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RESPITE Trial Collaborative Group

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Remifentanil patient controlled analgesia versus intramuscular pethidine for pain relief in labour: a randomised controlled trial

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A list of investigators and research nurses and midwives is provided within acknowledgements.

Summary

Background

Approximately a third of women receiving pethidine for labour pain subsequently require an epidural, which provides effective pain relief but increases the risk of instrumental delivery. Remifentanil patient controlled analgesia (PCA) in labour is an alternative to pethidine, but not widely utilized. We sought to determine epidural rates amongst women using remifentanil PCA compared to pethidine.

Methods

We conducted a randomised, parallel, open-label trial in 14 UK maternity units. Women at term gestation, in labour with a singleton cephalic presentation, requesting opioid pain relief, were randomly assigned (1:1) to remifentanil PCA (40µg bolus with a two minute "lock-out") or intramuscular pethidine (100mg, four-hourly, up to 400mg). Web-based or telephone randomisation minimised allocations by parity, age, ethnicity and mode of labour onset. The primary outcome was the proportion of women who received epidural analgesia after enrolment. To detect a reduction in epidural conversion from 30% to 15% with 90% power, with a 15% anticipated attrition from urgent delivery by emergency caesarean section, required 400 women. Primary analyses were unadjusted and by intention-to-treat. ISRCTN29654603.

Findings

Between May 2014 and September 2016, 201 women were randomised to remifentanil PCA and 200 to pethidine. Epidural conversion rates were 19% (39/201) and 41% (81/199) respectively (RR 0·48, 95% CI 0·34 to 0·66, $P<0·0001$).

Interpretation

Remifentanil intravenous PCA halves epidural conversion rates compared to intramuscular pethidine. These findings challenge routine pethidine use as standard care in labour.

Funding

NIHR Clinician Scientist award.

Research in context

Evidence before this study

The Cochrane review on Patient-controlled analgesia 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 IM/IV or by PCA. Three studies with 190 participants for the outcome 'additional analgesia required' showed a reduction for remifentanil compared to IM/IV pethidine (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 to1·28). 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 on 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 to pethidine administered by various routes from four poor quality studies (n=244 women) (RR 0·34, 95% CI 0·2-0·58).

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 conducted with sufficient rigor to inform practice. The requirement for epidural pain relief was halved in women who received remifentanil in comparison to pethidine. Epidural conversion rates were 19% (39/201) and 41% (81/199) respectively (RR 0·48, 95% CI 0·34 to 0·66, *P*<0·0001). Women randomised to remifentanil PCA were less likely to require instrumental vaginal delivery (15% vs 26%); RR 0.59 (95% CI 0.40 to 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, relative to intramuscular 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 prior low quality data that the rate of epidural rescue analgesia is halved, in women requesting opioid pain relief in labour with remifentanil PCA compared with IM pethidine. If the evidence from the studies included in the recent Cochrane Review and the results of RESPITE are considered together, the pooled risk ratio of a requirement for "rescue" analgesia with remifentanil, relative to pethidine yielded is 0·54, (95% CI 0·42 to 0·68). In the 3 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 foetal outcomes with remifentanil, relative to pethidine. The use of remifentanil PCA as a "first line" opioid for pain relief in labour in preference to pethidine would reduce epidural rates, instrumental delivery 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.

Introduction

Childbirth can be extremely painful and the provision of effective pain relief during labour is a vital 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 (IM) injection, and many more worldwide[1]. Despite widespread international use, pethidine is not uniformly effective in relieving labour pain[2] and has proven side effects including maternal sedation, nausea and potential transfer across the placenta to the foetus[3]. More than a third of women who receive pethidine subsequently require an epidural[4] for pain relief. 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 (IVD) and prolongation of the second stage of labour[5, 6]. This impact is reduced by modern "low-dose" epidural techniques, but not completely mitigated[5]. IVD 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 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 is 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 respiratory depression[12]. A Cochrane review evaluating remifentanil PCA relative to a range of other methods of labour pain management[13] reported remifentanil compared to intramuscular pethidine in three trials[14-16], to intravenous pethidine in one trial[4] and to PCA pethidine in three trials[17-19] but 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 foetal effects .

The aim of the RESPITE trial was to compare two "policies" of opioid pain relief in labour; intravenous remifentanil PCA with intra-muscular pethidine injection, to determine whether remifentanil PCA reduced progression to epidural analgesia and evaluate if it resulted in any adverse maternal or neonatal sequelae[20, 21].

Methods

Study design and participants

RESPITE was a two-group, parallel, randomised, open-label, multi-centre trial, conducted in 14 obstetric-led maternity units in the UK. Units were able to participate in RESPITE 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, aged 16 years or over and beyond 37+0 weeks' gestation, with a singleton live baby, in cephalic presentation, who were in established labour (defined as regular painful contractions irrespective of cervical dilatation), intending vaginal birth, were initially eligible and written informed consent was sought. All women booked for delivery at participating centres were informed about the study prior to labour at antenatal visits. Participants were eligible to consent in labour provided they had received information about the study beforehand. Women were randomised when they requested systemic opioid analgesia, provided they had not received such analgesia in the preceding four hours, had no contraindications to remifentanil, pethidine or epidural analgesia and were not participating in any other drug trial.

The trial had a favourable ethical opinion from the National Research Ethics Service Nottingham 2 Research Ethics Committee (reference: 13/EM0239). A Trial Steering Committee (TSC) provided independent oversight of the trial. Confidential interim analysis of all available data alongside anonymised reports of adverse events suffered by participants was reviewed by a Data Monitoring Committee (DMC) on three occasions. No reason to recommend halting or modifying the trial was identified. The trial protocol has been published elsewhere[22].

Randomisation and masking

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

Due to 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 healthcare providers could not be masked to the intervention group.

Procedures

Remifentanil was administered via a dedicated intravenous cannula. The patient controlled analgesia (PCA) pump was pre-programmed by physician anaesthetists, with a regime to provide a bolus of 40μg remifentanil on demand, with a "lockout" interval of two minutes. This dose regime 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 prior to 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 30μg with a lock-out interval of two minutes. Pethidine was given by the attending midwife in a dose of 100mg, by intramuscular injection, up to four hourly in frequency, to a maximum dose of 400mg in 24 hours.

Following administration of opioid analgesia, all women received one-to-one midwifery care, irrespective of study group allocation. Clinical observations were made every 30 minutes including recordings of respiratory rate and a numerical sedation score (1: Fully awake, 2: Drowsy, 3: Eyes closed, rousable by voice, 4: Eyes closed, rousable to physical stimulus, 5: Eyes closed, not rousable). A visual analogue pain score (VAS) was recorded every 30 minutes 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 minutes. Saturations recorded <94% when breathing room air was the threshold for mandatory maternal oxygen supplementation. Indications for contacting a physician anaesthetist were excessive maternal sedation; score 4 or greater (not rousable to voice), a respiratory rate <8 breaths/minute or oxygen saturation <94% despite supplemental 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. 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 visual analogue pain scores were discontinued after epidural analgesia. All data were collected prior to hospital discharge.

Outcomes

The primary outcome was the proportion of women who had an epidural placed for pain relief in labour after randomisation.

Pre-specified secondary maternal outcomes were the effectiveness of pain relief, quantified by Visual Analogue Scale (where 0 was no pain and 100 was worst possible pain) taken every 30 minutes; delivery mode (spontaneous vaginal delivery, instrumental vaginal delivery and caesarean section); excessive sedation score ≥ 4 (not rousable to voice); respiratory depression (respiratory rate <8 breaths/minute); oxygen saturation <94% whilst breathing room air; requirement for supplemental oxygen, anti-emetic administration and maternal satisfaction with pain relief, determined by postpartum questionnaire of childbirth experience, prior to hospital discharge. Pre-specified neonatal outcomes were the requirement for expedited interventional delivery to resolve foetal distress, persistent low Apgar score at five minutes (<4), foetal acidosis determined by umbilical cord gas analysis (if performed), the requirement for neonatal resuscitation, admission to neonatal special care and the rate of initiation of breast feeding within the first hour of birth.

Statistical Analysis

Epidural conversion rates after Remifentanil PCA were reported in a range of 5% to 19% in previous randomised trials,[4, 16-18] compared to conversion rates of greater than 30% (range 17% to 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 $\alpha=0{\cdot}05$, required 161 women in each arm 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 (percentages) for categorical variables, mean (standard deviation) for normally distributed continuous variables, or median (interquartile range) for non-normal continuous variables. Treatment effects were presented as risk ratios or mean differences, with 95% confidence intervals (CI).

The primary analysis was a comparison of the analgesic method assigned at randomisation (unadjusted intention-to-treat analysis). Two sided tests were considered significant if $p<0{\cdot}05$. In addition to the primary unadjusted analysis, a log-binomial model was fitted to account for the minimisation variables. A pre-specified subgroup analysis was performed for parity.

Two post-hoc sensitivity analyses were conducted to explore the impact of adherence to group allocation by trial participants. The first included only those women who were fully adherent to their group allocation i.e. received at least one dose of the analgesic to which they were originally randomised and no dose of the alternative analgesic. The second analysed women according to the analgesic they ultimately received.

All analyses were performed in SAS version 9.4 (SAS Corporation, USA)

There were no substantial changes to the main study protocol after recruitment commenced. The trial is registered at ISRCTN, number ISRCTN29654603.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the results for publication. 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 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 13th May 2014 and 2nd September 2016, 201 women were randomised to remifentanil PCA and 200 to pethidine. Figure 1 shows the trial profile. 186 women received the allocated drug, in compliance with the protocol, in the remifentanil group and 154 in the pethidine group. The main reasons for not receiving the allocated drug was women giving birth before it could be administered (n= 12 for remifentanil and 17 for pethidine) 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.

Figure 1 Trial profile

Table 1 Baseline characteristics of trial participants

Primary outcome

In the remifentanil group, 39 of 201 women (19%) had an epidural, compared to 81 of 199 (41%) women in the pethidine group, giving a risk ratio of 0·48 (95% CI 0·34 to 0·66, p<0·0001) in the unadjusted intention to treat analysis. Adjustment for the minimisation variables did not alter the risk ratio or its confidence intervals (Web table 1). 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: 36/186 women (19%) in the remifentanil group had an epidural compared to 56/152 women (37%) in the pethidine group with a risk ratio of 0·53 (95% CI 0·37-0·75, p<0·0003). Sensitivity analysis grouping participants by the analgesia ultimately received similarly demonstrated little effect (Web Table 2). In the pre-specified subgroup analysis, no interaction was found between parity and the treatment effect; 30/121 (25%) nulliparous women in the remifentanil group and 58/118 (49%) women in the pethidine group received an epidural, as did 9/80 (11%) and 23/81 (28%) parous women, respectively.

Secondary outcomes: Maternal (Table 2)

Median pain score was significantly reduced by 13·91 points (VAS Scale 0=No Pain, 100 = Worst Pain imaginable) in the remifentanil PCA, relative to the pethidine group (95% CI -21·40 to -6·43; p=0·0003) but there was no difference in maximum pain score between groups (mean difference -4·44 points; 95% CI -10·93 to 2·05: p=0·18). (Table 2)

The maternal outcomes of respiratory depression, defined as a maternal respiratory rate of <8 breaths per minute and excessive sedation, defined as not rousable by voice, did not differ between groups and were rare (respiratory depression: one in remifentanil; excessive sedation: two in remifentanil and three in pethidine group). Significantly more women in the remifentanil group had low maternal oxygen saturation (<94% whilst breathing room air) compared to the pethidine group, 26/191 (14%) vs 8/169 (5%) respectively, RR 2·65 (95% CI 1·23-5·68, p=0·007). Women randomised to remifentanil were more likely to receive supplemental oxygen than women in the pethidine group (Table 2). Significantly more women were given an anti-emetic in the pethidine than in the remifentanil group.

With regard to delivery mode, the intervention significantly reduced the number of instrumental vaginal deliveries, with 52 (26%) in the pethidine group and 31(15%) in the remifentanil group, with equal proportions of Caesarean section in both groups (Table 2). Interventional delivery for foetal distress was required for significantly fewer women in the remifentanil group 29/201(14%), compared to 51/199 (26%) who received pethidine (RR 0.56, 95% CI 0.37 to 0.85; p=0.005).

Secondary outcomes: Neonatal (Table 3)

All neonates had an Apgar score of ≥4 at five minutes after birth. There was no difference between groups in Apgar score <7 at 5 minutes after birth or the rate of foetal acidosis (Table 3). There were 20 (10%) infants born to women in the remifentanil group and 21 (11%) infants of women in the pethidine group who required resuscitation (RR 0·94, 95% CI 0·53 to 1·68; p=0·84), predominantly with supplemental oxygen, although one

baby in the pethidine group required complex resuscitation. There was no difference in the rate 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. Maternal satisfaction with their birth experience was assessed in nine domains and differences were found for two of these: more women in the remifentanil group agreed that their pain relief was effective and more agreed that they were satisfied with their pain relief than in the pethidine group (p=0.0003 in both cases). (Table 4).

The definition of expected, but unrelated adverse events was agreed at the outset of the trial, e.g. complications of labour and delivery, and as such could not be attributable to study interventions. Adverse events of concern 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

This multicentre randomised controlled trial has demonstrated that intravenous remifentanil PCA for pain relief in labour substantially reduced progression to epidural analgesia, in comparison to intramuscular pethidine. Women receiving remifentanil were more likely to have a spontaneous vaginal delivery, with the difference in delivery mode attributable to a reduction in instrumental vaginal delivery. An increased rate of low maternal oxygen saturation was observed with remifentanil in comparison to pethidine and an additional requirement for oxygen supplementation, 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. All outcome comparisons were pre-specified, with the exception of dichotomisation of 5 minute Apgar score at <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, although there was balance for this variable across the trial arms. This reflects the time available for the consent and randomisation processes to be completed. Women with induced labour were often admitted in advance of labour and therefore there was greater opportunity for providing trial information prior to 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 remifentanil PCA and pethidine groups. Twenty- two women, randomised to 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 pre-conceptions regarding pethidine, who nonetheless consented to randomisation. Episodes of non-adherence were distributed across study centres and no systematic pattern was identified by monitoring. The study protocol did not formally allow women to decline the analgesia to which they were randomised and opt immediately for epidural. However, once a woman 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.

Whilst the main unadjusted analysis of the primary outcome adhered to intention-to treat principles and included all participants randomised, 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 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. Blinding 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 intra-muscular 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 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 may 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 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 mother and baby, after randomisation. These methodological features should strengthen confidence that our findings are valid and reliable.

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 (i.e. dependent on maternal weight), was chosen to assist the ease of deployment of a pragmatic trial across multiple recruiting sites. It is feasible that other doses regimens could cause different treatment effects. However, most 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 relative to pethidine have been inconclusive as a result of inadequate size and quality. A review by Schnabel included 244 participants in four studies, all judged to be of low or poor quality with a relative risk of progression to epidural of 0·34 (95% CI 0·2-0·58) for remifentanil compared to pethidine administered by any route[11]. The relevant Cochrane review 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 IM/IV or by PCA[13]. Three studies comprising 190 participants for the requirement for "escape" analgesia showed a risk ratio of 0·57 for remifentanil compared to IM/IV pethidine (95% CI 0·4-0·81) and three studies of 215 participants showed a risk ratio of 0·76 (95% CI 0·45 to 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 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 to pethidine.

Our study has demonstrated an effect on mode of delivery, showing that remifentanil PCA resulted in a significant reduction in instrumental vaginal delivery, relative to pethidine. Previous studies included in the Cochrane review have not shown an impact of remifentanil PCA on IVD rates compared with IM or IV pethidine (RR 0·82, 95% CI 0·32 to 2·09) (18). Mode of delivery was a secondary outcome in our trial, however the treatment effect was marked. Adding RESPITE to this previous meta-analysis shows a statistically significant reduction in IVD rate (RR 0·62, 95% CI 0·43 to 0·90; I^2=0%). Given that IVD increases the risk of perineal trauma and the morbidity it causes, remifentanil PCA could indirectly reduce long term side effects from instrumental delivery, including faecal incontinence and sexual dysfunction after childbirth, if it were used in preference to pethidine.

Women who received remifentanil reported lower mean pain scores in labour and greater satisfaction with their pain relief in comparison to pethidine. These results are in keeping 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 since they were not always recorded contemporaneously by attending staff and could not be retrieved retrospectively. VAS were seldom returned for women who delivered before receiving study drugs. Since 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 arms. A lower rate of anti-emetic administration was also found with remifentanil, however, it was the practice of some participating centres to give an anti-emetic routinely with pethidine, so this finding should be interpreted with caution.

Remifentanil, like any potent opioid, has the capacity to induce sedation and respiratory depression. Some units, who have adopted remifentanil for routine use in labour, uniformly administer oxygen to women using remifentanil PCA. Anxiety amongst 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 (less than 8 breaths per minute) in the remifentanil group. Excessive sedation was similarly rare and equally distributed between remifentanil and pethidine (two and three cases respectively). Predictably, there was a greater incidence of low oxygen saturation when breathing room air with remifentanil and supplemental oxygen use far more likely. At trial inception, we made an active decision not to give supplemental oxygen uniformly with remifentanil, as some units using it choose to do, since not all women would ultimately require it, indeed 59% 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 DMC, 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/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. The predominant indication for supplemental oxygen was low maternal oxygen saturation. The threshold for oxygen supplementation was a maternal saturation of less than 94% whilst breathing room air. The use of maternal oxygen supplementation far exceeded the rate 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 potentially rarer safety outcomes. Despite the reassuring absence of negative sequelae on 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 were a halving of the epidural rate relative to pethidine, the provision of superior pain relief and a reduction in instrumental 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 impact on maternal or neonatal well-being. 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 pain relief in labour.

Contributors

The idea for the study originated from MW and he secured funding to conduct it. MW, CM and JD performed the literature search and were responsible for the study design, with assistance from FG, KH and LB. Study conduct and data collection was led by MW and LB with contributions from JD, CM and FG. Study analysis and figure generation was performed by CH, supervised by KH. All authors were involved in data interpretation. Writing of the paper was led by MW, CM and JD, with assistance from LB, FG, CH and KH.

Declaration of interests

The authors declare no competing interests.

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RESPITE collaborative group
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References

1. Ullman R, Smith LA, Burns E, Mori R, Dowswell T. Parenteral opioids for maternal pain management in labour. Cochrane Database of Systematic Reviews. 2010(9).

2. Wee MY, Tuckey JP, Thomas P, Burnard S. The IDvIP Trial: A two-centre randomised double-blind controlled trial comparing intramuscular diamorphine and intramuscular pethidine for labour analgesia. BMC Pregnancy and Childbirth. 2011;11(1):51.

3. Reynolds F. Labour analgesia and the baby: good news is no news. International Journal of Obstetric Anesthesia. 2011;20(1):38-50.

4. Evron S, Glezerman M, Sadan O, Boaz M, Ezri T. Remifentanil: A Novel Systemic Analgesic for Labor Pain. Anesthesia & Analgesia. 2005;100(1):233-8.

5. UK COMETCSG. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. The Lancet. 2001;358(9275):19-23.

6. Anim-Somuah M, Smyth RMD, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database of Systematic Reviews. 2011(12).

7. Macarthur C, Wilson D, Herbison P, Lancashire RJ, Hagen S, Toozs-Hobson P, et al. Faecal incontinence persisting after childbirth: a 12 year longitudinal study. BJOG : an international journal of obstetrics and gynaecology. 2013;120(2):169-78; discussion 78-9.

8. Barrett G, Pendry E, Peacock J, Victor C, Thakar R, Manyonda I. Women's sexual health after childbirth. BJOG: An International Journal of Obstetrics & Gynaecology. 2000;107(2):186-95.

9. Saurel-Cubizolles M-J, Romito P, Lelong N, Ancel P-Y. Women's health after childbirth: a longitudinal study in France and Italy. BJOG: An International Journal of Obstetrics & Gynaecology. 2000;107(10):1202-9.

10. Howie KM MS. Usage of Remifentanil patient controlled analgesia in labour in the UK. International Journal of Obstetric Anesthesia 2011:41.

11. Schnabel A, Hahn N, Broscheit J, Muellenbach RM, Rieger L, Roewer N, et al. Remifentanil for labour analgesia: a meta-analysis of randomised controlled trials. European Journal of Anaesthesiology (EJA). 2012;29(4):177-85.

12. Kranke P, Girard T, Lavand'homme P, Melber A, Jokinen J, Muellenbach RM, et al. Must we press on until a young mother dies? Remifentanil patient controlled analgesia in labour may not be suited as a "poor man's epidural". BMC Pregnancy Childbirth. 2013;13:139.

13. Weibel S, Jelting Y, Afshari A, Pace NL, Eberhart LH, Jokinen J, et al. Patient-controlled analgesia with remifentanil versus alternative parenteral methods for pain management in labour. The Cochrane database of systematic reviews. 2017;4:Cd011989.

14. Calderon E ME, Roman MD, Pernia A, Garcia-Hernandez R, Torres LM. Intravenous remifentanil delivered through an elastomeric device versus intramuscular meperidine comparative study for obstetric analgesia. Revista de la Sociedad Espanola del Dolor. **2006**;13:462–7.

15. Ng TK, Cheng BC, Chan WS, Lam KK, Chan MT. A double-blind randomised comparison of intravenous patient-controlled remifentanil with intramuscular pethidine for labour analgesia. Anaesthesia. 2011;66(9):796-801.

16. Thurlow JA, Laxton CH, Dick A, Waterhouse P, Sherman L, Goodman NW. Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour. British journal of anaesthesia. 2002;88(3):374-8.

17. Blair JM, Dobson GT, Hill DA, McCracken GR, Fee JPH. Patient controlled analgesia for labour: a comparison of remifentanil with pethidine*. Anaesthesia. 2005;60(1):22-7.

18. Douma MR, Verwey RA, Kam-Endtz CE, van der Linden PD, Stienstra R. Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour. British journal of anaesthesia. 2010;104(2):209-15.

19. Volikas I, Male D. A comparison of pethidine and remifentanil patient-controlled analgesia in labour. Int J Obstet Anesth. 2001;10(2):86-90.

20. Schnabel A, Hahn N, Muellenbach R, Frambach T, Hoenig A, Roewer N, et al. [Obstetric analgesia in German clinics. Remifentanil as alternative to regional analgesia]. Der Anaesthesist. 2011;60(11):995-1001.

21. Tveit TO, Halvorsen A, Rosland JH. Analgesia for labour: a survey of Norwegian practice - with a focus on parenteral opioids. Acta anaesthesiologica Scandinavica. 2009;53(6):794-9.

22. Wilson M, MacArthur C, Gao Smith F, Homer L, Handley K, Daniels J. The RESPITE trial: remifentanil intravenously administered patient-controlled analgesia (PCA) versus pethidine intramuscular injection for pain relief in labour: study protocol for a randomised controlled trial. 2016;17(1):591.

Figure 2: Trial Profile

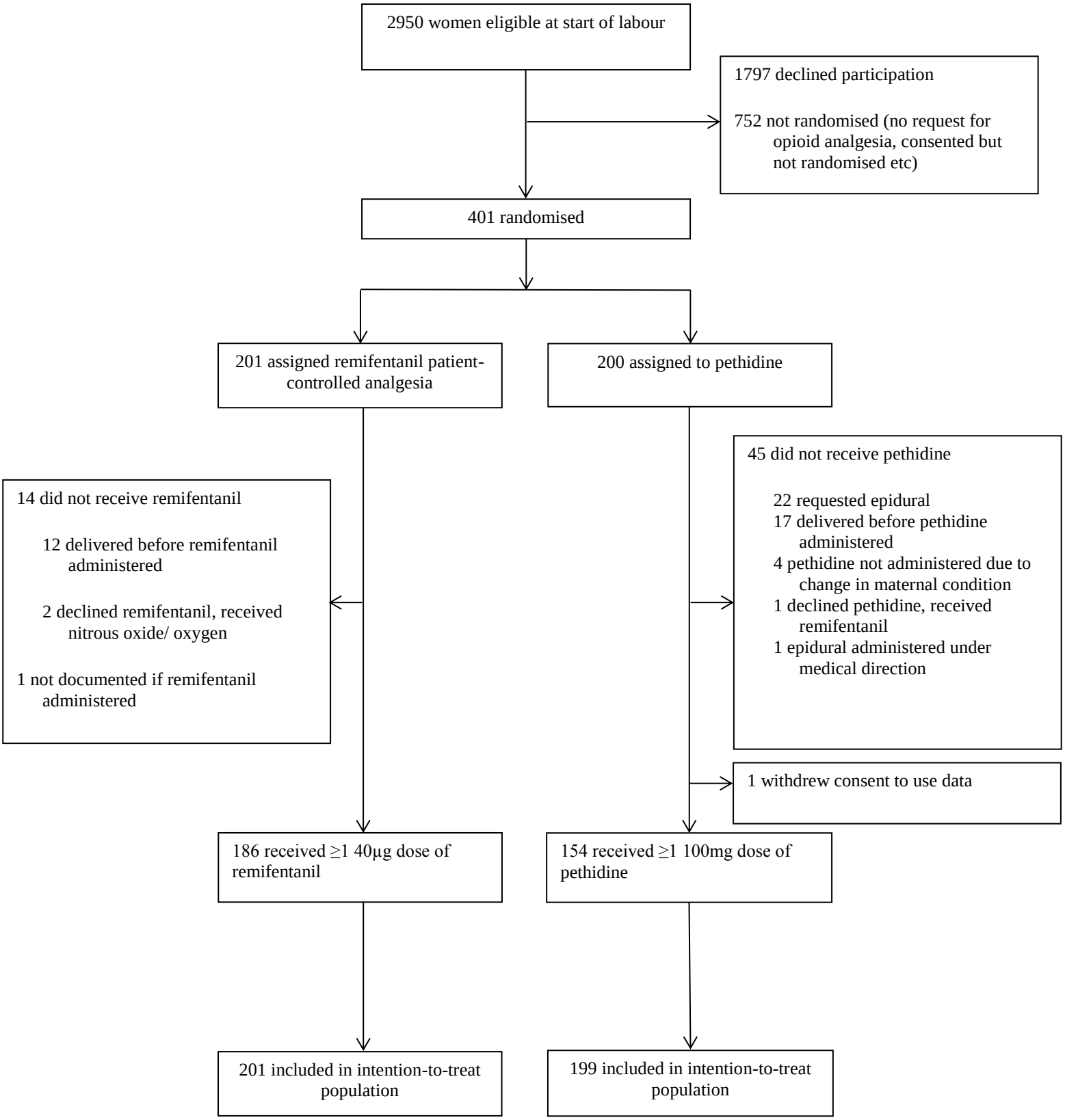

Table 2: Patient Characteristics

	Remifentanil (N=201)	Pethidine (N=199)
Patient Characteristics		
Age At Randomisation		
Mean (SD) years	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%)
≥40years	10 (5%)	9 (4%)
Ethnicity		
White	146 (73%)	157 (79%)
Black/Black British	8 (4%)	7 (3%)
Chinese/East Asian	4 (2%)	0 (-)
Asian (Indian)	7 (4%)	12 (6%)
Asian (Pakistani)	23 (11%)	17 (9%)
Asian (Bangladeshi)	1 (1%)	1 (1%)
Mixed	3 (1%)	0 (-)
Other	9 (4%)	5 (2%)
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%)
Previous Delivery Modes		
Unassisted vaginal	58 (74%)	50 (63%)
Instrumental vaginal	14 (18%)	19 (24%)
Elective caesarean section	7 (9%)	2 (3%)
Emergency caesarean section	12 (15%)	15 (19%)
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%)

Table 2: Maternal secondary outcomes

	Remifentanil (N=201)	**Pethidine** (N=199)	Estimate (95% C.I)	**p-value**
Mode of birth				
Spontaneous vaginal	128 (64%)	106 (53%)	-	**0.02**
Instrumental (forceps or suction)	31 (15%)	52 (26%)		
Caesarean section	42 (21%)	41 (21%)		
Supplementary oxygen				
Facial oxygen, to treat low saturation				
Yes	51/125 (41%)	1/119 (1%)	48.55[1] (6.82, 345.76)	**<0.001**
No	74/125 (59%)	118/119 (99%)		
Missing	0	4	-	-
Supplementary oxygen				
Yes	35/76 (46%)	1/76 (1%)	35.00[1] (4.92, 249.02)	**<0.001**
No	41/76 (54%)	75/76 (99%)		
Reasons for supplementary oxygen[4]				
Low oxygen saturation	31/76 (89%)	1/1 (100%)	-	-
Maternal sedation score (≥4)	0 (-)	0 (-)		
Physician request	6/76 (17%)	0 (-)		
Low respiration rate (<8 breaths/minute)	1/76 (3%)	0 (-)		
Other	0 (-)	0 (-)		
Pain scores				
Maximum VAS score[5]				
Mean (SD, N)	75.90 (27.09, 150)	80.34 (26.24, 117)	-4.44[2] (-10.93, 2.05)	**0.18**
Range	0-100	0-100		
Median VAS score[5]				
Mean (SD, N)	50.67 (29.41, 150)	64.58 (32.57, 117)	-13.91[2] (-21.40, -6.43)	**<0.001**
Range	0-100	0-100		
Respiratory depression (<8 breaths/minute)				
Yes	1 (1%)	0 (-)	-	**1.00**
No	186 (99%)	152 (100%)		
Missing	14	47	-	-
Low oxygen saturation (<94% whilst breathing room air)				
Yes	26 (14%)	8 (5%)	2.65[1] (1.23, 5.68)	**0.007**
No	163 (86%)	146 (95%)		
Missing	12	45	-	-
Excessive sedation (≥4)[6]				
Yes	2 (1%)	3 (2%)	0.54[1] (0.09, 3.20)	**0.49**
No	185 (99%)	149 (98%)		
Missing	14	47	-	-
Anti-emetic administration				
Yes	42 (21%)	134 (68%)	0.31[1] (0.23, 0.41)	**<0.0001**
No	159 (79%)	64 (32%)		
Missing	0	1	-	-
Breast feeding within first hour of birth				
Yes	90 (46%)	91 (47%)	0.99[3]	**0.92**

No	105 (54%)	104 (53%)	(0.80, 1.22)	
Missing	6	4	-	-

[1]Risk ratio, values <1 favour remifentanil.
[2]Mean difference, values <0 favour remifentanil.
[3] Risk ratio, values >1 favour remifentanil.
[4]Two participants in the Remifentanil arm selected both physician request and low oxygen saturation as the reason for supplemental oxygen. One participant in the Remifentanil arm selected both low respiratory rate and low oxygen saturation as the reason for supplemental oxygen.
[5]VAS score ranges from 0-100, where 0=no pain, 100=worst pain imaginable.
[6]Sedation scores range from 1-5 where 1=fully awake and 5=eyes closed and not rousable.
Missing data has been removed from denominators to generate % values

Table 3: Neonatal secondary outcomes

	Remifentanil (N=201)	**Pethidine** (N=199)	Estimate (95% C.I)	**p-value**
Apgar				
Apgar Score <4				
<4	0 (-)	0 (-)	-	-
≥4	201 (100%)	199 (100%)		
Apgar Score <7				
<7	1 (1%)	2 (1%)	0.50[1] (0.05, 5.42)	**0.56**
≥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 – 7.42	6.98 – 7.39		
Base Deficit (mmol/l)				
Mean (SD, N)	-2.93 (5.21, 88)	-2.69 (5.33, 97)	-	-
Range	-18.90 – 7.50	-12.30 – 9.70		
Fetal Acidosis				
Yes	2 (2%)	1 (1%)	2.18[1] (0.20, 23.64)	**0.51**
No	86 (98%)	95 (99%)		
Missing	113	103	-	-
Admission to Higher Level Care				
Yes	8 (4%)	9 (5%)	0.88[1] (0.35, 2.23)	**0.79**
No	193 (96%)	190 (95%)		
Requirement for Neonatal Resuscitation				
Yes	20 (10%)	21 (11%)	0.94[1] (0.53, 1.68)	**0.84**
No	181 (90%)	178 (89%)		
Interventional delivery for foetal distress				
Yes	29 (14%)	51 (26%)	0.56 (0.37, 0.85)	**0.005**
No	172 (86%)	148 (74%)		

[1]Risk ratio, values <1 favour remifentanil.

Table 4: Maternal satisfaction

	Remifentanil (N=184)	Pethidine (N=176)	p-value
1: I was satisfied with my overall childbirth experience			
Strongly disagree	4 (2%)	1 (1%)	0.27
Disagree	10 (6%)	8 (5%)	
Neutral	17 (9%)	11 (6%)	
Agree	66 (36%)	71 (40%)	
Strongly agree	87 (47%)	85 (48%)	
2: I was treated with respect by all of the staff			
Strongly disagree	1 (1%)	1 (1%)	0.21
Disagree	0 (-)	1 (1%)	
Neutral	7 (4%)	2 (1%)	
Agree	26 (14%)	18 (10%)	
Strongly agree	150 (81%)	154 (87%)	
3: I was involved in making decisions as much as I wanted to be			
Strongly disagree	1 (1%)	1 (1%)	0.19
Disagree	3 (2%)	2 (1%)	
Neutral	10 (5%)	2 (1%)	
Agree	39 (21%)	39 (22%)	
Strongly agree	131 (71%)	132 (75%)	
4: My expectations for labour and birth were met			
Strongly disagree	8 (4%)	5 (3%)	0.68
Disagree	13 (7%)	13 (7%)	
Neutral	27 (15%)	33 (19%)	
Agree	50 (27%)	51 (29%)	
Strongly agree	86 (47%)	74 (42%)	
5: I felt safe at all times			
Strongly disagree	1 (1%)	2 (1%)	0.41
Disagree	6 (3%)	1 (1%)	
Neutral	6 (3%)	4 (2%)	
Agree	35 (19%)	35 (20%)	
Strongly agree	136 (74%)	134 (76%)	
6: Good communication from the staff kept me well informed			
Strongly disagree	0 (-)	1 (1%)	0.87
Disagree	1 (1%)	0 (-)	
Neutral	6 (3%)	5 (3%)	
Agree	37 (20%)	32 (18%)	
Strongly agree	140 (76%)	138 (78%)	

	Remifentanil (N=184)	Pethidine (N=176)	p-value
7: I felt in control			
Strongly disagree	6 (3%)	4 (2%)	0.52
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 (-)	-
8: My pain relief was effective during labour			
Strongly disagree	4 (2%)	4 (2%)	0.0003
Disagree	9 (5%)	14 (8%)	
Neutral	12 (7%)	33 (19%)	
Agree	50 (27%)	57 (32%)	
Strongly agree	109 (59%)	68 (39%)	
9: I was satisfied with my labour pain relief			
Strongly disagree	3 (2%)	6 (4%)	0.0003
Disagree	9 (5%)	13 (7%)	
Neutral	11 (6%)	23 (13%)	
Agree	44 (24%)	60 (34%)	
Strongly agree	117 (63%)	74 (42%)	

Supplementary Information

Adjusted and sensitivity analyses of primary outcome

In addition to the primary unadjusted ITT analysis of the primary outcome, a further log-binomial model was fitted, adjusting for the minimisation variables:

- Ethnicity (south Asian, Other)
- Age (<20, 20-29, 30-39, ≥40 years)
- Parity (nulliparous, multiparous)
- Type of labour (induced, spontaneous)

Table 3: Primary adjusted intention to treat analysis

	Remifentanil (N=201)	**Pethidine (N=199)**	**Risk Ratio[1] (95% C.I)**	**p-value**
Woman received epidural				
Yes	39 (19%)	81 (41%)	0.47 (0.34, 0.65)	<0.0001
No	162 (81%)	118 (59%)		

[1]Remifentanil vs. Pethidine (values <1 favour Remifentanil).

Two 'per-protocol' analyses were undertaken for the primary outcome as sensitivity analyses to explore the potential effect of:

I. Non-adherence to the randomised allocation. The 'per-protocol' cohort was defined as only including those participants who complied with allocation and received only the randomised allocation. In the pethidine group, 45 women did not receive any pethidine and two participants received both pethidine and remifentanil. In the remifentanil group, 14 women did not receive any remifentanil and for one participant, it was not documented whether or not they received remifentanil and hence was excluded from this analysis. Results are reported in the main text.

II. Cross-over between treatment groups. Participants were grouped according to the intervention they ultimately received rather than the intervention to which they were randomised. Excluded from the analysis were 44 participants who did not receive their allocated pethidine, 13 participants who did not receive remifentanil, and the single participant for whom it was not documented whether they received their allocated remifentanil. Two participants in the pethidine group received pethidine and then went on to receive remifentanil, so are considered in the remifentanil group. One participant in the remifentanil group received only pethidine, and conversely one participant in the pethidine arm received only remifentanil. Results are in Table 4.

Table 4: Per-protocol sensitivity analysis: cross-over between treatment groups

	Remifentanil (N=189)	**Pethidine (N=153)**	**Risk Ratio[1] (95% C.I)**	**p-value**
Woman received epidural				
Yes	37 (20%)	57 (37%)	0.53 (0.37, 0.75)	0.0003
No	152 (80%)	96 (63%)		

[1]Remifentanil vs. Pethidine (values <1 favour Remifentanil