Clinical Trial/Experimental Study

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A randomized trial of remifentanil for analgesia in external cephalic version for breech presentation

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Abstract

Background: Although external cephalic version (ECV) can be effective for correcting the fetus in a cephalic presentation, it may be painful for the mother. This study aimed to evaluate the efficacy and safety of remifentanil for pain relief during ECV in China.

Methods: In all, 152 Chinese parturients with singleton breech presentation were randomly divided into 2 groups, each with 76 patients. All 152 patients were assigned to receive either remifentanil (infused at 0.1 μg/kg/min and demand boluses of 0.1 μg/kg) or saline placebo. The study was performed between January 2012 and December 2015. Outcome measurements included the Numerical Rating Pain Scale score (0–10) after ECV, success rate for ECV, and maternal satisfaction after ECV. Adverse events were also evaluated.

Results: The study was completed by 146 patients. Remifentanil showed greater efficacy than placebo in decreasing the pain score immediately after ECV (remifentanil 4.6±2.6 vs placebo 6.5±2.7; $P<0.001$). The success rate for ECV showed a significant difference between the 2 groups (remifentanil 56.5% vs placebo 39.5%; $P=0.04$). Maternal satisfaction also showed a significant difference between the 2 groups (remifentanil 9.6±1.4 vs placebo 6.4±3.7; $P<0.001$). However, the adverse events profiles were similar between both groups.

Conclusion: The results of this study demonstrate that remifentanil is an effective intervention for reducing pain, achieving successful ECV, and increasing maternal satisfaction during ECV, and is generally well-tolerated without additional adverse effects.

Abbreviations: ACOG = American College of Obstetricians and Gynecologists, AEs = adverse effects, BMI = body mass index, BP = breech presentation, CI = confidence interval, ECV = external cephalic version, ITT = intention to treat, NRPS = Numerical Rating Pain Scale, RR = risk ratio, SD = standard deviation.

Keywords: breech presentation, clinical trial, external cephalic version, randomized controlled trial, remifentanil

1. Introduction

Breech presentation (BP) has been associated with higher cesarean rates. It is estimated that 3% to 4% of single pregnancies are BPs.[1] A large proportion of pregnant women with BP undergo cesarean section, which leads to repeat cesarean section in subsequent pregnancies in many cases. Several interventions can help correct BP, such as moxibustion.[2] In addition, external cephalic version (ECV) can also change a fetal presentation from breech to cephalic by external pressure exerted through the maternal abdominal wall by the obstetrician. The American College of Obstetricians and Gynecologists (ACOG) has proposed the use of ECV to reposition the fetus to a cephalic presentation in an attempt to avoid caesarean delivery.[3] It has been reported that the mean success rate for ECV is 59%, with a range from 35% to 100%.[4]

External cephalic version (ECV) intervention is painful for most pregnant women, with mean scores of 4.6 to 8.5 out of 10, measured by the visual analog scale.[5] Some authors have explored the role of analgesia in ECV, mainly focusing on regional analgesia, which has been associated with reduced pain scores and increased success rates of ECV.[6–8] A recent Cochrane systematic review concluded that the use of regional analgesia did not show a corresponding decrease in cesarean rate.[6] However, it can increase the success rate of ECV.[6] In addition, regional analgesia is not free of potentially significant adverse effects (AEs), because of its invasive nature.[6]

Remifentanil, a μ-opioid receptor-antagonist, has a rapid onset of effect and a short half-life (3–4 minutes). Consequently, it does not have a cumulative effect in the mother or fetus. In addition, its action can be fully reversed with naloxone. Because of these characteristics, remifentanil is suitable for systemic analgesia in obstetrics.[9–11]

In this study, we tested the hypothesis that remifentanil would provide analgesic efficacy for ECV compared with placebo.

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The authors disclose no conflicts of interest.

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2. Methods

2.1. Design

This was a 2-parallel-arm, randomized, double-blind, placebo-controlled trial. In all, 152 parturients with singleton BP, including those undergoing screening, were scheduled for evaluation to determine baseline values and whether the patient met all the inclusion/exclusion criteria, and also for outcomes evaluation after ECV. The trial was conducted between January 2012 and December 2015 in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice: The People's Hospital of Yan'an. The study was approved by the Medical Ethical Committee of The People's Hospital of Yan'an. Eligible subjects were randomly allocated to a remifentanil or placebo group in a 1:1 allocation ratio.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: the study population consisted of singleton pregnancies with BP at term ($\geq 37^{+0}$ weeks), confirmed by ultrasound. Exclusion criteria were as follows: history of prior uterine surgery, uterine abnormalities, multiple pregnancy, contraindications to vaginal delivery, maternal cardiovascular disease, severe hypertension, American Society of Anesthesiologists class >2, allergy to the trial medications, prelabor ruptured membranes, placental abruption, fetal anomaly, intrauterine fetal death, and fetal weight above 3800 g. In addition, participants who received ECV, and also the moxibustion therapy,[2] to correct the BP before the study recruitment were also excluded.

2.3. Randomization and blinding

Patients who met all the inclusion/exclusion criteria were assigned to either the remifentanil or placebo group using a computerized number generator in the stratified block randomization method in SAS (version 8.3; SAS Institute, Inc., Cary, NC). The randomization was performed by a statistician who was blinded to treatment allocation. The treatment allocation was concealed in opaque, sequentially numbered, sealed envelopes containing the randomization assignments. The patients, investigators, and study site personnel were blinded to the treatment allocation. In addition, outcomes assessors and data analysts were also blinded in this study. Individuals who were directly involved in the study (including trial conduction and data analysis) did not have access to the randomization schedule until the trial was completed.

2.4. Participants and recruitment

All participants were recruited through the Clinic of the Obstetrics and Gynecology Department at The People's Hospital of Yan'an. All patients underwent a clinical assessment and ultrasound scan. After the clinical evaluation, patients were randomized to either the remifentanil or placebo group. Remifentanil or placebo was administered by the anesthetists, all of whom were trained in their administration. Then, all included patients were offered remifentanil or placebo intervention before ECV, and were informed about the research and given an information sheet. Consent was obtained from the patients who agreed to participate.

2.5. Intervention

All patients received intravenous paracetamol 1 g in 100 mL saline 5 minutes before ECV. In addition, patients assigned to the remifentanil group received remifentanil (0.1 μg/kg/min) for 3 minutes before beginning the ECV, with rescue boluses on demand of 0.1 μg/kg and a lockout period of 5 minutes.

2.6. Efficacy assessments

The primary outcome measurement was the Numerical Rating Pain Scale (NRPS) score (0 = no pain, 10 = worst pain imaginable). This was measured immediately after the ECV. Additionally, the level of satisfaction with ECV was assessed using another numerical rating scale (0 = completely dissatisfied, 10 = completely satisfied). This was evaluated 10 minutes after the ECV. The success rate after ECV was also evaluated.

2.7. Safety

Safety was evaluated by clinical review of AEs after the ECV intervention. AEs were documented by an investigator, who was also blinded to the randomization schedule. Safety data for all the treated patients were included in the analysis.

2.8. Statistical analysis

The estimated sample size for the remifentanil and placebo groups with a 1:1 ratio was 63 patients in each group, to detect a 50% difference in success rate, with $\alpha = 0.05$ (2-sided) and $\beta = 0.20$, assuming a baseline success rate of 55% in patients who received placebo. Assuming a 20% dropout rate, this estimate indicated that at least 152 patients with 76 in each group needed to be recruited for the study. The clinical outcome data were analyzed using an intention-to-treat (ITT) approach and the baseline value of patients randomized to the trial. For differences between the 2 groups, categorical data were analyzed using Fisher exact test, and *t* tests were used for continuous data with relative risks and 95% confidence intervals (CIs). Analysis was conducted blind to the study group by a study statistician.

3. Results

In all, 209 participants were initially screened for entry into the study (Fig. 1); 49 did not meet the inclusion criteria and 8 declined to participate. Therefore, 152 patients were randomized into the study. All included participants received study interventions and were involved in the ITT population for efficacy assessment using the NRPS, ECV satisfaction, and ECV success rate. Six patients withdrew from the study (Fig. 1).

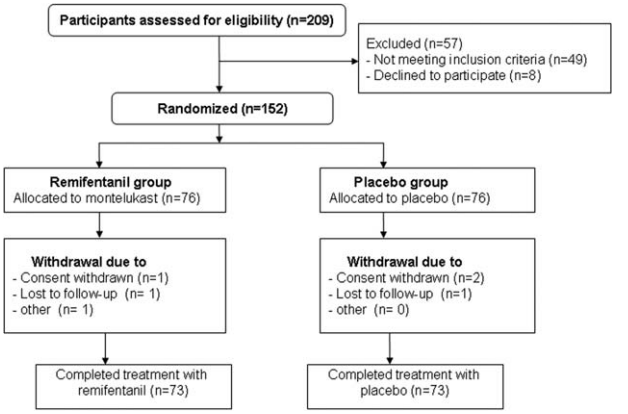

Figure 1. Flow of the participants through the trial.

Table 1

Baseline characteristics of participants at trial entry (ITT population).

	Remifentanil (n = 76)	Placebo (n = 76)	P
Maternal age, y: mean (±SD)	34.1 (4.2)	33.8 (3.9)	0.65
Maternal weight, kg	75.8 (11.8)	76.9 (12.1)	0.57
Maternal height, cm	162.6 (6.1)	163.4 (6.3)	0.43
Maternal BMI at ECV	28.6 (4.5)	28.9 (4.7)	0.69
Race, n (%)			
Asian (Chinese)	76 (100.0)	76 (100.0)	1.00
Parity, n (%)			
1	45 (59.2)	42 (55.2)	0.62
2	27 (35.5)	30 (39.5)	0.62
3	3 (3.9)	2 (2.6)	0.65
4^+	1 (1.3)	2 (2.6)	0.57
Weeks of gestation, n (%)			
37	68 (89.5)	71 (93.4)	0.39
38	4 (5.3)	3 (3.9)	0.70
39	1 (1.3)	1 (1.3)	1.00
40	2 (2.6)	1 (1.3)	0.57
41	1 (1.3)	0 (0)	0.50
Placental location, n (%)			
Anterior	34 (44.7)	39 (51.3)	0.81
Posterior	38 (50.0)	32 (42.1)	0.33
Other	4 (5.3)	5 (6.6)	0.34
Breech presentation, n (%)			
Frank	63 (82.9)	59 (77.6)	0.42
Complete	8 (10.5)	10 (13.2)	0.62
Footling	3 (3.9)	4 (5.3)	0.70
Transverse	2 (2.6)	3 (3.9)	0.65
Amniotic fluid, cm, n (%)			
Normal (5–19)	71 (93.4)	69 (90.8)	0.60
Low (<5)	3 (3.9)	4 (5.3)	0.70
High (≥20)	2 (2.6)	3 (3.9)	0.65
Amniotic fluid index, cm, mean (±SD)	12.4 (3.2)	12.2 (3.1)	0.70

BMI = body mass index, ECV = external cephalic version, ITT = intent to treat, SD = standard deviation.

The characteristics of the study participants at baseline are shown in Table 1. The 2 groups did not differ significantly in any demographic and clinical variables investigated at baseline.

The mean pain scores immediately after ECV in the remifentanil and placebo groups were 4.6 ± 2.6 and 6.5 ± 2.7, respectively ($P < 0.001$; Table 2). The mean number of bolus doses used in the remifentanil group was 5.3 ± 3.5, with 10.3 ± 4.8 in the placebo group ($P < 0.001$; Table 2). The success rate of ECV showed a significant difference between the remifentanil group (43/76, 56.5%) and the placebo group (30/76, 39.5%) ($P = 0.04$; Table 2). The satisfaction scores were also significantly higher in the remifentanil group (9.6 ± 1.4) than in the placebo group (6.4 ± 3.7) ($P < 0.001$; Table 2).

Table 2

Outcomes after ECV between 2 groups (ITT population).

	Remifentanil (n = 76)	Placebo (n = 76)	P
NRPS after ECV, mean (±SD)	4.6 (2.6)	6.5 (2.7)	<0.001
Number of PCA demands, mean (±SD)	5.3 (3.5)	10.3 (4.8)	<0.001
Satisfaction score, mean (±SD)	9.6 (1.4)	6.4 (3.7)	<0.001
ECV success, n (%)	43 (56.5)	30 (39.5)	0.04
Delivery after successful ECV, n (%)			
Spontaneous	50 (65.8)	52 (68.4)	0.73
Instrumental	14 (18.4)	18 (23.7)	0.43
Caesarean	12 (15.8)	6 (77.9)	0.14
Delivery after failed ECV, n (%)			
Breech	0 (0)	8/46 (17.4)	0.06
Caesarean	34/34 (100.0)	38/46 (82.6)	0.06

ECV = external cephalic version, ITT = intent to treat, NRPS = Numerical Rating Pain Scale, PCA = paracetamol, SD = standard deviation.

Table 3

Adverse events (n [%]: ITT population).

	Remifentanil (n = 76)	Placebo (n = 76)	P
Nausea	7 (9.2)	5 (6.6)	0.55
Vomiting	1 (1.3)	2 (2.6)	0.57
Dizziness	4 (5.3)	6 (7.9)	0.52
Transient fetal bradycardia	4 (5.3)	7 (9.2)	0.35
Drowsiness	0 (0)	1 (1.3)	0.50
Hypotension	1 (1.3)	0 (0)	0.50
Itchy nose	1 (1.3)	0 (0)	0.50

ITT = intent to treat.

All AEs in both groups are listed in Table 2. The most common AEs were nausea (remifentanil group, 9.2% vs placebo group, 6.6%, $P = 0.55$; Table 3); dizziness (remifentanil group, 5.3% vs placebo group, 7.9%, $P = 0.52$; Table 3); and transient fetal bradycardia (remifentanil group, 5.3% vs placebo group, 9.2%, $P = 0.35$; Table 3) There were no treatment-related deaths in either group.

4. Discussion

Pregnant women with BP undergoing ECV often experience moderate to high levels of pain.[4,7,12] In this study, the mean NRPS after ECV (±SD) was 4.6 (2.6) and 6.5 (2.7) in the remifentanil and placebo groups, respectively ($P < 0.001$). The satisfaction scores were 9.6 ± 1.4 in the remifentanil group and 6.4 ± 3.7 in the placebo group ($P < 0.001$). Moreover, the success rate of ECV also showed a significant difference between remifentanil and placebo groups (56.5% vs 39.5%; $P = 0.04$). The pain scores in the remifentanil group were significantly lower than in the placebo group. In addition, both maternal satisfaction rate and success rate after ECV were improved in the remifentanil group compared with those in the placebo group. These findings are consistent with other studies that have shown that remifentanil could reduce pain and increase maternal satisfaction.[13,14] However, our study found that remifentanil could also improve the success rate for ECV.

Previous studies reported results for the use of analgesics during the procedure of ECV.[13,14] One randomized controlled trial found no difference in the success rate for ECV between patients who received remifentanil with paracetamol and subjects who received placebo with paracetamol.[13] However, the mean pain score was significantly lower in the remifentanil group than in the control group.[13] Another randomized controlled trial also concluded that remifentanil analgesia decreased ECV-related pain, but failed to increase the success rate for ECV at term, and appeared to be associated with an increased frequency of mild AEs.[14]

Four systematic reviews and/or meta-analyses concluded that regional analgesia significantly improved the success rate of ECV.[5,15–17] However, controversy still exists because of the different techniques, drugs, and doses used during the procedure of ECV. Of these, the dose could be the most significant factor. The dose of analgesia is probably not sufficient to have a positive effect on the success of ECV (risk ratio [RR] 1.2, 95% CI

0.9–1.5). This may be because higher doses generate a higher degree of motor blockade on the abdominal muscles during the ECV, and thus prevent involuntary abdominal tensing.[15–17] The analgesic effect of remifentanil seems to be similar to that of regional analgesia, with effective pain relief, but no effect on ECV success rate. In contrast, regional anesthesia seems to increase the success rate of ECV.[18] Other studies also reported that regional anesthesia could not only increase the ECV success rate, but could also reduce costs, and minimize complications and morbidity.[19–21]

In this study, AEs were mild and infrequent. This suggested that remifentanil has an acceptable safety profile. The most common AEs were nausea, dizziness, and transient fetal bradycardia in both groups. No significant differences in any AEs were found between the 2 groups.

This study has several limitations. First, this study was conducted in a single center and only Chinese patients were recruited, which may influence the generalizability of our findings to other hospitals and other ethnicities. Second, the primary outcome measurement procedure using pain scores (numerical rating scale) was subjective and could have been affected by multiple unknown factors. Finally, an obstetric staff with varying levels of experience may cause bias in the patient's pain experience and success rate of ECV.

The results of this randomized, double-blind, controlled trial showed that the administration of remifentanil with bolus doses during the procedure of ECV achieved pain reduction, successful ECV, and increased maternal satisfaction, with no additional AEs.

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