morphine group at 2 and 6 h. Arterial carbon dioxide tension was significantly higher in the Epidural Morphine group

Table 1. Patient Data

Variable	Age (yr)	Wt (kg)	Ht (cm)	FEV ₁ (L)	FVC (L)	FEV ₁ /FVC ratio	Pneumonectomy	Lobectomy	Other
Tramadol									
Mean	46	59	165	1.86	2.81	69	11	16	3
sd	13	11	9	0.79	1.19	17			
Epidural morphine									
Mean	45	61	163	2.13	2.90	72	7	22	1
sd	16	13	8	0.78	0.82	13			
PCA morphine									
Mean	44	60	167	1.88	2.80	66	12	16	2
sd	13	11	10	0.73	0.81	13			

There were no significant differences.

Wt = weight; Ht = height; FEV₁ = forced expiratory volume at 1 s; FVC = forced vital capacity; PCA = patient-controlled analgesia.

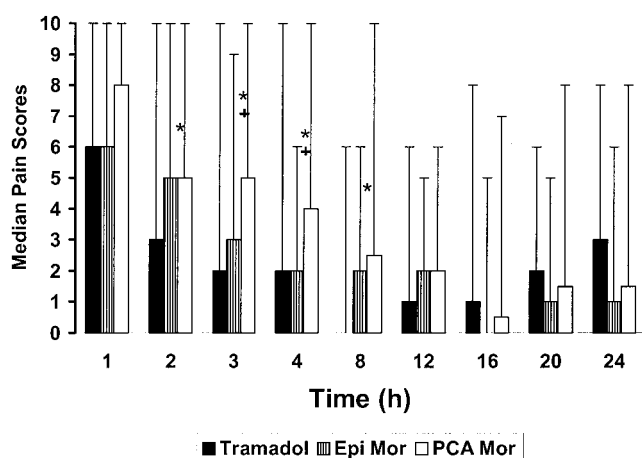


Figure 1. Median pain scores at rest in the three groups, with error bars showing upper ranges. All groups included zero as the lower range at all data points. Epi Mor = Epidural Morphine group; PCA Mor = Control group. **P* < 0.05, tramadol versus patient-controlled analgesia (PCA) morphine; +*P* < 0.05, epidural morphine versus PCA morphine.

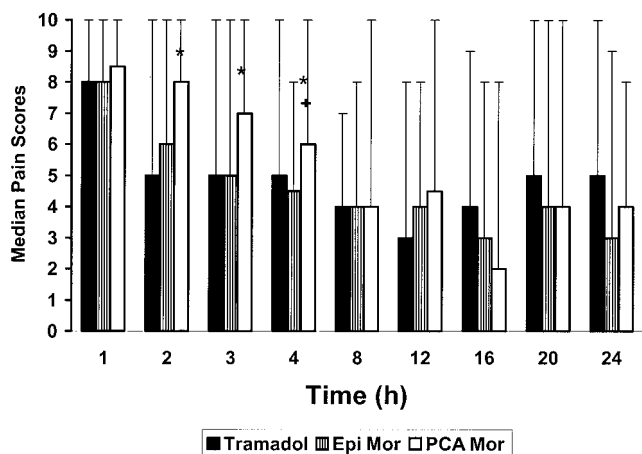


Figure 2. Median pain scores on coughing in the three groups, with error bars showing upper ranges. All groups included zero as the lower range at all data points. Epi Mor = Epidural Morphine group; PCA Mor = Control group. **P* < 0.05, tramadol versus patient-controlled analgesia (PCA) morphine; +*P* < 0.05, epidural morphine versus PCA morphine.

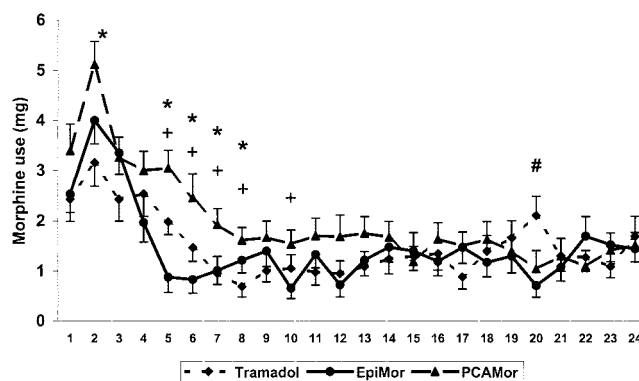


Figure 3. Mean (SEM) hourly patient-controlled analgesia (PCA) morphine consumption in the three groups. Epi Mor = Epidural Morphine group; PCA Mor = Control group. **P* < 0.05, tramadol versus PCA morphine; +*P* < 0.05, epidural morphine versus PCA morphine; #*P* < 0.05, tramadol versus Epidural Morphine and Control groups.

than the PCA Morphine group at 2 h postoperatively. Upon review of hemodynamic measures and other indicators of the stress response, there were no significant differences in cardiovascular variables or in catecholamine concentrations.

Discussion

A review on postthoracotomy pain relief (9) cites more than 100 publications between 1964 and 1994. It is difficult for clinicians to integrate this literature into functionally useful information. Prospective, concurrently controlled, double-blinded trials, although not necessarily representative of real-life postoperative pain management, may offer the only rational basis for adequate evaluation and comparison of various methods for managing pain. Thoracic epidural analgesia may result in earlier recovery of respiratory function after thoracotomy, because of an improvement in the mechanical function of the diaphragm related to decreased chest wall splinting (10).

The procedure is not without risk. One review reported 51 confirmed spinal hematomas associated

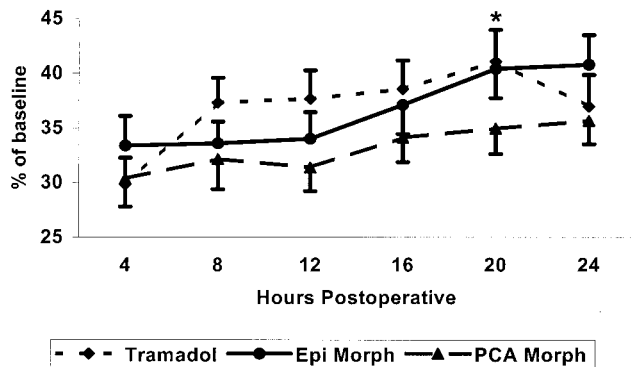


Figure 4. Vital capacity difference from preoperative baseline (mean, SEM) in the three groups. Epi Morph = Epidural Morphine group; PCA Morph = Control group. * $P < 0.05$, tramadol versus patient-controlled analgesia (PCA) morphine.

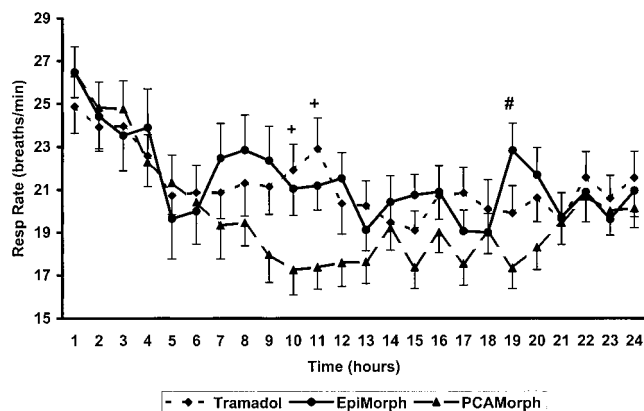


Figure 5. Respiratory rate (mean, SEM) in the three groups. Epi Morph = Epidural Morphine group; PCA Morph = Control group. + $P < 0.05$, tramadol and epidural morphine versus patient-controlled analgesia (PCA) morphine; # $P < 0.05$, epidural morphine versus PCA morphine.

with epidural anesthesia, suggesting an incidence of 1 in 190,000 (11), although most of these were in patients who may have had impaired coagulation. In addition, the use of even small concentrations of local anesthetics may be associated with hypotension. Considering these arguments and given that there are no randomized, controlled trials demonstrating that thoracic epidural analgesia is associated with a better outcome after thoracotomy than other treatment modalities, it is possible that this method should be reserved for selected patients (12).

The analgesic action of tramadol is based on a multimodal mechanism of action, which may also have advantages over conventional opioids in terms of side effects (13). In a study of 40 patients undergoing abdominal hysterectomy, it was concluded that tramadol administered intraoperatively was as effective as morphine for postoperative analgesia (14).

A previous study at our institution (8) showed that a single bolus of IV tramadol seemed as effective for

postthoracotomy pain relief as epidural morphine and offered marginal benefits in terms of oxygenation and respiratory depression. However, we concluded that these benefits were short lived and debated their value in the overall management of the postoperative patient. This study, conducted under similar circumstances, compared the analgesic efficacy of an IV bolus dose followed by infusion of tramadol for 24 hours to that of continuous thoracic epidural morphine, by using IV PCA morphine as control in an attempt to extend the benefits in high-risk patients requiring major thoracic surgery. This study matched the criteria set out in an extensive review of techniques for postthoracotomy pain relief (9).

The high pain scores in the first hour in this study are in keeping with the demonstrated time to peak analgesic effect of one hour for tramadol (14), which is similar to that of epidural morphine administered at the dermatomal level of nociceptive input. The pain scores for the Tramadol group were at least as good as those for the Epidural Morphine group until 16 hours postoperatively, and the amount of rescue medication in the Tramadol group was significantly less than that required in the Epidural Morphine group. Patients in the IV Tramadol and Epidural Morphine groups had significantly better pain scores both at rest and with movement than the PCA Morphine group, at specific time points during the first eight hours. It should be noted that if an initial loading dose of morphine had been administered in the patients receiving PCA morphine alone, this group might have been equivalent to the Tramadol group, but the persistent differences in pain scores and morphine consumption tend to argue against this. Furthermore, the administration of an initial dose of morphine to the patients receiving PCA morphine only would have meant that this would not have been a true control group, because an additional variable would have been introduced.

After the initial IV bolus and the infusion at 20 mg/h for the first six hours, the predicted serum tramadol concentration should have been in the order of 600 ng/mL. Pharmacokinetic predictions supplied by the manufacturer suggest that the serum tramadol concentration should have decreased to 350 ng/mL after reducing the infusion rate to 10 mg/h for the subsequent 18 hours (courtesy Grunenthal GMBH, Aachen, Germany). Therefore, the increase in pain scores in this group after 16 hours may be related to the reduction in the dose of tramadol at six hours and may support the maintenance of the larger dosage for a longer period than the initial six hours. Current dosage regimens, developed since the inception of this study, have been modified to account for this factor. The delay in increase in pain scores after the dose reduction at six hours may be explained by the fact that tramadol has a prolonged analgesic effect of five to six hours (15).

It was noteworthy that the vital capacity measurements for those patients receiving tramadol tended to be higher but were not significantly different from those in the Epidural Morphine group until 20 hours postoperatively, whereafter there was a decrease that did not reach statistical significance. The higher vital capacities recorded in the Tramadol group compared with the PCA Morphine group were probably due to improved pain relief.

Arterial oxygenation was significantly better in the Tramadol group than in the Epidural Morphine group over the first six hours; there were no hypoxic episodes, because all patients received supplemental oxygen. The $Paco_2$ was consistently lower (although not significantly so) in the Tramadol group when compared with epidural morphine, and no patient demonstrated dangerous respiratory depression. Overall, an infusion of tramadol did not prolong the early postoperative respiratory benefits conferred by this drug, as demonstrated in our previous study, which used a single bolus dose.

The most common side effects associated with tramadol are nausea, dizziness, drowsiness, tiredness, sweating, vomiting, and dry mouth, with an overall incidence of 1% to 6% (16). In this study, one patient in the Tramadol group required treatment for pruritus, and none experienced nausea or vomiting, compared with two in the Epidural Morphine group.

Morphine delays gastric emptying in healthy volunteers, whereas there was no demonstrable difference between placebo and tramadol (17). Tramadol may therefore have an important place as part of a multimodal recovery intervention approach, because it is a drug that does not impair the many peripheral benefits of good pain relief, which include improved perioperative nutrition and reduced postoperative ileus (13).

In conclusion, on the basis of pain scores, analgesic requirements, and respiratory variables, and considering the risks of thoracic epidural analgesia, this study suggests that an intraoperative bolus of tramadol, followed by a postoperative infusion, shows a good risk/benefit ratio as an analgesic regimen for

postthoracotomy pain relief and is at least as effective as thoracic epidural morphine.

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