—**Original**—

Efficacy of Intrathecal Morphine for Analgesia Following Elective Cesarean Section: comparison with Previous Delivery

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Abstract

Purpose: To determine the effect of intrathecal injection of morphine 0.2 mg on postoperative analgesia, activity and satisfaction after elective cesarean section.

Method: Forty-five parturients who had previously undergone cesarean section with spinal anesthesia without intrathecal morphine were enrolled in this randomized, double-blinded study. Group 1 received hyperbaric bupivacaine 10 mg intrathecally (IT) and group 2 received morphine 0.2 mg IT in addition to hyperbaric bupivacaine 10 mg IT. All subjects received 20 mg piroxicam rectally at the end of surgery and 18 hours after surgery. Side effects in the first 24 hours after delivery were recorded by a trained nurse. Pain, nausea, pruritus, and satisfaction during the first 24 hours were self-rated using a visual analog scale. Subjects also recorded their memories of these symptoms after their previous cesarean sections. The time to first request for additional analgesics (30 mg pentazocine intramuscularly), total dose of pentazocine within 24 hours postoperatively and nurse observations of walking status within 24 hours postoperatively were also recorded.

Results: In the present cesarean sections, the duration of complete analgesia and the time to first request for additional analgesics were longer in group 2 than in group 1. Group 2 had higher satisfaction scores than group 1 in spite of their more severe pruritus and nausea during the first 24 hours after surgery. The percentage of patients who could not walk during the first 24 hours after cesarean section was higher in group 1 than in group 2.

Conclusion: The addition of morphine 0.2 mg to hyperbaric bupivacaine 0.5% by intrathecal injection reduced postoperative pain and analgesic use, and increased patient satisfaction following cesarean section. The combination of intrathecal injection of morphine and preventive NSAIDs can be easily administered in most hospitals, and is substantially less expensive than the new pain management technologies currently in use.

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Key words: personal satisfaction, postoperative pain, complication, intrathecal injection

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Introduction

The provision of optimal analgesia after cesarean section remains a challenge, as satisfactory pain relief must be balanced with the ability of the mother to care for her newborn. The new technologies for postoperative pain control, such as patient-controlled analgesia (PCA) or patient-controlled epidural analgesia (PCEA), are expensive and may limit the ability of a woman to care for her child shortly after delivery because of the sedative effects of the opioids and motor blockade due to local anesthetics[1]. Moreover, administration of intravenous PCA with meperidine to breastfeeding patients after cesarean section has been associated with neonatal neurobehavioral depression[2].

Subarachnoid anesthesia is still popular for cesarean section, because the technique is easy and brief for the parturient who finds it difficult to hunch up her back, and spinal local anesthetics produce adequate relaxation of abdominal muscles with few effects on the neonate. However, spinal anesthesia provides insufficient postoperative analgesia, and additional analgesics are usually required in the postoperative period. Intrathecal (IT) morphine with hyperbaric bupivacaine 10 mg IT provides a simple method of pain control for patients undergoing cesarean section[3]. A single dose of IT morphine decreases post-cesarean opioid analgesic requirements and may reduce or prevent neonatal neurobehavioral depression associated with maternal analgesia[2]. Many previous studies have reported that IT morphine provides good analgesia after cesarean section, but the most of these included some emergency cases and cases in which parturient and/or fetal disorders led to the cesarean section. In emergency cesarean section, analgesia may be difficult to evaluate accurately because of the mother's strain, fear, and anxiety about her baby.

Effectiveness of analgesia in terms of pain relief, overall patient satisfaction, and nausea is subjective and can vary greatly depending on the character of the individual patient and her experience. A cesarean section is one of the few operations that patients routinely undergo more than once. An individual patient's postoperative status can therefore be compared with that following her previous delivery. No report has compared analgesia with and without intrathecal morphine administration in patients undergoing repeat cesarean section.

The perioperative circumstances for cesarian section are different from those of other operations. The mother is usually free of disease, and ideally she should be able to walk to the neonatal unit as soon as possible, to have contact with her child and to breast feed. Walking also decreases the postoperative risk of venous thrombosis. The quality of anesthesia and maternal satisfaction with childbirth are influenced by a number of factors including perioperative pain, side effects of anesthesia (e. g. nausea and vomiting, pruritus, somnolence and numbness of the legs), anxiety, impression of childbirth, condition of the newborn, and caregiver support. These factors can be summarized by a satisfaction score measured within 24 to 48 hours of cesarean section[4,5].

The aim of this study was to compare the pain relief, satisfaction, activity, and side effects with IT morphine following cesarean section with the same patients' previous experience of cesarean section without IT morphine.

Materials and methods

All parturients who had previously undergone cesarean section at Oyama Municipal Hospital (Tochigi, Japan) were recruited into this randomized, double-blind study, performed in the same hospital between April 2001 and February 2002. Forty-five American Society of Anesthesiologists (ASA) physical status 1 or 2 women scheduled for cesarean section with spinal anesthesia were included. The only reason for elective cesarian section in these subjects was the previous cesarian delivery. The average time elapsed from the previous cesarean section was 28.7±8.5 months (mean±SD). The term of all pregnancies was 35 weeks of gestation or longer and all subjects weighed between 50 and 100 kg. No patient had a

history of fetal compromise, respiratory insufficiency or heart disease. Written informed consent and Ethics Committee approval were obtained.

A visual analogue score (VAS) to assess postoperative pain, nausea, pruritus, and somnolence was explained to each patient before surgery. The VAS is a 100-mm scale with anchor points at 0 and 100 mm marked "no pain (or nausea, pruritus, somnolence)" and "worst possible pain (or nausea, pruritus, somnolence)," respectively. Each patient was randomly allocated to receive either hyperbaric bupivacaine 10 mg IT (group 1, n=22), or hyperbaric bupivacaine 10 mg IT and morphine 0.2 mg IT (group 2, n=23).

An anesthetist, who was not subsequently involved in the study, prepared the appropriate morphine solution prior to use. The spinal anesthesia and anesthetic management of all patients were standardized. Continuous ECG, noninvasive arterial blood pressure, and SpO_2 monitors were used before starting anesthesia, and the baseline arterial pressure was noted. Following a fluid preload of 1000 mL of Ringer's acetate solution, dural puncture was performed with the patient in the left-down lateral position in the L 3/4 or L 2/3 interspace using a 25-gauge needle, and the study drug (s) were injected over 10 seconds. The patients were then placed in the supine position with right hip up, and oxygen was supplied by facemask. Intravenous Ringer's acetate solution and incremental ephedrine boluses were given to maintain systolic arterial pressure at greater than 100 mm Hg or within 20% of the baseline value. The surgery was started when the sensory block, as measured using the loss of cold sensation, had reached the level of T 4. The umbilical cord was double clamped prior to placental separation. Methylergometrine maleate 0.2 mg was given intravenously after the separation. Apgar scores were recorded at 1 and 5 minutes. Fentanyl 0.1 mg was administered intravenously if the patient complained of intra-operative pain. In addition, all patients received droperidol 2.5 mg intravenously to prevent the side effects of IT morphine.

Piroxicam 20 mg was administrated per rectum at the end of surgery and 18 hours after surgery, the same doses which had been given after the previous cesarean section. For all patients, intramuscular pentazocine 30 mg was allowed every 4 hours postoperatively, if requested. Intravenous metoclopramide 10 mg was prescribed as the antiemetic of choice and intravenous diphenhydramine 10 mg was prescribed as the antipruritic agent of choice when required. A blinded researcher recorded the VAS scores for pain (at rest and attempting to turn over), pruritus, nausea, and satisfaction, any adverse effects, the time to first request for additional analgesic, the appearance of walking score, and the total dose of additional pentazocine, metoclopramide, and/or diphenhydramine during the first 24 hours postoperatively. Appearance of walking score was defined as follows: 1=almost normal gait, 2=able to walk, but only for a few minutes or very slowly, 3=cannot walk due to pain. Respiratory rates and oxygen saturations were recorded by the midwifery staff every 2 hours for the first 6 hours, and every 6 hours for the next 18 hours. We excluded the patients if they requested it during the study period or if the newborn had any malformation or other abnormality such as low body weight or fetal compromise. The endpoint of this study was 24 hours postoperatively, because 93% of the additional analgesics had been used within 24 hours postoperatively at the previous cesarean section (**Table 1**). The previous clinical recordings, the anesthesia charts, the nursing records, and the questionnaires were also reviewed.

Statistical analysis was performed by using Statview® version 5.0 (Abacus Concepts, Inc., Apple Computer, Cupertino, CA, USA) for Macintosh. The chi-square test and, where appropriate, Fisher's exact test, were used to compare the incidences of adverse effects. The Mann-Whitney u test was used to compare differences in postoperative VAS scores. Student's t test was used to analyze patient characteristics and infant data. The Wilcoxon signed-ranks test was used to compare intra-group differences in VAS scores. A p value < 0.05 was considered to be significant.

Results

Forty-two patients completed the study, and three

Table 1 Timing of requests for additional ahalgesia

the time from end of surgery (h)	0—6	6—12	12—24	24—36	36—
total no. of patients who requested request additional analgesics	26	27	14	5	0

Postoperative requests of additional analgesics at previous cesarean section are shown. Seventy-four percent of the total analgesics was administrated within 12 hours, and 93% was within 24 hours postoperatively.

were excluded. Two newborns in group 1 were excluded because they were small for dates and weighed less than 2000 g. One of these newborns was transferred to another hospital for admission to the neonatal intensive care unit. One newborn in group 2 was excluded due to polydactyly. All patients had adequate sensory and motor block intraoperatively, and no additional intraoperative analgesic supplements were required.

The patient characteristics and obstetric variables were similar in the two groups (**Table 2**). Demographic, analgesic, and adverse effect data in the previous operation also were similar in the two groups. Intraoperative crystalloid use and ephedrine dose were similar in the two groups in the previous and the present cesarean section. For the present cesarean section, however, the duration of complete analgesia and the time to the first request for additional analgesics were longer in group 2 than group 1. The VAS pain scores in group 2 were lower than in group 1. No patient in group 2 required postoperative analgesic supplements in the present operation, whereas for group 1 overall 30% of the permissible dosage of analgesia was requested. Only two patients in group 2 could not walk due to postoperative pain, while five patients in group 1 could not walk on post-operative day 1. The incidence of pruritus was higher in group 2 than in group 1, and the VAS nausea scores in group 2 were higher throughout the first 24 hours. Though the IT morphine group had more pruritus and nausea, the VAS satisfaction score was higher in this group.

No respiratory rate of less than 14 breaths/min was recorded, and no patient had an oxygen saturation reading of less than 90%. Neonatal conditions were similar in the two groups.

Discussion

The present study shows that additional IT morphine for elective cesarean section greatly reduces postoperative pain and analgesic requirements, and increases patient satisfaction. This study is the first to show that the effect of IT morphine was related not only to postoperative pain but also to satisfaction and postoperative activity compared with the previous operations in the same patients. It has previously been found that patients who have no additional analgesics with spinal anesthesia have higher pain scores and analgesia consumption during the first 4 hours postoperatively than patients who do[6] and that IT morphine is highly effective for managing postoperative pain[7]. However, IT morphine 0.1 to 0.3 mg has been shown to cause dose-dependent side effects[8]. Some patients who received only IT morphine demand additional analgesics for post-cesarean section pain[8,9]. When different classes of analgesics are administered simultaneously to the same patient, the drug can cause competitive, additive, or synergistic effects. In this study, IT morphine and NSAIDs seemed to act synergistically.

The administration of NSAIDs given preemptively to relive post-operative pain is controversial[10]. However, NSAIDs during spinal analgesia might prolong duration of the controversial. Subarachnoidal blockade induced prior to surgical trauma attenuates peripheral and central sensitization and NSAIDs act synergistically to decrease postoperative pain when used in combination[11]. Uterine contraction pain involves several chemical nociceptive pathways[12] and is mediated by prostaglandin cascade[13] that is inhibited by NSAIDs. Piroxicam has a marked analgesic effect directed selectively against pain induced by inflammation, and is used mainly for treating rheumatic disorders. If an NSAID with a short half-life, such as diclofenac[14]. is used, repeated doses may be needed.

Pruritus and nausea are common and troublesome side effects of neuraxial opioid administration after

Table 2 Patient characteristics, Anesthesia data, and Adverse effects

	previous cesarean delivery			*present cesarean delivery*		
	Group 1 (n=20)	Group 2 (n=22)	P value	Group 1 (n=20)	Group 2 (n=22)	P value
Patient characteristics						
Height (cm)	159 ± 7	159 ± 5	NS	159 ± 7	159 ± 5	NS
Weight (kg)	67.1 ± 9.5	67.4 ± 10.4	NS	66.5 ± 9.4	67.7 ± 10.6	NS
Age (yr)	27.6 ± 3.3	29.4 ± 3.5	NS	30.0 ± 3.9*	31.9 ± 3.7*	NS
Duration of pregnancy (wk)	38.3 ± 1.6	38.0 ± 1.4	NS	37.7 ± 0.7	37.8 ± 0.9	NS
Intraoperative Ringer's solution infused (mL)	1,241 ± 376	1,298 ± 337	NS	1,121 ± 428	1,341 ± 314	NS
Ephedrine dose (mg)	12.2 ± 8.2	13.3 ± 8.0	NS	10.5 ± 6.8	15.9 ± 11.9	NS
Weight of newborn (g)	2,930 ± 382	3,110 ± 359	NS	2,962 ± 267	3,132 ± 366	NS
Apgar score 1 min	8.5 ± 1.1	8.7 ± 0.6	NS	8.8 ± 0.4	8.7 ± 0.6	NS
Apgar score 5 min	9.0 ± 0.4	9.1 ± 0.5	NS	9.3 ± 0.4	9.3 ± 0.5	NS
Anesthesia data						
Complete analgesia (h)	2.9 ± 2.2	2.0 ± 1.2	NS	2.4 ± 2.5	19.8 ± 9.0*	<0.0001
Time to first request for additional analgesia (h)	9.6 ± 7.9	6.1 ± 6.2	NS	8.3 ± 6.8	24.0 ± 0.0*	<0.0001
Time to maximum pain from operation end (h)	5.7 ± 3.1	5.6 ± 2.8	NS	4.8 ± 2.9	22.3 ± 10.5*	<0.0001
Intraoperative pain (%)	0%	0%	NS	0%	0%	NS
Intraoperative analgesics request (%)	0%	0%	NS	0%	0%	NS
Pain score at maximum pain within 24 h						
At rest	71 ± 22	74 ± 22	NS	72 ± 20	29 ± 24*	<0.0001
During attemting to turn over	86 ± 15	91 ± 11	NS	88 ± 12	61 ± 23*	<0.0001
Requested analgesics within 24 h (%)	85%	91%	NS	90%	0%*	<0.0001
Total dose of pentazocine (mg/patient at 24 h)	45.0 ± 28.4	61.4 ± 28.5	NS	54.0 ± 34.6	0.0 ± 0.0*	<0.0001
Satisfaction score	44.0 ± 32.5	38.1 ± 18.7	NS	49.4 ± 33.8	86.8 ± 13.1*	<0.0001
Appearance of walking score	2.40 ± 0.60	2.64 ± 0.49	NS	2.15 ± 0.59	1.4 ± 0.67*	0.0005
Adverse effects						
Incidence of pruritus (%)	5%	14%	NS	5%	55%*	0.0003
Anti-pruritic use (%)	0%	0%	NS	0%	5%	NS
Maximum pruritus score within 24 h	1.4 ± 6.3	10.1 ± 27.0	NS	2.1 ± 9.4	32.4 ± 34.0*	0.0004
Incidence of nausea (%)	20%	10%	NS	20%	27%	NS
Frequency of vomiting (%)	10%	5%	NS	10%	14%	NS
Anti-emetic use (%)	5%	0%	NS	5%	0%	NS
Maximum nausea score within 24 h	1.8 ± 6.8	3.0 ± 13.9	NS	2.5 ± 7.9	20.9 ± 35.7*	0.03
Incidence of somnolence (%)	20%	32%	NS	30%	45%	NS
Maximum somnolence score within 24 h	8.9 ± 21.8	15.9 ± 25.8	NS	9.7 ± 20.3	19.1 ± 28	NS

Values are mean ± SD or number of patients or requests. Complete analgesia denotes the time from the intrathecal injection to the first report of pain (visual analog scale score>0). Effective analgesia denotes the time from the intrathecal injection to the first analgesic intervention. *p<0.05 versus 1st cesarean section. The columns of "P value" show the p value between group 1 and group 2. NS, not significant.

cesarean section. Intravenous droperidol[15], ondansetron[16], and dexamethasone[17] have all been reported to decrease nausea and pruritus in the first 24 hours after cesarean delivery. In the present study, all patients received droperidol 2.5 mg intravenously after the umbilical cord was clamped[18, 19]. The frequency and severity of nausea, vomiting and pruritus were higher in patients who receive intrathecal morphine than in those who did not. These side effects did not decrease the overall satisfaction score, but future studies should explore additional ways to decrease the incidence and severity of adverse effects. Administration of IT morphine at a dose lower than 0.2 mg might provide similar analgesia with fewer side effects. Investigations of the minimum IT morphine dose required when systemic NSAIDs are administered simultaneously should lead to further benefit for post cesarean patients. Droperidol also has some side effects, which include sedation, agitation, dysphoria,

and QT prolongation in the ECG. Droperidol may have analgesic potential or an opiate-sparing effect when administered to prevent nausea and pruritus after IT morphine[20]. However, this analgesic effect was not found in our study, because a small dose of droperidol bolus does not have a long analgesic effect. Some patients complained of more somnolence after the present operation than the last operation, but this was not significant.

Post cesarean section, patients who use PCA[21] or PCEA with opioids[22,23] may have increased opioid-induced somnolence. These new technologies are expensive and may compromise a woman's ability to care for her child immediately after delivery. When continuous epidural blockade for post-cesarean analgesia is used, local anesthetics may impair care of the newborn due to motor blockade, and subcutaneous morphine depresses respiration[24]. Furthermore, intravenous PCA with opioids is associated with neonatal neurobehavioral depression in nursing parturients[2]. We observed no adverse effects on the neonates in this study. Group 1 patients were not more sedated during the first postoperative day than patients in group 2. Patients in group 1 might have required less extra analgesia because they were limiting their activity due to postoperative pain. However if additional analgesics had been administered to eliminate all pain, both parturients and newborns might have been more sedated and there may have been additional side effects. The combination of spinal morphine and rectal NSAIDs is one strategy for avoiding the dose-dependent side effects of systemic opioid administration.

When used along with oral analgesics, small doses of spinal morphine provide adequate pain relief after cesarean delivery[25] without depressing respiration or compromising the woman's ability to care for her newborn[26]. Furthermore, small doses of spinal morphine are a time- and cost-effective method of providing adequate analgesia and patient satisfaction[24]. The present study suggests that the combination of IT morphine and rectal NSAIDs also might reduce the nursing workload related to postoperative pain[23] and lead to a decrease of time spent by patients in the recovery room. In addition, early return to normal activities of daily living, along with the use of low-molecular-weight heparins, may decrease complications such as thrombosis[27]. A walking score was included in this study as a practical indicator of patients' ability to care for their babies, whereas most previous assessments of postoperative recovery have used only cardiovascular and respiratory parameters such as the Aldrete score[28], but not accounted for the psychomotor function needed to care for the newborn. Cesarean section patients with ASA physical status 1 to 2 usually demand perioperative safety and comfort from their anesthesiologist. Despite the relatively high incidence of minor adverse effects, such as pruritus and nausea, the use of IT morphine increased patient satisfaction in this study.

Conclusion

IT morphine and NSAIDs following cesarean section provide satisfactory pain relief and might be a cost effective alternative to the new pain management technologies currently in use. This technique does not need any special equipment, so can be provided at most hospitals.

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