

Intrathecal Morphine for Analgesia After Postpartum Bilateral Tubal Ligation

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Postpartum bilateral tubal ligation (PPBTL) causes postoperative pain. We designed this study to determine the efficacy of 50 μg intrathecal morphine for analgesia after PPBTL. Sixty-five women received spinal anesthesia with 12.75 mg hyperbaric bupivacaine, 20 μg of fentanyl, and either 50 μg of morphine (morphine group) or 0.05 mL of saline (control group). Postoperative analgesia was provided with regular naproxen 500 mg and oxycodone 5 mg/acetaminophen 325 mg mixture as needed. Overall, satisfaction was higher ($P = 0.003$) and pain was less intense at rest ($P = 0.008$) and on movement ($P < 0.0001$) in the morphine group. There was no significant overall difference in nausea, pruritus, or sedation scores, but vomiting occurred more frequently in the morphine group (21.4% versus

3.5%; $P = 0.052$). In *post hoc* comparisons, pain at rest within the morphine group was significantly less at 4 h ($P = 0.006$), pain on movement was significantly less at 4 h ($P = 0.002$) and 12 h ($P = 0.0004$), and pruritus was significantly more frequent at 12 h ($P = 0.002$) compared with the control group. Oxycodone 5 mg/acetaminophen 325 mg mixture consumption was significantly smaller ($P = 0.006$) and the time to first request of analgesia was significantly longer ($P = 0.006$) in the morphine group. We conclude that the addition of 50 μg of morphine to intrathecal hyperbaric bupivacaine and fentanyl provides improved postoperative analgesia in women undergoing PPBTL.

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Postpartum bilateral tubal ligation (PPBTL) is a commonly performed procedure. It is associated with postoperative pain, the degree of which may be underestimated. It is commonly performed under neuraxial anesthesia (1,2). As the neuraxial sensory blockade recedes in the postanesthesia care unit (PACU), patients experience progressively increasing pain that can impair their ability to ambulate and look after their newborns. Postoperative pain originates from the infraumbilical skin incision, transection and suture ligation sites within the abdomen and on the fallopian tubes, and from uterine myometrial contractions associated with the normal regression of the uterus after delivery (2). Various methods have been used to provide postoperative analgesia with differing degrees of success, including nonsteroidal antiinflammatory drugs (NSAIDs) (3,4), preincisional infiltration of the skin incision with

local anesthetic (2), infiltration of the mesosalpinx and tubes with local anesthetic (2), and intrathecal fentanyl with and without added epinephrine (5).

The standard method to provide anesthesia for PPBTL at our institution is a spinal anesthetic using a mixture of hyperbaric bupivacaine and fentanyl. Postoperative analgesia is provided by oral NSAIDs and oxycodone 5 mg/acetaminophen 325 mg mixture. Intrathecal morphine is routinely used at our institution to provide postoperative analgesia after cesarean delivery but has been rarely used for analgesia after PPBTL. One recent study showed that the addition of 100 μg of intrathecal morphine to fentanyl and lidocaine provided good postoperative analgesia after PPBTL (1). There are limited data regarding the efficacy of smaller doses of intrathecal morphine for postoperative analgesia. In patients undergoing cesarean delivery under spinal anesthesia, small doses of intrathecal morphine (25–50 μg) combined with regular NSAIDs proved effective for controlling postoperative pain with an infrequent incidence of morphine-induced side effects (6). There are no published data for analgesia after PPBTL with similar doses of intrathecal morphine. We therefore designed this prospective, randomized, double-blind study to determine the efficacy

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and side effect profile of 50 μg intrathecal morphine for postoperative analgesia after PPBTL surgery.

Methods

After IRB approval and written informed consent, 65 women who had a vaginal delivery and were scheduled to undergo PPBTL under spinal anesthesia were enrolled. Patients were excluded if they had a contraindication to spinal anesthesia, history of opioid abuse or regular analgesic use, chronic pain syndromes, contraindication to NSAIDs, obesity (body mass index >40), or allergy to one of the study medications.

Patients received 30 mL of 0.3 M sodium citrate preoperatively. IV ketorolac 30 mg was also given before insertion of the spinal block. Women were allocated using sealed opaque envelopes, and randomization was grouped into blocks of 10 patients. Each patient received intrathecal 0.75% hyperbaric bupivacaine 1.7 mL (12.75 mg) and fentanyl 0.4 mL (20 μg). Patients in the morphine group also received 50 μg (0.05 mL) of preservative-free morphine sulfate, and women in the control group received 0.05 mL preservative-free normal saline for a total volume of 2.15 mL. The solution was prepared by an anesthesiologist not involved in the study. The preservative-free morphine sulfate (10 mg/10 mL) and fentanyl (250 μg /5 mL) were prepared using a 1 mL TB syringe.

Spinal anesthesia was performed in the sitting position at the L3-4 or L4-5 interspace by using a 25-gauge pencil point Pencan spinal needle (B. Braun, Bethlehem, PA). Immediately after removal of the spinal needle, each woman was placed in the supine position. Noninvasive arterial blood pressure, heart rate, and oxygen saturation were monitored. Hypotension, defined as a 20% decrease in systolic blood pressure from baseline, was treated with IV ephedrine 5–10 mg. Before skin incision, the surgeon infiltrated 5 mL of 0.5% bupivacaine along the planned incision line. Each patient was allowed up to 3 mg IV midazolam for sedation. Intraoperative pain or discomfort was managed with IV fentanyl.

Postoperative analgesia was provided using naproxen 500 mg every 12 h and oxycodone 5 mg with acetaminophen 325 mg tablets as needed. Postoperative nausea and vomiting (PONV) were treated with IV ondansetron 4 mg. Pruritus was treated with IV diphenhydramine 25 mg, followed by nalmefene 50 μg over 15 min if necessary. Respiratory rate was monitored every 2 h by the nursing staff as per our institution protocol for patients receiving neuraxial narcotics.

Research personnel unaware of the patient's randomization collected the data in PACU (time 0) and then at 4, 12, and 24 h postoperatively. Pain at rest (supine) and after movement (sitting at 4 h, walking around the room at 12 and 24 h), nausea, and pruritus

were assessed using a 100-mm visual analog score (VAS). Sedation was assessed on a four-point scale (0 = awake and alert, 1 = awake but drowsy, 2 = asleep but rousable, 3 = unresponsive). We also collected data concerning vomiting and need for rescue treatment of pain, pruritus, and PONV. At the 24-h assessment, women were asked about their satisfaction with anesthesia care and postoperative pain relief by using a 100-mm VAS.

Data from a previous study (1) indicated that a sample size of 29 patients per group would have 80% power to detect a reduction in pain scores from [mean (SD)] 20 (20) mm to 10 (7) mm at 24 h postoperatively with a type I error of 0.05. Data were analyzed using Student's *t*-test for continuous data and the χ^2 test for categorical data. Pain, nausea, and pruritus scores were compared in separate repeated-measures analyses of variance with group, time, and group \times time effects on log-transformed scores. *Post hoc* group comparisons at separate times were done with Wilcoxon's rank sum tests on raw scores and adjusted for multiple comparisons with the Bonferroni method. Sedation scores were compared with a Cochran-Mantel-Haenszel test of 2×2 tables for each of the occasions it was assessed. Satisfaction was compared by a single Wilcoxon's test. $P < 0.05$ was accepted as statistically significant.

Results

Eight women were excluded because of protocol violation. General anesthesia was needed for one woman, one patient stated that she was allergic to the oxycodone/acetaminophen mixture, and six patients did not receive postoperative naproxen. Of the remaining 57 patients, 28 were in the morphine group and 29 were in the control group. Demographic data are shown in Table 1. Patients in the morphine group were younger than patients in the fentanyl group ($P < 0.05$). There were no statistically significant differences between the two groups in weight, height, race, parity, characteristics of labor and delivery, time from delivery to placement of the spinal anesthetic, duration of surgery, or use of fentanyl or midazolam in the operating room.

Overall pain was less intense both at rest ($P = 0.008$) and on movement ($P < 0.0001$) in the group receiving morphine. In *post hoc* comparisons at specific times, pain at rest in the morphine group (Fig. 1) was significantly less at 4 h ($P = 0.006$) and pain on movement (Fig. 2) was significantly less at 4 h ($P = 0.002$) and 12 h ($P = 0.0004$). The consumption of oxycodone/acetaminophen tablets (median [interquartile range]) for rescue analgesia was significantly less in the morphine group (2 [0–4]) compared with the control group (4 [2–6]) ($P = 0.006$). Time to first request of rescue analgesia (minutes) was also significantly longer in the morphine group (447 [300–

Table 1. Patients demographics, labor and delivery characteristics, and intraoperative use of midazolam and fentanyl

	Control group (n = 29)	Morphine group (n = 28)
Age (yr)	26.4 ± 5.2	30.5 ± 6.1*
Weight (kg)	84.4 ± 13.7	83.7 ± 16
Height (cm)	162.2 ± 6.6	165.2 ± 10.2
Parity	3.2 ± 1.4	3.2 ± 1.2
Race (AA/C/H)	21/8/0	17/8/3
Spontaneous/induced or augmented labor	17/12	15/13
Mode of delivery (SVD/instrumental)	28/1	27/1
Episiotomy	3 (10)	0 (0)
Tears or lacerations	8 (27.6)	9 (32.1)
Breast feeding	13 (44.8)	16 (57.1)
Time from delivery to spinal anesthesia (h)	22.4 (1.7)	20.7 (1.7)
Duration of surgery (min)	39.2 ± 12	40.3 ± 10.2
Patients receiving midazolam in the OR	22 (75.9)	25 (89.3)
Midazolam dose in the OR (mg)	2 ± 0.2	2 ± 0.2
Patients receiving fentanyl in the OR	11 (37.9)	7 (25)
IV Fentanyl dose in the OR (µg)	57.3 ± 11.2	47.1 ± 7.1

Data are presented as mean ± SD or numbers (%).

AA = African-American; C = Caucasian; H = Hispanic; SVD = spontaneous vaginal delivery; OR = operating room.

*P < 0.05.

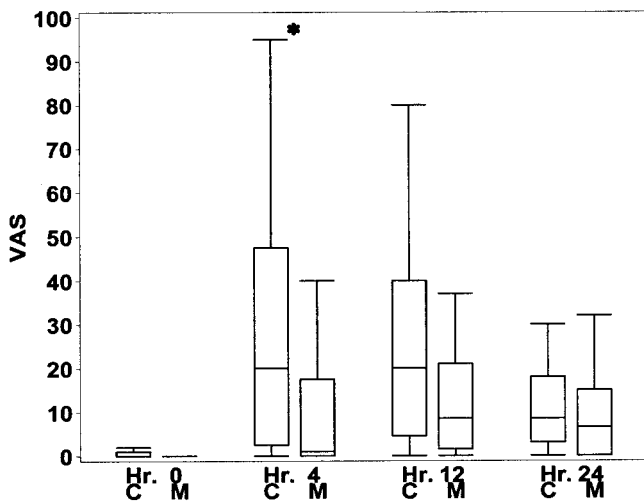


Figure 1. Pain scores at rest. Visual analog scale (VAS) scores (mm) for pain are shown on the y-axis and time (h) after admission to the postanesthesia care unit on the x-axis. Values are presented in box plot with median and interquartile range; the vertical lines extend to the most extreme point within 1.5 times the interquartile range. C = control group, M = morphine group. *P = 0.006 compared with the morphine group.

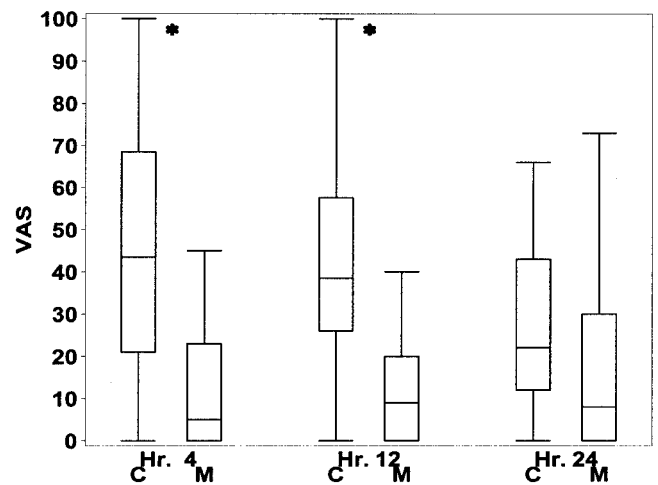


Figure 2. Pain scores on movement. Visual analog scale (VAS) scores (mm) for pain are shown on the y-axis and time (h) after admission to the postanesthesia care unit on the x-axis. Values are presented in box plot with median and interquartile range; the vertical lines extend to the most extreme point within 1.5 times the interquartile range. C = control group; M = morphine group. *P = 0.002 compared with the morphine group at 4 h and P = 0.0004 compared with the morphine group at 12 h.

667]) compared with the control group (178 [145-295]) (P = 0.006).

Postoperative opioid-related side effects are summarized in Table 2. "True" nausea and pruritus were defined as any VAS score >10. There were no differences between the two groups in the incidence of nausea or the need for treatment of PONV or pruritus. Overall nausea and pruritus scores did not differ between the 2 groups; however, in a *post hoc* comparison at specific times, the pruritus score was significantly higher at 12 h postoperatively in the morphine group compared with the control group (P = 0.002). There was a trend towards more

frequent pruritus (89.2% versus 79.3%, P = 0.056) and vomiting (21.4% versus 3.5%, P = 0.052) in the morphine group compared with the control group. No patients experienced respiratory depression, defined as a respiratory rate <8 breaths per minute. There was also no difference in sedation scores between the two groups at the different time points.

VAS satisfaction scores (median [interquartile range]) for satisfaction with anesthesia care and postoperative pain relief were significantly higher in the morphine group (100 [94-100]) compared with the control group (87 [40-98]) (P = 0.003).

Table 2. Postoperative adverse effects

	Control group (n = 29)	Morphine group (n = 28)
Nausea	4 (13.8%)	8 (28.6%)
Vomiting	1 (3.5%)	6 (21.4%)
Treatment for PONV	3 (10.3%)	7 (25%)
Pruritus	19 (65.5%)	25 (89.3%)
Treatment for pruritus	6 (20.7%)	6 (21.4%)
Nausea scores		
0 h	0 (0-0)	0 (0-0)
4 h	0 (0-0.5)	0 (0-4)
12 h	0 (0-0)	0 (0-4)
24 h	0 (0-0)	0 (0-0)
Pruritus scores		
0 h	0 (0-7)	0 (0-18)
4 h	3.5 (0-34.5)	12.5 (1-32.5)
12 h	0 (0-1.5)	15 (0-31.5)
24 h	0 (0-0)	0 (0-0.5)

Data are presented as number (%) or median (interquartile range).
VAS = visual analog score; PONV = postoperative nausea and vomiting.

Discussion

The severity of postoperative pain after PPBTL is often underestimated. In one study cumulative 24-hour IV patient-controlled analgesia morphine consumption after PPBTL was similar to that reported after cesarean delivery (1). Although long-acting intrathecal opioids are commonly used in many institutions for patients undergoing cesarean delivery, there is only one published report of patients undergoing PPBTL (1).

In this study, we found that a multimodal analgesic regimen incorporating 50 μ g intrathecal morphine, regular NSAIDs, and preincisional skin infiltration with bupivacaine was associated with lower pain scores, less need for analgesic rescue, and higher patient satisfaction compared with a similar regimen without intrathecal morphine.

A multimodal approach to the management of postoperative pain using a combination of drugs with different mechanisms of action has been recommended in an attempt to improve the quality of analgesia while minimizing the doses and side effects of opioids (7). Intrathecal morphine acts on the opioid receptors in the substantia gelatinosa of the dorsal horn of the spinal cord (8). The combination of NSAIDs and opioids may result in a synergistic action that provides satisfactory postoperative analgesia (9). NSAIDs may relieve incisional pain via an antiinflammatory action. They may also minimize cramping uterine pain (10). Although the package insert of ketorolac states that the drug is contraindicated in breast feeding mothers, the levels in breast milk are undetectable or small, being between 0.16% and 0.4% of the maternal exposure, suggesting that ketorolac has a more favorable profile than acetaminophen and other NSAIDs (11). In fact, both ketorolac and naproxen, like

other NSAIDs, are considered safe during breast feeding (12). Wound infiltration with bupivacaine also helps to reduce postoperative incisional pain (13).

Although intrathecal morphine provides reasonably satisfactory postoperative analgesia, side effects such as PONV and pruritus are frequent and dose-dependent (6,14,15). Previous studies have reported good postoperative analgesia after cesarean delivery with small doses of morphine combined with NSAIDs. In one study, the use of 100 μ g intrathecal morphine plus NSAIDs provided analgesia of similar quality to 250 μ g morphine but with less pruritus after cesarean delivery (16). In another study, the use of even smaller doses of intrathecal morphine (25-50 μ g) in combination with NSAIDs provided excellent analgesia after cesarean delivery and was associated with fewer side effects compared with 100 μ g morphine (6). There are, however, limited data regarding the efficacy and side effect profile of 50 μ g intrathecal morphine. Previous studies reported variable degrees of success after the use of this dose of intrathecal morphine. Yamaguchi et al. (17,18) have investigated postoperative analgesia produced by intrathecal morphine for abdominal hysterectomy and cholecystectomy. Intrathecal morphine doses of 0.04-0.1 mg for hysterectomy and 0.06-0.2 mg for cholecystectomy had comparable analgesic effects. In obstetrics, Uchiyama et al. (19) compared the quality of analgesia and the incidence of side effects of 50, 100, and 200 μ g of intrathecal morphine and reported that 100 μ g was the optimal dose for postoperative pain control after cesarean delivery. Intrathecal morphine was used as the sole analgesic in this study. When used as part of a multimodal regimen, 50 μ g of intrathecal morphine provided effective analgesia with an acceptable level of side effects after cesarean delivery (6,20,21).

Our data support the fact that 50 μ g of intrathecal morphine, in the context of a multimodal regimen, can produce good postoperative analgesia in the first 24 hours after PPBTL surgery. However, the use of even this small dose was associated with opioid-induced side effects. In our study, there was a trend towards a more frequent incidence of pruritus in the morphine group over the 24-hour study period (89.3% versus 65.5%, $P = 0.056$). At 12 hours postoperatively, pruritus was more severe in those receiving intrathecal morphine. The need for treatment, however, was not different from the control group. There was also a trend toward more vomiting ($P = 0.052$), more common nausea, and treatment of PONV in the morphine group. Although these differences did not reach statistical significance, this study was not designed to be able to exclude differences in these secondary outcomes. These results are different from those reported by Campbell et al. (1), who used a larger dose (100 μ g) of intrathecal morphine after PPBTL. In that study,

there was no difference between the two groups regarding the incidence of pruritus. The severity of pruritus and the occurrence of vomiting were not reported.

Higher patient satisfaction scores showed that improved analgesia outweighed the nuisance side effects of pruritus, nausea, and vomiting. We conclude that the addition of 50 μ g of morphine to intrathecal hyperbaric bupivacaine and fentanyl provides improved postoperative analgesia, less need for rescue analgesics, and a greater degree of patient satisfaction compared with a similar technique without morphine in women undergoing PPBTL.

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