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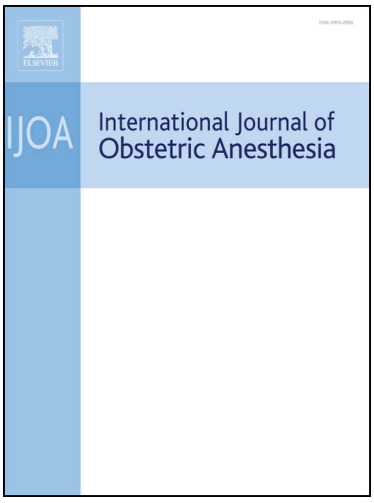

Original Article

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S Lomas, Z Minton, J Daniels

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Systematic review of the effectiveness of remifentanil in term breech pregnancies undergoing external cephalic version

S Lomas[1]*, Z Minton[1]*, J Daniels[2]

[1] School of Medicine, University of Nottingham, Nottingham, NG7 2UH, UK

[2] Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, NG7 2RD, UK

Corresponding author:

Professor Jane Daniels

Nottingham Clinical Trials Unit,

University of Nottingham,

Nottingham,

NG7 2RD

United Kingdom

Email: jane.daniels@nottingham.ac.uk

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Systematic review of the effectiveness of remifentanil in term breech pregnancies undergoing external cephalic version

S Lomas[1]*, Z Minton[1]*, J Daniels[2]

[1] School of Medicine, University of Nottingham, Nottingham, UK

[2] Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK

Corresponding author:

Professor Jane Daniels, Nottingham Clinical Trials Unit, University of Nottingham,

Nottingham, NG7 2RD, United Kingdom

Email: jane.daniels@nottingham.ac.uk

ABSTRACT

Background: External cephalic version (ECV) is a moderately painful procedure used to turn a fetus from a non-vertex to cephalic position. This systematic review and meta-analysis compared intravenous remifentanil with other analgesia or no analgesia or placebo on the success rate and associated pain of ECV.

Methods: Systematic searches for randomised controlled trials using remifentanil during ECV for non-cephalic term singleton pregnancies were conducted in EMBASE, MEDLINE and Cochrane Library to October 2021. The primary outcomes were successful ECV and maternal pain; secondary outcomes included mode of delivery and adverse effects. The Cochrane Risk of Bias tool was used and meta-analysis undertaken if there were ≥2 comparable studies.

Results: Four trials were identified, three placebo-controlled and one vs. no analgesia, totalling 482 participants. Comparisons against nitrous oxide or neuraxial anaesthesia were not analysed. Two studies had a low overall risk of bias, and two had some concern for bias. Remifentanil compared with placebo increased the success of ECV by 43% (risk ratio [RR] 1.43; 95% confidence interval [CI] 1.14 to 1.78). Pain scores (0-10) were lower (mean difference -1.97; 95% CI -2.49 to -1.46) whilst there was no impact on caesarean delivery rate (RR 0.97; 95% CI 0.81 to 1.17). Adverse events were rare, with fetal bradycardia observed less often with remifentanil than placebo.

Conclusions: Remifentanil increases the procedural success of ECV and reduces pain compared with placebo. Trials were at low risk of bias and contained a sufficient number of participants to have reasonable confidence in this finding.

Keywords

Analgesia

Breech presentation

Extracephalic version

Meta-analysis

Remifentanil

Introduction

Breech presentations complicate 3-4% of all deliveries.[1] Since the publication of the Term Breech Trial in 2000, [2] there has been a decrease in vaginal breech deliveries in favour of elective caesarean deliveries.[3] Consequently, there is renewed interest in the use of external cephalic version (ECV) to avoid caesarean birth and associated adverse events.[4] Evidence collated from a meta-analysis and observational studies has demonstrated the safety of ECV,[5, 6] reporting a reduction in non-cephalic vaginal births (RR 0.42, 95% CI 0.29 to 0.61),[7] and associated fetal and maternal morbidities.[8] Guidelines recommend that ECV be offered and attempted in the absence of contraindications,[9,10] for complete, incomplete, and frank breech and transverse presentations, with the ultimate goal of uncomplicated vaginal delivery.

Although ECV is usually well tolerated[11], analgesia may be offered for the course of ECV to facilitate the abdominal manipulation. Neuraxial anaesthesia increases success rates of ECV,[12-14] but with an increased incidence of adverse outcomes, such as maternal hypotension.[15] In recent years, the fast-acting opioid remifentanil has provided an alternative to standard anaesthetic techniques.

Remifentanil is an ultra-short μ-opioid receptor antagonist with a half-life of 3-4 min. The effectiveness of remifentanil delivered as patient-controlled analgesia during labour has been demonstrated.[16,17] Remifentanil offers a potential alternative to neuraxial anaesthesia for pain relief during ECV. We aimed to analyse the results of randomised control trials assessing the effectiveness of remifentanil in achieving successful ECV compared with other analgesics or no intervention.

Methods

This systematic review followed methods from the Cochrane Handbook for Systematic Reviews of Interventions,[18] and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[19] The review was registered with PROSPERO (CRD42021286674) before screening was undertaken.

Study Selection

Eligible studies were those involving women undergoing ECV at >36 weeks of pregnancy with a singleton fetus in a breech or non-vertex position. Trials exclusively involving fetuses with known birth anomalies, twins or other multi-fetus pregnancies, or fetuses with oligohydramnios, were excluded. The protocol stipulated that included studies compare remifentanil to placebo remifentanil, to other analgesics (including inhalational and neuraxial anaesthetics), or to no analgesic control. All intravenous remifentanil administration techniques were considered, including but not limited to, intravenous boluses, and continuous infusion or patient-controlled bolus techniques. Only randomised controlled trials were considered.

Searches were conducted in Ovid MEDLINE, EMBASE, AMED, MIDIRS, HMIC, and Cochrane Library CENTRAL, and included studies ranging from the inception of the respective

database to October 2021. All citations were exported into a bibliographic software package (Endnote) and duplicates automatically removed. In all databases, searches were carried out using the following key words: ("Fetal Version" OR "Pregnant Women" OR "Breech Presentation" OR "Pregnancy") AND "Remifentanil." An example database search strategy for Ovid MEDLINE is in Table S1. The reference lists of eligible studies were also screened.

Two authors (S.L. and Z.M.) worked in parallel to independently screen the studies for eligibility, first by reviewing the title and abstract, then a second round reviewing the whole paper. In the case of disparity, a third author (J.D.) helped to make a consensus decision.

Data extraction

Data from the eligible studies were independently extracted by S.L. and Z.M without alteration and compiled within custom-made data collection forms. Study characteristics, including year of publication, country, study design, study interventions, use of tocolytics, hydration, and additional analgesia, primary outcome, other key outcomes, and sample sizes for both the intervention and comparator(s).

The primary outcomes for review were 1) incidence of a successful external cephalic version, and 2) reported pain level identified during the procedure using either a numerical rating scale (NRS) or a visual analogue scale (VAS). The following secondary outcomes were also extracted if possible: mode of delivery, number of ECV attempts, reversion to a non-vertex position, adverse effects on the mother (e.g. maternal hypotension), and adverse effects on the fetus (e.g. fetal heart rate abnormalities and perinatal death). The intention-to-treat comparison data were extracted.

Risk of bias assessment

The Cochrane Risk-of-Bias Assessment Tool version 2 (RoB2 in MS Excel) was used for each of the included studies in duplicate by S.L and Z.M.,[18, 20] whilst J.D. facilitated the resolution of inconsistent judgements. Five domains of bias were assessed for each study: 1. Randomisation; 2. deviation from the intended intervention; 3. missing outcome data; 4. measurement of the outcome; and 5. selection bias. Eligible studies were categorised as high risk, low risk, or having some concerns of bias. The RoB2 tool provides an automated overall bias assessment for each domain based on the responses given by the assessor alongside assessor-based overall risk of bias category. In all cases, the assessors' determination was aligned with the algorithm's assessment.

Data synthesis

Three comparisons were prespecified: remifentanil vs placebo, remifentanil vs no analgesic, and remifentanil vs another analgesic or anaesthetic. Description of the data and meta-analyses were carried out if comparable data were available for two or more studies. The presence of a single trial is described, but the results not re-reported. A post-hoc comparison of remifentanil vs placebo or no analgesia was also undertaken. The synthesis of comparative data for success rate of ECV, incidence of caesarean section, and incidence of adverse effects was expressed as a risk ratio with 95% confidence intervals (CIs). Data relating to the reported pain score were reported using both the numerical rating scale (NRS, scored 0-10) and the visual analogue scale (VAS, scaled 0-100 mm); VAS results were reduced by a factor of 10. Pain scores and the number of attempts at ECV were expressed as a mean difference with 95% CI.

Meta-analysis was carried out using the Review Manager (RevMan) 5.4 software (The Cochrane Collaboration, 2020). For dichotomous measures, the Mantel-Haenszel method was used, as this method has been shown to have better statistical properties when data events are sparse.[21] For continuous measures, the inverse variance method was used to derive a mean difference.[18] A fixed-effects method was used within analyses in accordance with the assumption that all effect measures estimated the same underlying intervention effect.[18] Data generated from meta-analysis were presented within a forest plot.

Statistical heterogeneity was investigated using the I^2 statistic,[21] interpreted as 0% representing the absence of any heterogeneity, present if I^2 >0.50 and substantial if I^2 >0.75.[23] Sensitivity analysis to explore the impact of study level variables was planned if there were more than nine eligible studies. A formal assessment of publication bias, using a funnel plot, was planned if at least 10 eligible studies with primary outcome data were available. Finally, an overall assessment of the strength of evidence using the GRADE approach was not planned as there were too few studies for each comparison.

A post-hoc trial sequential analysis of the remifentanil vs placebo for the outcome of a successful turn was performed using Trial Sequential Analysis Viewer version 0.9.5.10 (Copenhagen Trials Unit, Denmark). The information size required to demonstrate either a 50% (chosen as target sample size by two included studies[24,25]) or a 43% relative increase in successful turns (obtained in the conventional meta-analysis), using a mean successful version rate in the placebo group of 40%, alpha at 0.01 or 0.05, power at 10% and a O-Brien-Fleming alpha spending function, was calculated.

Results

Study selection

The database searches generated 576 citations, 526 after automatic de-duplication (Fig. 1). From this, 384 papers were immediately excluded due to not being relevant to the review question. Of the remaining 142 citations, 75 were excluded for not being randomised controlled trials, 13 were duplicates missed by the software, 46 did not study ECV and three did not meet other eligibility criteria.

The remaining five studies were included in the review; four had data included in the analysis. A conference abstract,[26] identified from the reference list of a previous systematic review,[27] met the inclusion criteria, but on further inspection was deemed to be an interim report of one of the eligible studies, and thus was excluded.

Study characteristics

Characteristics of the five included studies are summarized in Table 1. Four studies were designed as two-arm randomised control trials, one comparing remifentanil with nitrous oxide (not included in the analysis),[28] and three with a placebo remifentanil comparator.[24, 25, 29] The final eligible study was a two-phase, three-arm trial; only those women who had been randomised to no analgesia or neuraxial anaesthesia in the first phase, and who failed to achieve successful ECV entered the second phase.[30] As the second phase participants are different in terms of risk of a failed ECV, only procedural success data from the first phase of the trial, randomising between remifentanil and no analgesia, was used and combined with the data for the placebo-controlled studies for a secondary comparison.

Two studies recruited women who were at least 36 weeks' gestation[29,30]; the remainder recruited women at 37 weeks' gestation or more.[24,25,28,30] All studies were restricted to singleton pregnancies, with one study exclusively recruiting nulliparous women.[25] Two studies were conducted in Spain,[28,29] the other three in China.[24,25,30] Sample size ranged from 63 to 189 participants per study.

Risk of bias assessment

Two studies were deemed to have an overall low risk of bias[24,29]; the remaining three studies were assessed as some concern for bias risk (Fig. 2).

All studies received a low risk of bias rating within the randomisation domain, with four studies using sequentially numbered sealed opaque envelopes,[24,25,28] and one study employing computer

randomisation.[29] The baseline characteristics of the participants was generally balanced between the different groups.

Three trials received a low risk of bias rating in the deviation from intended intervention domain, attributable to the interventions being blinded.[24,25,29] All trials followed the intention-to-treat principle. The other two trials had markedly different interventions: nitrous oxide was delivered via a facial mask in one trial,[28] and spinal anaesthesia required the participant to lie laterally, whilst remifentanil was delivered in the supine position in the second trial.[30] Low risks of bias were determined for missing outcome data and the description of the outcome, and even for the non-blinded studies, the risk of bias for the primary outcome was considered low as the determination of successful version is objective and unlikely to be influenced by knowledge of the analgesia used.[18] Only one trial was deemed to be at low risk of bias in the selective reporting domain, as the trial was prospectively registered and the data followed the publicly available record.[29]

One study, comparing remifentanil with inhalational analgesia, was closed to recruitment before the target sample size was reached, due to futility. The trial had anticipated a 20% absolute improvement in a successful ECV through use of remifentanil, requiring 180 participants, but an external data monitoring committee who reviewed interim data after 120 participants saw no evidence to suggest that predicted superiority over inhalational analgesia would ever be demonstrated.[28] No outcomes from this trial are presented in this review.

Data synthesis

All studies reported successful ECV rates (**Error! Reference source not found.**). The meta-analysis of the three studies using placebo as the comparator estimated that participants who received remifentanil were significantly more likely to have a successful ECV than if they received the placebo (RR 1.43, 95% CI 1.14 to 1.78) (**Error! Reference source not found.**). Including the study comparing remifentanil with no analgesia also demonstrated a benefit for remifentanil, albeit to a smaller extent (RR 1.27, 95% CI 1.07 to 1.51) (Fig. S1).

The meta-analysis shows that participants who received remifentanil reported a significantly lower pain score compared with those receiving the placebo (mean difference -1.97, 95% CI -2.49 to -1.46) (Fig. 4). Khaw et al. reported that pain was significantly reduced in the remifentanil groups (3.5, IQR 0-6.0) compared with control (5.0, IQR 3.0 to 7.5).[30] These data were not included in the meta-analysis because they were presented as median scores.

We interpreted the incidence of caesarean section as an indication of failed ECV in the absence of any further detail. No study reported a significant difference in the rate of caesarean section, with rates ranging from 49% to 60% for those using remifentanil (RR 0.97, 95% CI 0.81 to 1.17) (**Error! Reference source not found.**, Fig. S2).

A lower rate of adverse events from remifentanil was reported by Munoz et al. (remifentanil 7% [2/31] vs control 14% [4/29].[29] Fetal bradycardia was 60% lower in the remifentanil group compared with the placebo group (RR 0.4, 95% CI 0.19 to 0.83) (Table S2 and Fig. S3). Maternal adverse events were uncommon and there was no evidence of any difference between remifentanil and placebo (Table S2, Figs. S4-7).

Given that all meta-analyses generated I^2 values of 0% and as fewer than 10 studies were eligible for inclusion in the current review, neither a sensitivity analysis nor assessment of publication bias was conducted.

The post-hoc trial sequential analysis indicated an information size of 451 participants was required to determine a 43% risk reduction and 326 participants for a 50% risk ratio at a type I error of 1%, and 297 and 215 respectively for a 5%-type I error. The cumulative Z-score of the three meta-analysed trials crossed both boundaries at the 5% type I error threshold, but only for the 50% risk ratio at 1% threshold. This suggests reasonable, but not high, confidence that the observed risk

ratio in the meta-analysis was a significant finding and not a false positive result. Heterogeneity and diversity were both 0%.

Discussion

Compared with placebo, remifentanil was shown to significantly increase the success rate of ECV, whilst significantly decreasing maternal pain scores. Remifentanil also reduced the incidence of fetal bradycardia. Although remifentanil increased the success rates of ECV compared with placebo, this was not mirrored with a decreased rate of caesarean section. The relatively small sample sizes of the included studies may preclude a small, but clinically meaningful, increase in vaginal deliveries and caesarean section may be indicated for other medical reasons following a successful ECV. The prevailing rates of caesarean section for breech singleton pregnancies in China was 90% in 2016, [31] whilst data for a single centre in Spain suggests a rate of 45% of births by caesarean section in term breech pregnancies.[32]

Remifentanil reduced pain reported by participants throughout the ECV procedure by an average of 1.97 points on a 0-10 scale compared with placebo, which exceeds the minimal clinically important difference for peri-procedural pain.[33] The hypothesis is that analgesia reduces the risk of abandoning the ECV due to maternal discomfort, and the data analysed here support this hypothesis. Compared with an active comparator such as inhalational or spinal analgesia, the effect size would be expected to be smaller or even reversed, with remifentanil providing inferior analgesia, but we did not perform a network meta-analysis to rank the analgesic options.

Side effects of remifentanil, including maternal dizziness, hypotension, nausea, and vomiting were observed at rates consistent with the profile of this opioid drug, and with no evidence of an increased rate over background or placebo effects.

Hao et al.[27] conducted a network analysis of neuraxial, inhalational, and intravenous anaesthesia on the success rate of ECV, reporting results as odds ratios (OR). The wider inclusion criteria enabled a trial of fentanyl vs. combined spinal-epidural analgesia to be included in the intravenous versus neuraxial anaesthesia comparison.[34] An interim report of the study by Khaw et al. was treated as a separate trial, creating duplicate data.[26] Nonetheless, the Hao et al. meta-analysis of the same studies comparing remifentanil vs placebo on the rate of successful ECV produced a pooled odds ratio (OR) of 1.49 (95% CI 1.03 to 2.16), validating our results via a different statistical approach.[27] Similarly, Hao et al. found that remifentanil significantly decreased the odds of non-reassuring fetal responses (defined in the current review as fetal bradycardia) by 64% (OR 0.36, 95% CI 0.16 to 0.82) with no evidence of an impact on caesarean section rates (pooled OR 0.93, 95% CI 0.61 to 1.42), findings similar to our review.[27]

The review has been conducted according to the Cochrane Collaboration's standard methodology. The risk of bias assessment raised few concerns regarding the included studies and statistical heterogeneity was zero for all meta-analyses of placebo-controlled trials, and low when placebo and no analgesia were combined as comparators. There were sufficient numbers of participants to be confident at the 5% level that the risk ratio of 1.43 for the outcome of a successful ECV was not a false positive finding. Due to only one study each for the comparisons against inhalation and spinal anaesthesia, outcomes were not reported here as no additional interpretation is possible. The limited number of studies prevented sensitivity analysis and publication bias assessment.

Effective interventions to improve outcomes from ECV, such as the use of tocolytic agents,[11] and potential effect modifiers, such as paracetamol analgesia, were not deployed, or not reported. In the comparison of remifentanil with no analgesia, a potential for bias exists in participant-reported outcomes such as pain.[32]

Our results are generalisable, with review criteria and included studies reflecting the spectrum of women with term breech pregnancies that would be suitable for ECV, and studies only excluding women where accepted medical guidance precludes ECV, such as multi-fetus pregnancies.[35] The studies also report ECV success rates comparable to other reported literature.[12] The lack of geographic diversity in the included studies is a potential limitation, and differences in ECV technique may influence outcomes.

In conclusion, intravenous remifentanil increases the success rate of ECV compared with placebo and reduces maternal pain and fetal bradycardia. There is no evidence that maternal use of remifentanil causes harm to the baby. Remifentanil can be considered efficacious for use in ECV for singleton term breech presentations. The relative effectiveness of remifentanil in comparison with other analgesic options, including nitrous oxide and neuraxial analgesia, should be assessed in further robust randomised trials.

Acknowledgements

This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number: CRD42021286674. The protocol can be accessed via https://www.crd.york.ac.uk/prospero/ using the previously identified registration number.

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Declaration of interests

None.

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Figure legends

Fig. 1 Flow chart of study screening and selection

Fig. 2 Risk of bias summary, generated by the RoB2 Excel tool

Fig. 3 Meta-analysis of successful external cephalic version: remifentanil vs placebo

Fig. 4 Meta-analysis of reported maternal pain score (0-10 scale): remifentanil vs placebo.

HIGHLIGHTS

- External cephalic version (ECV) of breech fetuses increases cephalic presentation
- ECV is associated with moderate to severe pain for some women
- This meta-analysis compared remifentanil with no analgesia for ECV
- Remifentanil was associated with increased ECV success
- Remifentanil was associated with lower pain scores

Table 1 - Study characteristics of eligible trials

Study	**Study location**	**Sample size (n)**	**Type of malpresentation (n, intervention group: n, comparator group)**	**Gestation(weeks)**	**Remifentanil dose and lock-out period**	**Comparator**	**Primary outcome**	**Pain outcome measure**	**Tocolysis**	**Additional analgesia**	**Number of maximum ECV attempts**
Burgos et al. 2016	Spain	120	Frank 42:41 Complete 6:10 Incomplete 5:6 Footling 4:2 Transverse 3:1	≥37	0.1µg/kg/min for 3 min before ECV, additional bolus on demand	50% nitrous oxide : 50% oxygen	Successful ECV	Not reported	Ritodrine 6 mg	None reported	Not reported

Khawet al. 2015	China	189	Not reported	≥36	0.1μg/kg/min for 10 min before ECV	No intervention OR combined spinal-epidural: bupivacaine 9mg and fentanyl 15μg	SuccessfulECV, pain score	VAS	Hexo-prenaline 10μg/min as three doses at 2-min intervals	None reported	5
Liu, Xue 2016	China	152	Frank 63:59 Complete 8:10 Footling 3:4 Transverse 2:3	≥36	0.1 μg/kg/min for 3 min before ECV, additional bolus on demand with 5-min lockout	Placebo	Successful ECV, pain score	NRS	Not reported	Paracetamol (1 g)	Not reported
Wang et al. 2017	China	144	Frank 60:57 Complete 7:9 Footling 4:3 Transverse 1:3	≥37	0.1 μg/kg/min for 3 min before ECV, additional bolus on demand with 4-min lockout	Placebo	Pain score	NRS	Not reported	Paracetamol (1 g)	Not reported

Muñoz et al. 2014	Spain	63	Frank 17:20 Complete 9:5 Footling 3:1 Transverse 1:2	≥36	0.1 µg/kg/min for 3 min before ECV, additional bolus on demand with 4-min lockout	Placebo	Pain score	NRS	Ritodrine 200 µg/ min	Paracetamol (1 g)	Not reported

ECV: extra cephalic version; VAS: visual analogue scale; NRS: numerical rating scale

Table 2 Study level data for the outcomes of successful ECV, caesarean rate and reported pain score

Outcome study	**Remifentanil**	**Control**	
Successful ECV	**% (n/N)**	**% (n/N)**	**Relative risk (95% CI)**
Khaw et al.	64% (40/63)	64% (40/63)	1.00 (0.77 to 1.30)
Liu, Xue	56.5% (43/76)	39.5% (30/76)	1.43 (1.02 to 2.02)
Muñoz et al.	54.8% (17/31)	41.3% (12/29)	1.33 (0.77 to 2.27)
Wang et al.	56.9% (41/72)	38.9% (28/72)	1.46 (1.03 to 2.08)
Caesarean birth			
Khaw et al.	Not reported	Not reported	-
Liu, Xue	60.5% (46/76)	57.9% (44/76)	1.05 (0.80 to 1.36)
Muñoz et al.	54.8% (17/31)	55.2% (16/29)	0.99 (0.63 to 1.57)
Wang et al.	48.6% (35/72)	55.6% (40/72)	0.88 (0.64 to 1.20)

Reported pain score (0-10 scale)	Mean (SD); n (unless noted)	Mean (SD); n (unless noted)	Mean difference (95% CI)
Khaw et al.	Median 3.5 (range 0.0 to -1.0); 63	Median: 5.0 (range 0.0 to 1.0); 63	NA
Liu, Xue	4.6 (2.6); 76	6.5 (2.7);76	-1.90 (-2.74 to -1.06)
Muñoz et al.	4.7 (2.5); 31	6.5 (2.4); 29	-1.80 (-3.04 to -0.56)
Wang et al.	4.3 (2.2); 72	6.4 (2.5); 72	-2.10 (-2.87 to -1.33)

ECV: external cephalic version; CI: confidence interval; NA: not applicable.