

A comparison of intramuscular diamorphine and intramuscular pethidine for labour analgesia: a two-centre randomised blinded controlled trial

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Objective Intramuscular (i.m.) pethidine is used worldwide for labour analgesia and i.m. diamorphine usage has increased in the UK in the last 15 years. This trial aims to ascertain the relative efficacy and adverse effects of diamorphine and pethidine for labour pain.

Design Prospective, parallel-arm randomised controlled trial with blinding of participants, care-givers and outcome assessors.

Setting Maternity units in two District General Hospitals in the UK.

Population After written informed consent, 484 women were randomised and recruited (244 diamorphine, 240 pethidine). Inclusion criteria included women 16 years or older, established labour, singleton pregnancy, 37–42 weeks of gestation and weight 60–120 kg.

Methods On request of i.m. analgesia, participants received either 150 mg pethidine or 7.5 mg diamorphine based on computer-generated block randomisation.

Main outcome measures Maternal—reduction in pain intensity from baseline (10-cm visual analogue scale) at 60 minutes and over the 3-hour period after drug administration. Neonatal—requirement for resuscitation and Apgar score at 1 minute.

Results Diamorphine provided modestly improved pain relief at 60 minutes, mean difference 1 cm (95% confidence interval [CI] 0.5–1.5), and over the 3 hours, mean difference 0.7 cm (95% CI 0.3–1.1). However, average length of labour in women receiving diamorphine was 82 minutes longer (95% CI 39–124) and therefore they experienced more pain overall. There were no statistically significant differences in primary neonatal outcomes.

Conclusions There is a modest difference between the analgesia provided by diamorphine or pethidine for labour analgesia but diamorphine is associated with significantly longer labours.

Keywords Diamorphine, labour analgesia, meperidine, opiate, pethidine.

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Introduction

Labour is a painful experience and analgesia is often required. Most consultant-led obstetric units in the UK offer intramuscular (i.m.) opioids as well as regional analgesia. In the UK, 33% of women in labour use i.m. pethidine and it is the only opioid licensed for independent use by midwives.¹ Pethidine, otherwise known as meperidine, is a widely used i.m. analgesic for labour pain worldwide. Research has demonstrated that pethidine provides variable pain relief in labour; much of its effect is sedation rather than analgesia.^{2,3} Pethidine also has adverse effects in both

the mother and neonate. It may cause nausea, vomiting and dysphoria in women during labour.⁴ It crosses the placenta and may cause reduced fetal heart rate variability and fewer heart rate accelerations.⁵ Neonatal adverse effects include respiratory depression, impaired breastfeeding and altered crying.^{6,7}

Despite the disadvantages of pethidine, there are few well-designed studies comparing the relative adverse effects and effectiveness of different opioids in labour. Systematic reviews comparing parenteral opioids in labour have suggested the need for well-designed and adequately powered trials of pethidine versus other opioids.^{8,9} A small trial comparing i.m. pethidine with diamorphine, showed diamorphine to be more efficacious than pethidine when used for labour analgesia in multiparous women, but not nullipa-

Trial Registration EudraCT No: 2006-003250-18; ISRCTN14898678; <http://www.controlled-trials.com/ISRCTN14898678>.

rous women or both parities combined.¹⁰ The authors suggested that their trial was underpowered. A national survey relating to the use of i.m. opioids for analgesia in labour in the UK revealed that diamorphine was used in 34% of maternity units and this was a substantial increase in usage.¹¹ Where it is used, there is a perception that it provides superior analgesia with fewer adverse effects than pethidine, but there are no published large randomised controlled trials to support this impression. We undertook a two-centre blinded randomised controlled trial comparing i.m. diamorphine and pethidine in labour, investigating their analgesic efficacy and adverse effects in the mother, fetus and neonate during the immediate peripartum period.

Methods

A detailed protocol for this trial was published before completion of the trial and analysis of the data.¹² This two-centre blinded randomised controlled trial comparing i.m. diamorphine and pethidine was conducted at Poole Hospital NHS Foundation Trust (PHFT) the sponsor site, with 5800 deliveries, and the Royal United Hospital, Bath (RUH), 5300 deliveries per annum. Southampton and South West Hampshire Ethics Committee granted approval. Trial information was given to women and written informed consent was obtained in the antenatal period via clinics both in the community and in maternity hospitals. Consented women in labour were recruited to the trial on maternal request for opioid analgesia.

Inclusion criteria for randomisation included nulliparous and multiparous women aged 16 years or older who had given written informed consent, who were in active labour defined as regular uterine contractions of at least two in 10 minutes, with a singleton pregnancy, cervical dilatation of at least 3 cm, with gestation of 37–42 weeks, and weight between 60 and 120 kg. The weight eligibility criterion was reduced from 70 kg to 60 kg with a substantial amendment in June 2009 approximately 3 months after the start of recruitment. Exclusion criteria included allergy or previous adverse reaction to opioids or opioid dependency, use of parenteral opioids within the previous 24 hours or presence of severe systemic disease.

Interventions

Either i.m. pethidine 150 mg or diamorphine 7.5 mg was given into the muscles of the gluteus or lateral thigh by the midwife looking after the women from the trial syringes provided by the research midwife. These doses were considered to be equivalent and commonly used based on previous studies and from a national survey of opioid use in obstetrics.^{10,11} A maximum of two doses of opioid were given with a minimum interval of 2 hours if the women requested additional analgesia. Women also

received metoclopramide 10 mg with the first dose. Regional analgesia or Entonox were available as rescue analgesia.

Randomisation and masking

The trial statistician provided the computer-generated block randomisation using block sizes between two and ten to ensure approximately equal group sizes, and stratified by centre. The pharmacies of both trial centres prepared batches of two identical syringes labelled only with the trial number to conceal group allocation and to ensure that if two doses were given, the same opioid was given both times. This ensured that the women, researchers, maternity unit staff and trial statistician were blinded to allocation. Once recruited, women were randomly allocated to receive either opioid. To further reduce bias the actual identities of the two groups were not revealed until after full analysis and discussion of the results.

Measurements

General demographics and measurements recorded included age, weight, gestational age, cervical dilatation at first request for analgesia, frequency of contractions, parity, spontaneous or induced labour, use of oxytocin, fetal presentation and position, and mode of delivery. Further details are given on the data collection sheet (see Appendix S1).

Maternal primary outcomes

Pain severity during the last contraction was assessed using a Visual Analogue Scale (VAS) (with anchor points of 0 = no pain at all and 10 = the most excruciating pain) every 30 minutes during the 3-hour period after administration of the trial drug. This information was used to derive measures of pain relief at each time-point using absolute change in pain intensity (on a 10-cm VAS) from pre-analgesia (baseline). In addition to analysing all the time-points together (as described in the section on statistical analysis), a specific analysis of pain relief at 60 minutes was conducted, because it was anticipated that the maximum analgesic effect would occur then. Also, pain intensity at 60 minutes was the primary outcome used by Fairlie et al.¹⁰

Neonatal primary outcomes

The primary neonatal outcomes were need for neonatal resuscitation and Apgar score <7 at 1 minute.

Secondary outcomes

These are described in detail in the published protocol and detailed results are presented in the Supplementary material, Tables S2–S5.¹² Maternal secondary outcome measures included a four-point verbal pain intensity score and a four-point verbal rating scale (VRS) for midwife assessment of maternal pain relief. Other secondary maternal outcome measures were sedation, haemoglobin oxygen

saturation, nausea, vomiting, satisfaction with analgesia and time from first dose to delivery. Neonatal secondary outcome measures included cardiocograph trace, umbilical artery and vein pHs, time from delivery to first breath, Apgar score at 5 minutes, naloxone use, haemoglobin oxygen saturation, sedation, time from delivery to first feed and midwife assessment of neonatal breastfeeding behaviour during the first 2 hours after delivery.

Sample size

The sample size calculation was based on data from the comparable trial of pethidine versus diamorphine by Fairlie et al.¹⁰ With 406 women, the IDvIP trial was designed to have 90% power (at the 5% significance level) to detect a mean difference of 1 cm on a 10-cm VAS pain score and to detect approximately 50% reduction in occurrence of neonatal primary outcomes (see published protocol for further rationale).¹² Initially we planned to recruit 450 women to allow for withdrawals and incomplete data, but increased this to 484 towards the end of recruitment to take into account the observed 16% proportion with missing data for pain at 60 minutes. No interim analysis was planned or conducted.

Statistical analysis

A fuller description of the analysis plan is available in the published protocol.¹² Results are reported using CONSORT guidelines.¹³ Women were analysed in the group to which they were originally assigned, regardless of what subsequently occurred in labour. Missing maternal data were minimal except for the 30-minute interval measurements. Maternal data missing at 30 minutes and later was the result of the need for maternal examination or other intervention or immediate delivery. Data were analysed using IBM SPSS Version 19 (IBM, Armonk, NY, USA), MLWiN version 2.17 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK), and STATA 11.2 (Stata Corp., College Station, TX, USA). All analyses take into account the stratification variable of recruitment centre. Binary outcomes were compared between pain relief groups using logistic regression for single measures and Generalised Estimating Equations for repeated measures taken at 30-minute intervals. Continuous outcomes were compared using multiple regression for single measures and mixed models for repeated measures. Time effects were modelled using a categorical indicator variable. Further, prespecified analyses adjusting for maternal age, parity, gestation and pre-administration pain intensity were also conducted. These have not been reported unless they changed results. In addition to the a priori analyses specified in the protocol, area under the curve was used to compare total pain experience over the 3-hour period to take into account both amount and duration of pain (potential values ranging from zero to 30).

Trial governance, sharing and rights to the data

A Data and Safety Monitoring Committee (DSMC) had a remit to look at trial progress and adverse events. The National Institute for Health Research (NIHR) grant awarding body, Research for Patient Benefit, has rights of access to the anonymised data as stated in Sections 9 and 10 of the contract agreement with the Sponsor, Poole Hospital NHS Foundation Trust.

Results

A total of 1128 women were consented and 484 women were recruited to the trial (Figure 1). Two hundred and forty-four women were randomly allocated to the diamorphine group and 240 to the pethidine group. Baseline characteristics were comparable between the two groups (Table 1), and mean predose pain intensity measured using VAS was high in both groups. Baselines for outcome measures, where relevant, are shown (see Appendix S1 and Table S1).

Primary outcomes

Women in the diamorphine group had modestly better pain relief scores measured by VAS compared with pethidine at 60 minutes and summarised over the whole 3-hour period (Table 2 and Figure 2). However for the latter outcome there was a statistically significant interaction between time and pain relief group ($P = 0.001$), with further post hoc analyses indicating that the modest improved pain relief was mostly between the 30- and 60-minute time-points (Figure 2, and see Supplementary material, Table S2). There was no statistically significant difference in analgesic effect at 60 minutes between primiparae and multiparae (parity and study drug interaction effect $P = 0.94$). Of note, from the 60-minute measurement onwards there was significantly more missing data in the pethidine group than the diamorphine group (for example 19% versus 10% at 60 minutes, 53% versus 34% at 120 minutes). The difference in quantity of missing data was largely because the women in the pethidine group tended to deliver earlier. A second dose of study drug was requested by 87 women (36%) in the diamorphine group and 55 women (23%) in the pethidine group ($P = 0.003$). There were no significant differences in the neonatal primary outcome measures of neonatal resuscitation and Apgar scores < 7 at 1 minute (Table 2).

Results for secondary outcome measures are shown in the Supplementary material (Tables S2 to S5). There was no difference in analgesia between the drugs according to the VRS at any time-point although the overwhelming majority in both groups reported moderate or severe pain throughout. The midwife VRS for pain relief was statistically significantly better in the diamorphine group within the first hour after the dose. More women in the diamor-

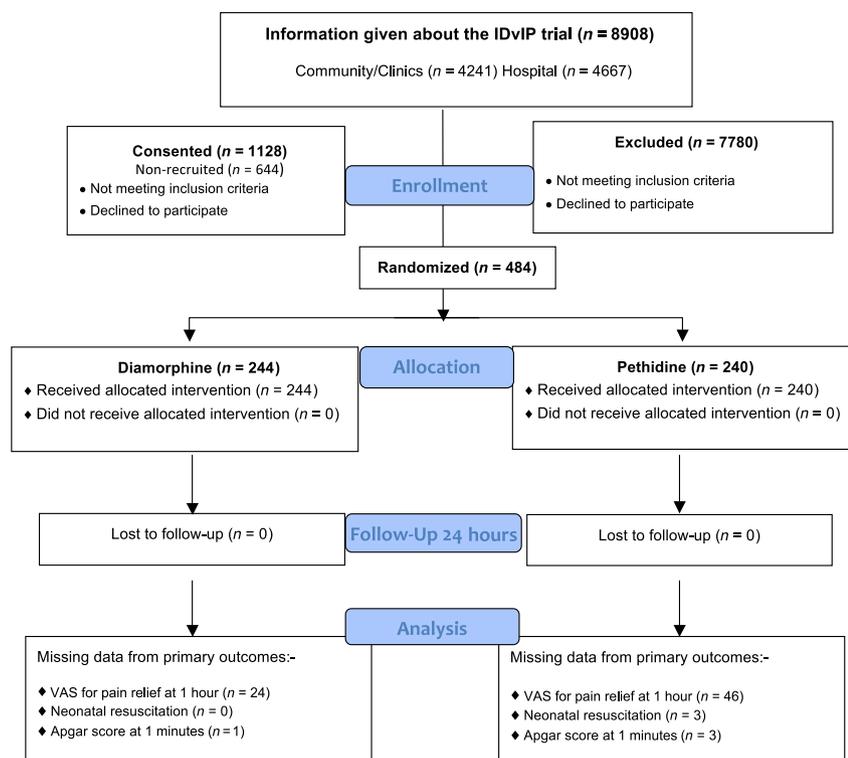


Figure 1. CONSORT flow chart—IDvIP Trial dated 13 Nov 2013..

phine group were very satisfied with their analgesia compared with the pethidine group (45% versus 34%; $P = 0.053$ and $P = 0.048$ after adjusting for pre-specified covariates in the supplementary analyses) and this may represent their improved sense of wellbeing. However, when asked within 24 hours of delivery, approximately 85% of women in both groups would have the same analgesia again. There were few differences in other maternal outcomes except that women in the diamorphine group were more likely to have haemoglobin saturation $\text{SpO}_2 < 97\%$ at 60 minutes ($P = 0.04$) but no women had clinically significant hypoxia and none required intervention such as oxygen supplementation. Also, women in the diamorphine group were less likely to have vomited at 30 minutes but more likely to have done so at 90 minutes ($P = 0.001$ for interaction between measurement occasion and study group). Supplementary analyses adjusting for prespecified covariates suggested that women in the diamorphine group were more likely to have one or more nausea events during the whole 3-hour period ($P = 0.047$). There were no differences in mode of delivery (see Table S6). There were no statistically significant differences in neonatal outcomes for the main analyses. After adjusting for prespecified covariates there appeared to be more moderate or severe neonatal sedation in the pethidine group ($P = 0.04$) 2 hours after delivery.

One unexpected but important observation was that women in the diamorphine group had significantly longer

labours from first dose to delivery, mean (SD)/median 362 (245)/323 minutes compared with pethidine 280 (228)/203 minutes, mean difference 82 minutes (95% confidence interval [CI], 39–124), $p < 0.001$. The distribution of labour length exhibited some skewness, but the difference between the two groups was also significant using the Mann–Whitney U -test ($P < 0.001$). In primiparae the means were 424 minutes and 357 minutes, respectively (mean difference 67 minutes, 95% CI 12–122 minutes; after adjusting for centre), and in multiparae were 258 minutes and 155 minutes (mean difference 104 minutes, 95% CI 52–156 minutes). Further post hoc analysis suggested that labour was more likely to have been augmented after randomisation in the diamorphine group (28% versus 18%, $P = 0.01$). The prolongation of delivery by diamorphine remained statistically significant when the analysis was confined to those not augmented after randomisation (55 minutes, 95% CI 14–97), those not having an epidural (68 minutes, 95% CI 27–108), and those with an occiput anterior presentation (87 minutes, 95% CI 35–139). Mean (SD) area under the curve of pain VAS scores was 13.8 (6.2) in the diamorphine group and 12.7 (6.8) in the pethidine group, mean difference 1.2 (95% CI 0–2.4, $P = 0.046$), suggesting that overall, although women in the diamorphine group had modestly better short-term pain relief they experienced more pain over the duration of labour due to their longer labours.

Table 1. Baseline characteristics—demographic and pregnancy variables

	Diamorphine (n = 244)	Pethidine (n = 240)
Maternal age (years), mean (SD)	28.7 (6.1)	28.7 (5.6)
Parity, n (%)		
0	153 (63%)	149 (62%)
1	62 (25%)	63 (26%)
2+	29 (12%)	28 (12%)
Gestational age (weeks), mean (SD)	40.3 (1.3)	40.3 (1.2)
Weight (kg), mean (SD)	81.7 (14.1)	84.3 (14.3)
Cervical dilation at first request for analgesia (cm), mean (SD)	4.6 (1.6)	4.6 (1.5)
Time between contractions (minutes), mean (SD)	3.6 (0.9)	3.7 (0.8)
Labour induced n (%)	93 (38%)	96 (40%)
Fetal position, n(%)		
OA	141 (58%)	147 (62%)
OP	60 (25%)	47 (20%)
Transverse	39 (16%)	45 (19%)
Other	3 (1%)	0 (0%)
Pain VAS		
Mean (SD)	8.1 (1.6)	8.0 (1.7)

Discussion

Main findings

To optimise the objectivity of pain measurement, we used a number of different measures: VAS and VRS for pain intensity scored by the women, midwife VRS for pain relief and maternal satisfaction.^{14,15} From the VAS, 7.5 mg diamorphine i.m. provided, on average, 1 cm better pain relief than 150 mg pethidine i.m., mostly in the period 30–60 minutes after administration. Although this was the effect size specified in the sample size calculation, the clinical significance

may be questioned. Some have suggested that the minimum difference in pain that can be subjectively measured by women is 1.3 cm, 1.4 cm or 1.8 cm.^{16–18} Further, expressed as standardised effect size, the difference is 0.39; a small to medium effect. We have therefore described the 1-cm effect as modest.¹⁶ For the VRS, the majority of women in both groups rated their pain as moderate or severe intensity throughout the study period. Women who received diamorphine showed greater levels of satisfaction with their analgesia but approximately 85% of women in both groups would choose the same analgesia in a future labour when questioned within 24 hours of delivery.

A significant finding of this trial was that women in the diamorphine group had significantly longer labours from first dose to delivery (mean difference 82 minutes). The area under the curve analysis that takes into account both levels of pain intensity and length of labour suggested that although diamorphine gave modestly improved short-term analgesia, overall women who received diamorphine experienced more pain over the duration of the labour as a result of their longer labours.

There were no significant differences in the neonatal primary outcomes of the need for resuscitation or Apgar scores <7 at 1 minute between the two groups. This was in contrast to the findings by Fairlie et al., who found that the Apgar scores at 1 minute were significantly lower in the pethidine group.¹⁰ There were minimal differences in maternal and neonatal secondary adverse effects.

Strengths and limitations

To our knowledge this is the largest adequately powered randomised controlled trial comparing pain relief and adverse effects between pethidine and diamorphine for analgesia in labour, and these are the most commonly used i.m. opioids for labour pain in the UK. Pethidine is the commonest opioid analgesic used worldwide. We acknowledge that the analgesic effect of a fixed dose may depend upon factors such as maternal weight; however, the doses used in the trial are those regularly used nationally in the

Table 2. Primary outcome measures

Maternal	Diamorphine Mean (SD)	Pethidine Mean (SD)	Mean difference (95% CI)	P-value
First dose—reduction from baseline in pain VAS @ 60 minutes	2.2 (2.4)	1.2 (2.7)	–1.0 (–1.5 to –0.5)	<0.001
First dose—reduction from baseline in pain VAS over 3 hours	See Table S2	See Table S2	–0.7 (–1.1 to –0.3)	<0.001
Neonatal	n (%)	n (%)	Odds ratio (95% CI)	P-value
Needed resuscitation	43 (18%)	44 (19%)	1.06 (0.67 to 1.69)	0.79
Apgar score < 7 at 1 minute	42 (17%)	36 (15%)	0.86 (0.53 to 1.39)	0.53

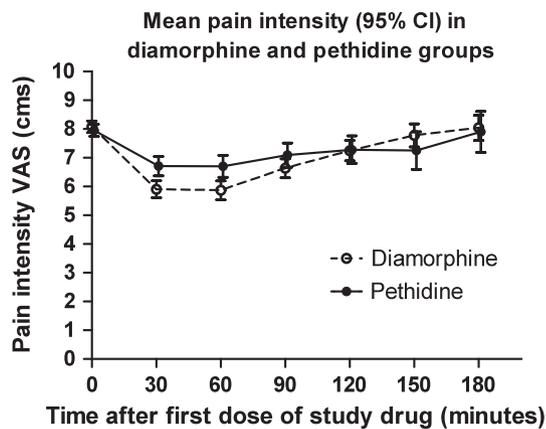


Figure 2. Mean pain intensity (95% CI) in diamorphine and pethidine groups.

UK and the weight ranges in both arms of the trial were comparable.¹¹ Strengths of the trial include concealed allocation of study drugs, blinding of researchers (including statistician) and clinical staff, the broad range of outcome measures employed and publication of the trial protocol before completion and analysis of the trial results. The trial was powered to detect a 50% change in primary neonatal outcomes. It is possible that the trial missed smaller clinically important effects, although estimates of effect size derived from the trial did not indicate this to be the case. There was some evidence in the supplementary analyses that neonates of women who received pethidine were more sedated at 2 hours and further longer-term observations would have informed us if this influenced their subsequent feeding behaviour and other longer-term adverse effects of both analgesics. This trial was not designed to study the longer-term adverse effects of these opioid analgesics in neonates. We have therefore not used other measures of neonatal health such as neuroadaptive capacity scores.

For the analysis of pain scores, we are unable to rule out bias resulting from women in the pethidine group tending to have shorter labours, and so being less likely to contribute to the analysis after the 30-minute time-point. The impact on the results is not known. Four primary outcomes (two maternal and two neonatal) were specified, increasing the possibility of type 1 error. Two were statistically significant. Under the null hypothesis that the two groups give identical outcomes, the probability that two or more independent outcome measures are statistically significant is 0.01 (i.e. unlikely).

Interpretation in the light of other evidence

In contrast to the smaller trial by Fairlie et al.¹⁰ this trial did not confirm that diamorphine resulted in fewer maternal, fetal, and neonatal adverse effects than pethidine. Furthermore, the Fairlie trial only found significant pain relief at 1 hour in multiparous but not nulliparous women who

received diamorphine compared with those receiving pethidine. As outlined above, a clinically and statistically significant finding was that women who received diamorphine tended to have longer labours by an average of 82 minutes (67 minutes for primiparae and 104 minutes for multiparae). This persisted when we excluded confounding factors that might affect the duration of labour such as abnormal foetal position, use of epidural analgesia and augmented labour. Using forty-four primary and secondary outcomes, we cannot exclude the possibility of type 1 error, though the *P*-value was small and remained significant after applying a Bonferroni correction ($P < 0.05$).

The prolongation of labour following diamorphine analgesia has been noted but not explained by other researchers.^{19,20} Oxytocin secretion is inhibited at the hypothalamus and the posterior pituitary by both μ and κ agonists.²¹ The mechanism for the prolongation of labour in the absence of obstetric factors is most likely a result of the effect of opioid metabolites on the reduction of oxytocin release from the pituitary gland. Overall, the greater μ agonist effect of diamorphine (via morphine metabolite) compared with pethidine (predominantly κ agonist) and the consequent greater inhibition of oxytocin release by diamorphine may explain the difference in effect of the two drugs on duration of labour.

Conclusions

This trial shows that there was a modest, short-term difference in the analgesia provided by 7.5 mg i.m. diamorphine compared with 150 mg i.m. pethidine for labour pain. The size and duration of this difference is of questionable clinical value. Further, diamorphine tends to prolong labour, resulting in women having greater total pain over the duration of labour. There were minimal, directionally inconsistent differences in short-term maternal and neonatal secondary outcomes between the two drugs. Diamorphine is approximately three times more expensive than pethidine and diamorphine use is largely limited to the UK. This trial does not support the use of diamorphine for labour pain.

Future research

We suggest there is a need for an adequately powered study to ascertain the mechanism of prolongation of labour by diamorphine and other opioids. We also suggest that the longer-term effects of diamorphine versus pethidine on the neonate should be ascertained.

Disclosure of interests

All authors have completed the Unified Competing Interest form and there are no competing interests. MW, JT and SB have received travel expenses for meetings in relation to the trial. PT received support for the study from the NIHR

RfPB grant. In addition, he receives support from another NIHR RfPB grant and from the NIHR Research Design Service. There are no financial activities declared outside the submitted work.

Contribution to authorship

MW and JT conceived the study, and contributed to the design and co-ordination of the trial. MW is chief investigator and principal investigator at the sponsor site, Poole Hospital NHS Foundation Trust. MW was responsible for leading the application of the Research for Patient Benefit (RfPB) programme for funding, obtaining ethics and MHRA approval and for providing regular reports to RfPB, research ethics and Data and Safety monitoring committees. MW and JT jointly chair the trial steering group meetings. JT is the principal investigator at the Royal United Hospital (RUH) Bath site. PT was responsible for statistical design and analysis of the trial and was a member of the trial steering group. SB had overall responsibility for setting up the study and management of the project at RUH Bath as well as overseeing the trial files at both sites, supervision of the research assistants and recruitment.

Details of ethics approval

Southampton and South West Hampshire Ethics Committee granted approval. REC Reference No: 06/Q1702/95 on 28 February 2007.

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Chris Miller, research midwife, set up the study in Poole Hospital NHS Foundation Trust (PHFT). Chris Miller and later Dawn Jackson, research midwife, undertook the administrative role at the Poole site including training, trial management, supervision of the research assistants, and recruitment. Sally Harries, research assistant (RA), PHFT, Deborah Randall (RA, PHFT), Susan Smith (RA, PHFT), Karen Ball (RA, RUH), Rachael Skinner (RA, RUH), Clare Fox (RA, RUH), and Susara Blunden (RA, PHFT) have all made contributions to the trial. All have contributed to informing, consenting, recruiting, collecting and recording maternal and neonatal data, maintaining trial files and are members of the trial steering group. Data entry was conducted by Louise Ward (Administrator, Bournemouth Uni-

versity Clinical Research Unit), and Zoe Sheppard (Research Fellow, Bournemouth University) contributed to the discussion of the analysis.

Mary Burrows (Research Governance Manager, PHFT) was responsible for the sponsor site responsibilities and research governance aspects of the trial and Lisa Austin (Research Manager, University of Bath and Wiltshire PCT) was responsible for the research governance aspect of the trial in RUH. Prof. Debra Bick, Prof. of Evidence Based Midwifery Practice, Kings College, London, Mr Robert Sawdy, Consultant Obstetrician and Mrs Elizabeth Davey (Senior Midwifery Lecturer, Bournemouth University) were members of the trial steering group. Prof. Philip Steer (Consultant Obstetrician and chair of the Data and Safety Monitoring Committee), Dr Minesh Khashu (Consultant Neonatologist) and Dr Hilary Swales (Consultant Anaesthetist) served on the DSMC. Mrs Noreen Hart and Amanda Paddock served as lay members of the steering group as well as the DSMC. Mrs Noreen Hart is also a member of the National Childbirth Trust.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics – outcome variables.

Table S2. Maternal and neonatal outcomes – Summary statistics for repeated measurements.

Table S3. Secondary outcome measures – Maternal Pain Variables.

Table S4. Secondary outcome measures – Other maternal variables.

Table S5. Secondary outcome measures – Neonatal variables.

Table S6. Mode of delivery.

Appendix S1. IDvIP Trial: Data Collection Sheet.

Data S1. Powerpoint slides summarising the study. ■

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Commentary on 'Why bother studying single shot opioids for labour analgesia?'

Wee et al. have conducted a blinded randomised controlled trial (RCT) comparing intramuscular diamorphine with intramuscular pethidine for labour analgesia. They report that diamorphine provides (very) slightly better analgesia with perhaps slightly better maternal satisfaction and less vomiting. A secondary finding was that women assigned to the diamorphine group had significantly longer labours (delivery ~ 6 hours after dosing compared with ~ 4.5 hours for pethidine). They conclude that the only marginally better analgesia with diamorphine, combined with evidence of prolongation of labour, suggests that pethidine should still be the opioid of choice for labour analgesia.

As an obstetric anaesthesiology practitioner and researcher in the USA, I have never used diamorphine, which is not available here, but am not surprised at the results of this study, which show that neither opioid leads to much analgesia. At maximum effect, the mean visual analogue scale score for the diamorphine group had decreased from 8 to 6, and the pethidine group from 8 to 7. Although this may be statistically detectable, a decrease in pain scores to 6–7 for half an hour hardly qualifies as 'analgesia'. It is somewhat disheartening to this obstetric anaesthesiologist that postpartum patient 'satisfaction' with analgesia was ~ 85%, confirming the common finding that many women are relatively pleased with any attempt at analgesia, once they have delivered a healthy baby. A reasonable conclusion from this study and multiple others would be that no single intramuscular dose of any opioid results in reasonably safe but effective analgesia for labour. Infusions of remifentanyl or patient-controlled infusions of pethidine at much higher doses (Alexander et al. *Anesth Analg* 2001;92:1524–8) can provide better analgesia than that seen in this study but with significant side-effects. Neuraxial techniques routinely result in visual analogue scale scores decreasing from the 7–10 to the 0–3 range. Between 60 and 65% of American women receive neuraxial analgesia, and the practice of using intramuscular opioids for women in active labour is disappearing from most larger US labour and delivery suites. The difference in practice regarding parenteral opioids on the two sides of the Atlantic is interesting, and surely reflects contributions of manpower and staffing patterns, culture, expectations and funding mechanisms.

The secondary finding of the study is more intriguing; that either diamorphine prolongs labour, or pethidine shortens it. A similar but smaller study more than a decade ago did not find this difference (Fairlie et al. *BJOG* 1999;106:1181–7), so caution is warranted in accepting this secondary outcome. However, there have been scattered

reports of pethidine speeding labour or cervical dilatation (Tournaire et al. *J Gynecol Obstet Biol.* 1980;9:261–6; Leighton et al. *Am J Obstet Gynecol* 2002;186:S69–77), and it has been suggested that a labour-enhancing effect of pethidine could explain some of the results of studies that suggest a labour-slowng effect of neuraxial analgesia when compared with a group receiving pethidine. Considering that we still really do not understand what initiates and maintains the labour process, further investigation of the reality and possible mechanism of such an effect would seem worthwhile.

Disclosure of interests

RS has no conflicts of interest to declare. ■

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Mini commentary on 'Comparison of the efficacy of intramuscular diamorphine with intramuscular pethidine in labour'

Wee et al. present a timely, well-designed trial to compare the efficacy of intramuscular diamorphine with intramuscular pethidine in labour. Pethidine (meperidine), developed in Germany during the First World War, is a synthetic opioid that is widely used to provide intramuscular analgesia in labour despite a paucity of data to suggest that it is particularly effective for this purpose (Olofsson et al. *Br J Obstet Gynaecol* 1996;103:968–72). The overwhelming majority of prospective trials report that pethidine is, at best, a poor analgesic in labour, and is probably less effective than Entonox (nitrous oxide) or transcutaneous electrical nerve stimulation (Harrison et al. *Acta Obstet Gynecol Scand* 1987;66:9–14). At the same time, the detrimental maternal and neonatal side effects have been widely reported.

Over the years, a number of other synthetic opioids have been developed as intramuscular alternatives with the promise of greater efficacy and reduced side effects for mother and baby—meptazinol (Meptid), pentazocine and nalbuphine for example. None have demonstrated clinical benefit. More recently, diamorphine, though not available for clinical use in many developed countries, has increased in popularity on labour wards in the UK. However, this is based largely on anecdotal reports and little robust evidence—hence the importance and timeliness of this paper.

The authors report a small 'statistically' significant reduction in pain as measured on a 10-cm visual analogue scale in the diamorphine group—1 cm at an hour and 0.7 cm over 3 hours. However, the *clinical* significance of this numerical reduction, as admitted by the authors, is very little; as shown by the verbal rating measurement of pain in which the overwhelming majority of all labouring mothers in the study describe their pain as moderate to severe throughout, regardless of which opioid they received. Of more concern, the study suggests that labour is prolonged in the diamorphine group by an average of 82 minutes—very significant both statistically and clinically. Hence, overall, the mothers in the diamorphine group suffered more. Neonatal side effects vary little, but it is important to note that data were only collected in the first few hours after delivery and no longer-term outcomes were investigated. To top all this, the authors point out that diamorphine is three times the price of pethidine.

Although it might be important to examine the long-term neonatal side effects and might be of interest to understand the mechanism by which labour may be prolonged, the take-home message from this study is clear: diamorphine should not be offered for intermittent intramuscular analgesia in labour. Indeed, perhaps it is time to reconsider the role any intramuscular opioid in this clinical setting.

Disclosure of interests

No interests to declare. ■

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Journal club

Scenario

On the labour ward, a woman in labour (G1 P0 at 40 weeks of gestation with no other medical history) has been using Entonox for labour analgesia. She is now requesting additional analgesia, but does not want epidural analgesia. How would you manage her pain?

Description of research

Participants	Women in active labour requiring opioid analgesia for labour pain
Intervention	Intramuscular diamorphine (7.5 mg), maximum two doses
Comparison	Intramuscular pethidine (150 mg), maximum two doses
Outcomes	Maternal: reduction in pain intensity from baseline at 60 minutes and over 3-hour period after drug administration Neonatal: requirement for resuscitation and Apgar score at 1 minute
Study design	1 : 1 Double-blind randomised controlled trial

Discussion points

1. What analgesia advice do you currently give to women in labour who request opioid analgesia?
2. How did the researchers determine the dosage of the opiates used? Is it similar to your current practice?
3. What are the purposes of block randomisation and stratification in this trial?
4. Define allocation, concealment and blinding in a randomised controlled trial—refer to the Cochrane handbook online (<http://handbook.cochrane.org>). Are they adequate in this trial?
5. What is the potential clinical relevance of the prolongation of labour observed in this trial?
6. Can you briefly summarise the results of this trial? How would the results of this trial influence your practice? (Data S1)

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