Acta Anaesthesiol Scand 1992: 36: 698–701

A two-dose epidural morphine regimen for cesarean section patients: therapeutic efficacy

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A single dose of epidural morphine (EM) usually produces 24 h of post-cesarean section (CS) analgesia and patients require supplemental analgesics beyond this period. This study assesses if a second dose of EM administered 24 h after the first one offers superior therapeutic efficacy compared to conventional analgesics. Patients (n = 100) were randomized to receive one or two doses of epidural morphine. In all patients, EM 5 mg was administered after delivery. After 24 h patients received epidurally either normal saline (n = 50, Group 1) or morphine 5 mg (n = 50, Group 2). An independent observer used a visual analogue scale to assess nausea, itching, and analgesia 24 h after each injection. Results were expressed as mean ± 1 s.e.mean and analyzed using nonparametric methods. The second dose of EM produced a significantly lower incidence and severity of nausea and itching than did the first dose ($P < 0.01$) in Group 2 with no difference in analgesia. The second day postoperative pain score in Group 1 was significantly greater than the first day score in the same group, and significantly greater than the severity score in Group 2. Only 36% of patients receiving two doses of EM required supplemental analgesics beyond 48 h compared to 76% of those receiving one dose ($P < 0.01$). No serious complications were noted. In summary, the use of a second dose of EM for post-CS analgesia produces better analgesia and reduces the need for oral analgesics. The second dose produced fewer side-effects, probably due to acute tolerance to morphine.

Received 24 June 1991, accepted in a revised version 24 February 1992

Key words: Cesarean section; epidural morphine; post-opertive analgesia; side-effects.

Epidural morphine is popular for post-operative analgesia in cesarean section patients (1, 2). A single 5-mg dose of epidural morphine provides analgesia lasting 20–24 h (2). However, up to 90% of patients in our institution require multiple parenteral or oral narcotic analgesics for pain relief after the first 24 h. Therefore, we examined the therapeutic efficacy and side effects of a second dose of 5 mg epidural morphine administered 24 h after the first dose in patients who underwent cesarean section.

PATIENTS AND METHODS

The protocol was approved by the Institutional Review Board and written informed consent was obtained. A total of 104 consecutive American Society of Anesthesiology Class I patients scheduled for elective cesarean section were studied.

Patients were alternately assigned to receive one dose of epidural morphine 5 mg (Group 1, n = 52), or two doses (Group 2, n = 52). Patients received 1500 ml lactated Ringer's solution intravenously before anesthesia.

An epidural catheter was inserted via the L2–L3 or L3–L4 interspace and secured in place with a transparent dressing such that the 10-cm mark on the catheter remained at the level of the skin. Epidural anesthesia to a T4 sensory level was induced by injecting 3-ml increments of bupivacaine 0.5%. Preservative-free morphine 5 mg in 10 ml normal saline was administered 1 h after the last local anesthetic dose.

Following surgery, patients were sent to the postpartum ward. Twenty-four hours later,the catheter position was verified by noting that the 10-cm mark still remained at the skin level, and that the aspiration of the catheter failed to yield blood or CSF.

The patients in Group 1 received 10 ml of preservative-free normal saline epidurally and those in Group 2 received 5 mg of morphine. Patients did not know whether they received morphine or saline for the second dose.

One patient in each group was omitted from the study due to inadequate epidural anesthesia. One patient in Group 1 refused the second dose of epidural medication, and one patient in Group 2 was excluded because blood was aspirated from the epidural catheter. The data from the remaining 100 patients (n = 50 in each group) were subjected to statistical analysis.

An independent observer who was blinded to the nature of the study and to the type of epidural solution administered asked patients to rate nausea/vomiting, itching, and post-operative pain on the first and second post-operative days on a 10-cm-long visual analog scale, with the 0-cm mark placed at the "no symptom" end and 10-cm mark at the "most severe symptom" end (3). Patients were asked to make a mark on the scale at a point which they thought corresponded to the severity of their symptom. The distance between the "no symptom" end (0 cm) and the mark was taken as the severity score in cm. A severity score greater than 0 cm for any symptom was considered a "yes" response.

Supplemental analgesic tablets (acetaminophen 325 mg with oxycodone HCl 5 mg) were given to patients who complained of post-operative pain. Additional tablets were given if required. Patients requesting treatment for itching were given diphenhydramine 50 mg IM and those requesting treatment for nausea prochlorperazine 10 mg IM. The time and dosages of supplemental narcotic administra-

tions were recorded. Nurses recorded the hourly respiratory rate for 48 h.

Results were expressed as mean ± s.e.mean. The frequencies of side effects produced by the two injections were compared with each other using Chi-square analysis within each group. The severity scores were treated as ordinal data and analyzed using Friedman rank-sum analysis of variance within each group (4). The frequencies of side-effects following dose 1 or 2 were compared between the two groups using Chi-square analysis and the severity scores using the Mann-Whitney rank-sum test. A P-value of <0.05 was considered significant.

RESULTS

The patients in Group 1 were 31 ± 0.6 years old, 161 ± 1.2 cm tall, and weighed 71 ± 1.8 kg. The corresponding figures for Group 2 were 32 ± 0.6 years, 163 ± 1.3 cm and 72.2 ± 2.0 kg. The patients in Groups 1 and 2, respectively, required 18 ± 0.4 ml and 19 ± 0.6 ml of local anesthetic for epidural anesthesia (p, NS).

In Group 1, fewer patients complained of nausea and itching following saline injection than following morphine injection (Table 1). However, more patients in Group 1 complained of post-operative pain despite oral analgesics on the second day (Table 1).

In Group 2, the incidence of nausea and itching was significantly less with the second dose of morphine compared to that with the first dose (Table 1). The incidence of nausea was not significantly different between the two groups following the first or the second injection. However, the incidence of itching was significantly greater, and that of pain significantly smaller with the second injection in Group 2 than in Group 1 (Table 1).

In Group 1, the severity scores for nausea and itching were significantly lower following saline injection compared to the corresponding score obtained following morphine injection, while the severity score of pain was significantly greater (Fig. 1).

In Group 2, nausea and itching scores were significantly less with the second injection of morphine compared to the first one while pain relief did not differ between the injections (Fig. 2).

Table 1
Frequency of side effects and post-operative pain.

	Nausea		Itching		Pain	
	Yes	No	Yes	No	Yes	No
Group 1						
Dose 1 – morphine	21	29	44	6	20	30
Dose 2 – saline	2	48*	3	47*	35	15*
Group 2						
Dose 1 – morphine	19	31	42	8	19	31
Dose 2 – morphine	3	47*	13	37*†	21	29†

* In comparison to Dose 1 within same group; $P<0.01$.
† In comparison to the corresponding dose in Group 1; $P<0.01$.

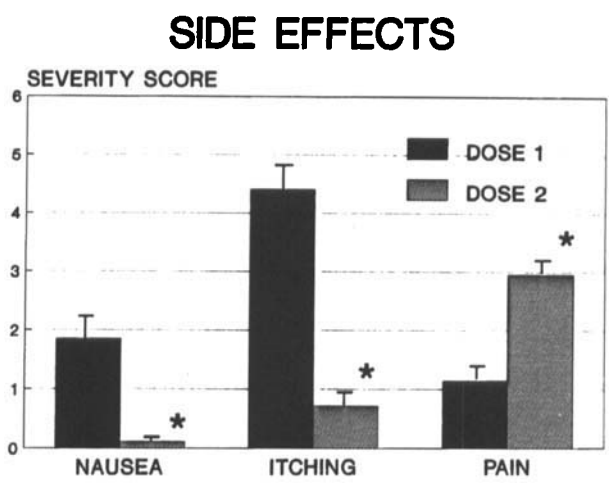

Fig. 1. Severity scores for nausea, itching and post-operative pain with the first and second injection in Group 1. The first injection (dose 1) was morphine and the second (dose 2) normal saline. Data are mean ± s.e.mean. *Significantly different from dose 1 ($P<0.01$).

Fig. 3 compares nausea, pain and itching scores obtained after the second injection in the two groups. Patients who received epidural morphine had significantly better pain relief on the second day than those given epidural saline injection and oral analgesics. However, there were no significant differences in severity scores for nausea and itching.

The number of patients requiring treatment for itching and nausea, respectively, were 12 and 5 following the first dose of morphine in Group 1. The corresponding figures in Group 2 were 14 and 6. None from either group required treatment for nausea or itching following the second injection ($P<0.01$ for comparison with the first dose for both groups).

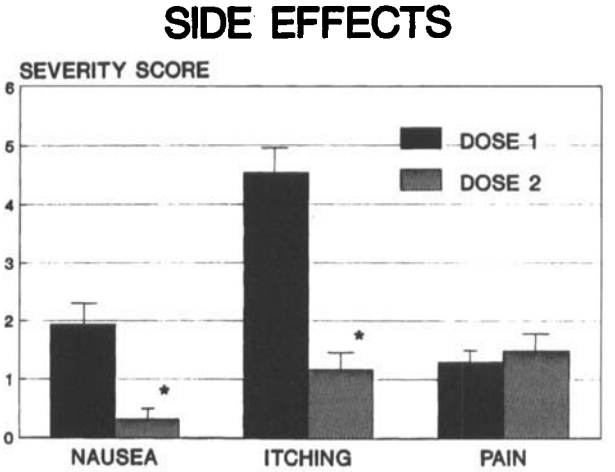

Fig. 2. Severity scores for nausea, itching and post-operative pain with the first and second doses of epidural morphine in Group 2. Data are mean ± s.e.mean. *Significantly different from dose 1 ($P<0.01$).

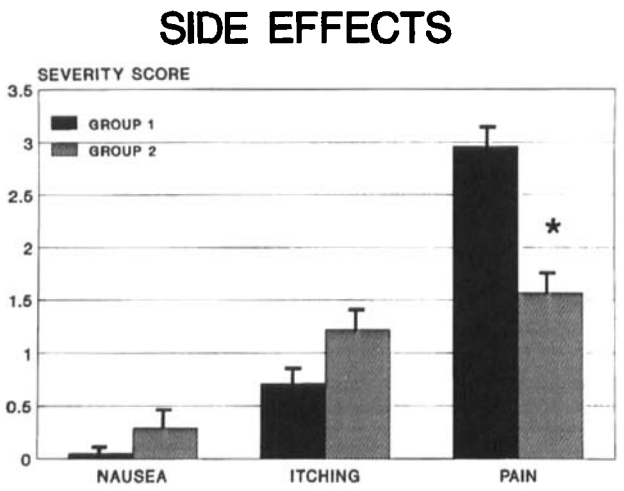

Fig. 3. Severity scores for nausea, itching, and post-operative pain for Group 1 and Group 2 after injection 2. Group 1 received epidural saline and oral analgesics and Group 2 received epidural morphine 5 mg. Data are mean ± s.e.mean. *Significantly different from Group 1 ($P<0.01$).

No patient in Group 1 required additional analgesics for the first 24 h. However, they required oral analgesics on day 2 (Table 2). In Group 2, patients did not require supplemental analgesics during the first 48 h. Patients in Group 1 required approximately twice the number of analgesic tablets after 48 h until discharge compared to Group 2. The number of patients not requiring any supplemental medication until discharge was significantly greater in Group 2 (Table 2). No patient from either group had a respiratory rate of <10/min and none required treatment for respiratory depression.

DISCUSSION

Our data show that the second epidural morphine dose is superior to oral analgesics in terms of overall therapeutic efficacy for post-cesarean section analgesia. With this regimen, the need for supplemental narcotics is minimized or eliminated. The decreased analgesic requirement beyond 48 h in Group 2 suggests the residual effect of morphine at the spinal opioid receptors. The second dose of epidural morphine produces fewer side-effects than the first dose. Indeed, the mean severity scores for nausea and itching with the second dose of morphine were comparable to those produced by saline injection.

Table 2
Supplemental analgesic requirement.

	Group 1	Group 2
Number of 5 mg oxycodone tablets:		
Day 1	0	0
Day 2	3.3 ± 0.8	0†
Day 3 and beyond	3.0 ± 0.7	1.4 ± 0.4†
Number of patients:		
No supplemental analgesics	12	32*

† $P<0.01$ compared to Group 1.

Administered orally or parenterally, morphine can produce itching (5). The decrease in both the incidence and severity of itching or nausea with the second dose in Group 2 in our study is probably related to the development of acute tolerance to morphine. Acute tolerance has been demonstrated in rabbits and rats within hours of exposure to that drug (6, 7). Data from humans are conflicting. One study showed that patients with cancer pain had an increasing epidural morphine requirement with time (8), while two others showed no evidence of such tolerance to the analgesic effects of epidural morphine (9, 10). A third study reported that previous exposure to parenteral morphine significantly decreased the likelihood of respiratory depression caused by epidural morphine in cancer patients without altering the degree of analgesia (11). In our study the analgesia with the second dose of epidural morphine was comparable to the first. The reason for the differential development of tolerance to side-effects is not clear but may be related to different mechanisms for different types of tolerance. In rats, acute tolerance to morphine analgesia (μ_1 receptor) occurred, while tolerance to respiratory depression (μ_2 receptor) did not (12). In fact, animal studies have shown that the mechanisms for acute tolerance are different from those for chronic tolerance (13, 14). Alternatively, the intensity of post-operative pain may have decreased on the second day in our patients, thus masking the development of tolerance to analgesia produced by the second dose of epidural morphine.

Early and delayed respiratory depression due to epidural opioids is known to occur in 0.2–0.4% of the general population (15, 16). Kafer et al. reported biphasic depression of ventilatory response to carbon-dioxide, with an early phase followed by a delayed one (17). In general, the predisposing factors for respiratory depression include old age, thoracic surgery, impaired respiratory function, and administration of supplemental narcotics (15, 18). However, experience accumulated with this technique in the past decade has vastly reduced the risk of respiratory depression (16, 19). Ready et al. who administered epidural narcotics to non-obstetrical patients on the surgical ward reported a 0.2% incidence of respiratory depression (16). Based on a nation-wide survey, Rawal et al. found a 0.09% incidence of serious respiratory depression (19).

Severe respiratory depression requiring naloxone

due to epidural morphine is rare in obstetrical patients because they are young and healthy. In over 5000 administrations, we have not seen a single case of severe respiratory depression requiring naloxone in obstetrical patients. In a retrospective study of 4880 obstetrical patients, Fuller et al. have reported bradypnea (6–9/min) in 12 patients (1). No patient in their report required endotracheal intubation and three required naloxone. However, a 0.9% incidence of respiratory depression was reported in hospitalized patients receiving oral or parenteral morphine (20). To ensure close observation of our patients, we had their respiratory rate monitored by the nurses hourly for 48 h.

In summary, our results show that a second dose of 5 mg epidural morphine administered 24 h after the first dose produces superior analgesia, reduces the requirement for oral analgesics during hospitalization, and produces fewer side-effects than the first dose does. We have used this two-dose regimen in over 1800 patients in the last 2 years without complications, and with staff and patient acceptance.

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