

Analgesic and Hemodynamic Effects of a Single 7.5-mg Intravenous Dose of Morphine in Patients with Moderate-to-Severe Postoperative Pain

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Study Objectives. To evaluate the analgesic and hemodynamic effects of a single dose of intravenous morphine 7.5 mg in patients experiencing moderate-to-severe postoperative pain, and to determine any gender differences in analgesic response.

Design. Randomized, double-blind, parallel-group, multicenter study.

Setting. Postanesthesia care unit of a university teaching hospital.

Patients. Eighty-eight patients who underwent total abdominal hysterectomy or prostatectomy.

Intervention. Thirty-seven patients received a single dose of morphine sulfate 7.5 mg and 51 patients received placebo, both administered intravenously for 1 minute.

Measurements and Main Results. Overall, morphine had no significant effect on systolic or diastolic blood pressure, heart rate, oxygen saturation, or respiratory rate. Compared with baseline, morphine significantly reduced pain intensity at 2, 5, and 10 minutes after administration ($p < 0.05$). The difference in pain intensity between patients who received morphine and those who received placebo, however, was significant only at the 5-minute time point ($p < 0.02$). Patients receiving morphine also reported mild pain relief at 2 and 5 minutes after its administration. Peak analgesic effect was reported 2 minutes after its administration in three quarters of the patients. Significant gender differences also were observed in response to analgesic effect. In women, no significant differences in pain intensity were seen at any time between the morphine and placebo groups, whereas in men receiving morphine, pain intensity was significantly less at 2, 5, and 10 minutes compared with baseline and that seen in the placebo group. Women were generally more satisfied with their pain treatment than were men.

Conclusion. A single 7.5-mg intravenous bolus dose of morphine did not appear to provide adequate reduction in perceived pain intensity in patients with moderate-to-severe postoperative pain. In addition, in contrast to the findings of other experimental pain studies, our data suggest that women are more tolerant of postoperative pain than are men.

Key Words: postoperative pain, morphine, gender differences, analgesia, hemodynamic effects.

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The degree and duration of postoperative pain are often proportionate to the extent of surgical

trauma.^{1,2} Little has been published with respect to the time course of pain after various surgeries.

Pain is usually most intense within the first 1–2 postoperative days.^{1,2} Factors other than surgical trauma that may contribute to the experience of postoperative pain include age and gender. Older subjects and men are believed to be more tolerant of pain.

Opioids are used widely to treat postoperative pain. The mechanisms by which these drugs relieve pain are not clearly understood. Opioids may act on injured tissues to reduce inflammation, impede the transmission of impulses in the dorsal horn,³ and reduce anxiety as well as the unpleasantness of pain.⁴ Although the total administered dose of an opioid analgesic is influenced by the severity of the pain, dosing guidelines for postoperative pain appear to follow fixed schedules. An initial dose of morphine for the treatment of postoperative pain is often in the range of 2–3 mg; subsequent doses may be even less. Little has been published regarding the analgesic or hemodynamic effects of larger doses of intravenous morphine in the immediate postoperative period. Most clinicians are reluctant to use higher doses due to anticipated adverse effects. Furthermore, there are scant data regarding the peak analgesic effect of single intravenous doses of morphine in postoperative patients. However, it is known that there is significant variability among patients with respect to postoperative opioid requirements⁵ and that postoperative pain continues to be undertreated.⁶

The objectives of our study were to evaluate the analgesic and hemodynamic effects of a relatively large (7.5-mg) dose of intravenous morphine in patients with moderate-to-severe postoperative pain, and to determine any gender differences in analgesic response.

Methods

This randomized, double-blind, parallel-group, multicenter study was approved by the participating hospitals' institutional review boards for the protection of human subjects. Informed consent was obtained from patients scheduled to undergo elective lower abdominal surgery. Patients were American Society of Anesthesiologists physical status I or II, aged

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Table 1. Patient Characteristics

Variable	Morphine Group (n=37)	Placebo Group (n=51)
Age ^a (yrs)	50 ± 8	50 ± 10
M/F	12/15	15/36
Body mass index (kg/m ²) ^a	27.2 ± 3.6	28.6 ± 3.7
Time in operating room ^a (min)	222 ± 97	191 ± 67
Time in postanesthesia care unit ^a (min)	144 ± 68	172 ± 84

^aData are mean ± SD.

18–70 years, and had a body mass index of 18–34 kg/m². Exclusion criteria were major organ dysfunction, history of epilepsy, history of alcohol or drug abuse, past idiosyncratic reactions to opioids, and use of an opioid within 24 hours before surgery.

Anesthetic management of the patients was standardized and consisted of propofol, fentanyl, nitrous oxide, oxygen, isoflurane, and a muscle relaxant. The maintenance dosage of fentanyl was limited to less than 3 µg/kg/hour, with the final dosage being administered before the commencement of skin closure. The residual neuromuscular block was reversed with appropriate dosages of reversal agents. All patients received an intraoperative dose of an approved 5-HT₃ antagonist.

After surgery, patients were transferred to the postanesthesia care unit. After recovery from general anesthesia (based on the investigator's assessment of the subject's ability to comprehend and respond to analgesic assessments), the presence and intensity of pain were assessed frequently in each patient. All patients received supplemental oxygen supplied by a nasal cannula with a flow rate of 2 L/minute and were given a continuous infusion of lactated Ringer's solution for hydration. Patients were monitored continuously with two-lead electrocardiography and pulse oximetry. Noninvasive blood pressure measurements were performed frequently as needed.

The presence and intensity of pain were assessed with use of a 4-point verbal rating scale of none, mild, moderate, or severe pain. If a patient reported moderate or severe pain, baseline hemodynamic measurements were obtained, and the patient was randomly assigned to receive either morphine sulfate 7.5 mg or an equal volume of normal saline administered intravenously for 1 minute. The dose of morphine selected for this study was approximately 2–3 times the usual initial dose. This dose was selected to reduce intrasubject

Table 2. Hemodynamic Data

Time (min)	Morphine Group (n=37)				Placebo Group (n=51)			
	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	RR (breaths/min)	HR (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	RR (breaths/min)	HR (beats/min)
0	137 ± 18	77 ± 17	17 ± 3	76 ± 15	135 ± 21	75 ± 15	17 ± 4	79 ± 12
1	132 ± 20	73 ± 15	16 ± 3	76 ± 16	132 ± 19	75 ± 14	17 ± 4	77 ± 13
2	132 ± 21	72 ± 16	—	76 ± 17	130 ± 20	74 ± 14	—	76 ± 12
5	130 ± 19	70 ± 16	16 ± 3	74 ± 15	131 ± 22	74 ± 12	17 ± 3	76 ± 13
7	130 ± 21	71 ± 15	—	74 ± 14	128 ± 21	73 ± 11	—	75 ± 12
10	128 ± 18	71 ± 16	16 ± 2 ^a	74 ± 15	131 ± 22	72 ± 13	18 ± 3 ^a	74 ± 13
15	130 ± 18	72 ± 16	16 ± 3	75 ± 18	135 ± 18	76 ± 11	17 ± 4	79 ± 16

Data are mean ± SD.

BP = blood pressure, RR = respiratory rate, HR = heart rate.

^ap<0.05.

variability with regard to the analgesic response.

Subject-rated pain intensity and hemodynamic measurements were recorded at 1, 2, 5, 7, 10, and 15 minutes after study drug administration. At 2, 5, 10, and 15 minutes, patients were asked to rate the degree of pain relief with use of a 5-point pain scale, with a score of -1 = worse pain, 0 = no pain relief, 1 = mild relief, 2 = moderate relief, and 3 = complete relief.

Patients were encouraged to wait 15 minutes but had access to rescue analgesics at any time after study drug administration. The choice of rescue drug was not standardized and was at the discretion of the attending physician. Immediately before the first dose of rescue drug was administered, both the patient and the investigator independently assessed their overall satisfaction with the analgesic efficacy of the study drug. They used a 5-point scale for efficacy, with a score of 1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent.

Data Analysis

Data were analyzed with use of the χ^2 test and repeated-measures analysis of variance (ANOVA) followed by the Duncan multiple range test. A p value of less than 0.05 was considered to indicate a statistically significant difference. Data were recorded as mean ± SD.

Results

Patient Characteristics

Eighty-eight patients who underwent either total abdominal hysterectomy (61 patients) or prostatectomy (27 patients) participated in this study. Data for the 37 patients who received morphine and the 51 who received placebo are

Table 3. Analgesic Data Based on Treatment Group

Variable	Morphine Group (n=37)	Placebo Group (n=51)
Pain intensity		
Baseline	2.5 ± 0.5	2.5 ± 0.5
At 2 min	2.0 ± 0.96 ^a	2.3 ± 0.76
At 5 min	1.86 ± 0.91 ^{a, b}	2.32 ± 0.79 ^b
At 10 min	2.06 ± 0.88 ^a	2.32 ± 0.78
Time to rescue drug (min)	20.4 ± 13.8	17.7 ± 13.8
Overall satisfaction score ^c		
Patient	1.9 ± 0.92 ^b	1.43 ± 0.76 ^b
Investigator	2.0 ± 1.0 ^b	1.5 ± 0.83 ^b

Data are mean ± SD.

^aStatistically significant difference compared with baseline in the morphine group (p<0.05).

^bStatistically significant difference between groups (p<0.02).

^cBased on a 5-point scale for efficacy: 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent.

summarized in Table 1. There were no significant differences in age, sex distribution, body mass index, time in the operating room, or time in the postanesthesia care unit between patients who received morphine and those who received placebo.

Hemodynamic Data

Overall, there were no significant differences between patients who received intravenous morphine 7.5 mg and those who received placebo with respect to systolic or diastolic blood pressure, heart rate, or oxygen saturation (Table 2). The difference in respiratory rate was significant between the two groups only at 10 minutes after administration of the study drug (morphine 16 ± 2 vs placebo 18 ± 3 breaths/min, p<0.05).

Table 4. Data on Gender Differences in Analgesic Response, Based on Surgical Groups

Variable	Total Abdominal Hysterectomy		Prostatectomy	
	Morphine Group (n=25)	Placebo Group (n=36)	Morphine Group (n=12)	Placebo Group (n=15)
Pain intensity				
Baseline	2.48 ± 0.5	2.6 ± 0.5	2.45 ± 0.52	2.33 ± 0.49
At 2 min	2.08 ± 0.91	2.28 ± 0.81	1.82 ± 1.08	2.4 ± 0.63
At 5 min	1.88 ± 0.95	2.25 ± 0.88	1.82 ± 0.87	2.47 ± 0.52
At 10 min	2.13 ± 0.76	2.26 ± 0.86	1.89 ± 1.17	2.5 ± 0.52
Time to rescue drug (min)	23 ± 15	18 ± 14	15 ± 9	16 ± 13
Overall satisfaction score ^a				
Patient	1.96 ± 0.93	1.47 ± 0.73	1.8 ± 0.92	1.33 ± 0.82
Investigator	2.08 ± 0.9	1.64 ± 0.9	1.8 ± 1.03	1.2 ± 0.56

Data are mean ± SD.

^aBased on a 5-point scale for efficacy: 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent.

Analgesic Data

The analgesic data for the morphine and placebo groups are summarized in Table 3. There was no significant difference in baseline pain intensity between patients in these two groups. Administration of morphine resulted in a significant reduction in the intensity of pain at 2, 5, and 10 minutes ($p < 0.05$). Very little change in pain intensity compared with baseline was noted in patients receiving placebo; however, the difference between patients receiving morphine and those receiving placebo was significant at the 5-minute measurement time ($p < 0.02$). (Analgesic data for the 15-min interval are not shown in Table 3 because almost 50% of patients had received a rescue drug by that time.)

The peak analgesic effect of morphine was seen most often at 2 minutes (76% of the time) and next most often at 5 minutes (17% of the time) after injection. Overall, patients receiving morphine had mild pain relief at 2 and 5 minutes after its administration, whereas those receiving placebo had no pain relief. Pain relief after morphine administration was also seen most frequently at 2 minutes (70% of the time).

There was no significant difference in the time to administration of rescue drugs between the two groups (Table 3). The choice and dosage of rescue drugs represent the diversity of opinion and practice among clinicians. These agents were morphine 1–4 mg, hydromorphone 0.2–1.25 mg, meperidine 12.5–50 mg, ketorolac 15–30 mg, and fentanyl 25–50 µg. Before treatment with rescue drugs, better overall satisfaction scores were given by both patients and investigators for morphine than for placebo (fair vs poor, $p < 0.02$). Patients receiving morphine rated their overall satisfaction with

analgesia as good or excellent twice as frequently as those receiving placebo (58% vs 29%). Investigators rated overall satisfaction as good or excellent in 56% of patients receiving morphine and in 31% of those receiving placebo.

Gender Differences in Analgesic Response

Total Abdominal Hysterectomy

Of the 61 female patients, 25 had received morphine and 36 had received placebo after total abdominal hysterectomy. There were no significant differences in any of the demographic data between these two groups of patients. Although pain intensity tended to decrease after morphine administration, only at the 5-minute measurement time was it significantly lower than baseline ($p < 0.05$; Table 4). There were no significant differences in pain intensity between the morphine and placebo groups at any time. Pain relief was significantly greater in the morphine group only at 2 minutes after administration ($p < 0.05$). The time to administration of rescue drugs was not significantly different between the morphine and placebo groups (range 5–55 and 3–82 min, respectively). There was no significant difference in investigators' overall satisfaction with the analgesic effect of morphine compared with placebo; however, patients were more satisfied if they had received morphine ($p < 0.05$).

Prostatectomy

Of the 27 male patients, 12 received morphine and 15 received placebo. There were no significant differences in any of the demographic data between the two groups. Pain intensity in patients receiving morphine was significantly less

than baseline and than that in the placebo group at 2, 5, and 10 minutes ($p < 0.05$; Table 4). There was no significant difference in the time to administration of rescue drugs between patients receiving morphine and those receiving placebo (15 ± 9 min [range 5–32 min] and 16 ± 13 min [range 5–51 min], respectively) after study drug administration. Patients receiving morphine reported significantly more pain relief than did those receiving placebo at 2, 5, and 10 minutes after study drug administration ($p < 0.05$). Neither patients nor investigators gave a significantly higher score for morphine's effectiveness as an analgesic agent than they did for that of placebo. Despite a greater reduction in pain intensity, male patients had lower overall satisfaction with pain therapy than did female patients, and they tended to receive rescue drugs earlier.

Discussion

Very few hemodynamic changes were observed after the administration of a relatively large (7.5-mg) intravenous dose of morphine in postoperative patients experiencing moderate-to-severe incisional pain. Compared with baseline, pain intensity was significantly lower for up to 10 minutes in patients who received morphine. However, more than half (58%) of patients who were given morphine continued to have moderate-to-severe pain compared with 80% of those given placebo until they received the rescue drug. Peak analgesic and hemodynamic effects of morphine, if any, were seen in most patients at 2 minutes after its administration.

Acute pain is a predictable response to surgery,³ particularly lower abdominal surgeries such as total abdominal hysterectomy or prostatectomy; however, little has been published with respect to the time course of pain after these procedures. The degree and duration of postoperative pain usually depend on the extent of surgical trauma.^{1,2} In addition, patients vary greatly in their analgesic requirements.

Postoperative pain treatment is often empiric, which may contribute to its well-documented inadequate management.^{6–8} Intravenous morphine administration is usually considered the standard for acute pain relief.⁷ The popularity of morphine may be due to clinicians' familiarity with the drug as well as to its relatively low cost. The usual intravenous dosage is approximately 2–3 mg every 5 minutes until an adequate response is obtained. Because of anticipated adverse effects, however, most institutions have a limit on the

maximum dose that can be administered in a given time period. The 7.5-mg intravenous dose selected for this study was approximately 2–3 times higher than the usual recommended initial dose. This dose was chosen to reduce between-subject variability in analgesic response and to differentiate the effects from those of placebo.

Gender differences were noted in the analgesic effects of morphine. In female patients, a single initial high bolus dose (7.5 mg) did not seem to significantly reduce the intensity of perceived pain; however, women gave a significantly higher overall satisfaction score than those who had received placebo. Similarly, in male patients, morphine did not appear to significantly decrease the intensity of pain, but they reported significant pain relief. Several studies have suggested that women are more sensitive to, and less tolerant of, experimental painful stimuli than are men.^{9–12} In our study, the baseline pain intensities were similar in men and women. Whether the extent of pain after total abdominal hysterectomy is the same as that after prostatectomy is not known, as the available measurement tools may not be sensitive enough to detect a difference. In addition, the results of experimental and clinical pain may not be interchangeable, as the two types of studies may elicit different behavioral responses.

Although not reporting significant differences in pain intensity or pain relief, female patients were generally more satisfied with their pain treatment than were men. Male patients had a greater reduction in pain and more pain relief but were less satisfied with the analgesic effect of morphine and received rescue drugs earlier than did female patients.

Satisfaction is a multidimensional variable that depends not only on the intensity of pain but also on factors such as age, expectations, and other psychological aspects of care.¹³ Some patients tend to be satisfied with pain treatment even when their pain is not relieved¹⁴; this was particularly true in our female patients. If satisfaction and delayed time to receiving a rescue drug represent toleration, then our data suggest that female patients are more tolerant of pain than are male patients. This finding is opposite to that reported after experimental pain.^{9–12}

Pain-relief ratings are related to, but distinct from, changes in pain intensity.¹⁴ Pain relief may reflect a change in pain encoding or pain perception. Morphine is a known anxiolytic with a perceptual effect, which may contribute to pain relief. As observed in this study, pain relief may occur without a parallel decrease in pain intensity

and thus may be a more sensitive indicator of the effects of analgesics than are pain-intensity ratings.¹⁴ Furthermore, a statistically significant reduction in pain intensity or an improvement in pain relief does not necessarily represent clinically significant change.¹⁵ Overall, patients receiving morphine had mild pain relief whereas those receiving placebo had none.

Conclusion

A single 7.5-mg intravenous bolus dose of morphine did not appear to provide adequate reduction in perceived pain intensity in patients with moderate-to-severe postoperative pain. The peak effect occurred 2 minutes after administration of the drug in most patients. This dose did not seem to cause clinically significant alterations in cardiovascular or respiratory parameters. Some investigators have advocated the administration of 3 mg every 5 minutes to relieve moderate-to-severe postoperative pain. Our data suggest that larger dosages, perhaps 5 mg every 3–5 minutes, may provide more adequate pain control. In addition, our data indicate that women are more tolerant of postoperative pain than are men.

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