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Low-dose Intrathecal Morphine for Postoperative Pain Control in Patients Undergoing Transurethral Resection of the Prostate

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Thirty patients undergoing lidocaine spinal anesthesia for transurethral resection of the prostate (TURP) were studied to evaluate the effectiveness of low-dose intrathecal morphine (ITM) for postoperative analgesia. In a double-blinded fashion, groups of ten patients received either 0.1 mg morphine, 0.2 mg morphine, or placebo (control group) intrathecally with lidocaine 75 mg. Standard postoperative analgesics were available to all patients. Patients receiving 0.1 mg or 0.2 mg morphine reported significantly less postoperative pain as assessed by an inverse numerical visual pain scale and required significantly fewer postoperative analgesic interventions than the control group. There was no difference between the 0.1 mg ITM and 0.2 mg ITM groups with regard to severity of postoperative pain or analgesic requirements. The incidence of nausea and vomiting was significantly higher in the group receiving 0.2 mg ITM than in the control group. Six patients (60%) in the 0.2 mg ITM group, two patients (20%) in the 0.1 mg ITM group, and one patient (10%) in the control group experienced nausea and vomiting. No clinically evident respiratory depression occurred in any of the subjects. The authors conclude that administration of 0.1 mg or 0.2 mg of morphine intrathecally is effective in reducing postoperative pain following TURP and that 0.1 mg ITM is not associated with nausea and vomiting. (Key words: Analgesics, intrathecal: morphine. Anesthetic techniques: spinal. Pain, postoperative: TURP. Surgery: TURP.)

SPINAL ANESTHESIA is a commonly used anesthetic technique for transurethral resection of the prostate (TURP), and is convenient for concomitantly introducing opioid into the intrathecal space. A single intrathecal injection of 1 mg morphine with local anesthetic has been reported to yield excellent postoperative analgesia for patients undergoing TURP, but results in a high incidence of undesirable side effects.[1] Doses of intrathecal morphine (ITM) less than 1 mg have been shown to provide excellent postoperative analgesia for a variety of surgical procedures while avoiding clinically significant respiratory depression.[2–4] Furthermore, when administered with local anesthetic agents, ITM may act synergistically, resulting in potentiation of morphine's antinociceptive effect and a reduction in the dose required for effective analgesia.[5]

In several pilot trials at our center, 0.15 mg and 0.20 mg ITM had proven effective in eliminating postoperative pain of TURP. We therefore undertook this study to determine the quality and duration of postoperative analgesia provided by 0.1 mg and 0.2 mg ITM, and the incidence and severity of side effects associated with these doses when administered along with the primary anesthetic. Whether these doses of ITM could provide superior postoperative analgesia compared to a more commonly used regimen of postoperative pain control was also investigated.

Materials and Methods

PATIENT SELECTION

This study was approved by the Human Subjects Committee of the University of Colorado Health Sciences Center and the Research and Development Committee, Human Subjects Subcommittee of the Denver Veterans Administration Medical Center. Informed consent was obtained from each subject.

In a double-blind study, 30 ASA Physical Status II and III patients undergoing elective TURP during spinal anesthesia were evaluated. Patients agreeing to participate in the study were randomly assigned to one of three treatment groups of ten subjects each.

ANESTHESIA

All patients received 75 mg lidocaine (5% solution with 7.5% glucose) injected intrathecally as the primary anesthetic. Intrathecal morphine doses of 0.1 mg and 0.2 mg were selected for study and compared with effects of a placebo. An individual not involved in anesthetic administration or postoperative assessment prepared each injectate. Patients in group 0 received no intrathecal narcotic and served as control. Group 1 patients received 0.1 mg preservative-free morphine sulfate (Duramorph 1 mg/ml) injected with the lidocaine. Group 2 patients received 0.2 mg preservative-free morphine sulfate injected with the lidocaine. The final volume of intrathecal injectate in groups 0 and 1 was adjusted to 1.7 ml with preservative-free NaCl 0.9% in order to equal the volume of injectate used for group 2.

All patients were maintained npo past midnight the day of surgery except for diazepam 2.5 mg po with 30

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ml of water administered 1 h prior to surgery. Ongoing drug therapy for concomitant medical problems was continued as deemed appropriate by the anesthesiologist. All patients received routine intraoperative care and monitoring.

Spinal anesthesia was performed with a 22 G disposable 3½ inch spinal needle inserted with the patient in either the lateral or sitting position depending on the anesthesiologist's preference. The needle was inserted at interspace L_{2-3} or L_{3-4} depending on the body habitus, and correct placement of the needle tip within the subarachnoid space was confirmed by aspiration of cerebrospinal fluid before and after injection. Peak anesthetic level was determined by loss of all sensation to pinprick.

Postoperatively, all subjects were observed in the postanesthesia care unit until evidence of a receding block was established, and were then transferred to the surgical intensive care unit for overnight observation for side effects associated with ITM. Respiratory rate monitoring was performed with an impedance pneumographic respiratory monitor (Edentec Model 2000W; Eden Prairie, MN) continuously for 24 h and by the nursing staff using direct observation throughout the study period.

Postoperative Analgesia

Identical analgesic orders were available for all patients so that we could compare the efficacy of ITM to the standard postoperative analgesic regimen used at our institution. The postoperative analgesic orders consisted of a belladonna (15.0 mg) and opium (60.0 mg) suppository every 4 h as needed for pain and/or bleeding attributed to bladder spasm, acetominophen 650 mg po for mild pain, and either acetominophen 650 mg with oxycodone 10 mg or acetominophen 600 mg with codeine phosphate 60 mg po for moderate to severe pain. For severe pain not controlled by the above medications, morphine sulfate was administered parenterally as deemed necessary on an individual basis.

Postoperative Measurements

Data collection was performed by one of the authors at 3, 5, and 7 h after the administration of the intrathecal medication, the morning and evening of postoperative day 1, and the morning of postoperative day 2 creating 6 scoring intervals.

Patients assessed their level of pain using an inverse numerical visual pain scale on which they had received a preoperative training session. This pain scale consisted of a 19 × 13 cm card with the numbers 1 through 10 printed vertically, the number 10 labeled NO PAIN at the top and the number 1 labeled WORST PAIN EVER at the bottom. Patients scored their pain in response to the question "How uncomfortable are you?" at the end of each scoring interval.

Analgesic requirements were measured by type of drug administered and number of doses received during each scoring interval. One analgesic intervention was considered to have occurred each time a patient asked for and received medication.

The occurrence of nausea, vomiting, and pruritus were noted for presence or absence of symptoms during each scoring interval. Respiratory depression was considered present during a scoring interval anytime the respiratory rate decreased below nine breaths per minute.

Somnolence was scored by the observer (author) and recorded at the end of each scoring interval using the following scale: 1. awake and alert; 2. sedated, responds to verbal stimulus; 3. sedated, responds to mild physical stimulus; 4. sedated, responds to moderate or strong physical stimulus; and 5. not arousable.

Statistical Analysis

Group height, weight, age, duration of surgery, pain scores, and number of analgesic interventions were analyzed by one-way analyses of variance in conjunction with the Student-NeumanKuells multiple comparisons procedure. Postoperative pain scores as a function of peak anesthetic dermatomal level, and as a function of duration of surgery, were examined by linear regression. Level of anesthesia was analyzed by Wilcoxon's Rank-Sum Test. The associations between morphine dosage and pruritus, nausea/vomiting, and drowsiness were analyzed with chi-square measures of association.§

Results

Age, weight, duration of surgery and sensory level of the spinal anesthetic did not differ significantly between the three groups (Table 1). There was no association between the duration of surgery and the total pain scores for any of the groups nor was there an association between peak level of anesthesia and pain scores. All patients had adequate surgical anesthesia from the initial spinal anesthetic and no patient required or received supplemental analgesia intraoperatively.

There was no significant difference in pain scores between the three groups at 3 h, but patients in group 0 (control) experienced significantly more postoperative pain than that experienced by patients in either group 1

§ Any occurrence of pruritus, nausea or vomiting during the study period resulted in that subject being classified as symptom present, whereas absence of these symptoms resulted in a classification of symptom absent for the chi-square analyses. When significance was found by chi-square for an overall association, each combination of two groups was analyzed separately.

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TABLE 1. Demographics of Study Patients (Mean ± SE)

	Group 0	Group 1	Group 2
Dose of ITM	0	0.1 mg	0.2 mg
Number of patients	10	10	10
Age (years)	61.2 ± 2.8	66.5 ± 3.7	63.1 ± 3.3
Height (cm)	179.8 ± 2.2	178.1 ± 1.0	173.0 ± 1.9*
Weight (kg)	90.5 ± 8.8	76.1 ± 3.4	89.3 ± 3.9
Duration of surgery (min)	55.3 ± 4.5	59.3 ± 8.4	51.0 ± 5.6
Range of peak anesthetic level	T_6–T_{12}	T_4–T_{10}	T_4–L_1

* Significantly different from group 0 at $P < 0.05$.

(0.1 mg) or group 2 (0.2 mg) from the 3 h point to completion of the study (fig. 1). There was no significant difference in pain scores between patients in groups 1 and 2 at any point. Figure 2 shows the frequency distributions of all pain scores. Of the 60 scores obtained for each group, 98.3% of scores in group 1 and 96.6% of scores in group 2 were 9 or 10, indicating little or no pain. In contrast, only 33.3% of group 0 scores were 9 or 10; the remaining 66.6% of scores ranged between 1 and 8.

Patients in group 0 required significantly more analgesic interventions from 3 h postoperatively to the second postoperative day than did patients in group 1 or group 2. There was no significant difference between patients in groups 1 and 2 in the number of analgesic interventions at any point during the study (table 2).

Six patients in group 2, two patients in group 1, and one patient in group 0 developed nausea and vomiting, all between 3 and 7 h postoperatively. The greater incidence of nausea and vomiting in group 2 compared with that in group 0 proved to be statistically different. Two patients in group 1 developed mild pruritus, but this was not statistically significant.

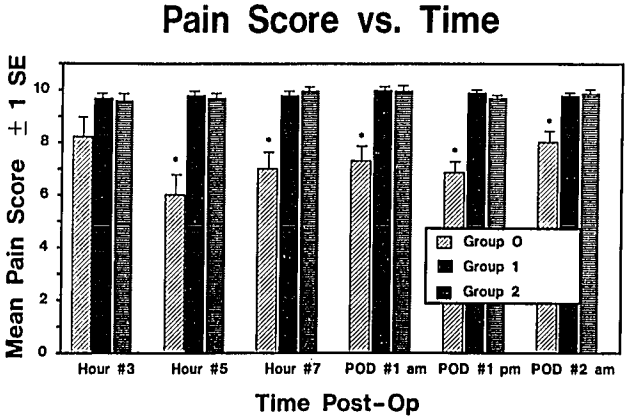

FIG. 1. Group pain scores at the end of each scoring interval. *Group 0 statistically different from Groups 1 and 2 at $P < 0.05$; 10 = no pain. Group 0 = control.

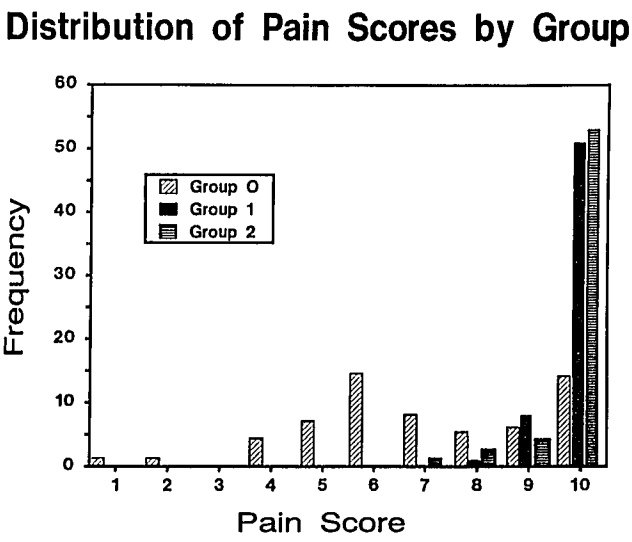

FIG. 2. Frequency distribution of all pain scores plotted by group; 10 = no pain, 1 = worst pain.

No patients developed clinically evident respiratory depression and there was no significant difference in the degree of somnolence between groups.

Discussion

The benefits of intraspinal opioid administration for postoperative pain control are just now being realized for a variety of surgical procedures and yet, despite the widespread and expanding role of this technique, the potential for catastrophic side effects remains a major concern. The wide range in doses of ITM previously reported[3,6,7,8] and the variability in incidence of respiratory depression associated with these doses raises the question of the relationship between dose and other variables such as patient positioning, baricity of injectate, individual susceptibility, and variability[9] to the occurrence of respiratory depression. However, morphine concentrations in the CSF following ITM are dose dependent[10] and, indeed, the inci-

TABLE 2. Analgesic Interventions (Mean ± SE)

	Group 0	Group 1	Group 2
3 h post-ITM	0.5 ± 0.31	0.0 ± 0.00	0.0 ± 0.00
5 h post-ITM	0.8 ± 0.20	0.2 ± 0.20*	0.1 ± 0.10*
7 h post-ITM	0.8 ± 0.29	0.0 ± 0.00*	0.0 ± 0.00*
PPD #1 A.M.	2.2 ± 0.42	0.0 ± 0.00*	0.1 ± 0.10*
POD #1 P.M.	1.4 ± 0.31	0.0 ± 0.00*	0.4 ± 0.16*
POD #2 A.M.	1.4 ± 0.56	0.2 ± 0.20	0.4 ± 0.16
Total Interventions	7.1 ± 1.29	0.4 ± 0.4*	1.0 ± 0.30*

* Significantly different from group 0 at $P < 0.05$.

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dence of problems does appear lower as the dose decreases.[3,4,7,11]

Poorly lipid-soluble narcotics such as morphine tend to remain within the CSF for relatively long periods of time, flowing cephalad with the CSF from the point of introduction, eventually reaching those areas of the brain responsible for control of respiration. Even at the small doses we used, nausea and vomiting did occur which may be indicative of rostral spread.

Does ITM of 0.1 mg or 0.2 mg present a safe dose with regard to postoperative respiratory depression? In a retrospective questionnaire study of over 1100 patients, Gustafson *et al.*[7] reported delayed respiratory depression in 0.36% of the patients receiving ITM in the dosage range of 0.2–0.8 mg. None of the patients in that study, however, who received less than 0.3 mg were among those that developed respiratory depression. Other studies further support the lack of respiratory complications following the ITM administration of doses less than 0.4 mg.[3,4,12]

Nausea and vomiting are troublesome side effects of ITM. Group 2 patients demonstrated a significantly higher incidence of nausea and vomiting than did the control group, but all affected patients responded well to small doses of intravenous naloxone (0.1 mg bolus). Our experience differs from a previous report showing a relatively high incidence of nausea and vomiting in patients receiving ITM doses as low as 0.1 mg.[4]

A small dose of ITM is consistently effective in minimizing postoperative pain in patients undergoing TURP even when administered in doses that are inadequate to produce a similar effect for other surgical procedures.[13] Opioids and specific opioid receptors are known to play a role in mediation of bladder activity and bladder reflexes both at spinal and supraspinal levels.[14–16] Clinical studies have provided evidence that administration of ITM quickly results in elimination of uninhibited detrusor contractions and pain associated with bladder spasm.[17–21] We speculate that our patients who received ITM may well have experienced analgesia by detrussor relaxation and suppression of any reflex bladder activity associated with the surgical procedure yielding a quality of analgesia significantly greater than would be expected from a purely direct opiate-receptor mediated analgesic effect.

In conclusion, ITM administration of 0.1 or 0.2 mg proved equally effective in reducing postoperative analgesic requirements and in eliminating postoperative pain associated with TURP. In our patients, 0.1 mg ITM was not associated with significant side effects.

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