Clinical trial results:
The introduction and use of Entonox as an alternative method of pain relief for intrauterine contraception device insertions.

Summary

EudraCT number	2015-003628-29
Trial protocol	GB
Global end of trial date	04 August 2016
Results information	
Result version number	v1 (current)
This version publication date	12 October 2019
First version publication date	12 October 2019

Trial information

Trial identification	
Sponsor protocol code	REGC-15-035.R1
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT number: 2015-003628-29

Notes:

Sponsors	
Sponsor organisation name	University of Brighton
Sponsor organisation address	Village Way, Brighton, United Kingdom, BN1 9PH
Public contact	Theofanis Fotis, University of Brighton, +44 (0)1273 644512, T.Fotis@brighton.ac.uk
Scientific contact	Theofanis Fotis, University of Brighton, +44 (0)1273 644512, T.Fotis@brighton.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	04 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research objective is to see if Entonox® helps to reduce the level of pain experienced by women during intrauterine contraception device insertions in a community contraception and sexual health clinic compared to local anaesthetic intracervical injection.

Protection of trial subjects:

Entonox has recognised benefits for its use as a method of pain relief for procedural pain, however there is no published data into its benefits for IUC insertion. There is the potential for it to be inadequate for this purpose and the client may experience a greater level of pain and or anxiety than if she were receiving a commonly used method. Some women may experience side effects to the Entonox that they find unacceptable, such as nausea. Participants will be informed that should they require additional or alternate analgesia during the procedure they can opt out of the study at that point and receive an alternative method of pain relief.

Women who are allocated to receive intracervical LA injection will be counselled pre procedure regarding the possibility of discomfort at the administration of the anaesthesia and can opt out of participation if they feel this is unacceptable to them or they require additional pain relief.
Intracervical injection has the minimal but serious risks of accidental intravenous administration and anaphylactic reaction. Practitioners undertaking this procedure are trained to recognise signs and symptoms of these, are trained in basic life support, anaphylaxis and the administration of emergency drugs. Emergency drugs of Adrenaline and Atropine are available in the clinical room during all procedures. All women choosing IUC as their preferred method of contraception are offered local anaesthetic intracervical injection as routine for IUCD insertion currently and women will only be eligible for the study if they are requesting analgesia for this procedure.

Background therapy:

As per standard care, participants were asked to take oral over the counter pain relief prior to their appointment which was optional.

Evidence for comparator:

Local anaesthetic intracervical and paracervical injections are widely used as pain relief for intrauterine device insertion although evidence supporting it's efficacy is conflicting (Lopez et al 2015, Pergialiotis et al 2014,). Lidocaine 1% solution for injection is a local aesthetic of the amide group which acts by suspending the sensation of pain without effecting consciousness (Braun 2005). Injection into mucosa provides an anaesthetising effect within one to five minutes, lasts for one to three hours and is confined area of application.

Entonox (nitrous oxide 50/air 50%) is a low potency inhalation anaesthetic and high potency analgesic which acts on the pain centres of the brain and spinal cord, releasing endogenous neurotransmitters and activating opioid receptors (BOC 2014, Emmanouil and Quock 2007). It works within two to three minutes of inhalation with a rapid fall in arterial concentration within thirty seconds of discontinuation making it highly suitable for procedures where the pain is predictable (Pedani 2003).

B.Braun. (2005). 1% w/v Lidocaine Injection:Summary of product characteristics. Germany. B.Braun Melsungen AG
Emmanouil, D.E., and R.M. Quock. 2007. Advances in understanding the actions of nitrous oxide. Anesthesia Progress 54 (1): 9-18.
Lopez, L.M., A. Bernholc, Y. Zeng, R.H. Allen, D. Bartz, P.A. O'Brien, and D. Hubacher. 2015. Interventions for pain with intrauterine device insertion. The Cochrane database of systematic reviews, 2015 (7).

Pediani, R. 2003. Patient-administered inhalation of nitrous oxide and oxygen gas for procedural pain relief. World Wide Wounds. [Online]. Available from: www.worldwidewounds.com/2003/october/Pediani/Entonox-Pain-Relief.html. [20/11/14]
Pergialiotis, V., D.G. Vlachos, A. Protopappas, and G.D. Vlachos. 2014. Analgesic options for placement of an intrauterine contraceptive: A meta-analysis. The European Journal of Contrac

Actual start date of recruitment	01 December 2015
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: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	0
Adults (18-64 years)	51
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All women over the age of 16 years attending the contraceptive service requesting and eligible for intrauterine contraception were advised of the trial from the period December 2015 to August 2016 from two sites within a community based sexual health service.

Pre-assignment

Screening details:

Participants were women between the ages of 18-54 years, requesting and eligible for intrauterine contraception with no contraindications to the use of Entonox inhalation analgesia or local anaesthetic injection and desiring of pain relief for this procedure.
103 participants were eligible for inclusion.

Period 1

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

Blinding implementation details:

no blinding occured

Arms

Are arms mutually exclusive?	Yes
Arm title	pain relief - Entonox

Arm description:

Entonox will be administered through a one way demand valve system mouthpiece. The participant will begin inhalation of the anaesthetic following speculum insertion until they begin to feel sedated and have adequate analgesic effect for the procedure. They will be informed to discontinue inhalation if minor side effects occur and that they will soon recover. Inhalation can be repeated through the procedure as required by the participant. The participant will be advised to discontinue Entonox if they experience ear ache and an alternative method of analgesia will be offered. Pain will be scored on a visual analogue scale at two points, following tenaculum placement and following IUC insertion.

Arm type	Experimental
Investigational medicinal product name	Entonox
Investigational medicinal product code	0735/5017
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

self administered inhalation throughout procedure

Arm title	pain relief - LA injection

Arm description:

If recruited to receive intracervical LA injection, following speculum insertion, participants will be given 0.5ml lidocaine 1% placed superficially to the cervix at the 12 and/or 6 o'clock position using a 22mm gauge needle, tenaculum will be placed at the 12 and/or 6 O'clock position and 2ml lidocaine 1% will be administered intracervicaly at the 4 and 8 o'clock positions on the cervix. Participants will be asked to score their pain on a visual analogue scale following LA injection at two points, following tenaculum placement and following IUC insertion.

Arm type	Active comparator
Investigational medicinal product name	Lidocaine 1%
Investigational medicinal product code	PRD568902
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intracervical use

Dosage and administration details:

If recruited to receive intracervical LA injection participants will be given 0.5ml lidocaine 1% placed superficially to the cervix at the 12 and/or 6 o'clock position using a 22mm gauge needle, pre tenaculum placement and 2mls lidocaine 1% intracervicaly at both the 4 and 8 o'clock positions on the cervix following tenaculum placement. This will be given following speculum insertion.

Investigational medicinal product name	Entonox
Investigational medicinal product code	0735/5017
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Participant directed self administered inhalation throughout procedure

Number of subjects in period 1	pain relief - Entonox	pain relief - LA injection
Started	23	28
Completed	23	28

Baseline characteristics

Reporting groups	
Reporting group title	pain relief - Entonox

Reporting group description:

Entonox will be administered through a one way demand valve system mouthpiece. The participant will begin inhalation of the anaesthetic following speculum insertion until they begin to feel sedated and have adequate analgesic effect for the procedure. They will be informed to discontinue inhalation if minor side effects occur and that they will soon recover. Inhalation can be repeated through the procedure as required by the participant. The participant will be advised to discontinue Entonox if they experience ear ache and an alternative method of analgesia will be offered. Pain will be scored on a visual analogue scale at two points, following tenaculum placement and following IUC insertion.

Reporting group title	pain relief - LA injection

Reporting group description:

If recruited to receive intracervical LA injection, following speculum insertion, participants will be given 0.5ml lidocaine 1% placed superficially to the cervix at the 12 and/or 6 o'clock position using a 22mm gauge needle, tenaculum will be placed at the 12 and/or 6 O'clock position and 2ml lidocaine 1% will be administered intracervicaly at the 4 and 8 o'clock positions on the cervix. Participants will be asked to score their pain on a visual analogue scale following LA injection at two points, following tenaculum placement and following IUC insertion.

Reporting group values	pain relief - Entonox	pain relief - LA injection	Total
Number of subjects	23	28	51
Age categorical			
women between the ages of 18 to 54			
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)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults 18-54	23	28	51
Age continuous			
Women aged between 18 to 54 years			
Units: years			
arithmetic mean	30	30	
standard deviation	± 5.5	± 5.2	-
Gender categorical			
Female only			
Units: Subjects			
Female	23	28	51
Male	0	0	0

End points

End points reporting groups

Reporting group title	pain relief - Entonox

Reporting group description:

Entonox will be administered through a one way demand valve system mouthpiece. The participant will begin inhalation of the anaesthetic following speculum insertion until they begin to feel sedated and have adequate analgesic effect for the procedure. They will be informed to discontinue inhalation if minor side effects occur and that they will soon recover. Inhalation can be repeated through the procedure as required by the participant. The participant will be advised to discontinue Entonox if they experience ear ache and an alternative method of analgesia will be offered. Pain will be scored on a visual analogue scale at two points, following tenaculum placement and following IUC insertion.

Reporting group title	pain relief - LA injection

Reporting group description:

If recruited to receive intracervical LA injection, following speculum insertion, participants will be given 0.5ml lidocaine 1% placed superficially to the cervix at the 12 and/or 6 o'clock position using a 22mm gauge needle, tenaculum will be placed at the 12 and/or 6 O'clock position and 2ml lidocaine 1% will be administered intracervicaly at the 4 and 8 o'clock positions on the cervix. Participants will be asked to score their pain on a visual analogue scale following LA injection at two points, following tenaculum placement and following IUC insertion.

Subject analysis set title	overall satisfaction with pain relief received
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were asked two questions- how satisfied were you with the method of pain relief you received and would you recommend this method to a friend or family member.
Results were compared from descriptive data as percentages.
82.6% of participants found Entonox helpful or very helpful.
92.9% of participants found LA injection helpful or very helpful.
72.6% of participants would recommend or highly recommend Entonox to a friend or family member
82.2% of participants would recommend or highly recommend LA injection to a friend or family member.
7.1% of participants would not recommend LA injection.

Subject analysis set title	Age of participants
Subject analysis set type	Full analysis

Subject analysis set description:

Age range is described as percentages from descriptive data.
The mean age of participants was 31 years.
The highest percentage of participants was in the age range 26-35 years.
The lowest percentage of participants was in the age range 46-55 years.

Primary: Pain as scored on a visual analogue scale following intrauterine insertion

End point title	Pain as scored on a visual analogue scale following intrauterine insertion

End point description:

End point type	Primary

End point timeframe:

Participants were asked to score the level of pain experienced following Intrauterine insertion on a 0-100 visual analogue scale

End point values	pain relief - Entonox	pain relief - LA injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	28		
Units: ordinal				
arithmetic mean (standard deviation)	54 (± 30.5)	42 (± 28)		

Statistical analyses

Statistical analysis title	Post IUC insertion

Statistical analysis description:

Participants were asked to rate the level of pain experienced following IUC insertion on a 0-100 VAS. Data was normally distributed and parametric testing was applied. An independant samples T-test was performed to compare VAS pain scores between the two groups, Entonox and LA injection.

Comparison groups	pain relief - Entonox v pain relief - LA injection
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	> 0.05 [2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.7
upper limit	5.2
Variability estimate	Standard deviation
Dispersion value	47.5

Notes:

[1] - Analysis was performed using IBM SPSS , Armonk, NY, USA.

[2] - Entonox, M= 53.7 SD 30.5 N23
LA Injection M=42.46 SD 27.8 N28
T= (49) -1.378 p=.175
r=0.059

Primary: Pain as scored on a visual analogue scale following tenaculum placement .

End point title	Pain as scored on a visual analogue scale following tenaculum placement .

End point description:

Participants were asked to assess the level of pain experienced following tenaculum placement on a 0-100 mm visual analogue scale (VAS). Data was of non normal distribution and non parametric testing was applied. A Mann_Whitney U test was performed to compare VAS pain scores in two groups, LA injection and Entonox

End point type	Primary

End point timeframe:

Participants were asked to assess the level of pain following tenaculum placement.

End point values	pain relief - Entonox	pain relief - LA injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	28		
Units: ordinal				
median (standard deviation)	24 (± 18.2)	15.5 (± 24.6)		

Statistical analyses

Statistical analysis title	Post tenaculum placement

Statistical analysis description:

Participants were asked to rate the level of pain experienced following tenaculum placement on a 0-100 mm visual analogue scale (VAS). Data was non normally distributed and parametric testing was applied. A Mann-Whitney U test was performed to compare pain scores from two groups, Entonox and LA injection.

Comparison groups	pain relief - Entonox v pain relief - LA injection
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	> 0.05 [4]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	75
Variability estimate	Standard deviation
Dispersion value	21.7

Notes:

[3] - Data was analysed using IBM SPSS version 25

[4] - comparison of two groups;
Both methods combined Md=20 M=25 SD21.7 N=51
LA injection Md=15.5 M=24.8 SD 24.4 N=23
Entonox MD=24 M=25.3 sd18.2 n=28
u=299 z=.436 R=0.017

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: within 3 days of event.	
Adverse event reporting additional description: Any serious adverse event will be documented and reported as per Part 5, medicines for Human Use (Clinical trials) Regulations 2004.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	2004

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

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: This was a student lead research project comparing a method of pain relief offered and commonly accepted for the procedure of IUC insertion within the research setting with an inhalation anaesthetic know to have limited side effects and/or complications when used within the research parameters.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported