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Epidural Morphine for Postoperative Pain Relief: A Dose-response Curve

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Different doses of epidural morphine were studied in order to determine their effectiveness in providing postoperative pain relief after surgery of the lower extremities and their relationship to the incidence of untoward reactions. The study was carried out in a double-blind fashion using five dosages of epidural morphine (0.5, 1.0, 2.0, 4.0, and 8.0 mg) and included 60 patients. The higher doses of morphine (2.0, 4.0, and 8.0 mg) were equally effective and more effective than the lower doses (0.5 and 1.0 mg) in providing postoperative analgesia. Nausea and vomiting were encountered more frequently with the highest dose (8.0 mg) and this finding was statistically significant ($P < 0.03$). No statistically significant difference was found between the doses studied with regard to itching, urinary retention, and respiratory depression; the latter was evaluated in a subgroup of 20 patients. These data suggest that effective postoperative pain relief after surgery of the lower extremities can be achieved with relatively low doses of morphine sulfate and with minimal side effects. For the type of surgery studied, 2 mg morphine sulfate appeared to be the optimum dose. (Key words: Analgesics: morphine. Anesthetic technique: epidural. Pain: postoperative.)

CLINICAL STUDIES have proved the effectiveness of epidural or intrathecal morphine.[1–13] Nevertheless, some untoward effects have already been described following its administration.[13–18]

The following study was undertaken to determine the most effective dose for pain relief with the fewest side effects.

Materials and Methods

This study included 60 patients of ASA class I or II undergoing orthopedic surgery of the lower limb under epidural anesthesia. The Ethic Committee (Faculté de Médecine) approved the protocol but refused the inclusion of a placebo group. Informed consent was obtained from each patient. The studied population was distributed into five groups of 12 patients each according to a table of random numbers. These groups were also subdivided into randomized blocks according to the identity of the two surgeons performing the operations and according to the site of operation (surgery on the knee and surgery elsewhere on the lower extremity).

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One hour preoperatively each patient was given 10 mg diazepam per os as premedication. Continuous epidural anesthesia was performed at the L3–L4 level using lidocaine hydrocarbonate with epinephrine (1/200,000) injected through a catheter introduced 2 cm cephalad into the epidural space. No narcotic or any other drug, or volatile agent was administered during the operation and the anesthesia was maintained exclusively through the epidural catheter using the local anesthetic.

When the patients began to experience pain in the recovery room, preservative-free morphine sulfate diluted to 10 ml normal saline was administered through the epidural catheter in a double-blind fashion. Each patient of the five groups received one of the following doses of morphine: Group I, 0.5 mg; Group II, 1.0 mg; Group III, 2.0 mg; Group IV, 4.0 mg; Group V 8.0 mg.

Five variables were assessed in a double-blind fashion for each one of the patients in the following order: (1) The residual sensory level of anesthesia was determined by one of the authors (R.M. or J.S.) with a Wartenberg pinwheel, just before epidural morphine administration and then one hour later. (2) The patients reported their degree of pain before epidural morphine injection (to one of those two authors) using the following scale: 0 = no pain; 1 = slight pain; 2 = moderate pain; and 3 = severe pain. (3) They also assessed their pain relief and reported it to one of the two authors every 15 min during the first hour after epidural injection by means of the following scale: 0 = no relief; 1 = partial relief; 2 = marked relief; and 3 = total relief. After the first hour, 5.0 mg intramuscular morphine sulfate was prescribed PRN every 4 h for the next 24 h, during which time the respiratory rate was recorded regularly. (4) Twenty-four hours later each patient was interviewed and reported the postoperative analgesia according to the following scale: 3 = excellent; 2 = very good; 1 = good; and 0 = unsatisfactory; the presence or absence of side effects such as nausea, vomiting, itching, or urinary retention was also determined at this time. (5) The total dose of im morphine received during the first postoperative day as well as the time interval between the epidural morphine injection and the first im administration were recorded.

Twenty of the 60 patients (four from each of the five groups) were sampled at random and underwent the following respiratory tests: $P_{E_{CO_2}}$ (Godart's capnograph); mouth occlusion pressures ($P_{0.1}$) at a normal $P_{E_{CO_2}}$ and at a $P_{E_{CO_2}}$ of 50 mmHg.[16] The mouth oc-

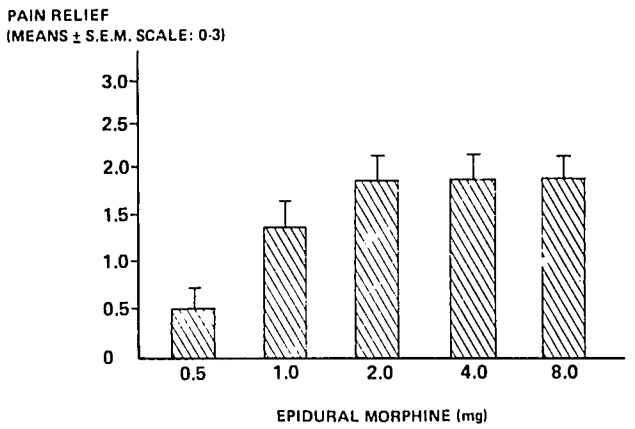

FIG. 1. Pain relief 45 min following the epidural injection of five different doses of morphine. 2.0 mg *vs.* 0.5 mg: $P < 0.002$; 2.0 mg *vs.* 8.0 mg: P = NS (Mann-Whitney U tests).

(Standard errors of the mean were calculated only for descriptive purposes. The analysis and the conclusion are based on nonparametic ranking techniques.)

clusion pressure measurements were performed using a semi-closed circuit system and a Trantec® pressure transducer. These tests were performed before the epidural morphine administration, then one hour, and 6–8 h later.

Analysis of variance was performed on weight, height and age of the patients as well as the $P_{E_{CO_2}}$, and mouth occlusion pressure values. Chi-square tests were done for the following variables: sex, cutaneous level of anesthesia pre- and postmorphine injection, the occurrence of nausea, urinary catheterization, and itching. Because of the small number of patients, a Fisher exact probability test evaluated the occurrence of nausea among all groups. Nonparametric one-way analyses of variance (Kruskall-Wallis) were used in pain relief score at 15, 30, 45, and 60 min following epidural morphine injection, and on the time interval between the first hour after epidural morphine injection and the first injection of im morphine. These same techniques were also utilized for the total 24-h dose of im morphine and the quality of the first postoperative day analgesia. Mann-Whitney U test were performed afterwards for two by two comparisons on: the time interval between the hour after epidural morphine injection and the first injection of im morphine, the pain relief at 45 and 60 min, and on the first postoperative day analgesia quality as well as on the total im morphine. Finally, with correlation analysis, the relationship between weight and pain relief as well as height and pain relief was measured on Group III (2.0 mg) at 60 min following epidural morphine injection, and for all the groups on the height and pain relief relationship at 45 min.

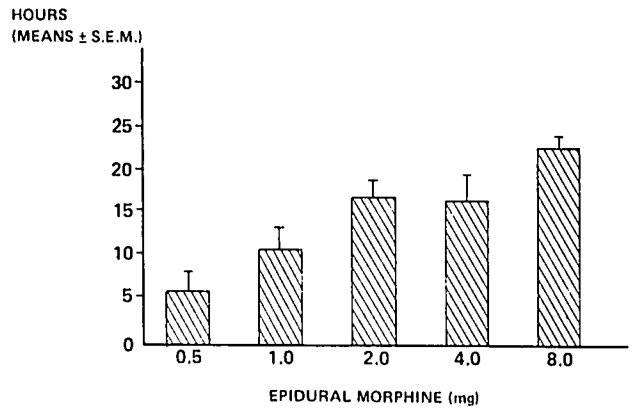

FIG. 2. Length of action of epidural morphine estimated by the time between the epidural injection and the first intramuscular injection. 2.0 mg *vs.* 0.5 mg: $P < 0.02$; 2.0 mg *vs.* 8.0 mg: P = NS (Mann-Whitney U Tests).

Results

No significant difference was found between the five groups concerning age, height, weight, and sex. The mean age of the 60 patients was 41.3 ± 16.4 (SD) years, their average height was 165.9 ± 10.9 (SD) cm, and their average weight was 69.3 ± 14.9 (SD) kg. Thirty-three were male and twenty-seven, female. In the same way, no variations were caused by the two surgeons nor the two types of surgery. According to these variables the five groups of patients were comparable.

A majority of patients (39 of the 60) had a residual cutaneous level of anesthesia at the onset of postoperative pain when they received epidural morphine. These 39 patients were equally distributed among the five groups. One hour after epidural morphine injection, only six of 60 patients had a cutaneous sensory level and the six patients were once more evenly distributed among the five groups. The pre-injection pain was evaluated by the patients as moderate to severe and there was no difference among the groups. There was no obvious relief after 15 and 30 min among any of the five groups. At 45 and 60 min, Kruskall-Wallis test demonstrated a significant difference among the five groups in relation to pain relief ($P < 0.01$ at 45 min and $P < 0.001$ at 60 min). Mann-Whitney U tests indicated a significant pain relief difference among the 2-mg morphine group compared to the morphine 0.5-mg group at 45 min ($P < 0.002$) (fig. 1). However, with this same test, we did not find any significant difference concerning pain relief at 45 min between the 2.0-mg group and the 8.0-mg group (fig. 1). At 60 min the tests led to the same conclusions: there was a great difference in pain relief between the 0.5-mg group (I) and the 2.0-mg group (III) ($P < 0.002$), while there was no significant difference between the 2.0-mg group and the 8.0-mg group (IV).

There was a significant difference among the five groups for duration of analgesia ($P < 0.001$), the quality

of the first postoperative day analgesia ($P < 0.003$), and the total dose of im morphine ($P < 0.001$). When the Mann-Whitney U test was used to study those three variables, once again a significant difference was shown to the advantage of the 2.0-mg group over the 0.5-mg group: duration of analgesia ($P < 0.02$, fig. 2); analgesia quality ($P < 0.02$, fig. 3), and im morphine dose ($P < 0.002$, fig. 4). However, again there was no significant difference between the 2.0-mg group and the 8.0-mg group.

We found no statistical difference among the five groups according to PE_{CO_2} and mouth occlusion pressures ($P_{0.1}$) at pre-epidural morphine injection time nor at 1, and then 6 to 8 h later. However, one young patient (ASA I) who received 8.0 mg epidural morphine (Group V) and not included in the subsample studied with mouth occlusion pressure, developed respiratory depression 10 h after injection with a Pa_{CO_2} of 49 mmHg, and a respiratory rate of 8/min, requiring the administration of naloxone. A single dose of 0.2 mg, iv, resolved the problem. Side effects such as nausea, vomiting, itching, and urinary retention relieved by urinary catheterization appeared among the five groups of patients. There was no significant difference in the occurrence of itching or urinary retention among all groups but the Group V patients (8.0 mg) suffered a significantly higher incidence of nausea and vomiting than the others (table 1).

Correlation analysis on Group III (2.0 mg) between height and pain relief, as well as weight and pain relief at 60 min after epidural morphine injection did not demonstrate any significant relationship. The same conclusions were obtained for the height-pain relief relationship at 45 min after epidural morphine injection among all the 60 patients.

Discussion

This study performed on orthopedic surgical patients operated under epidural anesthesia demonstrated that a preservative-free 2.0-mg dose of morphine sulfate diluted to 10 ml with normal saline and administered postoperatively into the epidural space produced the desired effect of long lasting analgesia.

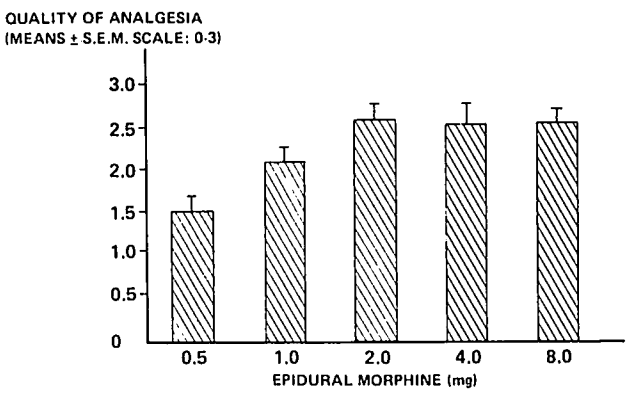

FIG. 3. Quality of the analgesia for the 24 h following the epidural injection of morphine. 2.0 mg *vs.* 0.5 mg: $P < 0.02$; 2.0 mg *vs.* 8.0 mg: P = NS (Mann-Whitney U tests).

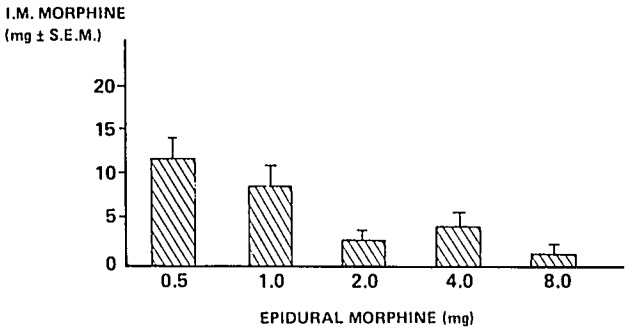

FIG. 4. Total intramuscular quantity of morphine needed by the patients for the first 24 h following the epidural injection of morphine. 2.0 mg *vs.* 0.5 mg: $P < 0.002$; 8.0 mg *vs.* 2.0 mg: P = NS (Mann-Whitney U tests).

No cutaneous level of anesthesia followed any of the doses of epidural morphine and there was no correlation between pain relief and weight or pain relief and height of the patients. Consequently, when utilizing preservative-free morphine sulfate diluted to 10 ml in normal saline, it does not seem necessary to dose morphine on a weight or height basis.[11,18] According to our study 2.0 mg was the optimum dose. With this dose fewer analgesics or none at all were required during the first postoperative day. Furthermore, even if itching, urinary retention or nausea appear (one-third of the patients), these side effects are well-tolerated as the patient is relieved of pain. These side effects are not dose-related except for the nausea and vomiting; patients in Group V (8.0 mg) showed a significantly higher incidence of nausea and vomiting than the others (table 1). Nausea was relieved by 2.5 mg droperidol, im, and occured 8 to 10 h after the injection of epidural morphine.

No statistically significant respiratory depression as evaluated by the PE_{CO_2} and the mouth occlusion pressures was observed in the subsample of 20 patients. The protocol, however, was not designed to test for the occurrence of a reaction that is relatively rare.

TABLE 1. Complications of Epidural Morphine Injection

Morphine	Number of Patients	Complications (Number of Patients)		
		Nausea and Vomiting	Urinary Retention	Itching
0.5 mg	12	4	6	5
1.0 mg	12	5	4	4
2.0 mg	12	5	4	8
4.0 mg	12	4	5	3
8.0 mg	12	10*	4	8

* $P < 0.03$ (Fisher's Test).

Whatever the dose, itching often appears when morphine is injected into the epidural space; however, this does not seem to have greatly affected our patients. The initial epidural block is probably responsible for the urinary retention affecting many patients in this study, since its occurrence was not enhanced by higher doses of epidural morphine.

Among most of the patients the onset of epidural morphine analgesia began at 30 or 45 min, which confirms previous findings.[5] However, this analgesia lasted far beyond the maximum level of serum morphine which occurs during the first 15 minutes.[19]

We conclude that for the relief of postoperative pain following lower limb orthopedic surgery, 2.0 mg epidural morphine sulfate is as effective and less likely to cause undesirable side effects as all the higher doses used during this study.

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