Continuous Ropivacaine Subfascial Wound Infusion Compared With Intrathecal Morphine for Postcesarean Analgesia: A Prospective, Randomized Controlled, Double-Blind Study

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BACKGROUND: After cesarean delivery, postoperative pain management allows early rehabilitation and helps prevent postpartum depression and chronic pain. Our present prospective, randomized controlled, double-blind study assessed the duration and effect of intrathecal analgesia and continuous ropivacaine wound infiltration versus a control group after cesarean delivery. The primary outcome was analgesia duration, defined as time to first morphine request. Secondary outcomes were cumulative postoperative morphine consumption, number of patients who did not require IV morphine, incidence of adverse effects, and time to first ambulation.

METHODS: A total of 192 full-term parturients undergoing elective cesarean delivery were randomly allocated into 3 groups (control, morphine, and catheter). All patients received spinal anesthesia with 10 mg bupivacaine 0.5% hyperbaric bupivacaine (2 mL) + 5 µg of sufentanil (1 mL) and a multiholed catheter inserted into the wound. In the control group, NaCl 0.9% was administered intrathecally (0.1 mL) and through the catheter. The morphine group received 100 µg morphine (0.1 mL) intrathecally and NaCl 0.9% infused through the wound catheter. The catheter group received 0.1 mL NaCl 0.9% intrathecally and ropivacaine 0.2% infused in the catheter. Each patient received a 15-mL bolus of the dedicated solution through the catheter, which was connected to an elastomeric pump infusor delivering the same solution at a rate of 10 mL/h for 30 hours. All patients also received multimodal analgesia including acetaminophen and diclofenac. Analgesia duration was defined as the time from spinal injection (T0) to first IV morphine requirement (T1) administered via a patient-controlled IV analgesia pump. Statistical data analyses included use of the Kruskal-Wallis rank-sum test followed by the post hoc Tukey test and χ^2 test.

RESULTS: The duration of postoperative analgesia was increased with intrathecal morphine (380 minutes; 215–1527) and ropivacaine wound infusion (351 minutes; 227–594) compared with the control (247 minutes; 182–338) with effect sizes of 0.171 (0.043–0.293) for morphine versus control and 0.164 (0.052–0.271) for catheter versus control. There was no difference between the morphine group and catheter group (effect size, 0.007; −0.118 to 0.132). Cumulative postoperative morphine consumption was also significantly lower in the morphine group and catheter group compared with the control group. The incidence of adverse effects did not differ between groups.

CONCLUSIONS: After elective cesarean delivery, 100 µg intrathecal morphine and ropivacaine wound infusion both increased the duration and effect of postcesarean analgesia without increased incidence of side effects.   (Anesth Analg 2017;125:907–12)

C esarean delivery is a common intervention performed with steadily increasing frequency.[1] To avoid the complications associated with general anesthesia, spinal anesthesia has become the method of choice for this procedure.[2] Postoperative pain management allows early rehabilitation and helps to prevent postpartum depression and chronic pain.[3,4] For cesarean delivery, spinal anesthesia is often performed using a combination of 0.5 hyperbaric bupivacaine (HB) with a lipophilic opioid such as fentanyl or sufentanil.[5] In elective cesarean deliveries, intrathecal addition of 25 to 500 µg morphine during spinal anesthesia effectively extends postoperative analgesia[6] but at the expense of increasing adverse effects such as nausea, vomiting, or pruritus.[7–10]

Technologic innovations, including multiholed catheters and elastomeric pumps, open the door to novel analgesic approaches such as continuous wound infiltration with ropivacaine through a multiholed catheter.[11] Such practices could lead to lower the incidences of nausea, vomiting, and pruritus, enabling a better breastfeeding experience. Adverse effects of multiholed catheters are rare with no reports showing increased incidences of sepsis or delayed healing when

standard aseptic precautions are observed.[12] Continuous wound infusion with local anesthetic has shown potential benefits in abdominal surgery[13,14] and with Pfannenstiel incisions,[15–19] including reduced pain at rest and during mobilization as well as decreases in postoperative morphine consumption; incidences of nausea, vomiting, and pruritus; and length of hospital stay. However, scarce data are available comparing postcesarean analgesia with intrathecal morphine injection versus continuous wound infusion with local anesthetic with regard to efficacy and relative risks.

We performed a study in women undergoing elective cesarean delivery performed under spinal anesthesia with the aim of comparing the efficacies of intrathecal morphine injection and continuous wound infusion with local anesthetic versus a control group. The primary outcome was duration of analgesia until first IV morphine request via a patient-controlled IV analgesia pump. Secondary outcomes were postoperative IV morphine consumption, number of patients who did not require IV morphine, and incidence of adverse effects.

METHODS

This prospective randomized controlled, double-blind study included pregnant women admitted for planned cesarean delivery with Pfannenstiel incision at Brugmann University Hospital. This institute is a tertiary public hospital that performs approximately 3500 deliveries per year and a referral center for complicated patients. Inclusion criteria were age ≥18 years, an American Society of Anesthesiologists physical status of 1 or 2, and being ≥34 weeks of gestation Exclusion criteria were contraindication to regional anesthesia, allergy to products used in the study, American Society of Anesthesiologists score ≥3, sleep apnea syndrome, obesity (body mass index >35 kg/m²), height <155 cm, patient refusal, and the presence of a language barrier. All patients received verbal and written information about the study and wrote informed consent. This study was approved by the ethics committee of Brugmann on January 10, 2012 (EC No. 2012/02) and was validated in the register of clinical trials EudraCT on February 21, 2012 (No. 2012-000647-27; Clinical Trials Registry NCT02264821).

Recruitment was accomplished by the anesthesiologist in charge of the patient. A pharmacist who was not otherwise involved in the study used a computer program (Randomization.com) to randomize the participants into three parallel study groups in blocks of 12 with 1:1:1 randomization. The utilized products were prepared by a member of the anesthesia team who was otherwise not involved in the study. Each patient received spinal anesthesia and a multiholed catheter (PAINfusor catheter 7.5 cm; Baxter SA, Lessines, Belgium) inserted into the wound below the fascia by the obstetrician at the end of surgery.[16]

Each parturient in the control group received 10 mg bupivacaine 0.5% HB (2 mL) + 5 μg of sufentanil (1 mL) + 0.1 mL NaCl 0.9% intrathecally and a bolus of 15 mL of NaCl 0.9% through the multiholed catheter, which was connected to an elastomeric pump infuser (FOLFusor LV 10 mL/h; Baxter) delivering NaCl 0.9% at a rate of 10 mL/h for 30 hours.

Each parturient in the morphine group received 10 mg bupivacaine 0.5% HB (2 mL) + 5 μg of sufentanil (1 mL) + 100 μg of morphine (0.1 mL) intrathecally and a bolus of 15

mL of NaCl 0.9% through the multiholed catheter, which was connected to an elastomeric pump infuser delivering NaCl 0.9% at a rate of 10 mL/h for 30 hours.

Finally, patients in the catheter group received 10 mg bupivacaine 0.5% HB (2 mL) + 5 μg of sufentanil (1mL) + 0.1 mL NaCl 0.9% intrathecally and a bolus of 15 mL of 0.2% ropivacaine through the multiholed catheter, which was connected to an elastomeric pump infusor delivering ropivacaine 0.2% at a rate of 10 mL/h for 30 hours.

In all patients, the injected spinal anesthesia volume was standardized as 3.1 mL and the time of injection was recorded as time zero (T0). Hypotensive episodes—defined as a systolic blood pressure decrease of >20% from baseline measurements or a systolic blood pressure <100 mm Hg—were treated with a bolus of ephedrine (5 mg) and/or phenylephrine (50 μg) based on the patient's heart rate. Unless contraindicated, all patients also received multimodal analgesia with 1 g acetaminophen every 6 hours and 75 mg diclofenac every 12 hours starting at the end of surgery. Patients could also receive IV morphine (1 mg/mL) delivered through a patient-controlled IV analgesia (Gemstar pump; Hospira Inc, Lake Forrest, IL), which was programmed to deliver a bolus of 1 mg with a 7-minute lockout time and a maximum dose of 20 mg/4 hours.

Ten minutes after intrathecal injection, the patient's level of sensory block was verified by the cold test with ether. We recorded the incidence of intraoperative hypotensive episodes. Postintervention pain at rest was assessed using a visual analog scale (0–10). Nausea (N) and vomiting (V) were graded on a scale of 0 to 3 with 0 indicating no N or V, 1 indicating mild N requiring no treatment, 2 indicating moderate N responsive to treatment, and 3 indicating severe N unresponsive to treatment and/or V. Pruritus (P) was also graded on a scale from 0 to 3 with 0 indicating no P, 1 indicating mild P requiring no treatment, 2 indicating moderate P responsive to treatment, and 3 indicating severe P unresponsive to treatment. These evaluations were performed hourly during the first 4 hours after intrathecal anesthesia and then every 4 hours until 30 hours postoperatively. Nausea and vomiting episodes were treated with IV droperidol at a dose of 0.625 to 1.25 mg repeated once in 24 hours. If this was unsuccessful, 4 mg ondansetron was administered and repeated every 8 hours if necessary. Antipruritic treatment consisted of 10 mg IV propofol with a maximum dose of 50 mg. In cases of persistent itching, a 10-mg tablet of cetirizine was administered.

The primary outcome of this study was analgesia duration, defined as the time from the completion of spinal anesthesia (T0) to the patient's first morphine request. Secondary outcomes were cumulative morphine consumption during the first 30 postoperative hours (until the infusion was stopped and the IV line withdrawn), the number of patients who did not require IV morphine, the incidence of adverse effects (nausea, vomiting, and pruritus), and the time of the first ambulation. From randomization until completion of the statistical analyses, the patient, the anesthesiologist in charge, and the study staff responsible for collecting data were blinded to the treatment group. The collected data were stored in a locked cupboard in the department of anesthesiology.

Statistical Analyses

Statistical analyses were performed using R software version 3.2.2.[20] For the primary and secondary outcomes, we used the Shapiro-Wilks test to determine whether the analysis of variance had normal residuals and the Bartlett's χ^2 test to assess whether the group variances were homogeneous. For all analyzed continuous variables, at least 1 test indicated that the underlying hypotheses of the analysis of variance were violated (results not shown). Thus, we used the nonparametric Kruskal-Wallis rank test. Binary secondary outcomes were compared using the χ^2 test. For discrete and nonparametric data regarding the primary and secondary outcomes, we performed Tukey's multiple comparison tests using the multcomp R package[21] and nparcomp R package.[22] We used the rank-based multiple test procedures and simultaneous confidence intervals for unbalanced designs with independent observations developed by Konietschke et al.[23] Their mathematical solution provides confidence intervals that do not include the null value when there is a treatment effect and include the null value when there is no treatment effect.

Data are expressed as median and quartiles or percentage. A P value of < .05 was considered statistically significant.

Sample Size Justification

To determine the sample size required for our study based on our primary objective, we used previous results showing a 362-minute mean duration (standard deviation, 330 minutes) of analgesia with spinal anesthesia containing 10 mg bupivacaine 0.5% HB + 5 µg of sufentanil.[24] We determined that we required 54 patients per group to demonstrate a 50% increase of analgesia duration resulting from intrathecal addition of morphine or wound infusion with ropivacaine with a power of 0.8 and an α of .05/3 (0.0167) to account for multiple testing. This would indicate a difference of 181 minutes in the mean duration between the control and the tested groups, a hypothesized standard deviation of 530 minutes, and a superiority margin of 50. We included 60 patients per group to account for potential loss of results and/or protocol violations. Finally, to account for exclusions after randomization, we recruited an additional block of 12 patients with the same random sequence as initially used, achieving a total of 192 recruitments.

RESULTS

From the date of our first recruitment (September 5, 2012) to our last recruitment (May 26, 2014), a total of 1127 patients underwent cesarean delivery in our hospital. Of these patients, 182 were included in our study (Figure 1). Patient demographic and intraoperative data were comparable among the 3 study groups (Table 1). The required thoracic sensory level was achieved in all patients, and all patients received multimodal analgesia including acetaminophen and diclofenac.

Analgesia duration was significantly longer in the morphine group (380 minutes; 215–1527) and the catheter group (351 minutes; 227–594) compared with in the control group (247 minutes; 182–338) (P < .01) (Figure 2). Table 2 presents the estimated treatment effects.

Morphine consumption during the first 30 postoperative hours was significantly lower in the morphine group (4.0 mg; 1.0–10.0) and the catheter group (8.0 mg; 4.5–19.0) compared with in the control group (20.5 mg; 10.0–30.5) and was lower in the morphine group than the catheter group (Figure 3; Table 2). The time to reach a visual analog scale score of >3 was significantly lower in the morphine group and the catheter group than in the control group but did not differ between the morphine group and the catheter group (Table 3). The number of patients who did not require IV morphine was significantly lower in the morphine group than in the control group, but did not differ between the morphine group and the catheter group. There were no significant between-group differences in the incidences of intraoperative and postoperative complications or in the time to the first ambulation (Table 3).

Figure 1. Flowchart of patient recruitment and randomization. Of the 6 exclusions of patients in the control group, 4 were the result of pump technical problems, 1 the result of catheter misplacement, and 1 because the obstetrician refused to insert the catheter. Of the 3 exclusions of patients in the morphine group, 1 was the result of pump technical problems, 1 because a midline incision was performed, and 1 resulting from drains. The 1 exclusion in the catheter group was because of a vaginal delivery.
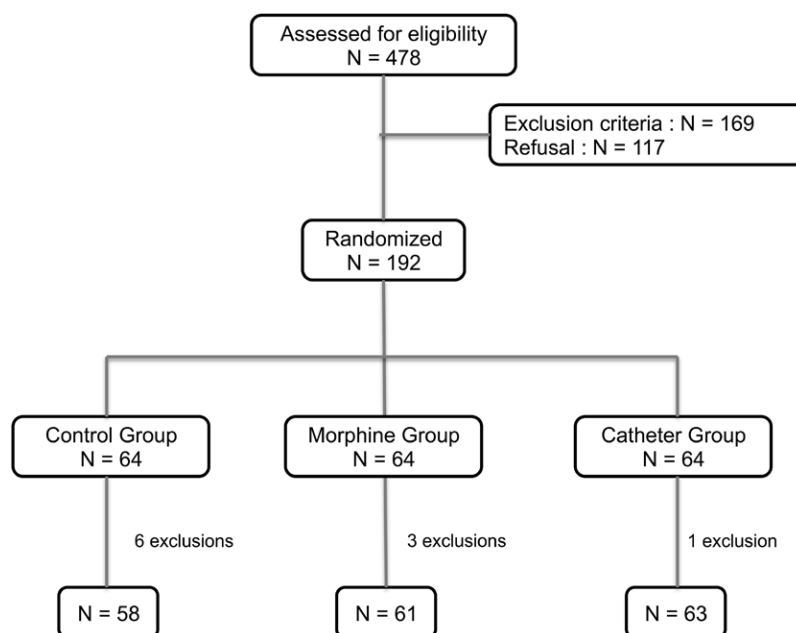
Table 1. Patient Characteristics and Demographic Data

	Control Group (N = 58)	Morphine Group (N = 61)	Catheter Group (N = 63)
Age (y)	32 [28–37]	32 [28–34]	30 [27–34]
Height (cm)	162 [157–167]	164 [160–170]	163 [157–170]
Weight (kg)	78 [72–86]	78 [72–86]	78 [70–88]
Body mass index (kg/m^2)	29 [27–35]	28 [26–32]	30 [27–33]
Multiparous	41 (71)	40 (66)	42 (67)
History of cesarean delivery	34 (59)	30 (49)	27 (43)
Twin pregnancy	4 (7)	8 (13)	9 (14)
Thoracic anesthetic level	4 [3–4]	3 [3–4]	4 [3–4]
Duration of surgery (min)	57 [44–75]	59 [48–74]	56 [45–71]
Apgar score at 1 min	9 [9–10]	9 [9–10]	9 [9–10]
Apgar score at 5 min	10 [10–10]	10 [10–10]	10 [10–10]
Apgar score at 10 min	10 [10–10]	10 [10–10]	10 [10–10]

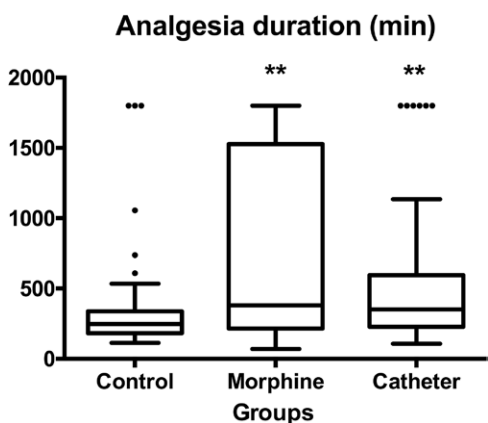Data are presented as number (percentage) or median [quartiles].

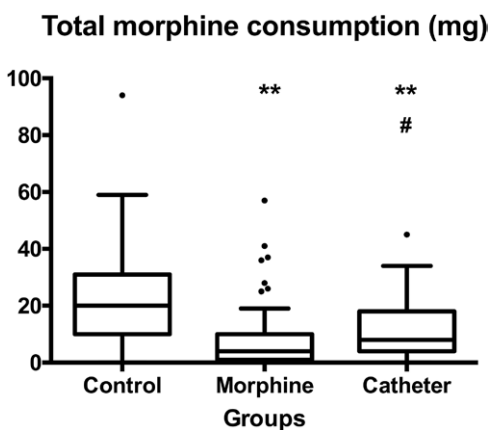**Figure 2.** Boxplot of analgesia duration for the 3 groups. **$P < .01$ versus control group.

Figure 3. Boxplot of cumulative morphine consumption over 30 hours postoperation in the 3 groups. **$P < .01$ versus control group. #$P < .05$ versus morphine group.

Table 2. Treatment Effect Estimates for Duration of Analgesia (A) and Cumulative Morphine Consumption (B)

	Estimator	95% Confidence Interval	P Value
A			
Catheter versus control	0.164	0.052–0.271	.0022
Spinal morphine versus control	0.171	0.043–0.293	.0058
Spinal morphine versus catheter	0.007	−0.118 to 0.132	.9904
B			
Catheter versus control	−0.181	−0.287 to -0.071	<.001
Spinal morphine versus control	−0.310	−0.414 to −0.198	<.001
Spinal morphine versus catheter	−0.128	−0.238 to −0.016	.022

DISCUSSION

Our present results showed that both intrathecal morphine and wound infusion with 0.2% ropivacaine significantly increase analgesia duration after elective cesarean delivery when compared with placebo. We also established that both intrathecal morphine and wound infusion with ropivacaine significantly reduced postoperative morphine consumption without increased incidence of adverse effects.

Although previous studies have evaluated the efficacy of intrathecal morphine and of wound infusion with a local anesthetic, few have compared both approaches for postcesarean analgesia. Several randomized controlled trials have

also demonstrated that intrathecal morphine significantly increases analgesia duration and decreases postoperative morphine consumption.[7–10,25] Among previously tested doses ranging from 25 to 500 µg, 100 µg appears to provide the best effectiveness without increased side effects.[7,9,10,25] Therefore, we used 100 µg morphine in our present study.

Previous randomized controlled trials have investigated the effectiveness of multiholed catheters at delivering local anesthetic for postoperative analgesia in elective cesarean delivery. Most have reported decreased postoperative analgesic consumption.[17–19,26,27] However, it is difficult to compare these studies, because they have used different local anesthetics (ropivacaine, levobupivacaine, and bupivacaine) at different concentrations and volumes, alone or in combination with other adjuvants, and with different patterns of administration.

Catheter position (below or above the fascia) has also varied among studies, which appears to be a determinant of its effectiveness. Indeed, Rackelboom et al[16] compared these two different anatomic positions of the catheter in cesarean delivery and reported lower postoperative opioid consumption when the catheter was positioned below the fascia, as was done in our study. The choice of ropivacaine 0.2% as the local anesthetic was based on the fact that this molecule has lower systemic toxicity than bupivacaine as well as a shorter elimination half-life than bupivacaine and levobupivacaine,

Table 3. Secondary Outcomes in the 3 Groups

	Control Group (N = 58)	Morphine Group (N = 61)	Catheter Group (N = 63)	Global P	Morphine Versus Control	Catheter Versus Control	Catheter Versus Morphine
Time to reach a VAS >3 (min)	480 [240–1440]	1440 [480–1440]	1200 [480–1440]	0.007	0.024	0.018	0.471
Patients not requiring IV morphine	3 (5.2)	14 (23.0)	5 (8.0)	0.005	0.0287	0.8138	0.0652
Hypotension	30 (52)	23 (38)	22 (35)	0.1364	0.276	0.152	0.944
Nausea or vomiting							
0	49 (84)	43 (70)	53 (84)				
1	3 (5)	4 (7)	5 (8)	0.5783	0.127	0.999	0.114
2	5 (9)	8 (13)	4 (6)				
3	1 (2)	6 (10)	1 (2)				
Pruritus							
0	34 (64)	26 (43)	32 (51)				
1	13 (22)	20 (33)	11 (17)	0.0565	0.056	0.123	0.967
2	7 (12)	13 (21)	16 (25)				
3	1 (2)	2 (3)	4 (6)				
Time to ambulation (min)	1423 [1268–1483]	1305 [1138–1460]	1403 [1246–1496]	0.0653	0.081	0.939	0.150

Data are presented as number (percentage) or median [quartiles].
Abbreviation: VAS, visual analog scale.

decreasing the risk of accumulation during prolonged infusion.[28] The ropivacaine concentration and infusion rate were determined based on the study by Beaussier et al,[28] which reported beneficial effects in patients undergoing colorectal surgery. The catheter length was determined after discussion with the obstetricians with the aim of minimizing the length of the surgical incision.

Only 1 previous study has compared wound infusion with local anesthetic with the use of intrathecal morphine for postcesarean analgesia.[29] In their small prospective randomized double-blind, placebo-controlled study, Kainu et al[29] compared continuous wound infusion with ropivacaine 0.375% with 160 µg intrathecal morphine for analgesia after cesarean delivery. Compared with a control group, intrathecal morphine reduced postoperative opioid consumption and pain scores, whereas continuous infusion with ropivacaine did not. The difference between their results and our present findings may be explained by differences in the local anesthetic concentration (0.375% vs 0.2%) and infusion rate (5 vs 10 mL/h). Although similar ropivacaine doses were administered hourly in both studies, the higher infusion rate used in our study may be associated with better diffusion of the local anesthetic and, therefore, with a better analgesic effect. Despite numerous studies published in this field, no optimal concentration and flow rate have been determined. The improved analgesia observed with intrathecal morphine administration could have been related to the higher dosage used by Kainu et al. However, this better analgesic effect was achieved at the expense of a higher incidence of pruritus, a dose-dependent side effect.[7,10,25] We used a dose of 100 µg morphine because we believe it to be the most appropriate in terms of efficacy and reduced risks of adverse effects such as respiratory depression.[7–10] Overall, the presently observed incidences of nausea and vomiting were lower than those reported in the literature. This might be explained by differences in the studied populations and/or scoring system used to assess this side effect.

Limitations of the study include the single-center design and the fact that breastfeeding outcomes were not evaluated. Finally, it must be noted that a multimodal analgesia approach including acetaminophen and diclofenac was used in all of our patients. Nonsteroidal anti-inflammatory drugs reportedly decrease both pain scores and opioid consumption and are now recommended after cesarean delivery.[30,31]

CONCLUSIONS

Under the conditions of our present study, ropivacaine wound infusion and intrathecal morphine were both effective with regard to the duration and effect of postcesarean analgesia. As a result of the cost of wound catheters, they should be reserved for patients for whom intrathecal morphine is not an option. ∎

DISCLOSURES
Name: Manon Lalmand, MD.
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