Comparison of 0.25 mg and 0.1 mg intrathecal morphine for analgesia after Cesarean section

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Purpose: To test the hypothesis that 0.1 mg intrathecal morphine plus NSAIDs provides satisfactory analgesia post-Cesarean section with fewer side effects than 0.25 mg intrathecal morphine.

Methods: Sixty women, scheduled for elective Cesarean section under spinal anesthesia, were randomized to receive either 0.1 mg or 0.25 mg intrathecal morphine combined with hyperbaric bupivacaine 0.75% and 20 µg fentanyl. All patients received a 100 mg indomethacin suppository at the end of surgery and 500 mg naproxen *po* b.i.d. was started the evening of surgery and continued until discharge. A blinded researcher recorded the pain, pruritus, and nausea scores, the time to first request for additional analgesics, a visual analogue scale (VAS) satisfaction score, and the use of additional opioids, antipruritics, and/or antiemetics.

Results: Of the 60 patients enrolled, two were not included in the data analysis because of protocol violations leaving 30 patients in the 0.1 mg group and 28 in the 0.25 mg group. There were no differences in the VAS pain scores or the number of women requesting an opioid other than codeine between the two groups. The VAS pruritus scores in the 0.1 mg group were lower throughout the 24 hr ($P < 0.001$). Fewer women in the 0.1 mg group (4/30 vs 12/28) requested nalbuphine to treat itching ($P = 0.018$). Nausea scores were lower in the 0.1 mg group ($P < 0.001$).

Conclusion: The use of 0.1 mg intrathecal morphine plus NSAIDs provides analgesia of similar quality to 0.25 mg but with fewer undesirable side effects following Cesarean section.

Objectif : Vérifier l'hypothèse qui veut que 0,1 mg de morphine intrathécale combinée à des AINS fournissent une analgésie satisfaisante à la suite d'une césarienne et moins d'effets secondaires que 0,25 mg de morphine intrathécale.

Méthode : Soixante femmes, admises pour une césarienne planifiée sous rachianesthésie et réparties au hasard ont reçu 0,1 mg ou 0,25 mg de morphine intrathécale combinée à de la bupivacaine hyperbare 0,75 % et à 20 µg de fentanyl. Toutes ont reçu un suppositoire de 100 mg d'indométhacine à la fin de l'opération et 500 mg de naproxène *po* b.i.d. à partir du premier soir jusqu'au jour du départ. Un anesthésiologiste impartial a enregistré les scores de douleurs, de prurit et de nausées, le temps avant la première demande d'analgésiques supplémentaires, le degré de satisfaction à l'échelle visuelle analogue (EVA) et l'usage d'opioïdes, d'antiprurigineux et/ou d'antiémétiques additionnels.

Résultats : Des 60 patientes recrutées, deux n'ont pu participer à la cueillette de données à cause de violations au protocole de recherche; il est resté 30 patientes dans le groupe de 0,1 mg et 28 dans celui de 0,25 mg. Il n'y a pas eu de différence intergroupe pour les scores à l'EVA ou le nombre de femmes qui ont demandé un opioïde autre que la codéine. Le degré de prurit fourni par l'EVA a été plus bas dans le groupe de 0,1 mg pendant 24 h ($P < 0,001$). Moins de femmes du groupe de 0,1 mg (4/30 vs 12/28) ont demandé de la nalbuphine contre le prurit ($P = 0,018$) et les scores de nausées ont été plus bas dans ce groupe également ($P < 0,001$).

Conclusion : L'utilisation, après la césarienne, de 0,1 mg de morphine intrathécale combinée à des AINS a fourni une analgésie de qualité semblable à celle qui a été produite avec 0,25 mg, mais comportant moins d'effets secondaires.

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INTRATHECAL morphine, 0.25 mg, is widely used for analgesia following Cesarean section under spinal anesthesia. However, there are bothersome side effects associated with this dose such as nausea, vomiting, and particularly itching. Because of a possible "ceiling effect",^{1,2} a dose of intrathecal morphine lower than 0.25 mg following Cesarean section may be indicated. This "ceiling effect" refers to a dose above which there is no additional analgesia but an increased incidence of side effects. Doses as low as 0.1 mg have been sporadically reported in studies suggesting it may provide adequate post-operative analgesia.²⁻⁴ This may be especially true when non-steroidal anti-inflammatory drugs (NSAIDs) are part of the post-operative analgesic regimen.

It was hypothesized that a lower dose of intrathecal morphine, 0.1 mg, could provide satisfactory analgesia following Cesarean section when combined with indomethacin/naproxen (NSAIDs), because of their possible additive analgesic effects. We hoped that this lower dose would produce fewer side effects, notably pruritus, than that with 0.25 mg of intrathecal morphine.

Methods

Pruritus was the primary outcome measured. Previous studies²⁻⁶ have demonstrated an 80% incidence of pruritus with 0.25 mg intrathecal morphine and 40% with 0.1 mg. At a power ($1-\beta$) of 0.80 and $P(\alpha)$ of 0.05, 30 patients per group would allow detection of a 50% difference in the incidence of pruritus between the higher *vs* the lower dose of intrathecal morphine.

The study was prospective, randomized and double-blind. Following Medical Research Ethics Board approval, written informed consent was obtained from patients who were then entered into the study. All women scheduled for elective Cesarean section who met the inclusion criteria and did not have any of the exclusion criteria were eligible for the study. The inclusion criteria were: informed consent, ASA classification I or II, age ≥ 18 yr, and gestational age ≥ 36 wk. The exclusion criteria were: allergy to morphine, indomethacin, or naproxen, contraindications to spinal anesthetic, contraindications to NSAIDs, and/or inability to speak English.

The parturients were randomized when they presented for their Cesarean section under a spinal anesthetic. The women received 1.2 - 1.8 ml hyperbaric bupivacaine 0.75%, 20 μ g fentanyl, and either 0.1 mg or 0.25 mg intrathecal morphine (0.5 mg·ml⁻¹ solution). At the completion of surgery, all patients received 100 mg indomethacin *pr*. Then naproxen, 500 mg twice daily *po* was started, and the patients

remained on this dose for the duration of their stay in hospital. Post-operative analgesics included: 325-650 mg acetaminophen *po* q4h *prn*, 1-2 tabs Tylenol #3 *po* q4h *prn*. The attending physician ordered additional analgesics as necessary. Nalbuphine, 5 mg, *im/sc* q3h *prn* and 50 mg gravol *im* q4h *prn* were ordered for pruritus and nausea respectively. The women were told to ask for antipruritics and/or antiemetics when they were required. Any analgesics, antipruritics, and/or antiemetics given intra-operatively were included in the analysis.

Demographic data were obtained including: age, gravida, parity, height, and weight. Assessment of the effectiveness of analgesia as well as the presence of side effects between the two doses of intrathecal morphine was performed by a blinded researcher. The time intervals at which the patients were assessed were: 0 hours (before the dose), on arrival in post-anesthetic recovery room (PARR), 2, 4, 8, and 24 hr after the dose. In addition, overall patient satisfaction was also measured at 24 hr. Pain, pruritus, and satisfaction were measured on a 10 cm visual analogue scale (VAS) labeled "no pain/itch and complete unsatisfaction" at one end and "worst imaginable pain/itch and complete satisfaction" at the other. Nausea was measured on a 5-point ordinal scale, where 0 = no nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea, and 4 = vomiting in the last hour. The time for a patient to first request additional analgesics was also documented. Finally, the use of additional medications including analgesics other than codeine and acetaminophen, antipruritics, and/or antiemetics were noted.

Pain, pruritus, and nausea scores were analyzed with two-way repeated analysis of variance (ANOVA). Post-hoc analysis using multiple independent sample t tests with Bonferroni correction was performed to determine the time interval(s) where significant differences (if any) occurred. The independent sample t test and Mann-Whitney U test were applied where it was appropriate. The Fisher's exact test was applied to the frequencies of additional analgesic, antipruritic, and/or antiemetic use. A *P*-value of ≤ 0.05 was deemed to be significant.

Results

Sixty patients of the first 62 patients approached were enrolled and two were not included in the data analysis because they did not receive NSAIDs. Of the remaining 58, 30 were in the 0.1 mg group and 28 in the 0.25 mg group.

There were no differences between the two groups with respect to demographic data (Table I). There

TABLE I Comparison of demographic data

	0.1 mg (N = 30)	0.25 mg (n = 28)	P
Age (yrs)	31.2 ± 4.4 (22-39)	28.0 ± 5.4 (19-41)	0.88
Height (cm)	161.2 ± 7.3 (150-173)	164.4 ± 6.6 (150-175)	0.09
Weight (kg)	82.2 ± 16.5 (60-127)	80.1 ± 13.2 (64-111)	0.59

Values are expressed as mean ± standard deviation (range)

TABLE II Proportion of women requesting additional medications

	0.1 mg (number/total)	0.25 mg (number/total)	P
Additional narcotics (other than codeine)	4/30	4/28	0.99
Antipruritics	4/30	12/28	0.018
Antiemetics	11/30	15/28	0.29

were also no differences between the two groups in terms of the VAS pain scores over time ($P = 0.33$) and the number of women requesting an opioid(s) other than codeine ($P = 0.99$, Table II). The additional opioids requested were lertine *po*, percocet *po*, morphine *im*, or demerol *im*. There were, however, differences with respect to pruritus. The 0.1 mg group had consistently lower pruritus scores throughout the 24 hr postoperative period ($P < 0.001$, Figure 1). Post-hoc analysis demonstrated lower pruritus scores at four and eight hours in the 0.1 mg group. Fewer women in the 0.1 mg group (4/30) than in the 0.25 mg group (12/28) requested nalbuphine for itching ($P = 0.018$, Table II). The nausea scores were also lower in the 0.1 mg group over the 24 hr postoperative period ($P < 0.001$, Figure 2). Post-hoc analysis failed to determine the specific time interval(s) in which these differences occurred. There were no differences in the number of women between the two groups requesting antiemetics post-operatively.

The time for patients to first request acetaminophen and/or codeine was not different between the groups ($P = 0.8$); average time approximately 700 min. There were also no differences in the satisfaction scores between the two groups ($P = 0.13$).

Discussion

Providing pain relief following Cesarean section is one of the many uses of intrathecal opioids, specifically morphine. Because of the low lipid solubility of morphine,⁷ it is retained in the cerebrospinal fluid, prolonging the

FIGURE 1 Comparison of VAS pruritus scores in the 0.1 mg group vs the 0.25 mg group postoperatively.

FIGURE 2 Comparison of 5-point nausea scores in the 0.1 mg group vs the 0.25 mg group postoperatively.

duration of action as well as promoting its cephalad spread. Morphine not only acts on the opioid receptors in the substantia gelatinosa of the dorsal horn of the spinal cord, but exerts a supraspinal effect to provide analgesia.⁸ However, morphine produces undesirable side effects such as pruritus, which may result from a

direct action of the opioid on the trigeminal nucleus in the medulla.⁹ Morphine may also interact in the substantia gelatinosa of the spinal cord to cause pruritus.⁹ Its cephalad spread to the chemoreceptor trigger zone on the floor of the fourth ventricle and the pons results in nausea/vomiting and respiratory depression respectively.¹⁰ However, respiratory depression is unlikely with the doses currently used.²⁻⁶

Various authors have shown that NSAIDs can decrease the amount of other analgesic drugs required in the post-operative period.^{11,12} The combination of opioids and NSAIDs may result in a synergistic action that provides satisfactory postoperative pain control.¹² After Cesarean section, NSAIDs may relieve pain via an anti-inflammatory effect at the surgical wound. They may also depress uterine contractility through their inhibition of prostaglandin synthesis, minimizing the pain associated with uterine cramping post-operatively.^{11,14} The risk of post-partum bleeding from NSAIDs in this patient population is theoretical and has not been reported in previous studies.¹¹⁻¹⁴ An additional mechanism of action may involve reduction of both the acute and the delayed pain via central mechanisms.¹² At the Foothills hospital, it is standard practice to administer a 100 mg indomethacin suppository at the end of a Cesarean section followed by 500 mg naproxen *po* twice daily.

As shown in this study, 0.1 mg intrathecal morphine in combination with naproxen provided satisfactory postoperative analgesia following Cesarean section when compared with 0.25 mg - the current standard dose. This was demonstrated by no differences in the VAS pain scores 24 hr post-operatively, in the use of additional opioid(s) other than codeine, and in the time to the first request of additional analgesia between the 0.1 mg and the 0.25 mg group. Pain scores with mobilization were not obtained and may have provided additional useful information. However, there were no differences between the two groups in terms of the use of additional opioids (other than codeine) post-operatively.

A clinically relevant additional finding was the smaller number of women who experienced pruritus and who required treatment with nalbuphine in the 0.1 mg group. Although there are effective methods for treating side effects from intrathecal morphine, such as pruritus, the avoidance of the side effects altogether may be more sensible. As shown, this can be achieved by lowering the intrathecal morphine dose used.

Although 60 women is a small sample size, the initial power analysis showed that this number would detect differences in the side effect profile, specifically pruritus, between the two different intrathecal morphine doses.

We recommend the use of 0.1 mg intrathecal morphine, a lower dose than commonly used, with NSAIDs following Cesarean section to provide effective analgesia with less pruritus.

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