Clinical trial results:
High Or Low Dose Syntocinon® (Oxytocin) for delay in labour. HOLDS: a pilot study.

Summary

EudraCT number	2009-012752-24
Trial protocol	GB
Global end of trial date	30 September 2011

Results information

Result version number	v1 (current)
This version publication date	19 July 2019
First version publication date	19 July 2019

Trial information

Trial identification

Sponsor protocol code	RG_09-016

Additional study identifiers

ISRCTN number	ISRCTN23847193
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	MREC number : 10/H0406/30, Funder I.D. : PB-PG- 0407-13193, CTA number: 21761/0249/001-0001

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B152TT
Public contact	Dr Birgit Whitman, University of Birmingham, +44 0121 4158011, B.Whitman@bham.ac.uk
Scientific contact	Dr Birgit Whitman, University of Birmingham, +44 0121 4158011, B.Whitman@bham.ac.uk
Sponsor organisation name	Birmingham Women's and Children's NHS Foundation Trust
Sponsor organisation address	Mindelsohn Way, Birmingham, United Kingdom, B15 2TG
Public contact	Elizabeth Adey, Birmingham Women's and Children's NHS Foundation Trust, +44 01213338749, e.adey@nhs.net
Scientific contact	Elizabeth Adey, Birmingham Women's and Children's NHS Foundation Trust, +44 01213338749, e.adey@nhs.net

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	31 August 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2011
Global end of trial reached?	Yes
Global end of trial date	30 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This pilot study based in three maternity units will recruit approximately 100 women. It is the pilot for a proposed multicentre trial which would compare standard and high dose oxytocin in approximately 4300 women from 24 centres. The main hypothesis of the trial is that the use of high dose oxytocin will achieve more effective uterine contractions resulting not only in shorter labours but in a higher chance of vaginal birth in women who are diagnosed as having delay in the first stage of labour. The regimen we will evaluate has a higher starting dose, earlier attainment of conventional maximum doses (at 2 hours rather than over 4 hours) and the use of higher maximum doses of oxytocin compared to the standard regimen used at present.

Protection of trial subjects:

The study was discussed with women and written information presented detailing no less than: the exact nature of the study; the implications of the protocol for both her and her baby. It was clearly stated that the woman was free to withdraw from the study at any time and for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Women received information about the study in advance during the antenatal period with the process for providing information being individulised for each hospital. The administration of oxytocin does carry known side effects, which particiapnts were made aware of. In these cases the opinion of an obstetrician was sought. The side effects of oxytocin are that the uterus contracts too much (hyperstimulates) which can cause the baby to become distressed. For this reason women on oxytocin were more intensively monitored. Participating in the study did not alter the care the woman or baby received in the instance of any anticipated or unanticipated problem and standard procedures, as defined within the local Maternity Unit protocols, were then followed. An Independent Oversight Committee reviewed Serious Adverse Events and information was fed back to the Project Management Group and Sponsor as appropriate. Participant's could be unblinded to treatment allocation if necessary.

Background therapy:

Oxytocin is routinely given to nulliparous women who become delayed in labour and it is given via an intravenous cannula, which is attached to intravenous fluid to which oxytocin is added. This is usual practice for these women and their participation in the study will not alter the route of oxytocin administration.
The dose of oxytocin will usually be administered using an infusion pump and will be routinely increased every half hour until contractions are occurring 4-5 every 10 minutes. The dose increments are "titrated" against uterine activity. If there is evidence of excess uterine activity the dosage increase is stopped or reversed (the half life of oxytocin is 5 minutes) and once effective contractions are achieved it is not increased further.
Delay in labour is an everyday occurrence on UK Labour Wards and the titration of oxytocin to re-establish effective uterine contractions is a situation clinicians are used to managing effectively. Women receiving oxytocin for delay in labour are routinely monitored more intensively by the midwife caring for the woman and this would normally include monitoring of the strength and frequency of contractions, the woman's observations and fluid balance. She will also be offered support and effective pain relief. Electronic Fetal heart Monitoring (EFM) would routinely be offered to detect signs of fetal hypoxia should they occur.
Care of women having continuous EFM in the presence of oxytocin will follow that advocated by the NICE Intrapartum Care Guideline. Should uterine tachysytole occur (defined as more than 5 contractions in 10 minutes for 20 minutes) this will be documented and obstetric opinion sought, as is usual practice. Should uterine hyperstimulation occur (defined as tachysystole with suspicious or pathological fetal heart rate) this will be documented and obstetric opinion sought, as is usual practice.

Evidence for comparator:

A major cause of failure to achieve spontaneous vaginal birth (SVB) is delay in labour caused by presumed inefficient uterine action. This is relatively common as it occurs in over a third of women in their first labours. Current practice is to augment uterine activity with an intravenous infusion of oxytocin in the belief that this will maximise the number giving birth spontaneously. However, this has been challenged by a systematic review undertaken for the National institute of Clinical Excellence (NICE) Intrapartum Guideline which found that the use of standard escalating low dose oxytocin regimens was associated with a shorter labour without change in mode of birth. It is plausible that the lack of effect of oxytocin is due to either an inadequate dose or delay in achieving effective doses and there is some evidence to suggest that high starting doses of oxytocin and more rapid escalation may increase the numbers of women having a SVB. The published trials are too small to reliably detect a meaningful difference. Furthermore they do not have enough information on neonatal outcomes or the impact on women's experience of childbirth or the relationship with her baby.
Maximising the number of women who have a SVB is an objective that clinicians strive to achieve. Women who experience delay in labour pose particular challenges as they often give birth either by caesarean section (CS) or by assisted vaginal birth. Information from University Hospitals Leicester (UHL) over 2005 and 2006, showed that of nulliparous women who become delayed in labour and are given oxytocin, 40% will have a SVB, 40% an instrumental birth and 20% CS. The latter two are associated with higher maternal and neonatal mortality and morbidity and associated health service costs. Many women who have a CS will go on to have another CS in subsequent pregnancies and this group of women are currently the single largest group of elective CSs.

Actual start date of recruitment	01 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	3
Adults (18-64 years)	91
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 94 consenting nulliparous women at term with confirmed delay in labour were recruited from 3 UK teaching hospitals between November 2010 and May 2011.

Pre-assignment

Screening details:

Women were eligible for inclusion if they were consenting nulliparous women with a singleton pregnancy at term (37-42 weeks) gestation and had confirmed delay in labour as defined by NICE Intrapartum Care Guideline and with ruptured membranes.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The study drug will be blinded, randomised and packaged by a Bilcare pharma, which is a Clinical Trial Supplier and holds an MHRA IMP Manufacturers Licence (May 2004), together with an Manufacture and Assembly Licence Specials. Should unblinding be required, unblinding codes will be held in the Pharmacy Departments of each Maternity Unit, as well as by the Trial Statistician. Reasons for unblinding will be documented.

Arms

Are arms mutually exclusive?	Yes
Arm title	High dose Oxytocin

Arm description:

The high dose oxytocin regimen started at 4 mU/min and increased to a maximum dose of 64 mU/min. The high dose solution contained 2 x 10iu in 50 mls.

Arm type	Experimental
Investigational medicinal product name	Syntocinon injection ampoules 10 IU/ml
Investigational medicinal product code	N/A
Other name	High dose Oxytocin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The high dose regimen starts at 4 mU/min and increases to a maximum dose of 64 mU/min.

Oxytocin is routinely given to nulliparous women who become delayed in labour and it is given via an intravenous cannula, which is attached to intravenous fluid to which oxytocin is added. This is usual practice for these women and their participation in the study will not alter the route of oxytocin administration.
The dose of oxytocin will usually be administered using an infusion pump and will be routinely increased every half hour until contractions are occurring 4-5 every 10 minutes. The dose increments are "titrated" against uterine activity. If there is evidence of excess uterine activity the dosage increase is stopped or reversed (the half life of oxytocin is 5 minutes) and once effective contractions are achieved it is not increased further.

Arm title	Standard Dose Oxytocin

Arm description:

The standard dose is recommended by NICE in their Induction of Labour Guideline and has been widely adopted in the United Kingdom (UK). This regimen has never been evaluated in a clinical trial and fulfils the requirements of the "low dose" defined in the systematic review. It starts at 2 mU/min and increases to a maximum dose of 32 mU/min (as advocated by NICE).

Arm type	Active comparator

Investigational medicinal product name	Syntocinon injection ampoules 5 IU/ml
Investigational medicinal product code	N/A
Other name	Standard Dose Oxytocin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxytocin is routinely given to nulliparous women who become delayed in labour and it is given via an intravenous cannula, which is attached to intravenous fluid to which oxytocin is added. This is usual practice for these women and their participation in the study will not alter the route of oxytocin administration.
The dose of oxytocin will usually be administered using an infusion pump and will be routinely increased every half hour until contractions are occurring 4-5 every 10 minutes. The dose increments are "titrated" against uterine activity. If there is evidence of excess uterine activity the dosage increase is stopped or reversed (the half life of oxytocin is 5 minutes) and once effective contractions are achieved it is not increased further. The dose starts at 2 mU/min and increases to a maximum dose of 32 mU/min.

Number of subjects in period 1	High dose Oxytocin	Standard Dose Oxytocin
Started	47	47
Completed	46	46
Not completed	1	1
Withdrawn	1	1

Baseline characteristics

Reporting groups	
Reporting group title	High dose Oxytocin
Reporting group description:	
The high dose oxytocin regimen started at 4 mU/min and increased to a maximum dose of 64 mU/min. The high dose solution contained 2 x 10iu in 50 mls.	
Reporting group title	Standard Dose Oxytocin
Reporting group description:	
The standard dose is recommended by NICE in their Induction of Labour Guideline and has been widely adopted in the United Kingdom (UK). This regimen has never been evaluated in a clinical trial and fulfils the requirements of the "low dose" defined in the systematic review. It starts at 2 mU/min and increases to a maximum dose of 32 mU/min (as advocated by NICE).	

Reporting group values	High dose Oxytocin	Standard Dose Oxytocin	Total
Number of subjects	47	47	94
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	3	0	3
Adults (18-64 years)	44	47	91
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	26	28	
standard deviation	± 5.0	± 5.2	-
Gender categorical Units: Subjects			
Female	47	47	94
Smoking Units: Subjects			
Smoking throughout pregnancy	10	5	15
Stopped during pregnancy	0	1	1
Non-smoker	36	40	76
Not known (withdrew)	1	1	2
Ethnicity Units: Subjects			
African	0	0	0
Asian	6	6	12
Caribbean	1	0	1
European	38	35	73
Middle Eastern	0	0	0
Mixed	0	1	1

Other	1	4	5
Not known (withdrew)	1	1	2

Gestation (weeks)			
Units: Weeks			
arithmetic mean	40.5	40.2	
standard deviation	± 1.0	± 1.0	-
BMI			
Units: BMI			
arithmetic mean	25.2	25.8	
standard deviation	± 3.7	± 4.4	-
Baby weight			
Units: Grams			
arithmetic mean	3519	3363	
standard deviation	± 543	± 429	-

End points

End points reporting groups

Reporting group title	High dose Oxytocin

Reporting group description:

The high dose oxytocin regimen started at 4 mU/min and increased to a maximum dose of 64 mU/min. The high dose solution contained 2 x 10iu in 50 mls.

Reporting group title	Standard Dose Oxytocin

Reporting group description:

The standard dose is recommended by NICE in their Induction of Labour Guideline and has been widely adopted in the United Kingdom (UK). This regimen has never been evaluated in a clinical trial and fulfils the requirements of the "low dose" defined in the systematic review. It starts at 2 mU/min and increases to a maximum dose of 32 mU/min (as advocated by NICE).

Primary: Rate of Spontaneous Vaginal Birth

End point title	Rate of Spontaneous Vaginal Birth

End point description:

Mode of birth

End point type	Primary

End point timeframe:

At birth

End point values	High dose Oxytocin	Standard Dose Oxytocin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[1]	47[2]		
Units: Number of women				
Spontaneous Vaginal Birth	12	10		
Instrumental Birth (IB)	17	21		
Caesarean Section	15	13		
Caesarean Section following failed IB	2	2		
Not known (withdrew)	1	1		

Notes:

[1] - Includes 1 woman that withdrew

[2] - Includes 1 woman that withdrew

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary clinical endpoint for the HOLDS pilot study is the rate of Spontaneous Vaginal Birth (SVB). SVB rates for each arm will be calculated, and an odds ratio (OR) together with a 95% confidence interval (CI) will be calculated.

Comparison groups	High dose Oxytocin v Standard Dose Oxytocin

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Risk ratio (RR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.5
Variability estimate	Standard error of the mean

Notes:

[3] - No hypothesis testing proposed as this was a pilot study.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from randomisation until discharge from hospital.

Adverse event reporting additional description:

All expected SAEs will be reported on the data collection forms and will be reviewed by the Project Management Group (PMG) at the end of the pilot study. If any of the serious adverse events occur they will be reported to the Oversight Group (OG) and will also be reviewed by the PMG at the end of the pilot study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	High Dose Oxytocin

Reporting group description:

2 women did not receive the intervention due to giving birth before the intervention could be given

Reporting group title	Standard Dose Oxytocin

Reporting group description:

1 woman did not receive the intervention due to giving birth before the intervention could be given

Serious adverse events	High Dose Oxytocin	Standard Dose Oxytocin	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	1 / 46 (2.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Hypertension	Additional description: Mother admitted to High Dependency Unit with hypertension for 24 hours. Discharged home with baby on 06/04/2011.		
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: Baby admitted to Neonatal Unit with congenital pneumonia and required ventilation for 3 days in intensive care. Infection screen negative - treated with 7 days antibiotics. Discharged home		
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (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: 5 %

Non-serious adverse events	High Dose Oxytocin	Standard Dose Oxytocin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 45 (6.67%)	4 / 46 (8.70%)	
Pregnancy, puerperium and perinatal conditions			
Fetal hypoxia requiring FBS	Additional description: Fetal hypoxia (defined as fetal scalp pH as <7.20) requiring Fetal Blood Sampling		
subjects affected / exposed	1 / 45 (2.22%)	2 / 46 (4.35%)	
occurrences (all)	1	2	
Neonatal hyperbiliruninaemia	Additional description: Neonatal hyperbiliruninaemia requiring phototherapy		
subjects affected / exposed	2 / 45 (4.44%)	2 / 46 (4.35%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2010	Changes to the protocol (updated to v3.0 20/09/2010): • An addition to the Expected Serious Adverse Events of maternal admission to HDU/ITU (page 20 and 29) • Removed reference to collecting a copy of the consent form for the Study Office (page 17) We have also added a sentence to the consent form regarding the participant giving consent for contact details to be collected and for data to be transferred to the Study Office. This is clearly explained in the Participant information leaflet. Questionnaires 1 and 2 also have minor changes to the wording for clarity.
20 January 2011	Changes to the protocol (updated to v4.0 20/01/2011): • To increase the numbers of women we are hoping to recruit as recruitment is going well and we have enough treatment packs to continue. • We are also having a disappointing response to the postal questionnaire after birth and would like the local midwife to ask the women they make contact with (as part of our agreed processes) who have not returned a questionnaire or agreed to be interviewed a few questions about their experiences.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The pilot study was not powered to detect differences in clinical outcomes. Only explored women's experiences following a diagnosis of delay in labour, when the majority of women had an epidural in situ. Lack of non-European participants

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23786339