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Remifentanil analgesia during external cephalic version for breech presentation in nulliparous women at term

A randomized controlled trial

Zhi-Hong Wang, MD, Yi Yang, MD, Gui-Ping Xu, MD, PhD*

Abstract

Background: The aim of the study was to assess the efficacy and safety of remifentanil for pain relief during external cephalic version (ECV) for breech presentation in nulliparous women at term.

Methods: A total of 144 nulliparous women with singleton breech presentation were randomly divided into the intervention group and the placebo group, with 72 subjects in each group. The subjects in the intervention group received remifentanil (infused at 0.1 μg kg^{-1} min^{-1} with demand boluses of 0.1 μg/kg), whereas those in the placebo group were given saline placebo. This study was conducted from May 2013 to April 2016. The outcomes measures include pain (measured with the visual analog scale, VAS), success rate of ECV, maternal satisfaction for ECV, and adverse events.

Results: A total of 137 participants completed the study. The intervention with remifentanil showed greater efficacy than did placebo in decreasing the VAS score immediately after ECV (intervention group 4.3 ± 2.2 vs placebo group 6.4 ± 2.5, $P < 0.01$). A significant difference in the ECV success rate was also found between the 2 groups (intervention group 56.9% vs placebo group 38.9%, $P = 0.03$). In addition, a significant difference in the satisfaction score was also detected (intervention group 9.3 ± 0.9 vs placebo group 6.7 ± 1.2, $P < 0.01$). The observed adverse events were similar between the 2 groups.

Conclusion: This study shows that remifentanil could decrease pain, improve the ECV success rate, and improve satisfaction in nulliparous women at term during the period of ECV. Furthermore, it is also well tolerated with few adverse events.

Abbreviations: AEs = adverse events, BP = Breech presentation, ECV = external cephalic version, ITT = intention to treat, VAS = visual analog scale.

Keywords: Breech presentation, external cephalic version, nulliparous women, randomized controlled trial, remifentanil

1. Introduction

Breech presentation (BP) occurs in 3% to 4% of all pregnancies.[1,2] Among pregnant women presenting with BP, 90% of those subjects undergo caesarean delivery in many countries.[3–4] Cephalic presentation and vaginal delivery have been reported to be associated with reduced maternal and fetal morbidity.[5] To avoid caesarean delivery and reduce the incidences of BP, the American College of Obstetricians and Gynecologists has proposed performing external cephalic version (ECV) to change the fetal presentation from breech to cephalic through the use of external pressure.[5] Previous studies have reported that the success rate of ECV is from 50% to 74%, with a reduction rate of 9% to 16% in BP and caesarean delivery.[6–8] Furthermore, ECV can also reduce the surgical risks for both the mother and baby, and decrease the cost of delivery.[9]

Burgos and colleagues reported that ECV is a very painful intervention for most pregnant women, especially for nulliparous women.[5] Their study found that the mean pain scores measured with the visual analog scale (VAS) ranged from 4.6 to 8.5 of the maximum of 10.[5] Although previous studies have used neuraxial analgesia for ECV,[10,11,12] which has been associated with improved pain scores and increased success of ECV, those drugs may also be associated with maternal hypotension, sedation, and other adverse events (AEs).[13,14] Cluver and colleagues conducted a Cochrane systematic review and found that use of regional analgesia did not produce a corresponding decrease in the cesarean rate,[6] although it can increase the success rate of ECV.[6] In addition, regional analgesia may also have significant adverse effects.[14] Thus, the best approach for pain control during the period of ECV is still unclear.[11]

Remifentanil, an ultra-short μ-opioid receptor-antagonist, has a rapid onset of effect and can be quickly metabolized by nonspecific esterases in blood and other tissues, with a half-life of 3 to 4 minutes. Thus, it does not have a cumulative effect and is therefore safely used for analgesia in obstetrics.[15]

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Department of Anesthesia, The People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China.

** Correspondence: Gui-Ping Xu, Department of Anesthesia, The People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Uygur Autonomous Region, Urumqi, China (e-mail: guiping830001@outlook.com).*

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In this study, we tested the hypothesis that remifentanil could reduce pain and improve the success rate of ECV in nulliparous women at term.

2. Methods

2.1. Design

This study was designed as a randomized, double-blind, placebo-controlled trial. In total 144 nulliparous women with singleton BP were recruited in this study. The study was conducted at The People's Hospital of Xinjiang Uygur Autonomous Region from May 2013 to April 2016. The trial was approved by the Medical Ethical Committee of The People's Hospital of Xinjiang Uygur Autonomous Region. All suitable participants were identified by using our inclusion/exclusion criteria. All included participants were randomly divided and allocated to the intervention group or the placebo group (1:1 allocation ratio).

2.2. Inclusion and exclusion criteria

The inclusion criteria selected nulliparous women with singleton BP at term ($\geq 37^{+0}$ weeks), and the eligibility of all subjects was confirmed with ultrasound examination. Subjects were excluded in the presence of fetal abnormalities, intrauterine fetal death, multiple pregnancy, prior uterine surgery, maternal cardiovascular disease, severe hypertension, fetal weight >3800 g, American Society of Anesthesiologists class >2, allergy to remifentanil and its placebo, ruptured membranes, and placental abruption.

2.3. Randomization and blinding

Randomization was performed by using a computerized number generator in the stratified block randomization method in SAS (version 8.1; SAS Institute Inc., Cary, NC). Thereafter, the randomization assignments were concealed in opaque, sequentially numbered, sealed envelopes. The participants, investigators, outcome assessors, and the statistician who conducted the randomization and data analysis were blinded to the treatment allocation.

2.4. Participants and recruitment

All participants were recruited through the clinic of the obstetrics and gynecology department at The People's Hospital of Xinjiang Uygur Autonomous Region. All subjects were randomized to either the intervention group or placebo group only after the clinical evaluation and ultrasound scan. All anesthetists and investigators were trained in their tasks. The participants were informed about the research and given an information sheet. Consent was obtained from all subjects. Thereafter, all included subjects were administered remifentanil intervention or placebo before ECV.

2.5. Intervention

All participants were given intravenous paracetamol 1 g in 100 mL saline 5 minutes before ECV. Subsequently, they received a patient-controlled analgesia at 0.1 μg/kg/min for 3 minutes and then rescue boluses on demand of 0.1 μg/kg and a lockout period of 4 minutes.

2.6. Outcome measurements

The primary outcome was pain, which was measured by the VAS scale (0 = no pain, 10 = worst pain imaginable). After ECV, the pain was immediately measured for all participants. In addition, maternal satisfaction for ECV was also evaluated by another numerical rating scale (0 = completely dissatisfied, 10 = completely satisfied) at 10 minutes after the ECV, as well as the success rate after ECV.

2.7. Adverse events

AEs were recorded after the ECV. All safety data for all included participants were analyzed and included in the analysis.

2.8. Statistical analysis

The estimated sample size was 63 patients in each group with a 50% difference in success rate, $\alpha = 0.05$ (2-sided) and $\beta = 0.20$. Assuming a 10% dropout rate, at least 144 patients with 72 in each group should be recruited in this study. All outcome data were analyzed by an intention to treat (ITT) approach. Fisher's exact test and *t* tests were used to analyze the categorical and continuous data, respectively, with relative risks and 95% confidence intervals.

3. Results

A total of 198 nulliparous women were initially recruited for entry into the study (Fig. 1). However, 54 subjects were excluded that they failed to meet to inclusion criteria and rejected to participate. Thus, 144 patients were included and were randomly divided into intervention and placebo group, each group 72 participants. Seven patients withdrew from the study, 3 from the intervention group, and 4 from the placebo group (Fig. 1). The patients' characteristics at baseline are shown in Table 1. No significant differences in any demographic and clinical variables at baseline were found.

The VAS score was 4.3 ± 2.2 in the intervention group, which is significantly lower than the score of 6.4 ± 2.5 in the placebo group ($P < 0.01$, Table 2). The number of bolus doses used was 5.1 ± 3.3 in the intervention group, which is much fewer than the 10.2 ± 4.4 bolus doses used in the placebo group ($P < 0.01$, Table 2). The ECV success rate was 56.9% in the intervention group, which is significantly higher than the 38.9% success rate in the placebo group ($P = 0.03$, Table 2). The satisfaction score was 9.3 ± 0.9 in the intervention group, which is also significantly higher than the score of 6.7 ± 1.2 in the placebo group ($P < 0.01$, Table 2).

All AEs are listed in Table 2. The most common AEs were nausea (intervention group 4.2% vs placebo group 6.9%, $P = 0.47$, Table 3) and transient fetal bradycardia (intervention group 2.8% vs placebo group 8.3%, $P = 0.17$, Table 3). No treatment-related deaths were found in both groups.

4. Discussion

Pregnant women undergoing ECV for correcting BP often experience moderate to high levels of pain, especially for nulliparous women at term.[16] The key finding of this study is that remifentanil not only can reduce pain and improve satisfaction but also can improve the success rate of ECV in nulliparous women at term. These findings are consistent with those of other studies showing that remifentanil could reduce pain and increase maternal satisfaction.[15,17,18] In addition, analgesia with remifentanil could also improve the success rate of ECV.[15]

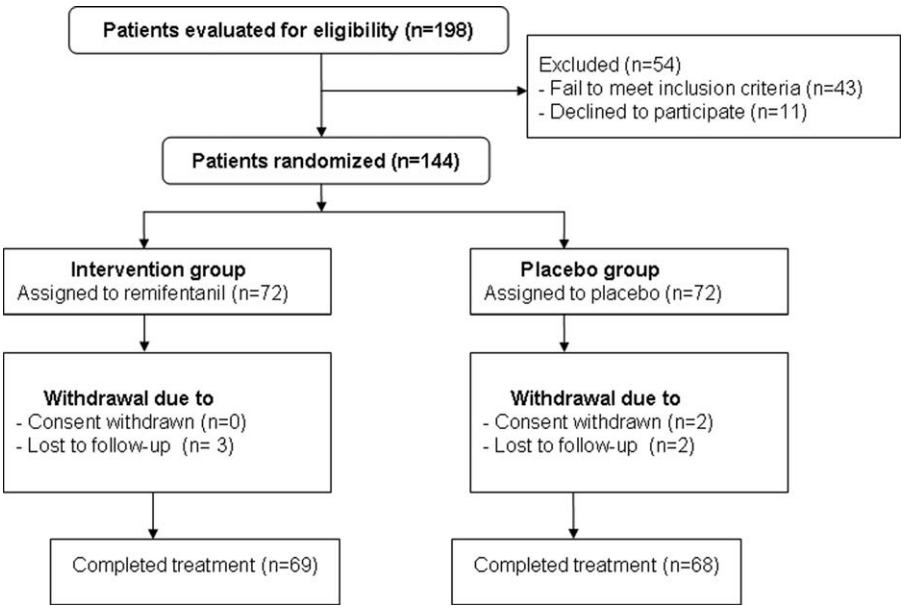

Figure 1. Flow of participants through the trial.

Although several previous studies have reported that analgesia can be effectively used for multiparous women for correcting BP during the period of ECV,[15,17–18] no study has focused on the use of remifentanil for pain relief during ECV for BP in nulliparous women at term. Of the previous studies, 1 study found 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.[15] Another study demonstrated that remifentanil could effectively decrease pain, but found no difference in the success rate of ECV between patients who received remifentanil and those who received placebo.[17] A similar result was reported by Burgos and colleagues,[18] although they also found an increased frequency of mild AEs.[18]

Although several systematic reviews concluded that regional analgesia could significantly enhance the success rate of ECV,[14,19–21] controversy still exists because of the different techniques, drugs, and doses used during the procedure of ECV. Of all those factors, dose difference may be the most important. Previous studies found that higher doses could generate a higher degree of motor blockade on the abdominal muscles during ECV, and thus could prevent involuntary abdominal tensing.[19–21]

In this study, only mild and infrequent AEs were found, which suggests that remifentanil has an acceptable safety profile for pain relief during ECV for BP in nulliparous women at term. The most common AEs were nausea, dizziness, and transient fetal

Table 1

Patients characteristics.

	Intervention group (n=72)	Placebo group (n=72)	*P*
Age, y	33.2 (4.6)	32.9 (5.1)	0.71
Body mass index, kg/m^2	27.4 (3.5)	27.5 (3.4)	0.86
Race			
Uyghur ethnicity	65 (90.3)	63 (87.5)	0.60
Han ethnicity	7 (9.7)	9 (12.5)	0.60
Parity			
1	41 (56.9)	37 (51.4)	0.50
2	27 (37.5)	31 (43.0)	0.50
3	3 (4.2)	2 (2.8)	0.65
≥4	1 (1.4)	2 (2.8)	0.57
Gestation week			
37	66 (91.7)	64 (89.0)	0.57
38	3 (4.2)	4 (5.6)	0.70
39	1 (1.4)	2 (2.8)	0.57
40	2 (2.8)	1 (1.4)	0.57
41	0 (0)	1 (1.4)	0.50
Placental			
Anterior	33 (45.8)	31 (43.1)	0.74
Posterior	26 (36.1)	25 (34.7)	0.86
Fundal	13 (18.1)	16 (22.2)	0.53
Breech presentation			
Frank	60 (83.3)	57 (79.1)	0.52
Complete	7 (9.7)	9 (12.5)	0.53
Footling	4 (5.6)	3 (4.2)	0.70
Transverse	1 (1.4)	3 (4.2)	0.33
Amniotic fluid index, cm	12.3 (3.2)	12.4 (3.0)	0.85

Data are present as mean ± standard deviation or number (%).

Table 2

Outcome measurements.

	Intervention group (n=72)	Placebo group (n=72)	*P*
VAS score after ECV	4.3 (2.2)	6.4 (2.5)	<0.01
Number of PCA demands	5.1 (3.3)	10.2 (4.4)	<0.01
ECV success	41/72 (56.9)	28/72 (38.9)	0.03
Satisfaction score	9.3 (0.9)	6.7 (1.2)	<0.01
Delivery after successful ECV			
Spontaneous	29/41 (70.7)	19/28 (67.9)	0.80
Instrumental	8/41 (19.5)	5/28 (17.9)	0.86
Caesarean	4/41 (9.8)	4/28 (14.2)	0.57
Delivery after failed ECV			
Breech	0 (0)	8/44 (18.2)	0.07
Caesarean	31/31 (100.0)	36/44 (81.8)	0.07

Data are present as mean ± standard deviation or number (%).
ECV = external cephalic version, PCA = paracetamol, VAS = visual analog scale.

Table 3

Adverse events between 2 groups.

Adverse events	Intervention group (n = 72)	Placebo group (n = 72)	*P*
Nausea	3 (4.2)	5 (6.9)	0.47
Vomiting	1 (1.4)	3 (4.2)	0.33
Dizziness	1 (1.4)	2 (2.8)	0.57
Transient fetal bradycardia	2 (2.8)	6 (8.3)	0.17
Drowsiness	2 (2.8)	0 (0)	0.29
Hypotension	1 (1.4)	0 (0)	0.50

Data are present as number (%).

bradycardia, in both groups. No significant differences in any AE were found in both groups.

Despite revealing the efficacy and safety of remifentanil for ECV in nulliparous women at term, this study still has several limitations. First, this study was conducted only at the People's Hospital of Xinjiang Uygur Autonomous Region, and most of the participants were Uyghur Chinese, which may have an influence on the generalizability of our findings to patients in other hospitals and of other ethnicities. Second, pain relief was evaluated by using the VAS, which is a subjective tool and may be affected by multiple unknown factors. Finally, although all investigators underwent training before this study, the variety of their experience levels may still cause bias in the pain experience of patients and the success rate of ECV.

The results of this study showed that the administration of remifentanil for ECV in nulliparous women at term could not only achieve pain reduction and enhance maternal satisfaction, but could also facilitate a successful ECV and has few AEs.

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