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A randomized trial to compare pain control using oral analgesia with epidural analgesia after cesarean section following combined spinal-epidural anesthesia

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ABSTRACT. This study aimed to evaluate whether combined oral oxycodone hydrochloride-controlled release tablets plus paracetamol and tramadol hydrochloride tablets are more effective than epidural analgesia for postoperative pain control and side effects after cesarean section. We randomly enrolled 60 patients scheduled for cesarean section into either: patient-controlled epidural analgesia with 0.1% ropivacaine + 0.1 µg/mL sufentanil (for postoperative 48 h) + injected pethidine on demand (E group); or controlled-release oxycodone (2 x 15 mg for the first postoperative 24 h; 2 x 10 mg for the second postoperative 24 h) + paracetamol and tramadol hydrochloride tablets (8 x 1 tablet for the postoperative 48 h) orally + injected pethidine on demand (O group). The E group experienced more evoked pain and uterine cramping pain at all times postoperatively. The patients who received oral analgesia had less resting pain at 6, 12, 24, and 36 h after surgery. Two patients in the E group injected pethidine

(150 mg total) during the oxytocin infusion, whereas none of the O group patients injected pethidine. Pruritus was more common in the E group ($P < 0.05$). Maternal satisfaction with the analgesia regimen was lower in the E group ($P < 0.01$). The median duration of hospital stay was about 5 days for both groups. Postoperative pain control after cesarean section with oral oxycodone hydrochloride-controlled release tablets plus paracetamol and tramadol hydrochloride tablets is preferable to epidural analgesia, even when side effects and maternal satisfaction are taken into account.

Key words: Cesarean section; Epidural analgesia; Oxycodone; Acetaminophen; Ropivacaine; Pruritus

INTRODUCTION

Differences in postoperative pain control between cesarean section and other surgeries are as following: first, pain after cesarean section involves two components, somatic pain from the wound and visceral pain from uterine cramps (Lavand'homme, 2006); and, second, women are expected to recuperate in a short period of time to take care of their infants after surgery. Therefore, effective postoperative analgesia is crucial. Patient-controlled analgesia (PCA), traditional parenteral opioids and intrathecal or epidural opioid administration can all offer effective analgesia. However, parenteral opioids and intrathecal opioid administration have known side effects, including nausea, vomiting, urinary retention, pruritus, and respiratory depression. Additionally, PCA devices are expensive and cumbersome, require trained personnel and special equipment, and could potentially interfere with infant care. The potential benefits of oral opioids include easy administration, high maternal satisfaction, fewer opioid-related side effects than intrathecal opioids, and the avoidance of complications associated with an indwelling epidural catheter (Swart et al., 1997; Holt, 2000; American College of Obstetricians and Gynecologists, 2002).

The main purpose of this study was to confirm whether oral-controlled release oxycodone (2 x 15 mg for the first postoperative 24 h; 2 x 10 mg for the second postoperative 24 h) + paracetamol and tramadol hydrochloride tablets (8 x 1 tablet for the postoperative 48 h) provides better analgesia than patient-controlled epidural analgesia with 0.1% ropivacaine + 0.1 μg/mL sufentanil.

MATERIAL AND METHODS

Subjects

Using a table of random numbers, 60 women scheduled for elective primary cesarean section were randomized to two groups. Exclusion criteria included: an unplanned cesarean section, contraindications to combined spinal-epidural anesthesia, failure to identify the subarachnoid space at the time of anesthesia, a known allergy/hypersensitivity to oxycodone, tramadol, or paracetamol, a history of pain syndrome or pruritus; and concurrent opioid therapy, and a duration of the indwelling of the urethral catheter that exceeded 36 h. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Zhejiang University. Written informed consent was obtained from all participants.

Methods

All patients received no premedication and were fasted from solid food from midnight but allowed clear oral fluids up to 4 h before surgery. Spinal anesthesia was administered with hyperbaric bupivacaine (5 mg/mL, 10-12 mg). The woman was in the right lateral position and a combined spinal-epidural technique (18 g Tuohy needle and 27-G pencil point spinal needle) was performed at a low lumbar interspace (L3-4 or L2-3). The catheter was advanced 3-4 cm into the epidural space. Hypotension was treated with *iv* 6 mg ephedrine. If surgery was delayed or intraoperative pain experienced, 2% lidocaine was given through the epidural catheter. Cesarean section was performed without injecting local anesthetic into the incision and no long-acting intrathecal narcotics were administered. After the peritoneum closed, all patients received *iv* 40 mg parecoxib and *iv* 0.3 mg ramosetron as antiemetic prophylaxis. The operation was performed with a Joel-Cohen or a Pfannenstiel skin incision.

If randomly assigned to the epidural analgesia group (E group), patients received epidural analgesia with 0.1% ropivacaine + 0.1 μg/mL sufentanil (continuous, 8 mL/h; bolus, 4 mL; lockout interval, 15 min; 1-h limitation, 16 mL) in a PCA device (Gemstar, Abbot) for the postoperative 48 h. Immediately after the peritoneum closed, the PCA device was connected to the epidural catheter and the 5-mL loading dose was given.

If randomly assigned to the oral analgesia group (O group), patients received 5 mL 2% lidocaine after the peritoneum closed. At the end of the surgery, the epidural catheter was removed. On arrival in the recovery room, every patient received 15 mg controlled release oxycodone (Mundipharma Pharmaceutical Ltd., Beijing, China) + 1 tablet paracetamol and tramadol hydrochloride tablets (containing 37.5 mg tramadol and 325 mg paracetamol) (Xian-Janssen Pharmaceutical Ltd., Xian, China) orally. This was followed by controlled release 15 mg oxycodone every 12 h for the first postoperative 24 h [including the first dose in the Adult Postanesthesia Unit (PACU)], 10 mg every 12 h for the second postoperative 24 h + 1 tablet paracetamol and tramadol hydrochloride tablets every 6 h for the postoperative 48 h (including the first dose in the PACU).

If requested by the patient, rescue analgesia for breakthrough pain was administrated with intramuscular pethidine (50 mg). A patient could receive the second dose 15 min later. Postoperative pruritus was treated with *iv* 4 mg ondansetron every 6 h on demand or, if this was ineffective, with hourly *iv* 50 μg naloxone.

Observation indexes

Maternal age, height, weight, gestation, and the type of skin incision were recorded. At 6, 12, 24, 36, and 48 h after the surgery, the sedation score was also recorded and pain control was assessed using a visual analog scale (VAS) of 0 (no pain) to 100 (worst pain imaginable). Three categories of pain were assessed: wound pain at rest (VAS-R), evoked wound pain (VAS-E), and uterine cramping pain (VAS-U). We evaluated evoked wound pain during two patient activities: while changing position in bed and while walking to the toilet. The uterine cramping pain was defined as the intermittent, dull, cramping pain associated with uterine contraction and felt inside the abdominal cavity. The wound pain was defined as the constant, sharp, burning, and evoked pain over the wound and adjacent region. The uterine cramping pain was assessed in the first 15 min while the oxytocin was administrated as an infusion with

20 U in 500 mL 5% dextrose doses, which were infused within 1 h. Oxytocin infusions were administered at our hospital at about 6, 24, and 48 h after surgery to prevent postpartum hemorrhage.

Time to free mobilization (walking without assistance), hospital stay, pethidine consumption and its side effects (nausea and vomiting, pruritus, dizzy), bowel function, and maternal satisfaction were also recorded.

Statistical analysis

The primary endpoints were the VAS scores of resting, evoked, and uterine cramping pain. The secondary endpoints were side effects, hospital duration, and maternal satisfaction. Data were analyzed using an independent Student *t*-test for continuous variables with a nearly normal distribution. The chi-square test or the Fisher exact test was used for categorical data. Multivariate analysis of variance (MANOVA) was used for VAS scores at different times after surgery. Data were analyzed using SPSS 16.0. The level of statistical significance was set to $P < 0.05$.

RESULTS

The epidural catheter was dislodged by accident in 6 patients in the E group, who were excluded when the data were analyzed. No difference was found between the treatment groups regarding maternal age, height, weight, gestation, or type of skin incision (Table 1). Patients who received oral analgesia had less resting pain at 6, 12, 24, and 36 h after surgery ($P < 0.05$; Table 2 and Figure 1A) and had less evoked pain at all times assessed postoperatively ($P < 0.05$; Table 2 and Figure 1B). VAS scores were significantly higher in the E group than in the O group at the oxytocin infusions ($P < 0.05$; Table 2 and Figure 1C).

Table 1. Maternal characteristics between E and O group.

Group	Age (years)	Height (cm)	Weight (kg)	Gestation (weeks)	Type of skin incision (Joel-Cohen/Pfannenstiel)
E group	29 ± 3	160.7 ± 4.1	69.8 ± 7.9	39.1 ± 0.8	15/9
O group	28 ± 3	160.0 ± 3.8	69.1 ± 10.1	39.3 ± 1.3	16/14
P	0.33	0.51	0.79	0.55	0.84

Table 2. Postoperative visual analog scale (VAS) of pain score.

	E group	O group	P value
Rest Pain			
6 h	25.0 ± 19.1	13.0 ± 16.6	0.02*
12 h	26.7 ± 17.6	13.0 ± 16.0	0.00*
24 h	19.6 ± 13.6	6.3 ± 10.3	0.00*
36 h	12.5 ± 12.2	3.7 ± 8.5	0.00*
48 h	5.4 ± 9.8	1.3 ± 5.1	0.53
Evoked pain			
6 h	0	0	-
12 h	48.3 ± 17.4	36.3 ± 17.4	0.00*
24 h	48.8 ± 15.7	31.0 ± 13.0	0.00*
36 h	50.4 ± 16.5	39.3 ± 19.5	0.03*
48 h	40.0 ± 11.0	31.0 ± 15.8	0.02*
Uterine cramping pain			
First oxytocin infusion	40.0 ± 31.2	23.7 ± 20.8	0.02*
Second oxytocin infusion	56.2 ± 27.3	21.3 ± 17.8	0.00*
Third oxytocin infusion	35.0 ± 26.0	10.3 ± 15.7	0.00*

*$P < 0.05$.

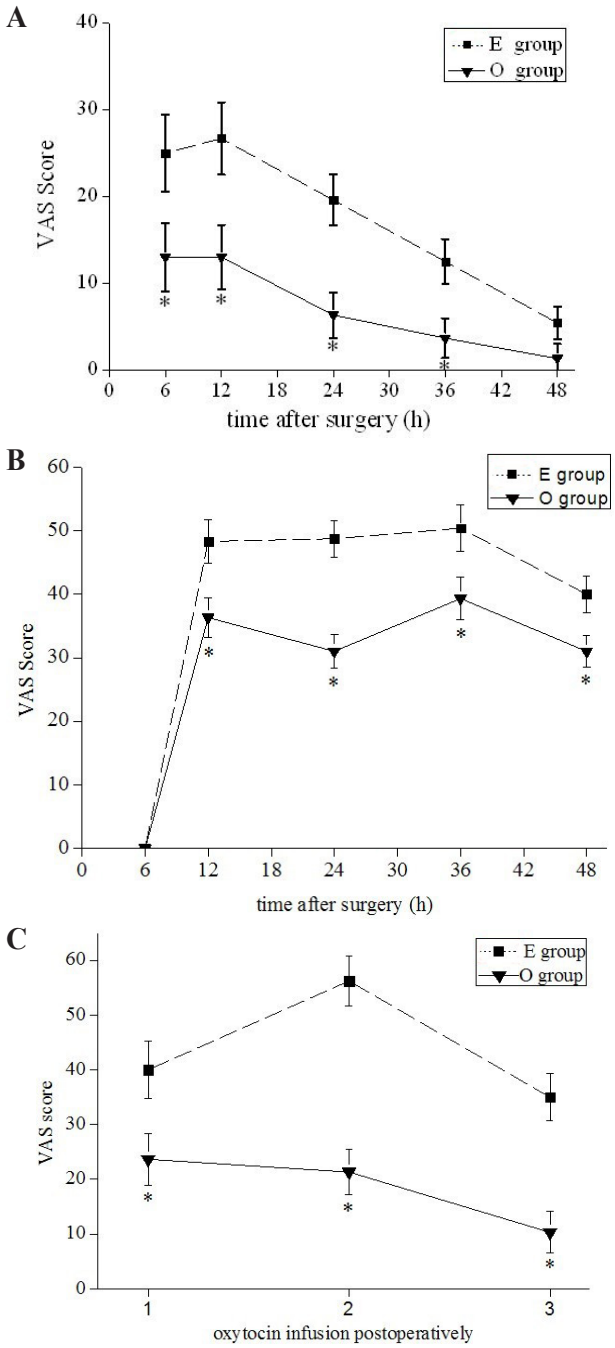

Figure 1. A. Visual analog scale (VAS) of pain score at rest 0-48 h postoperatively (mean and 95% confidence interval) using multivariate analysis ($P < 0.05$); **B.** VAS score of the evoked pain 0-48 h postoperatively (mean and 95% confidence interval) using multivariate analysis ($P < 0.05$); **C.** VAS score of the uterine cramping pain at the oxytocin infusion three times postoperatively (mean and 95% confidence interval) using multivariate analysis ($P < 0.05$).

Two patients in the E group requested pethidine (150 mg total) when the oxytocin was infused, whereas none of the O group requested this injection. There was a significantly higher incidence of pruritus in the E group (P = 0.03). There were no significant differences between groups for the incidence of dizziness, nausea, or vomiting (Table 3). No significance was found in anus exhaustion time, free to mobilization time, or hospital duration. At the 48 h review, patients in the O group had higher satisfaction scores (90.0 ± 9.8 *vs* 82.0 ± 10.0; P < 0.01; Table 4). Sedation scores were 0-1 in all patients.

Table 3. Postoperative recovery status.

Group	Time to anus exhaustion (h)	Time to free mobilization (h)	Hospital duration (d)	Satisfaction
E	19.1 ± 15.6	39.4 ± 8.6	5.4 ± 1.2	82.0 ± 10.0
O	21.9 ± 11.0	37.5 ± 7.7	5.4 ± 1.3	90.0 ± 9.8
P value	0.47	0.40	0.96	0.00*

Postoperative recovery status using the independent sample *t*-test (*P < 0.05).

Table 4. Side effects.

Group	Dizzy	Nausea	Vomiting	Pruritus
E group	4	0	0	4
O group	8	1	1	0
P value	0.35	1.00	1.00	0.03*

Side effects using the independent sample *t*-test (*P < 0.05).

DISCUSSION

In this randomized, non-blinded trial, we confirmed that a well-planned analgesia regimen consisting of oral non-opioids and oxycodone was more efficacious than the epidural patient-controlled analgesia after cesarean section, resulting in superior pain control with less pruritus and greater satisfaction.

Our results correlated well with a previous report showing that oral oxycodone and paracetamol for postoperative pain control after radical retropubic prostatectomy was preferable to epidural analgesia (Hohwü et al., 2006). McDonnell et al. (2010) reported that oral oxycodone produced comparable postoperative pain relief after cesarean section to intrathecal morphine with a lower incidence of pruritus. Davis et al. (2006) also pointed out that oral oxycodone-acetaminophen offered superior pain control with fewer side effects than morphine patient-controlled analgesia after cesarean section in a randomized controlled trial. Dieterich et al. (2012) showed that oral oxycodone was cheaper, more convenient, and a comparable analgesic to PCA devices with intravenous piritramide after cesarean section in a randomized controlled trial.

Because all patients were not allowed to move until 6 h after surgery, the VAS-E score at 6 h was zero. Until the urethral catheter was removed, the patients were permitted to walk. The catheter was removed about 24-36 h after surgery; therefore, before that patients could only change position in bed. That is why the VAS-E score at 36 h was higher than the 24 h score in the O group, but this trend was not observed in the E group.

Oxycodone is a semi-synthetic opioid agonist that is derived from thebaine with affinity for the κ-receptor and, to a less degree, for the μ-receptor (Ordóñez et al., 2007). In the

opioid κ-receptor-deficient mice, Simonin et al. (1998) found that the κ-receptor is implicated in the perception of visceral pain. Oxycodone may be more effective in treatment of visceral pain than morphine (Olkkola and Hagelberg, 2009). Visceral pain of uterine cramping caused by oxytocin infusion postoperatively may result from myometrial ischemia, leading to the release of potassium, bradykinin, histamine, and serotonin. These toxic chemicals stimulate mechanoreceptors and impulses follow sensory-nerve fibers that accompany sympathetic nerve endings that pass the paracervical region and the pelvic and hypogastric plexus to enter the lumbar sympathetic chain. Although the white rami communicantes of the L1-T10 spinal nerves, they enter the dorsal horn of the spinal cord (Eltzschig et al., 2003). The block levels of the patients in E group cannot all reach T10 and, if this happened, patients would feel visceral pain when the oxytocin was infused postoperatively, but this would not happen in the O group. Therefore, the VAS-U is higher in the E group compared with the O group. Drug combinations with paracetamol have been demonstrated to have an opioid-sparing effect, which can decrease opioid-related side effects (Elia et al., 2005). Combinations of paracetamol with tramadol, a weak opioid agent, are widely used, because of the well-established complementary pharmacokinetics and mechanisms of action of the drugs (Schug, 2006).

Previous studies have found that the oral administration of oxycodone (in doses ≤90 mg in a 24-h period) for post-cesarean analgesia, up to 3 days postoperatively, posed a minimal risk to neonates. Effective analgesia brings the parturient comfort and successful initiation of breast feeding, and the benefits appear to outweigh the risk of oxycodone exposure during the breast-feeding period (Seaton et al., 2007).

Our study has a number of limitations. Nafisi (2007) found that exteriorization of the uterus for closing the uterine incision significantly increased the first- and second-night postoperative visceral pain following cesarean section. We did not consider the method of repairing the uterine incision. Because of the absence of immediate-release oxycodone or morphine in our hospital, we have to relieve severe pain through *im* pethidine rather than orally, which may increase side effects.

Oral analgesia with controlled release oxycodone and paracetamol and tramadol hydrochloride tablets for treatment of post-cesarean pain appears to be a more effective and convenient option than patient-control epidural analgesia, resulting in less pruritus and greater maternal satisfaction.

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