Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): an open-label, multicentre, randomised controlled trial

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Summary

Background About a third of women receiving pethidine for labour pain subsequently require an epidural, which provides effective pain relief but increases the risk of instrumental vaginal delivery. Remifentanil patient-controlled analgesia (PCA) in labour is an alternative to pethidine, but is not widely used. We aimed to evaluate epidural analgesia progression among women using remifentanil PCA compared with pethidine.

Methods We did an open-label, multicentre, randomised controlled trial in 14 UK maternity units. We included women aged 16 years or older, beyond 37 weeks' gestation, in labour with a singleton cephalic presentation, and who requested opioid pain relief. We randomly assigned eligible participants (1:1) to either the intravenous remifentanil PCA group (40 µg bolus on demand with a 2 min lockout) or the intramuscular pethidine group (100 mg every 4 h, up to 400 mg in 24 h), using a web-based or telephone randomisation service with a minimisation algorithm for parity, maternal age, ethnicity, and mode of labour onset. Because of the differences in routes of drug administration, study participants and health-care providers were not masked to the group allocation. The primary outcome was the proportion of women who received epidural analgesia after enrolment for pain relief in labour. Primary analyses were unadjusted and analysed by the intention-to-treat principle. This study is registered with the ISRCTN registry, number ISRCTN29654603.

Findings Between May 13, 2014, and Sept 2, 2016, 201 women were randomly assigned to the remifentanil PCA group and 200 to the pethidine group. One participant in the pethidine group withdrew consent, leaving 199 for analyses. The proportions of epidural conversion were 19% (39 of 201) in the remifentanil PCA group and 41% (81 of 199) in the pethidine group (risk ratio 0·48, 95% CI 0·34–0·66; p<0·0001). There were no serious adverse events or drug reactions directly attributable to either analgesic during the study.

Interpretation Intravenous remifentanil PCA halved the proportion of epidural conversions compared with intramuscular pethidine. This finding challenges routine pethidine use as standard of care in labour.

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Introduction

Childbirth can be extremely painful. Thus the provision of effective pain relief during labour is an important element of a positive maternal experience. More than a quarter of a million women per year in the UK receive the opioid drug pethidine by intramuscular injection, and many more worldwide.[1] Despite widespread international use, pethidine is not uniformly effective in relieving labour pain,[2] and it has proven side-effects including maternal sedation, nausea, and potential transfer across the placenta to the fetus.[3] More than a third of women who receive pethidine subsequently require an epidural for pain relief.[4] Epidural analgesia is the most effective form of pain relief in labour and is associated with high levels of maternal satisfaction; however, there is an increased likelihood of instrumental vaginal delivery and prolongation of the second stage of labour.[5,6] This effect is reduced by modern low-dose epidural techniques, but is not completely mitigated.[5] Instrumental vaginal delivery is associated with perineal trauma and long-term morbidity thereafter, such as faecal incontinence[7] and sexual dysfunction.[8,9]

Remifentanil is a potent synthetic opioid with novel pharmacokinetic properties, including very rapid onset and an ultra-short duration of action, making it effective for pain relief in labour when administered by intravenous patient-controlled analgesia (PCA) and thus a potential alternative to pethidine. However, most maternity units in the UK rarely use remifentanil PCA in routine practice,[10] restricting it to circumstances when epidural analgesia is contraindicated. This pattern of use is similar in other European countries.[11] The main reasons for this limited use are the paucity of high-quality evidence for its benefit, relative to pethidine as the traditional opioid used in labour, and concerns regarding the potential for opioid-induced maternal

Research in context

Evidence before this study

The Cochrane review on patient-controlled analgesia (PCA) with remifentanil versus alternative parenteral methods for pain management in labour was published in April, 2017. It separately meta-analysed comparisons with remifentanil according to whether pethidine was administered intramuscularly, intravenously, or by PCA. Three studies with 190 participants for the outcome of requiring additional analgesia showed a reduction for remifentanil compared with intramuscular or intravenous pethidine (relative risk [RR] 0·57, 95% CI 0·40–0·81) and no difference in three studies with 215 participants for PCA pethidine (RR 0·76, 95% CI 0·45–1·28). In all but one study, the additional analgesia was epidural. None of the studies in these reviews were designed to examine epidural conversion as a primary outcome. The Cochrane review concluded that the evidence was too low in quality to inform practice and that future research was needed including data for potential maternal and neonatal side-effects. Prior to the RESPITE trial being designed, our searches had found four small, heterogeneous trials comparing remifentanil with pethidine for labour analgesia (see original protocol). A systematic review published in 2012, before RESPITE commenced recruitment, showed a reduction in progression to epidural with remifentanil compared with pethidine administered by various routes from four poor-quality studies (n=246 women; RR 0·34, 95% CI 0·20–0·58).

Added value of this study

This study has provided conclusive evidence of the benefit of remifentanil PCA for women in labour, relative to intramuscular pethidine. It is the first randomised controlled trial done with sufficient rigour to inform practice. The requirement for epidural pain relief was halved in women who received remifentanil PCA compared with pethidine. Proportions of epidural conversion were 19% (39 of 201) in the remifentanil PCA group and 41% (81 of 199) in the pethidine group (RR 0·48, 95% CI 0·34–0·66; p<0·0001). Women randomly assigned to the remifentanil PCA group were less likely to require instrumental vaginal delivery than those assigned to the pethidine group (15% *vs* 26%; RR 0·59 [95% CI 0·40–0·88], p=0·008). A reduction in instrumental delivery has the potential to accrue long-term benefit by avoiding associated morbidity. There was a greater requirement for supplemental maternal oxygen with remifentanil PCA than with pethidine, although we found that it was not uniformly required. Maternal side-effects were transient, easily recognised, and managed, and no neonatal effects were detected. This study is unique in examining epidural rescue as a primary outcome, reporting neonatal resuscitation requirement at birth and maternal satisfaction with pain relief.

Implications of all the available evidence

The high-quality evidence from RESPITE is consistent with previous low-quality data that the proportion of epidural rescue analgesia is halved in women requesting opioid pain relief in labour with remifentanil PCA compared with intramuscular pethidine. If the evidence from the studies included in the recent Cochrane review and the results of RESPITE are considered together, the pooled RR of a requirement for rescue analgesia with remifentanil, relative to pethidine, is 0·54 (95% CI 0·42–0·68). In the three studies included in the Cochrane review to generate this comparison, epidural was a possible rescue in two trials with further pethidine or Entonox in one. Our study demonstrated no excess risk of maternal respiratory depression or adverse fetal outcomes with remifentanil PCA compared with pethidine. The use of remifentanil PCA as a first-line opioid for pain relief in labour in preference to pethidine would reduce the need for epidurals, instrumental deliveries, and consequent morbidity for large numbers of women worldwide. The implications are that a fundamental re-evaluation of opioid pain relief in labour is required, challenging the routine use of pethidine in childbirth.

respiratory depression.[12] A Cochrane review[13] evaluating remifentanil PCA relative to a range of other methods of labour pain management reported remifentanil compared with intramuscular pethidine in three trials,[14–16] intravenous pethidine in one trial,[4] and PCA pethidine in three trials.[17–19] This Cochrane review[13] concluded that all these studies provided low-quality evidence, limited by inconsistency and imprecision, and that more robust research was needed to evaluate possible maternal and fetal effects.

Therefore, the aim of the RESPITE trial was to compare intravenous remifentanil PCA with intramuscular pethidine injection in labour to determine whether the intervention reduced progression to epidural analgesia and to evaluate any subsequent adverse maternal or neonatal sequelae.[20,21]

Methods

Study design and participants

RESPITE was an open-label, multicentre, randomised controlled trial, conducted in 14 obstetric-led maternity units in the UK. Units were able to participate in this trial if intramuscular pethidine was the standard care for pain relief in childbirth. The study established a care pathway that allowed eligible women to promptly receive intravenous remifentanil PCA; however, it was not routinely available, on maternal request, at participating centres outside the context of the study.

Women were initially eligible if they had met the following inclusion criteria: 16 years or older and beyond 37 weeks' gestation, with a singleton live baby, in cephalic presentation, who were in established labour (defined as regular painful contractions irrespective of cervical

dilatation), and intending vaginal birth; written informed consent was sought. All women booked for delivery at participating centres were informed about the study before labour at antenatal visits. Participants were eligible to consent in labour provided they had received information about the study beforehand. Eligible women were enrolled to the study when they requested systemic opioid analgesia provided they had not received such analgesia in the preceding 4 h, had no contraindications to remifentanil, pethidine, or epidural analgesia, and were not participating in any other drug trial.

RESPITE had a favourable ethical opinion from the National Research Ethics Service Nottingham 2 Research Ethics Committee (13/EM0239). A Trial Steering Committee provided independent oversight of the trial. Confidential interim analysis of all available data alongside anonymised reports of participants' adverse events was reviewed by a Data Monitoring Committee on three occasions. No reason to recommend halting or modifying the trial was identified. There were no substantial changes to the main study protocol after recruitment commenced. The trial protocol has been published elsewhere.[22]

Randomisation and masking

Women were randomly assigned (1:1) to either intravenous remifentanil PCA (ie, the intervention group) or intramuscular pethidine (ie, the control group), via a web-based central service or a 24-h, 7-day interactive telephone-based service. A minimisation algorithm was used to avoid chance imbalances in four variables: parity (nulliparous *vs* multiparous), maternal age (<20 years, 20 to <30 years, 30 to <40 years, and ≥40 years), ethnicity (south Asian *vs* other), and onset of labour (induced *vs* spontaneous).

Because of the differences in routes of drug administration and the fact that recipients of remifentanil became immediately aware of the drug's effect and therefore of their group allocation, study participants and health-care providers were not masked to the study group allocation.

Procedures

Remifentanil was administered via a dedicated intravenous cannula. The PCA pump was pre-programmed by physician anaesthetists, with a regimen that provided a bolus of 40 µg remifentanil on demand, with a lockout interval of 2 min during which further remifentanil could not be received. This dose regimen was based on sample guidelines adapted from those used in the introduction of remifentanil PCA into clinical practice in some UK labour wards and reflects those used in the largest study before the start of RESPITE.[18] In the event of excess sedation being recorded by regular observation of sedation score and respiratory function, the regimen was reduced to 30 µg with a lockout interval of 2 min. Pethidine was given by the attending midwife in a dose of 100 mg, by intramuscular injection, up to 4 h in frequency, to a maximum dose of 400 mg in 24 h.

Following administration of opioid analgesia, all women received one-to-one midwifery care, irrespective of study group allocation. Clinical observations were made every 30 min including recordings of respiratory rate and a numerical sedation score (1=fully awake; 2=drowsy; 3=eyes closed and rousable by voice; 4=eyes closed and rousable to physical stimulus; 5=eyes closed and not rousable). A Visual Analogue Scale (VAS) pain score was recorded every 30 min from trial entry (0=no pain to 100=worst pain imaginable). Pain scores were discontinued after epidural placement, delivery, or transfer to theatre. Maternal oxygen saturation was monitored continuously by pulse oximetry and recorded every 30 min. A saturation less than 94% when breathing room air was the threshold for mandatory maternal oxygen supplementation. Indications for contacting a physician anaesthetist were excessive maternal sedation, defined as a score of 4 or greater (not rousable to voice), a respiratory rate less than eight breaths per minute, or oxygen saturation less than 94% despite supplementary inspired oxygen therapy.

Women were free to request epidural pain relief at any point after trial entry. Neither the consenting physicians nor research midwives or nurses were involved with a decision to proceed to epidural analgesia. A maternal request for epidural analgesia was treated according to local practice and administered according to individual labour ward protocols. Once effective epidural pain relief was established, the administration of the study drugs was discontinued irrespective of group allocation. Maternal VAS pain scores were discontinued after epidural analgesia. All data were collected before hospital discharge.

Outcomes

The primary outcome was the proportion of women who had an epidural placed for pain relief in labour after randomisation. Maternal and neonatal adverse safety outcomes, potentially attributable to study interventions, were defined as secondary outcomes and collected. Prespecified secondary maternal outcomes were the effectiveness of pain relief, quantified by the VAS pain score taken every 30 min; delivery mode (spontaneous vaginal delivery, instrumental vaginal delivery, and caesarean section); excessive sedation score of 4 or more (ie, not rousable to voice); respiratory depression (respiratory rate <8 breaths per minute); oxygen saturation less than 94% while breathing room air; requirement for supplementary oxygen and antiemetic administration; and maternal satisfaction with pain relief, determined by postpartum questionnaire of childbirth experience, before hospital discharge.

Prespecified neonatal outcomes were the requirement for expedited interventional delivery to resolve fetal distress, persistent low Apgar score at 5 min (ie, Apgar score <4), fetal acidosis determined by umbilical cord gas analysis (if performed), the requirement for neonatal resuscitation, admission to neonatal special care, and the

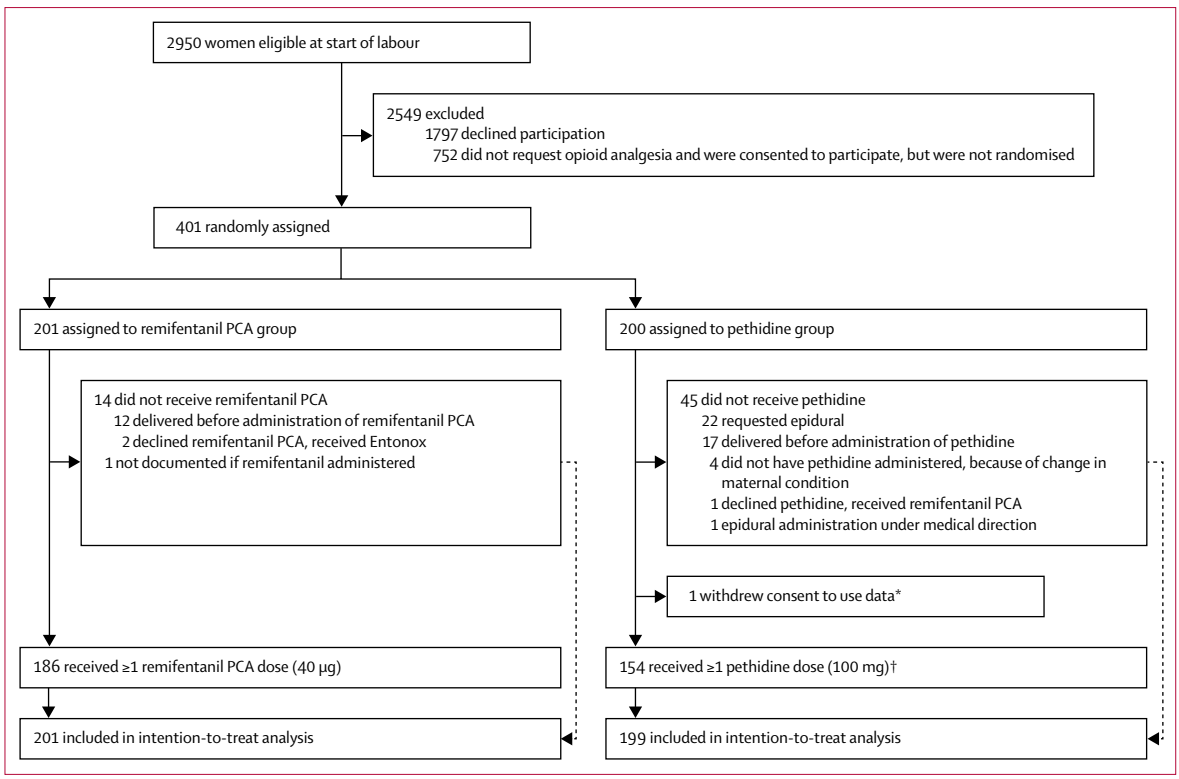

Figure: **Trial profile**
PCA=patient-controlled analgesia. *This woman also did not receive pethidine. †Two women received pethidine as allocated, but subsequently received remifentanil and were therefore non-adherent and not included in the sensitivity analysis.

rate of initiation of breast feeding within the first hour of birth.

Statistical analysis

The proportions of epidural conversion after remifentanil PCA were reported in a range of 5% to 19% in previous randomised trials,[4,16–18] compared with proportions of greater than 30% (range 17–39) in women receiving pethidine. Taking a deliberately conservative estimate of intervention effect using these data, a reduction in epidural conversion from 30% (pethidine) to 15% (remifentanil PCA) was considered reasonable. To detect such a reduction with 90% power at an α level of 0·05, 161 women were required in each group of the trial, yielding a sample size of 322 in total. Adjustment was made to account for attrition of the study population as labour progressed, anticipating that no more than 15% of the women would require urgent delivery by emergency caesarean section before a request for further analgesia could be made. Accounting for a modest unavailability of primary outcome data and non-adherence of 6%, a total sample size of 400 was required.

Demographic factors and clinical characteristics were summarised with counts and percentages for categorical variables, mean and SD for normally distributed continuous variables, or median and IQR or range for non-normal continuous variables. Treatment effects were presented as risk ratios (RRs) or mean differences, with 95% CIs. The primary analysis was a comparison between the analgesic methods assigned at randomisation, using an unadjusted intention-to-treat analysis. Two-sided tests were considered significant if $p<0·05$. In addition to the primary unadjusted analysis, a log-binomial model was fitted to account for the minimisation variables. A prespecified subgroup analysis was done for parity.

Two post-hoc sensitivity analyses were done to explore the effect of adherence to group allocation by trial participants. The first sensitivity analysis included only those women who were fully adherent to their group allocation—ie, received at least one dose of the analgesic to which they were originally assigned to and no dose of the alternative analgesic. The second sensitivity analysis analysed women according to the analgesic they ultimately received.

All analyses were done in SAS (version 9.4). This study is registered with the ISRCTN registry, number ISRCTN29654603.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and trial statisticians had full access to all the data in the study. All authors in the writing team shared final responsibility

for the decision to submit for publication. The manufacturers of the analgesic pump equipment for remifentanil PCA used in the trial were not involved in any aspect of the study. Members of PRIME (Public and Researchers Involvement in Maternity and Early pregnancy group), a group of maternity service users convened by the University of Birmingham, were involved in reviewing the participant information and were represented on the Trial Steering Committee.

Results

Between May 13, 2014, and Sept 2, 2016, 401 women were randomly assigned to receive either intravenous remifentanil PCA (n=201) or intramuscular pethidine (n=200). The figure shows the trial profile. 186 (93%) of 201 women received the allocated drug, in compliance with the protocol, in the remifentanil PCA group and 154 (77%) of 200 in the pethidine group. The main reasons for not receiving the allocated drug were women giving birth before it could be administered (n=12 for the remifentanil PCA group and n=17 for the pethidine group) or a maternal decision to immediately request an epidural after randomisation, without receiving the allocated opioid, which only occurred in the pethidine group (n=22). Participants had a mean age of 29·3 years and 60% were nulliparous. Table 1 provides more details of participant characteristics.

In the remifentanil PCA group, 39 (19%) of 201 women had an epidural compared with 81 (41%) of 199 in the pethidine group (unadjusted intention-to-treat analysis RR 0·48, 95% CI 0·34–0·66; p<0·0001). Adjustment for the minimisation variables barely altered the RR or its CIs (appendix). The sensitivity analysis, which excluded participants non-adherent to the study protocol, had little effect on the magnitude of the difference shown in the unadjusted analysis: 36 (19%) of 186 women in the remifentanil PCA group had an epidural compared with 56 (37%) of 152 in the pethidine group (RR 0·53, 95% CI 0·37–0·75; p=0·0003). Sensitivity analysis, grouping participants by the analgesia ultimately received, similarly showed little effect (appendix). In the pre-specified subgroup analysis, no interaction was found between parity and the treatment effect: 30 (25%) of 121 nulliparous women in the remifentanil PCA group and 58 (49%) of 118 in the pethidine group received an epidural, as did nine (11%) of 80 parous women in the remifentanil PCA group and 23 (28%) of 81 in the pethidine group.

See Online for appendix

Median VAS pain score was significantly reduced by 13·91 points (95% CI –21·40 to –6·43; p=0·0003) in the remifentanil PCA group than in the pethidine group; however, there was no difference in the maximum VAS pain score reported between both groups (mean difference –4·44 points, 95% CI –10·93 to 2·05: p=0·18; table 2).

The maternal outcomes of respiratory depression and excessive sedation did not differ between groups and were rare: respiratory depression occurred in one (1%) of 187 women in the remifentanil PCA group and excessive sedation occurred in two (1%) of 187 in the remifentanil PCA group and three (2%) of 152 in the pethidine group. Significantly more women in the remifentanil PCA group had low maternal oxygen saturation than those in the pethidine group (26 [14%] of 189 *vs* eight [5%] of 154; RR 2·65 [95% CI 1·23–5·68], p=0·007). Women randomly assigned to the remifentanil PCA group were more likely to receive supplementary oxygen than those assigned to the pethidine group (table 2). Significantly more women were given an antiemetic in the pethidine group than in the remifentanil PCA group (table 2).

With regards to delivery mode, there was a significant difference between the intervention groups (p=0·02). Relative to other delivery modes combined, instrumental delivery was significantly reduced in the remifentanil

	Remifentanil PCA group (n=201)	Pethidine group (n=199)
Patient characteristics		
Age at randomisation		
Mean years (SD)	29·4 (6·1)	29·3 (6·1)
<20 years	12 (6%)	13 (7%)
20–29 years	99 (49%)	97 (49%)
30–39 years	80 (40%)	80 (40%)
≥40 years	10 (5%)	9 (5%)
Ethnicity		
White	146 (73%)	157 (79%)
Black or Black British	8 (4%)	7 (4%)
Chinese or east Asian	4 (2%)	0
Asian (Indian)	7 (3%)	12 (6%)
Asian (Pakistani)	23 (11%)	17 (9%)
Asian (Bangladeshi)	1 (<1%)	1 (1%)
Mixed	3 (1%)	0
Other	9 (4%)	5 (3%)
Weight (kg)		
Mean (SD; n)	73·1 (18·4; 194)	74·0 (17·2; 192)
Range	45–147	38–125
Obstetric history		
Gravidity		
Median (IQR)	2 (1–3)	2 (1–3)
Parity		
Median (IQR)	0 (0–1)	0 (0–1)
Nulliparous	121 (60%)	118 (59%)
Multiparous	80 (40%)	81 (41%)
Current pregnancy		
Induced	137 (68%)	136 (68%)
Pre-eclampsia	8 (4%)	8 (4%)
Continuous electronic fetal monitoring	188 (94%)	184 (92%)
Syntocinon commenced before randomisation	100 (50%)	103 (52%)

Data are n (%) unless otherwise specified. PCA=patient-controlled analgesia.

Table 1: **Patient characteristics**

	Remifentanil PCA group (n=201)	Pethidine group (n=199)	Estimates (95% CI)	p value
Mode of birth				0·02
Spontaneous vaginal	128 (64%)	106 (53%)	..	
Instrumental (forceps or suction)	31 (15%)	52 (26%)	..	
Caesarean section	42 (21%)	41 (21%)	..	
Facial oxygen to treat low saturation			48·55* (6·82 to 345·76)	<0·0001
Yes	51/125 (41%)	1/119 (1%)	..	
No	74/125 (59%)	118/119 (99%)	..	
Missing	0	4	..	
Supplementary oxygen			35·00* (4·92 to 249·02)	<0·0001
Yes	35/76 (46%)	1/76 (1%)	..	
No	41/76 (54%)	75/76 (99%)	..	
Reasons for supplementary oxygen†				
Low oxygen saturation	31/35 (89%)	1/1 (100%)	..	
Maternal sedation score ≥4	0	0	..	
Physician request	6/35 (17%)	0	..	
Low respiration rate (<8 breaths per minute)	1/35 (3%)	0	..	
VAS pain scores				
Maximum VAS pain score‡			−4·44§ (−10·93 to 2·05)	0·18
Mean (SD; n)	75·90 (27·09; 150)	80·34 (26·24; 117)	..	
Range	0–100	0–100	..	
Median VAS pain score‡			−13·91§ (−21·40 to −6·43)	0·0003
Mean (SD; n)	50·67 (29·41; 150)	64·58 (32·57; 117)	..	
Range	0–100	0–100	..	
Respiratory depression (<8 breaths per minute)				1·00
Yes	1 (1%)	0	..	
No	186 (99%)	152 (100%)	..	
Missing	14	47	..	
Low oxygen saturation (<94% while breathing room air)			2·65* (1·23 to 5·68)	0·007
Yes	26 (14%)	8 (5%)	..	
No	163 (86%)	146 (95%)	..	
Missing	12	45	..	
Excessive sedation (sedation scores ≥4)¶			0·54* (0·09 to 3·20)	0·49
Yes	2 (1%)	3 (2%)	..	
No	185 (99%)	149 (98%)	..	
Missing	14	47	..	
Antiemetic administration			0·31* (0·23 to 0·41)	<0·0001
Yes	42 (21%)	134 (68%)	..	
No	159 (79%)	64 (32%)	..	
Missing	0	1	..	
Breastfeeding within first hour of birth			0·99‖ (0·80 to 1·22)	0·92
Yes	90 (46%)	91 (47%)	..	
No	105 (54%)	104 (53%)	..	
Missing	6	4	..	

Data are n (%) or n/N (%) unless otherwise specified. Data that were missing have been removed from the denominators to generate percentages. PCA=patient-controlled analgesia. RR=risk ratio. VAS=visual analogue scale. *RRs less than 1 favour remifentanil PCA. †Two participants in the remifentanil PCA group had both physician request and low oxygen saturation as the reasons for supplementary oxygen. One participant in the remifentanil PCA group had both low respiratory rate and low oxygen saturation as the reasons for supplementary oxygen. ‡VAS pain score ranges from 0 to 100, in which 0 is no pain and 100 is worst pain imaginable. §Mean differences less than 0 favour remifentanil PCA. ¶Sedation scores range from 1 to 5, in which 1 is fully awake and 5 is eyes closed and not rousable. ‖RRs more than 1 favour remifentanil.

Table 2: **Maternal secondary outcomes**

PCA group compared with the pethidine group (31 [15%] of 201 *vs* 52 [26%] of 199; RR 0·59 [95% CI 0·40–0·88], p=0·008), with equal proportions of caesarean section in both groups (table 2). Interventional delivery for fetal distress was required for significantly fewer women in the remifentanil PCA group than in the pethidine group

	Remifentanil PCA group (n=201)	Pethidine group (n=199)	RR (95% CI)	p value
Apgar scores				
Apgar score				
<4	0	0	..	
≥4	201 (100%)	199 (100%)	..	
Apgar score			0·50* (0·05–5·42)	0·56
<7	1 (<1%)	2 (1%)	..	
≥7	200 (99%)	197 (99%)	..	
Fetal acidosis				
Umbilical cord pH				
Mean (SD; n)	7·24 (0·09; 91)	7·24 (0·09; 97)	..	
Range	6·89 to 7·42	6·98 to 7·39	..	
Base deficit (mmol/L)				
Mean (SD; n)	−2·93 (5·21; 88)	−2·69 (5·33; 97)	..	
Range	−18·90 to 7·50	−12·30 to 9·70	..	
Presence of fetal acidosis			2·18* (0·20–23·64)	0·51
Yes	2 (2%)	1 (1%)	..	
No	86 (98%)	95 (99%)	..	
Missing	113	103	..	
Admission to higher level care			0·88* (0·35–2·23)	0·79
Yes	8 (4%)	9 (5%)	..	
No	193 (96%)	190 (95%)	..	
Requirement for neonatal resuscitation			0·94* (0·53–1·68)	0·84
Yes	20 (10%)	21 (11%)	..	
No	181 (90%)	178 (89%)	..	
Interventional delivery for fetal distress			0·56 (0·37–0·85)	0·005
Yes	29 (14%)	51 (26%)	..	
No	172 (86%)	148 (74%)	..	

Data are n (%) unless otherwise specified. PCA=patient-controlled analgesia. RRs=risk ratios. *RRs less than 1 favour remifentanil PCA.

Table 3: **Neonatal secondary outcomes**

(29 [14%] of 201 women *vs* 51 [26%] of 199; RR 0·56 [95% CI 0·37–0·85], p=0·005).

All neonates had an Apgar score of 4 or more at 5 min after birth. There was no difference between groups in Apgar score of less than 7 at 5 min after birth or the number of neonates with fetal acidosis (table 3). There were 20 (10%) of 201 infants born to women in the remifentanil PCA group and 21 (11%) of 199 in the pethidine group who required resuscitation (RR 0·94, 95% CI 0·53–1·68; p=0·84), predominantly with supplementary oxygen, although one baby in the pethidine group required complex resuscitation. There was no difference in the number of neonatal transfer to a higher level of neonatal care between study groups.

There was no difference in the proportion of women successfully initiating breastfeeding within an hour of birth between groups (table 2). Maternal satisfaction with their birth experience was assessed in nine domains and differences were found for two of these; more women in the remifentanil PCA group than in the pethidine group agreed that their pain relief was effective during labour (p=0·0003) and more agreed that they were satisfied with their pain relief (p=0·0003; table 4).

The definition of expected but unrelated adverse events was agreed at the beginning of the trial—eg, complications of labour and delivery—and as such could not be attributable to study interventions. Relevant maternal and neonatal safety outcomes were defined as secondary outcomes, to be formally compared. There were no serious adverse events or drug reactions directly attributable to either analgesic recorded during the study.

Discussion

In this multicentre, randomised controlled trial, we showed that intravenous remifentanil PCA for pain relief in labour significantly reduced progression to epidural analgesia in comparison with intramuscular pethidine. Women receiving remifentanil were more likely to have a spontaneous vaginal delivery than those receiving pethidine, with the difference in delivery mode attributable to a reduction in instrumental vaginal delivery. An increased proportion of low maternal oxygen saturation and additional requirement for oxygen supplementation was observed with remifentanil than with pethidine; however, it did not result in adverse maternal or neonatal sequelae.

The strengths of our study include robust trial methodology, secure randomisation, rigorous analysis, and transparent reporting. We recruited to target, achieved comparability at baseline, had independent data monitoring throughout, and minimal patient or data loss, with the primary outcome available for all but one trial participant that withdrew consent. All outcome comparisons were prespecified, with the exception of dichotomisation of 5 min Apgar score of less than 7, which was requested during the review process of this report. The diversity of our population across many centres adds to generalisability of the findings. Women with induced labour were somewhat over-represented in the study population, reflecting the time available for the consent and randomisation process, although there was balance for this variable across the intervention groups. Women with induced labour were often admitted in advance of labour and therefore there was greater opportunity for providing trial information before consent in active labour. Induction of labour is a very common procedure; therefore, our findings are relevant to a routine clinical population, given the very wide inclusion criteria for the study.

There was a disparity in compliance to allocated treatment between the remifentanil PCA group and pethidine group. 22 women, who were randomly assigned to receive pethidine, requested immediate progression to epidural, and three had an epidural placed for medical indications, without pethidine being administered. The non-adherent women in the pethidine group most likely represent participants with an undisclosed preference for remifentanil or women with preconceptions regarding

pethidine, who nonetheless consented to participating. Episodes of non-adherence were distributed across study centres and no systematic pattern was identified. The study protocol did not formally allow women to decline the analgesia to which they were randomly assigned and opt immediately for epidural. However, once a participant made a request for epidural analgesia, it could not ethically be denied, even if the request was made before the analgesia allocated by randomisation had been administered.

Although the main unadjusted analysis of the primary outcome adhered to intention-to-treat principles and included all participants randomly assigned, regardless of the analgesia actually received, the difference in compliance between groups raised the possibility that observed treatment effects could potentially have been distorted by the disparity in adherence. However, when these episodes of non-adherence were excluded, analysis of women only deemed compliant with the randomised allocation yielded almost identical results both in the direction and magnitude of treatment effect, confirming that the intention-to-treat analysis was robust to the outcomes of non-adherent participants. Thus, the observed benefits of remifentanil PCA cannot be attributed to the difference in compliance between groups.

A potential weakness of the study was the inability to mask clinical staff and women to the treatment allocation, made inevitable by the dissimilar technical aspects of intravenous PCA and intramuscular injection. Masking trial participants and clinical staff to the group allocation was impossible without the use of a double-dummy design and sham interventions, which would have included intravenous PCA with an inactive placebo and an inactive intramuscular injection. These possibilities were explored thoroughly at the study design stage. Sham interventions were ultimately rejected as a result of strongly negative opinions expressed by women in the Patient and Public Involvement group assisting in the study design. Clinical staff were also unwilling to administer inactive, invasive procedures required for sham intervention or control. The matter was explored at the stage of ethical approval with similarly unfavourable opinion from both medical and lay representatives. Even if a sham design had been pursued, it might well not have been effective, since in practice it was found that women receiving remifentanil PCA immediately became aware of its effect, after a single intravenous bolus; therefore, their group allocation would have been made immediately obvious. The limitations of an open-label study design in terms of potential for performance or ascertainment bias were mitigated by precluding research staff from any involvement in the request for or decision to proceed to epidural, or any additional or subsequent clinical care of the mother and baby, after randomisation. These methodological features should strengthen confidence that our findings are valid and reliable.

	Remifentanil PCA group (n=184)	Pethidine group (n=176)	p value
I was satisfied with my overall childbirth experience			0·27
Strongly disagree	4 (2%)	1 (1%)	
Disagree	10 (5%)	8 (5%)	
Neutral	17 (9%)	11 (6%)	
Agree	66 (36%)	71 (40%)	
Strongly agree	87 (47%)	85 (48%)	
I was treated with respect by all of the staff			0·21
Strongly disagree	1 (1%)	1 (1%)	
Disagree	0	1 (1%)	
Neutral	7 (4%)	2 (1%)	
Agree	26 (14%)	18 (10%)	
Strongly agree	150 (82%)	154 (88%)	
I was involved in making decisions as much as I wanted to be			0·19
Strongly disagree	1 (1%)	1 (1%)	
Disagree	3 (2%)	2 (1%)	
Neutral	10 (5%)	2 (1%)	
Agree	39 (21%)	39 (22%)	
Strongly agree	131 (71%)	132 (75%)	
My expectations for labour and birth were met			0·68
Strongly disagree	8 (4%)	5 (3%)	
Disagree	13 (7%)	13 (7%)	
Neutral	27 (15%)	33 (19%)	
Agree	50 (27%)	51 (29%)	
Strongly agree	86 (47%)	74 (42%)	
I felt safe at all times			0·41
Strongly disagree	1 (1%)	2 (1%)	
Disagree	6 (3%)	1 (1%)	
Neutral	6 (3%)	4 (2%)	
Agree	35 (19%)	35 (20%)	
Strongly agree	136 (74%)	134 (76%)	
Good communication from the staff kept me well informed			0·87
Strongly disagree	0	1 (1%)	
Disagree	1 (1%)	0	
Neutral	6 (3%)	5 (3%)	
Agree	37 (20%)	32 (18%)	
Strongly agree	140 (76%)	138 (78%)	
I felt in control			0·52
Strongly disagree	6 (3%)	4 (2%)	
Disagree	8 (4%)	12 (7%)	
Neutral	30 (16%)	35 (20%)	
Agree	62 (34%)	54 (31%)	
Strongly agree	77 (42%)	71 (40%)	
Missing	1 (1%)	0	
My pain relief was effective during labour			0·0003
Strongly disagree	4 (2%)	4 (2%)	
Disagree	9 (5%)	14 (8%)	
Neutral	12 (7%)	33 (19%)	
Agree	50 (27%)	57 (32%)	
Strongly agree	109 (59%)	68 (39%)	

(Table 4 continues on next page)

	Remifentanil PCA group (n=184)	Pethidine group (n=176)	p value
(Continued from previous page)			
I was satisfied with my labour pain relief			0·0003
Strongly disagree	3 (2%)	6 (3%)	
Disagree	9 (5%)	13 (7%)	
Neutral	11 (6%)	23 (13%)	
Agree	44 (24%)	60 (34%)	
Strongly agree	117 (64%)	74 (42%)	

Data are n (%). PCA=patient-controlled analgesia.

Table 4: **Maternal satisfaction**

The remifentanil PCA dose regimen was chosen carefully to reflect the one most commonly used in current practice in the UK. A fixed remifentanil bolus dose, as opposed to a variable dose (ie, dependent on maternal weight), was chosen to assist the ease of doing a pragmatic trial across multiple recruiting sites. It is feasible that other doses regimens could cause different treatment effects. However, most maternity units adopting remifentanil PCA into practice opt for a fixed-dose regimen for clarity and continuity. The trials to date that have investigated the effectiveness of remifentanil in comparison with pethidine have been inconclusive as a result of inadequate size and quality. A review[11] of 246 participants from four studies, which were all judged to be of low or poor quality, reported a relative risk of progression to epidural of 0·34 (95% CI 0·20–0·58) for intravenous remifentanil PCA compared with pethidine administered by any route. The relevant Cochrane review[13] published in 2017 compared remifentanil PCA with a range of other analgesic regimes and stratified its meta-analyses according to the route of pethidine administration (intramuscular, intravenous, or by PCA). Three studies comprising 190 participants for the requirement of so-called escape analgesia, including Entonox or epidural analgesia, showed a RR of 0·57 (95% CI 0·40–0·81) for remifentanil compared with intramuscular or intravenous pethidine, and three studies of 215 participants showed a RR of 0·76 (95% CI 0·45–1·28) for pethidine PCA. None of the studies included in these reviews were designed to examine epidural conversion as a primary outcome; and in all but one study, the outcome of escape analgesia was epidural. Since the Cochrane review[13] concluded that the evidence was too low in quality to inform practice or future research, the findings from our study therefore represent the first robust evidence that remifentanil reduces the requirement for epidural analgesia compared with pethidine.

Our study has shown an effect on mode of delivery, showing that remifentanil PCA resulted in a significant reduction in instrumental vaginal delivery compared with pethidine. The Cochrane review[13] did not show an effect of remifentanil PCA on the number of instrumental vaginal deliveries compared with intramuscular or intravenous pethidine (RR 0·82, 95% CI 0·32–2·09). Mode of delivery was a secondary outcome in our trial; however, the treatment effect was marked. Adding RESPITE to this previous meta-analysis[13] shows a significant reduction in instrumental vaginal delivery (RR 0·62, 95% CI 0·43–0·90). Given that instrumental vaginal delivery increases the risk of perineal trauma and the morbidity it causes, remifentanil PCA could indirectly reduce long-term side-effects, including faecal incontinence and sexual dysfunction after childbirth, if it were used in preference to pethidine.

Women who received remifentanil PCA reported lower mean VAS pain scores in labour and greater satisfaction with their pain relief in comparison with pethidine. These results are in accordance with other studies in the field, and set in the context that no policy of opioid analgesia in labour is as effective as epidural pain relief. VAS data were incomplete because they were not always recorded contemporaneously by attending staff and could not be retrieved retrospectively. VAS pain scores were seldom given from women who delivered before receiving study drugs. Because pain scores were discontinued at epidural placement, none were recorded for women in the pethidine group who requested epidural immediately after randomisation, accounting for the imbalance in missing denominator values between trial groups. A lower proportion of antiemetic administration was also found with remifentanil PCA than with pethidine; however, it was the practice of some participating centres to give an antiemetic routinely with pethidine, so this finding should be interpreted with caution.

Remifentanil, similar to any potent opioid, has the capacity to induce sedation and respiratory depression. Some maternity units, who have adopted remifentanil for routine use in labour, uniformly administer oxygen to women using remifentanil PCA. Anxiety in some clinicians regarding the potential for serious adverse maternal respiratory side-effects, including desaturation and apnoea, has limited the widespread uptake of remifentanil into routine practice.[12] We recorded a single episode of low respiratory rate (<8 breaths per minute) in the remifentanil PCA group. Excessive sedation was similarly rare and equally distributed between both groups. Predictably, there was a greater incidence of low oxygen saturation when breathing room air with remifentanil than with pethidine, and supplementary oxygen use was far more likely too. At trial inception, we made an active decision not to give supplementary oxygen uniformly with remifentanil, as some maternity units using it choose to do, because not all women would require it; indeed more than half of the study population did not. From the outset of the study, supplementary oxygen use was recorded as facial oxygen to treat low oxygen saturation. On the advice of the Data Monitoring Committee at interim review, the precise indication for oxygen administration was collected in the last 152 women recruited to the study. The data for these participants

recorded whether supplementary oxygen was used (yes or no); and if yes, an indication was identified. These two sets of data could not subsequently be combined and have therefore been reported alongside each other in this study. The predominant indication for supplementary oxygen was low maternal oxygen saturation. The threshold for oxygen supplementation was a maternal saturation of less than 94% while breathing room air. The use of maternal oxygen supplementation far exceeded the proportion of low saturation and probably represents caution on the part of clinical staff.

It was a goal of the study to generate reliable evidence for the maternal effects of pethidine and remifentanil PCA in the study population. Respiratory rate, sedation score, and oxygen saturation were the principal observations used to evaluate opioid side-effects and one-to-one midwifery care of participants was maintained throughout the study. End tidal carbon dioxide monitoring to detect apnoea is not routinely available in labour wards. The study sample size was calculated to detect differences in epidural conversion rather than to detect potentially rarer safety outcomes. Despite the reassuring absence of negative sequelae in mothers or neonates, larger populations would be required to establish their true prevalence.

This study has answered the call for an adequately powered, robust, rigorously conducted, controlled trial to evaluate the effectiveness of remifentanil PCA in labour. The benefits of remifentanil compared with pethidine were a halving of the proportion of epidurals administered, the provision of superior pain relief, and a reduction in instrumental vaginal delivery. Maternal respiratory side-effects of remifentanil did not occur in all women. When they did occur, they were transient, quickly identified, easily managed, and did not affect maternal or neonatal wellbeing. The evidence generated by this trial challenges the role of pethidine as a usual standard of care for women in childbirth and requires a fundamental re-evaluation of opioid-based pain relief in labour.

Contributors

MJAW conceived the idea for this study and secured funding. MJAW, CM, and JD did the literature search and were responsible for the study design, with assistance from KH, FG, and LB. Study conduct and data collection was led by MJAW and LB, with contributions from CM, FG, and JD. Study analysis and figure generation was done by CAH, supervised by KH. All authors were involved in data interpretation. Writing of the paper was led by MJAW, CM, and JD, with assistance from CAH, KH, FG, and LB.

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Declaration of interests

We declare no competing interests.

Data sharing

No additional data are available for this Article.

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