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Cesarean analgesia using levobupivacaine continuous wound infiltration: a randomized trial☆

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ABSTRACT

Objective: Neuraxial morphine is considered as a "gold standard" for pain relief after cesarean section, however it causes bothersome side effects. Alternative analgesia including nonsteroidal antiinflammatory drugs (NSAID) has been proposed. We aimed to assess the morphine sparing effect of continuous wound infiltration with a local anesthetic, when added to multimodal systemic analgesia including NSAID without subarachnoid morphine.

Study design: Sixty-eight women scheduled for elective cesarean section under spinal anesthesia were included in a randomized controlled open-label trial. Patients received bupivacaine spinal anesthesia without intrathecal morphine. Postoperative analgesia consisted for all patients in multimodal systemic analgesia with acetaminophen, nefopam, celecoxib, and patient-controlled intravenous morphine for 24 h. The intervention group also received subfascial levobupivacaine infiltration through a multi-holed catheter, at 6.25 mg/h for 48 h. The primary endpoint was total morphine consumption at 24 h postoperatively; and secondary endpoints were pain scores, side effects, breastfeeding comfort, maternal satisfaction, and nurse workload. Student *t* test, Mann–Whitney test or χ^2 test were used when appropriate.

Results: The intervention group had 6.7 mg less morphine consumption (95%CI −1.3 mg; −12 mg, $P = 0.02$), and 0.8 pain point less at rest on the numerical rating scale 0–10 (95%CI −0.3; −1.3, $P = 0.002$). The intervention was associated with significantly better breastfeeding comfort (+1.7 at numerical rating scale score 0–10, 95%CI +0; +3.3, $P = 0.0498$). Wound dressing changes were required in a significantly higher proportion of intervention-group women (12/34 vs. 1/34, $P = 0.002$).

Conclusion: Adding continuous levobupivacaine infiltration to multimodal analgesia after cesarean section without subarachnoid morphine decreased postoperative morphine consumption and pain, facilitated breastfeeding initial comfort, and slightly increased nurse workload.

Introduction

Cesarean section is a common surgical procedure, performed at an increasingly high rate [1,2]. Cesarean postoperative pain is a major concern [3], as it could generate persistent pain and postnatal depression [4–6].

Intrathecal morphine efficiently reduces post-cesarean pain [7–9], but it induces numerous side effects including pruritus, nausea, vomiting, sedation, urinary retention, ileus and respiratory depression [7,9–11].

Multimodal analgesia including nonsteroidal antiinflammatory drugs (NSAIDs) decreases both pain scores and opioid consumption [10,12], and is now recommended after cesarean section [13].

Continuous local anesthetic infiltration into the surgical wound is a safe procedure which reduced both postoperative pain and opioid consumption after cesarean delivery in most, but not all studies [14–18]. The place of this technique is not yet well established among analgesia procedures.

☆ Trial Registry Number: ClinicalTrials.gov NCT01751256.

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Using a randomized controlled trial, we aim to assess the additional analgesic effect of a continuous wound infiltration with a local anesthetic, on women delivered with cesarean section and treated with systemic analgesia including NSAID but no intrathecal morphine.

Methods

Ethics approval

The study was approved by the *Comité de Protection des Personnes* of Ile-de-France XI, France, and registered on ClinicalTrials.gov (NCT01751256). Written Informed consent was obtained from each patient before study inclusion.

Trial design

We conducted a randomized controlled trial to assess the additional analgesic effect of continuous wound infiltration with a local anesthetic compared to optimal conventional multimodal analgesia alone. This trial was performed at the Poissy Saint Germain-en-Laye university hospital (France).

Randomization

Patients were included by 10 senior anesthesiologists during the preanesthesia visit or after admission for cesarean section. FJ, who had no role in the eligibility assessments or patient inclusions, manually achieved the randomization in a 1:1 ratio and in blocks of 4. Using a list of random numbers, FJ placed each number in an opaque sealed envelope before study initiation. This envelope was opened by the treating anesthesiologist immediately before the patient entered the operating room. Neither the patients nor the physicians were blinded to the treatment arm.

Patients' inclusion and exclusion criteria

We approached all pregnant patients, aged 18–50 years, at full term (37–42 weeks after the last menstrual period as confirmed by early ultrasound), scheduled for elective cesarean delivery under spinal anesthesia. Exclusion criteria were emergency cesarean section, contraindication to morphine, acetaminophen or local anesthetics, coagulation abnormalities, active infection, insulin-treated diabetes, history of opioid use for more than 6 months, and insufficient comprehension of French. No selection was made concerning breastfeeding project.

Conduct of the study

Surgery was performed under spinal anesthesia using 10 mg of hyperbaric bupivacaine and 5 mcg of sufentanil. No morphine was administrated intrathecally. Cesarean section was carried out according to the Misgav Ladach method [19]. Briefly, incision was transversal, skin, muscle fascia, and uterus wall were only lightly incised and tissues were separated by pulling. Uterus wall, peritoneum when applicable and muscle fascia were sutured with polyglactin ligatures (Vicryl, Johnson and Johnson, Neuilly, France). Skin was sutured with poliglecaprone ligatures with separated inverting subcuticular stitch (Monocryl, Johnson and Johnson, Neuilly, France). Both groups received the same multimodal analgesic regimen: during cesarean section, 20 mg of intravenous (IV) nefopam and 1 g of IV acetaminophen. At postanesthesia care unit (PACU) discharge: 400 mg of oral celecoxib followed by 200 mg *bid* (in patients without contraindications), 1 g of oral acetaminophen *qid* for 3 days, and 20 mg of oral nefopam *qid* for 24 h. An IV-PCA pump was provided for 24 h and delivered boluses of 1.2 mg of morphine and 0.06 mg of droperidol, with a 7-min lockout period.

In the intervention group, a 15-cm multi-holed PAINfusor® catheter (Baxter, Maurepas, France) was inserted subfascially (when achievable) by the surgeon after peritoneum closure. It entered the skin 5 cm laterally and above the scar. An initial 20-mL bolus of levobupivacaine 2.5 mg mL^{-1} was followed by continuous levobupivacaine 1.25 mg mL^{-1} delivered at a rate of 5 mL h^{-1} for 48 h (at all, 350 mg in 260 mL were delivered) using an LV5® elastomeric infusion pump (Baxter, Maurepas, France). In the control group, neither infusion catheter was placed, nor wound infiltration was given and the peritoneum was left open.

Prophylactic antibiotic consisted of 2 g of IV cefazolin 30 min before incision. Postoperative nausea and vomiting were prevented using 4 mg of IV betamethasone and 0.625 mg of IV droperidol after umbilical cord clamping. Ulcer prevention and thromboembolism prophylaxis were performed in compliance with European recommendations [20]. The urinary catheter was removed just before the patient left the PACU, i.e. 2–3 h after skin closure.

Data handling and outcomes

General and obstetrical characteristics were collected at inclusion.

The primary outcome was morphine consumption by PCA over the first day after cesarean section.

Secondary outcomes included pain intensity, periodically measured using a 0–10 numerical rating scale (NRS), at rest and during lower-limb mobilization, along the first 3 days after skin closure. We also recorded time from skin closure to first ambulation and to first flatus.

Pruritus and nausea were evaluated using a 0–10 NRS.

Nursing staff checked 4 times daily catheter occlusion or premature withdrawal, absence of local anesthetic intolerance, and surgical and medical complications. Nurse workload was daily evaluated during the first 2 postoperative days by FJ. Every intervention concerning dressing change, help with caring for the baby or breastfeeding were recorded. All study outcomes were routinely collected by the nursing staff using a specific monitoring chart and entered daily into the study database by FJ, who had no role in patient care.

At the second postoperative day, women were asked to answer a questionnaire. Comfort since birth when taking different breastfeeding positions was assessed using a 0–10 NRS. Treatment side effects, discomfort caused by the equipment, and pain at catheter removal were also recorded using 0–10 NRSs, as for maternal satisfaction with analgesia.

Sample size

Morphine consumption during the first post-cesarean day was 30 ± 10 mg in our ward. We expected a 25% decrease in morphine consumption in the intervention group [17]. To detect this difference with 80% power with two-sided alpha set at 0.05, we needed at least 28 patients in each group. To compensate for possible early discontinuation of the study treatment due to technical issues reported in a previous trial [21], we decided to include 12 additional women, i.e., 68 women in all.

Statistical methods

Qualitative data were expressed as size and percentage (n (%)). Quantitative data were expressed as mean and standard deviation (mean $\pm$ SD) if normally distributed, or median (interquartile range) if not. Comparisons were performed using the intention-to-treat approach. The distribution of continuous variables was evaluated