Clinical trial results:
Remifentanil intravenous patient controlled analgesia (PCA) versus intramuscular pethidine for pain relief in labour: a randomised controlled trial

Summary

EudraCT number	2012-005257-22
Trial protocol	GB
Global end of trial date	03 September 2016

Results information

Result version number	v1 (current)
This version publication date	03 November 2017
First version publication date	03 November 2017
Summary attachment (see zip file)	RESPITE Clinical Trial summary report (RESPITE Clinical Trial Summary Report v1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_12-151

Additional study identifiers

ISRCTN number	ISRCTN29654603
ClinicalTrials.gov id (NCT number)	NCT02179294
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS number: 116638

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B152TT
Public contact	Sean Jennings, University of Birmingham, Research Support Group, +44 01214143794, researchgovernance@contacts.bham.ac.uk
Scientific contact	Sean Jennings, University of Birmingham, Research Support Group, +44 01214143794, researchgovernance@contacts.bham.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2016
Global end of trial reached?	Yes
Global end of trial date	03 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To conduct a RCT to determine if remifentanil PCA administered for pain relief in labour, reduces the proportion of women who subsequently require an epidural for pain relief in comparison to intermittent intramuscular pethidine (current practice).

Protection of trial subjects:

The trial protocol dictated that all women randomised were to receive one-to-one midwifery care. Observations including excessive sedation score, oxygen saturation and respiratory depression were recorded every 30mins until delivery or transfer to theatre. Women who were randomised to receive remifentanil PCA, in the event of excess sedation being recorded by regular observation of respiratory function, the regimen was altered by reduction of the remifentanil bolus dose to 30µg with a lock-out interval of 2 minutes.

Background therapy:

After the administration of analgesia, all women received one-to-one midwifery care and had observations recorded including:

- Respiratory rate and continuous oxygen saturation monitoring by pulse oximetry
- Sedation score every 30 minutes
- Visual analogue pain score every 30 minutes

Evidence for comparator:

Remifentanil is a novel synthetic opioid with a very rapid onset (blood-brain equilibration 1.2-1.4 minutes) and short duration of action (context specific half-life 2-3 minutes), giving it an analgesic profile which potentially makes it ideal for providing pain relief over 1-2 uterine contractions after a single intravenous dose. It is subject to rapid redistribution and metabolism by non-specific blood and tissue esterases, negating the potential for accumulation in mother or foetus. Administration of remifentanil by PCA has been investigated in several small studies in comparison to pethidine and shown to provide useful, although not complete, pain relief in labour. Thus far, there is no evidence of detrimental neonatal effects in comparison to other opioids.

Some units are starting to offer this form of pain relief in cases where pain relief is requested, but an epidural is contraindicated, for example in the case of maternal clotting abnormality or platelet dysfunction. However the use of remifentanil PCA is not currently widespread or routine. Crucially, there is some evidence from the studies performed thus far that the proportion of women who require rescue pain relief with an epidural after remifentanil PCA is reduced in comparison to pethidine, although no study has yet investigated this as a primary end-point. If such an effect were proven and remifentanil demonstrated to be at least as safe and effective as pethidine, the number of women requiring an epidural in labour could potentially be reduced with a concomitant beneficial reduction in instrumental vaginal delivery and associated morbidity including incontinence and sexual dysfunction, relative to spontaneous delivery.

Actual start date of recruitment	13 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 401
Worldwide total number of subjects	401
EEA total number of subjects	401

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	6
Adults (18-64 years)	395
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited and randomised into the trial on 13/05/2014 and the last patient was randomised into the trial on 02/09/2016.

The study was open in the UK only and was open in 16 centres in total. 2 centres closed prematurely after failing to recruit any women and 1 centre closed prematurely after only recruiting one woman.

Pre-assignment

Screening details:

A total of 2950 eligible women were screened for the trial. Of those 2549 women were not randomised and 401 women were randomised. Of the 2549 women not randomised, 1797 declined and 752 women were not recruited due to an 'other' reason e.g consented but did not proceed to randomisation.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Pethidine

Arm description:

100mg by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Pethidine
Investigational medicinal product code	N/A
Other name	Pethidine hydrochloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

100mg by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.

Arm title	Remifentanil PCA

Arm description:

- Dedicated intravenous cannula for remifentanil administration
- PCA protocol
  - PCA bolus remifentanil 40 µg
  - Lockout interval 2 minutes

Arm type	Experimental
Investigational medicinal product name	Remifentanil PCA
Investigational medicinal product code	N/A
Other name	Remifentanil hydrochloride
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Dedicated intravenous cannula for remifentanil administration
- PCA protocol

o PCA bolus remifentanil 40 µg
o Lockout interval 2 minutes

Number of subjects in period 1[1]	Pethidine	Remifentanil PCA
Started	199	201
Completed	199	201

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 200 women were randomised to the Pethidine arm. 1 woman in the Pethidine arm withdrew her consent to use her data. I have attempted to document this as 200 'started' in the Pethidine arm and 199 'completed' in the Pethidine arm with 1 lady withdrawing consent therefore the total decreases from 200 to 199. This has not been accepted within the system and I have been advised by a member of the EudraCT team to enter the information as 199 'started' and 199 'completed'.

Baseline characteristics

Reporting groups	
Reporting group title	Pethidine
Reporting group description:	
100mg by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.	
Reporting group title	Remifentanil PCA
Reporting group description:	
• Dedicated intravenous cannula for remifentanil administration • PCA protocol o PCA bolus remifentanil 40 µg o Lockout interval 2 minutes	

Reporting group values	Pethidine	Remifentanil PCA	Total
Number of subjects	199	201	400
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	29.3	29.4	
standard deviation	± 6.1	± 6.1	-
Gender categorical Units: Subjects			
Female	199	201	400
Parity Units: Subjects			
Nulliparous	118	121	239
Multiparous	81	80	161
Ethnicity Units: Subjects			
South Asian	30	31	61
Other	169	170	339
Type of labour Units: Subjects			
Induced	136	137	273
Spontaneous	63	64	127

End points

End points reporting groups

Reporting group title	Pethidine

Reporting group description:

100mg by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.

Reporting group title	Remifentanil PCA

Reporting group description:

- Dedicated intravenous cannula for remifentanil administration
- PCA protocol
  - PCA bolus remifentanil 40 µg
  - Lockout interval 2 minutes

Primary: The proportion of women who have an epidural placed for pain relief in labour, in each group

End point title	The proportion of women who have an epidural placed for pain relief in labour, in each group

End point description:

End point type	Primary

End point timeframe:

During labour

End point values	Pethidine	Remifentanil PCA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: Number of women				
Woman received epidural	81	39		
Woman did not receive epidural	118	162		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Primary ITT (Intention-to-Treat) Unadjusted Analysis. The primary analysis is a comparison of the rate of conversion to epidural between Remifentanil PCA and Pethidine (usual care) using a log-binomial model.

Comparison groups	Pethidine v Remifentanil PCA

Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.05 [2]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.7
Variability estimate	Standard deviation

Notes:

[1] - Primary ITT (Intention-to-Treat) Unadjusted Analysis. The primary analysis is a comparison of the rate of conversion to epidural between Remifentanil PCA and Pethidine (usual care) using a log-binomial model.

[2] - P value result for the primary analysis of the primary outcome was <0.0001. P-value stated above relates to the significance level in calculating the sample size

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The time period for occurrence of SAEs relevant to reporting is from the participant's entry to the study until hospital discharge. In the case of a neonatal SAE, the period is from birth to discharge.

Adverse event reporting additional description:

*1 x neonatal SAE included diagnosis of sepsis and pyrexia (Remifentanil arm)
† 1 x neonatal SAE included diagnosis of hypertrophic cardiomyopathy, pneumonia and pulmonary hypertension (Pethidine arm)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Pethidine

Reporting group description:

100mg by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.

Reporting group title	Remifentanil PCA

Reporting group description:

- Dedicated intravenous cannula for remifentanil administration
- PCA protocol
  - PCA bolus remifentanil 40 µg
  - Lockout interval 2 minutes

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Low respiratory rate, high sedation score and low oxygen saturation were considered adverse reactions that would require attention from an anaesthetist. Observations were collected and recorded in the Pain Relief and Maternal Observations form but were not reported specifically using an Adverse Event form. Non-serious adverse events, not directly linked to trial interventions, were not collected.

Serious adverse events	Pethidine	Remifentanil PCA	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 154 (4.55%)	9 / 186 (4.84%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 154 (0.65%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Post-partum haemorrhage	Additional description: Maternal		

subjects affected / exposed	0 / 154 (0.00%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia	Additional description: Maternal		
subjects affected / exposed	1 / 154 (0.65%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress	Additional description: Neonatal. 1 in remifentanil arm and 1 in pethidine arm (pethidine not administered)		
subjects affected / exposed	1 / 154 (0.65%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea	Additional description: Neonatal		
subjects affected / exposed	2 / 154 (1.30%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium aspiration	Additional description: Neonatal		
subjects affected / exposed	0 / 154 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension	Additional description: Neonatal		
subjects affected / exposed	1 / 154 (0.65%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis	Additional description: Sepsis (neonatal) - 2 in remifentanil arm, 1 in pethidine arm (not administered) Sepsis (post delivery; maternal) - 1 in remifentanil arm		
subjects affected / exposed	1 / 154 (0.65%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 154 (0.65%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection	Additional description: Neonatal		
subjects affected / exposed	1 / 154 (0.65%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Neonatal		
subjects affected / exposed	1 / 154 (0.65%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Pethidine	Remifentanil PCA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 154 (0.00%)	0 / 186 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2013	Substantial amendment 2. Change in wording of eligibility criteria to make in line with the randomisation form. Section 5.1.2 of protocol 'continuous' added to oxygen saturation monitoring and removal of '30 mins' from timing. Protocol updated to v1.2.
14 October 2014	Substantial amendment 5. Addition of TSC and DMC members, amended TMG members, updated BCTU address and addition of Clinicaltrials.gov NCT number. Section 3.3 wording amended so consent can be obtained once patient enters established labour up to and including the point that the patient requests opioid analgesia. Section 3.4 removed patient initials, parity and gestational age as these are not being collected on screening logs. Section 5.1.3 clarification that no additional temperature monitoring of trial drugs is required beyond established Trust protocols. Section 5.2 clarification that consenting investigator nor research midwife are party to the decision to progress to epidural. Section 6.1.3 list of anticipated SAEs added which are not considered to be related to Pethidine and/or Remifentanil. Protocol updated to v1.3
15 October 2015	Substantial amendment 10. Various clarifications around eligibility assessment, delegated roles, SAE assessment, definition of established labour, scope for co-enrolment, data transferred to University of Aberdeen for randomisations performed via the 24/7 automated telephone system, drug storage and dispensing and the exclusion criteria regarding systemic opioids. Additional information has been added regarding breastfeeding with Pethidine and Remifentanil, incentives for sites in recognition of reaching recruitment targets and extending the recruitment end date. Addition of DMC member, addition of collaborator, change of details for Trial Coordinator. Protocol updated to v2.0
25 July 2016	Substantial amendment 12. Change of BCTU logo, update to table 1 - list of previous studies of remifentanil for analgesia in labour, clarification of secondary outcomes and update to the reference list. Protocol updated to v3.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 October 2015	Further clarification was required on governance aspects of the trial within protocol v1.4. This resulted in a temporary halt to the trial which was not related to safety of trial patients or data integrity. This was submitted to REC and MHRA via a substantial amendment (substantial amendment 10, dated 15th October 2015) and a serious breach regarding this was also reported to REC and MHRA.	26 November 2015

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27955688