The Impact of Nalmefene on Side Effects Due to Intrathecal Morphine at Cesarean Section

Introduction

Spinal anesthesia is used commonly for cesarean section because of the simplicity of the technique and its rapid onset of anesthesia. Often, intrathecal morphine sulfate is administered at the time of the spinal anesthetic for postoperative analgesia. Compared with groups of patients given parentally or orally administered analgesics for postoperative pain control, those who received intrathecal morphine had improved analgesic satisfaction scores, ambulated earlier, and were discharged earlier from the hospital.14 When administered intrathecally, morphine produces profound analgesia by direct action on the spinal cord that begins approximately 1 hour after administration with a duration of up to 24 hours.7,8 However, intrathecal morphine is associated with a high incidence of side effects that can last up to 12 hours. These side effects include pruritus, nausea, vomiting, urinary retention, and respiratory depression.9

Intrathecal morphine is an attractive option in the obstetrical population because it has been shown that when the dose is limited to less than 0.3 mg, no effect on fetal heart rate, neonatal Apgar scores, umbilical acid-base status, or blood gas tensions are seen.10-12 While no adverse effects are seen in the neonate with this small dose, a high incidence of maternal side effects occurs. Maternal side effects increase proportionally to the dose of the intrathecally administered morphine sulfate. Therefore, the dose typically administered to patients undergoing cesarean section for postoperative analgesia is small, most commonly 0.25 mg. Despite this small dose, the incidence of side effects is high, with a reported incidence of pruritus ranging from 40% to 60%, followed by nausea and vomiting at 20% to 40%, urinary retention at 20%, and respiratory depression at less than 2%.10-12 Often these side effects are resistant to the standard treatment protocols of administering an antihistamine for pruritus or an antiemetic for nausea and vomiting and usually require an opioid antagonist for full reversal of side effects.9,12

Naloxone, the most commonly administered antagonist, typically is given in small intravenous doses ranging from 200 to 400 µg. Studies have shown that this will reverse most cases of intrathecal morphine–induced side effects without an adverse effect on the level and quality of analgesia.9 However, due to the short duration of action of naloxone (1-1.5 hours), patients often require supplemental doses for complete reversal of side effects, which can result in a decrease in analgesic efficacy.13 To avoid the need for supplemental doses of naloxone, some clinicians advocate using the long-acting opioid antagonist naltrexone.15 Studies have shown that naltrexone is efficacious for providing long-term relief from opioid induced side effects. In fact, some studies have shown that naltrexone can be administered prophylactically following intrathecal morphine and result in a significant reduction in the occurrence and severity of side effects. However, when the dose exceeds 6 mg, a reduction in the level and quality of analgesia occurs, and patients often require supplemental analgesia. In addition, naltrexone must be given orally; thus, its usefulness is limited for most post-

Nalmefene is a long-acting opioid antagonist that provides long-term relief from side effects of intrathecal morphine sulfate. A randomized, double-blind, placebo-controlled study was conducted to determine whether prophylactic nalmefene could decrease side effects of intrathecal morphine given during cesarean section, without affecting analgesia. Sixty parturients were given 0.25 mg of intrathecal morphine, 12.5 µg of fentanyl, and 11.25 to 15 mg of bupivacaine. A dose of 0.25 µg/kg of nalmefene or placebo was given by intravenous piggyback immediately after delivery of the neonate.

Nausea, vomiting, pruritis, and level of sedation were assessed for a 24-hour period using a 4-point ordinal scoring system. Pain was assessed by using a 0- to 10-point verbal analogue scale. A 5-point analgesic satisfaction survey also was completed.

Subjects who received nalmefene required supplemental analgesia at a median of 6.00 hours after intrathecal morphine, compared with 14.12 hours in the placebo group (P = .037). No differences were found between the groups in the incidence of pruritis, nausea and vomiting, level of sedation, or analgesic satisfaction.

We concluded that nalmefene at a dose of 0.25 µg/kg does not decrease the incidence of side effects but increases the need for supplemental analgesics.

Key words: Cesarean section, intrathecal opioids, nalmefene, neuraxial side effects of morphine, obstetrical anesthesia.

CDR Joseph E. Pellegrini, CRNA, DNSc, NC, USN
Bethesda, Maryland
CAPT Steven L. Bailey, MD, MC, USN
Portsmouth, Virginia
Jeffery Graves, MD
Louisville, Kentucky
Judith A. Paice, RN, PhD, FAAN
CDR Joseph E. Pellegrini, CRNA, DNSc, NC, USN
Chicago, Illinois

Margaret Faut-Callahan, CRNA, DN Sc, FAAN
Susan Shott, PhD

Capt Steven L. Bailey, MD, MC, USN
Portsmouth, Virginia

Judith A. Paice, RN, PhD, FAAN

Margaret Faut-Callahan, CRNA, DNSc, FAAN

Chicago, Illinois

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operative patients because they are unable to take oral medications during the immediate postoperative period.14

In 1986, nalmefene, a new long-acting, pure opioid antagonist for parenteral administration, was introduced. Nalmefene is a water-soluble form of naltrexone with a mean beta elimination half-life of 8.5 hours. Studies have shown that it has the ability to reverse all side effects from opioids for approximately 10 to 18 hours.15-18 Brown and associates19 were the first to study the effect of nalmefene on intrathecal morphine-induced pruritis in a population of patients after cesarean section. They administered an average dose of 0.25 µg/kg of nalmefene when patients complained of pruritus and compared results with those for a group of patients given naloxone. Nalmefene reversed the pruritis for a significantly longer period of time than the naloxone and was reported to have no effect on the quality and duration of analgesia. While nalmefene has been shown to be efficacious for reversing all side effects from intrathecal morphine, no study to date has analyzed the effect of the administration of a prophylactic dose of nalmefene on these same variables. Therefore, we performed the present study.

Methods

All patients requiring a subarachnoid block for a non-emergent, nonurgent cesarean section were approached for inclusion in this institutional review board–approved study. Patients were excluded from the study if they had a history of sensitivity to morphine, naloxone, or nalmefene; preoperative nausea, vomiting, pruritus, or hypotension; or a history of diabetes, renal failure, bleeding disorders, preeclampsia, eclampsia, cardiac anomalies, central nervous system disorders, or opioid addiction. Once the inclusion criteria were met and informed consent was obtained, subjects were assigned to the experimental (nalmefene) or the control (placebo) group, using computer-generated randomization. Before initiation of the study, a sample size of 30 subjects per group was estimated by power analysis. Inclusion of 30 subjects per group ensured 80% power for detecting a difference between the groups using a 2-sided Mann-Whitney test with a .05 significance level if the probability that an observation in one group is less than an observation in the other group is 0.71.20 Some assumptions were based on previously published data that reported a reversal of pruritis by nalmefene in patients after cesarean section who had received intrathecal morphine.19

Assessments for pain, pruritis, nausea and vomiting, and level of sedation were performed preoperatively to serve as a baseline and postoperatively every hour for the first 12 hours following surgery and every 2 hours thereafter, for a total of 24 hours. Pain was assessed using a 0- to 10-point ordinal verbal analog scale with 0 designating “no pain” and 10 indicating “the worst possible pain.” A 0- to 3-point ordinal scale was used to measure levels of pruritis, nausea and vomiting, and level of sedation. Pruritis was analyzed by the following scale: 0, none; 1, occasional; 2, bothersome but relieved with medications; and 3, intolerable with no relief with medications. The nausea and vomiting scale was as follows: 0, none; 1, minimal; 2, moderate with no emesis; and 3, severe with emesis. For level of sedation, the subjective 0- to 3-point ordinal scale included the following: 0, alert; 1, drowsy; 2, sleeping but arousable; and 3, unarousable. In addition, a 5-point analgesia satisfaction survey was performed during the postoperative interview approximately 16 to 24 hours after the cesarean section.

Before transport to the operative suite, a preoperative measurement of vital signs and fetal heart tones was performed. A bolus of 15 mL/kg of lactated Ringer’s solution was given over a 45-minute period immediately before entry into the operative suite. After entry into the operative suite, standard monitors were placed, and a subarachnoid block was performed using aseptic technique. The subarachnoid block was placed with the patient in the sitting position; a 25-gauge Whitacre spinal needle was inserted at either the L2-3 or L3-4 interspace and advanced to yield free-flowing cerebral spinal fluid. The patient then was given a spinal anesthetic consisting of 11.25 to 15 mg of bupivacaine, 0.25 mg of preservative-free morphine, and 12.5 µg of fentanyl. This combination of fentanyl and morphine was used because it is the routine intrathecal opioid combination in our clinical practice setting to facilitate postoperative analgesia in patients undergoing cesarean section. After injection of the opioid-bupivacaine mixture into the subarachnoid space, the spinal needle was removed, and the patient was placed immediately in the supine position. Maternal vital signs were monitored and recorded every 5 minutes intraoperatively. After a sensory level of at least T5 was established, the obstetrician performed the cesarean section. Neonatal Apgar scores were determined by the resident pediatricians and recorded.

Patients were randomized into either an “A” or “B” group according to subject number before initiation of the study. Those randomized to group A were assigned to receive medication from a vial designated as the “A” vial, while those assigned to group B received medications from the “B” vial. The pharmacy
pain. In addition, 0.4 mg of naloxone was placed at hydrochloride, 5 mg intravenously every 4 hours as needed. Breakthrough pain was treated with acetaminophen for mild pain and oxycodone for moderate pain. In addition, 0.4 mg of naloxone was placed at every patient’s bedside with instructions that it was to be given intravenously if clinically significant respiratory depression or excessive somnolence occurred.

On postoperative day 1 (after data were collected for at least 16 hours by nursing personnel), each patient’s chart was reviewed. All data including demographics (age, height, weight, race, gravida, and parity), pain scores, side effect scores, and any necessary interventions were recorded on a data flow sheet by the primary or associate investigators. A postoperative interview also was performed, which included an analgesic satisfaction survey with ordinal scoring as follows: 1, completely dissatisfied, poor pain control with continuous severe pain; 2, dissatisfied, poor pain control with frequent severe pain; 3, somewhat dissatisfied, poor pain control with infrequent severe pain; 4, satisfied, adequate pain control with only mild to moderate pain; and 5, completely satisfied, good pain control with only mild pain.

All data were evaluated for entry errors, missing data, and consistency before statistical analysis. Statistical analysis was done using SPSS for Windows, version 7.5 (SPSS, Chicago, Ill.). Normality assumptions were examined, and the data were found to be statistically nonnormal. For this reason, nonparametric methods were used to analyze the data. The chi-square test of association was done to compare the study groups with respect to nominal demographic data. A Mann-Whitney test was used to compare the groups with respect to nonnominal data. Kaplan-Meier curves and the log-rank test were used to compare the groups with respect to the time until a request for supplemental analgesia and the times until risk of breakthrough pain and the occurrence of side effects. All data are expressed as the median or mean ± SD. A P value of less than .05 was considered significant.

Results
A total of 62 subjects were enrolled in the study. One subject was dropped from the study due to failure to answer questions in the postpartum period, and the data for another subject were removed from the analysis because the spinal anesthetic was converted to a general anesthetic due to extensive hemorrhaging and extension of the surgical site. Data for 60 subjects were analyzed. No statistically significant demographic differences were found between the groups (Table 1).

Pain scores were higher in the nalmefene group than in the placebo group, with statistically significant differences at 9 (P = .033), 10 (P = .044), and 22 (P = .045) hours following intrathecal morphine sulfate administration (Figure 1). There was a statistically significant difference between the groups with respect to the time until supplemental analgesia was requested during the 24-hour period following cesarean section (P = .037). Figure 2 shows that the placebo group took longer than the nalmefene group department performed vial designation, and both vials were exchanged weekly. These vials contained either the study medication of nalmefene 20 µg/mL or a placebo (bacteriostatic water) in 30 mL of bacteriostatic water. All intravenous piggybacks then were formulated using these vials to contain 0.25 µg/kg nalmefene or placebo in 50 mL of 0.9% sodium chloride solution and given over a 20-minute period immediately after delivery of the neonate. A log was kept in the pharmacy that contained the code that identified the nalmefene and placebo vials. This code was not disclosed to the researchers until completion of the study.

Upon entry to the recovery room, maternal vital signs were obtained and recorded every 15 minutes and a spinal-epidural order sheet was written that detailed the treatment regimens for breakthrough pain, pruritis, nausea and vomiting, and excessive sedation. This treatment regimen was ordered to remain in effect for the length of the study period, a period of 24 hours. In addition, orders were written to perform postoperative assessments using the 0- to 3-point ordinal scoring system every hour for the first 12 hours following surgery and every 2 hours thereafter. Postpartum assessments were conducted by nursing staff who were blinded as to whether the patient had received a placebo or the study drug.

Nursing staff were instructed to not awaken patients at night to perform assessments. Nursing personnel were instructed to contact the obstetrical anesthesia department immediately in all instances of a pain score greater than 7, if a respiratory rate of less than 8 breaths per minute was noted, or if an ordinal score of 3 was recorded for side effects. Before initiation of the study, the nursing staff members were educated about proper use of the data flow sheet and assessment techniques used in this study. Complaints of nausea were treated with ondansetron, 4 mg intravenously every 4 hours as needed. Nursing personnel were instructed to contact obstetrical anesthesia staff if the subject experienced unresolved nausea after a total dose of 8 mg (2 4-mg doses or a total of 8 mg) of ondansetron was given or in the presence of protracted vomiting. Pruritis was treated with nalbuphine hydrochloride, 5 mg intravenously every 4 hours as needed. Breakthrough pain was treated with acetaminophen for mild pain and oxycodone for moderate pain. In addition, 0.4 mg of naloxone was placed at every patient’s bedside with instructions that it was to be given intravenously if clinically significant respiratory depression or excessive somnolence occurred.

On postoperative day 1 (after data were collected for at least 16 hours by nursing personnel), each
to request supplemental analgesia. The median times until subjects' first request for supplemental analgesia in the nalmefene group was 6.00 hours compared with 14 hours in the placebo group (Table 2).

Oxycodone was requested by 87% (n = 26) of patients for first request for analgesia in the nalmefene group, compared with 45% (n = 13) of patients in the placebo group. Second requests for analgesia were similar between the 2 groups, with approximately 40% (12 patients) of both groups requesting oxycodone for analgesia and approximately 60% (18 patients) requesting acetaminophen.

When pruritis scores were analyzed, we noted overall higher scores in the placebo group than in the nalmefene group, but the differences were statistically significant only at the 10th (P = .008) and 11th hours (P = .018) following nalmefene administration. The placebo group had a higher incidence of requests for treatment for complaints of pruritis than did the nalmefene group, but this difference was not statistically significant. The median time until first request for treatment of pruritis was shorter in the placebo group than in the nalmefene group (10.92 vs 12.46 hours), but this difference was not statistically significant (P = .281) (Figure 3).

No statistically significant difference was found between the groups with respect to reported nausea and vomiting (P = .201). Median times until treatment for nausea and vomiting also were similar between the groups, with a median of 9.3 hours in the nalmefene group and 7.50 hours in the placebo group. In addition, there were no statistically significant differences between the groups with respect to the level of sedation (P = .378) or the analgesic satisfaction rating (P = .561). No subject in either group experienced a profound degree of sedation, and most reported satisfactory postoperative analgesia. No respiratory depression was seen in either group.

**Discussion**

To our knowledge, this study is the first to examine...
the effects of prophylactic nalmefene on side effects in parturients receiving intrathecal opioids for cesarean section. The duration of analgesia was reduced significantly in the nalmefene group compared with the placebo group. This finding conflicts with the results of the study by Brown et al.\textsuperscript{10} which found no decrease in analgesia when a median dose of 0.25 µg/kg of nalmefene was given for reversal of intrathecal morphine-induced pruritis. However, Brown et al.\textsuperscript{10} did not report an increased need for supplemental analgesia in their study population; they reported only that analgesic satisfaction scores were similar between the groups. The findings of our study also conflict with those of studies that reported that the administration of small amounts of other opioid antagonists (naltrexone, naloxone) have no effect on the quality or duration of analgesia.\textsuperscript{14,21,22}

In the present study, statistically significant increases in reported pain scores occurred at 9, 10, and 22 hours following intrathecal morphine administration. The 9th and 10th hours correspond to nalme-fene’s mean beta-elimination half-life, suggesting a possible relationship between the peak beta-elimination time of nalme-fene and the relative antagonistic potency. However, there are no data to confirm such a relationship, and further studies are needed. The increased analgesic requirements at the 22nd hour following intrathecal morphine administration could be explained by the relative increase in most postpartum patients’ activity levels following the cesarean section. In addition, the nalmefene group required more aggressive treatment for breakthrough pain with oxycodone compared with the placebo group, thus adding credence to the theory that nalme-fene causes a marked reversal in analgesia supplied by intrathecal morphine.

Another possible explanation for the diminished analgesia in the nalme-fene group could be related to intrathecal morphine’s pharmacokinetics and dynamics, coupled with the timing of nalme-fene administration. The early administration of nalme-fene may not allow for the intrathecal morphine to fully occupy the opioid receptor sites during the time of rostral spread, thereby decreasing analgesic duration and potency. Prophylactic administration of nalme-fene before the onset of analgesia from the intrathecal morphine may have allowed for a greater concentration of nalme-fene at the opioid mu, kappa, and delta receptors in the central nervous system, thereby decreasing analgesic efficacy. Further studies are needed to evaluate this possibility.

Many of the findings in the present study mirror results in other studies of the use of intrathecal morphine sulfate in patients undergoing cesarean section.\textsuperscript{23–25} Pruritis was the most frequent complaint, with 57% (34) of the patients requiring treatment for pruritis followed by an approximate 35% (21 patients) incidence of nausea. No incidence of respiratory depression or excessive somnolence was observed, which is consistent with clinical reports of no incidence of respiratory depression or marked sedation when a dose of 0.3 mg or less of intrathecal morphine sulfate was used for postoperative analgesia.

No differences in analgesic satisfaction scores were noted when age, ethnic origin, and parity were analyzed. The majority of subjects in both groups reported analgesic satisfaction scores of 4 (satisfied) or 5 (completely satisfied). When the analgesic satisfaction scores were compared for patients reporting the highest pain scores and patients reporting the lowest pain scores, no statistically significant differences were found. This suggests that analgesic satisfaction may not be a good indicator of overall postoperative analgesia. However, patient perception about overall analgesic satisfaction is one of the most important variables to consider in any study measuring such subjective variables as pain and satisfaction. One possible explanation for the similar findings between the high-pain and low-pain groups could be adequacy of the supplemental analgesics given for breakthrough pain.

The primary limitations of this study pertain to method and design. Of the parturients, 78% (47 out of 60) were undergoing scheduled cesarean sections. This was unavoidable because of limitations of including only subjects requiring a nonurgent, non-emergent cesarean section. Other limitations included the demographic makeup of the study population, the large number of individuals involved in hourly assessments, and a possible influence of a “rescue phenom-
enon.” All subjects were informed that medications were ordered for side effects and breakthrough pain. Since this information was stressed, we do not know whether subjects or nursing personnel had a lower threshold for using supplemental medications, thus initiating the possible rescue phenomenon. The study population added a limitation because all parturients were active duty military or dependents and possibly not a true representation of the general population. Data collection occurred over a 24-hour period; thus, a large number of nursing personnel were used to collect the data. This variability in nursing personnel made it difficult to ensure that consistent assessments were performed.

Conclusions
Because of the benefits that intrathecal morphine offers over parentally administered morphine for patients undergoing cesarean section, it will continue to be widely used despite the high incidence of side effects. The prevalence of intrathecal morphine use and the severity of side effects dictate that studies of the control of side effects must continue. The present study did not show that nalmefene, when given prophylactically, is efficacious for decreasing side effects, but study results invite consideration of whether we should try to provide prophylaxis against side effects or simply treat them as they occur. The use of nalmefene may be particularly attractive to an anesthesia practice that routinely uses intrathecal morphine for labor analgesia for vaginal deliveries. Nalmefene can be administered to these parturients during the immediate postpartum period when analgesic considerations are not as predominant as for patients immediately after cesarean section. The use of nalmefene in this postpartum population may prove beneficial for allaying or reducing the side effects of intrathecal morphine sulfate, thereby resulting in overall increased patient comfort. However, based on the findings in the present study, prophylactic administration of nalmefene to the patients after cesarean section cannot be recommended.

Many obstetrical anesthesia practices often administer prophylactic opioid antagonists to parturients after they have received neuraxially placed opioids. This prophylaxis often is given in the form of a naloxone infusion administered over a 24-hour period. Based on the results of the present study, this practice may not be prudent or in the best interests of patients. A reexamination of this clinical practice is warranted, as the prophylactic administration of opioid antagonists may be more detrimental than beneficial to patients given neuraxially placed opioids.

REFERENCES


**AUTHORS**

CDR Joseph E. Pellegrini, CRNA, DNSc, NC, USN, is director of Research, Navy Nurse Corps Anesthesia Program, Bethesda, Md.

CAPT Steven L. Bailey, MD, MC, USN, is department head, Anesthesia, Naval Medical Center, Portsmouth, Va.

Jeffery Graves, MD, is the department head, Anesthesiology, Caritas Hospital, Louisville, Ky.

Judith A. Paice, RN, PhD, FAAN, is a research professor of Medicine, Hematology/Oncology Department, at Northwestern University, and a member of the Palliative Care and Home Hospice Program, Northwestern Memorial Hospital, Chicago, Ill.

Susan Shott, PhD, is a consultant in the Department of Biostatistics, Rush University, Chicago, Ill.

Margaret Faut-Callahan, CRNA, DNSc, FAAN, is program director, Nurse Anesthesia Program, Rush University, Chicago, Ill.

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