Clinical trial results:
A Randomised Controlled Double-Blind Trial of Intranasal Fentanyl versus Intravenous Morphine in the Emergency Department Treatment of Severe Painful Sickle Cell Crises in Children

Summary

EudraCT number	2011-005161-20
Trial protocol	IE
Global end of trial date	14 November 2013

Results information

Result version number	v1 (current)
This version publication date	28 July 2019
First version publication date	28 July 2019
Summary attachment (see zip file)	Intranasal fentanyl versus intravenous morphine in the emergency department treatment of severe painful sickle cell crises in children: study protocol for a randomised controlled trial (Barrett et al. - 2012 - Intranasal fentanyl versus intravenous morphine in.pdf)

Trial information

Trial identification

Sponsor protocol code	SCC01

Additional study identifiers

ISRCTN number	ISRCTN67469672
ClinicalTrials.gov id (NCT number)	NCT03682211
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Our Lady's Children's Hospital, Crumlin
Sponsor organisation address	Cooley Road, Dublin, Ireland,
Public contact	Dr Michael Barrett, Our Lady's Children's Hospital, Crumlin, 353 014096814,
Scientific contact	Dr Michael Barrett, Our Lady's Children's Hospital, Crumlin, 353 014096814,
Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield, Dublin, Ireland,
Public contact	Clinical Research Centre, University College Dublin, 353 17164582,
Scientific contact	Clinical Research Centre, University College Dublin, 353 17164582,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	02 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to illustrate the comparative efficacy of intranasal fentanyl to IV morphine in reducing severe pain associated with Painful Sickle Cell Crises in the Emergency Department.

Protection of trial subjects:

Informed written consent was obtained from parent(s) and age appropriate assent from each eligible patient attending the hospital's outpatient hemoglobinopathy service prior to patient recruitment in the ED. Each consented family and trial patient was provided with a Contact card so that trial personnel could be contacted about impending acute presentations. Verbal re-consent and assent were obtained at ED presentation.

Harm and stress were minimised as per the clinical guidelines for this patient cohort in Our Lady's Children's Hosptial, Crumlin. Trial subjects were treated and monitored in the hospital accidents and emergencies unit where immediate care was available to minimise pain and distress.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2012
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	Ireland: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	16
Adolescents (12-17 years)	10
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Informed written consent was obtained from parent(s) and age-appropriate assent from each eligible patient attending the hospital's outpatient hemoglobinopathy service prior to patient recruitment in the emergency department

Pre-assignment

Screening details:

Eligible patients were children and adolescents aged between 1 and 21 years with SCD consecutively presenting to the ED with acute severe pain. Severe pain was defined as pain due to SCD in the extremities, back, abdomen or chest that was rated 7 or greater on a 0–10 numeric pain scale or equivalent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intravenous Morphine Group

Arm description:

Trial Subjects were randomly assigned to receive 0.1mg/kg of intravenous Morphine with intranasal placebo

Arm type	Active comparator
Investigational medicinal product name	Morphine Sulphate 10mg/ml BP
Investigational medicinal product code	
Other name	Morphine Sulphate
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single administration of Intravenous solution within 2 minutes after patient receives intranasal solution
Dose was morphine calculated based on patient receiving an immediate dose of 0.1mg/kg.
Intravenous preparation administered via an IV cannula.

Investigational medicinal product name	Water for injection
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Administration of intranasal solution first followed within 2 minutes by administration of the IV solution.
The matched shape and size of the placebo is a 2ml water for injection glass ampule.
Intranasal medications will be administered using the Mucosal Atomiser Device (MAD) with a 1ml syringe. 1ml dose administered to each nostril.

Arm title	Intranasal Fentanyl Group

Arm description:

Trial Subjects were randomly assigned to receive 1.5mcg/kg intranasal Fentanyl and intravenous placebo (water for injection).

Arm type	Experimental

Investigational medicinal product name	Fentanyl Citrate 50 microgram/mL
Investigational medicinal product code	
Other name	Fentanyl Citrate
Pharmaceutical forms	Solution for injection
Routes of administration	Intranasal use

Dosage and administration details:

Administration of Intranasal solution first followed within 2 minutes by administration of IV solution.
The volume of intranasal solution calculated is based on each patient receiving an immediate dose of 1.5mcg/kg of Fentanyl.
Intranasal solution will be administered between both nostrils via Mucosal atomiser device (MAD) with a 1ml syringe.

Investigational medicinal product name	Water for Injection
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Intravenous use

Dosage and administration details:

Administration of IV solution within 2 minutes after patient receives Intranasal solution.
1ml Water for Injection glass ampoule is matched placebo for Intravenous Morphine and volume is calculated based on patient receiving an immediate dose of 0.1mg/kg. Intravenous preparation administered via an IV cannula.

Number of subjects in period 1	Intravenous Morphine Group	Intranasal Fentanyl Group
Started	16	15
Completed	16	15

Period 2

Period 2 title	Endpoint period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intravenous Morphine Group

Arm description:

Trial Subjects were randomly assigned to receive 0.1mg/kg of intravenous Morphine with intranasal placebo

Arm type	Active comparator

Investigational medicinal product name	Morphine Sulphate 10mg/ml BP
Investigational medicinal product code	
Other name	Morphine Sulphate
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single administration of Intravenous solution within 2 minutes after patient receives intranasal solution
Dose was morphine calculated based on patient receiving an immediate dose of 0.1mg/kg.
Intravenous preparation administered via an IV cannula.

Investigational medicinal product name	Water for injection
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Administration of intranasal solution first followed within 2 minutes by administration of the IV solution.
The matched shape and size of the placebo is a 2ml water for injection glass ampule.
Intranasal medications will be administered using the Mucosal Atomiser Device (MAD) with a 1ml syringe. 1ml dose administered to each nostril.

Arm title	Intranasal Fentanyl Group

Arm description:

Trial Subjects were randomly assigned to receive 1.5mcg/kg intranasal Fentanyl and intravenous placebo (water for injection).

Arm type	Experimental
Investigational medicinal product name	Fentanyl Citrate 50 microgram/mL
Investigational medicinal product code	
Other name	Fentanyl Citrate
Pharmaceutical forms	Solution for injection
Routes of administration	Intranasal use

Dosage and administration details:

Administration of Intranasal solution first followed within 2 minutes by administration of IV solution.
The volume of intranasal solution calculated is based on each patient receiving an immediate dose of 1.5mcg/kg of Fentanyl.
Intranasal solution will be administered between both nostrils via Mucosal atomiser device (MAD) with a 1ml syringe.

Investigational medicinal product name	Water for Injection
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Intravenous use

Dosage and administration details:

Administration of IV solution within 2 minutes after patient receives Intranasal solution.
1ml Water for Injection glass ampoule is matched placebo for Intravenous Morphine and volume is calculated based on patient receiving an immediate dose of 0.1mg/kg. Intravenous preparation administered via an IV cannula.

Number of subjects in period 2	Intravenous Morphine Group	Intranasal Fentanyl Group
Started	16	15
Completed	16	15

Baseline characteristics

Reporting groups	
Reporting group title	Intravenous Morphine Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 0.1mg/kg of intravenous Morphine with intranasal placebo	
Reporting group title	Intranasal Fentanyl Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 1.5mcg/kg intranasal Fentanyl and intravenous placebo (water for injection).	

Reporting group values	Intravenous Morphine Group	Intranasal Fentanyl Group	Total
Number of subjects	16	15	31
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			
median	11.7	9.1	
inter-quartile range (Q1-Q3)	7.0 to 15.2	5.9 to 14.4	-
Gender categorical Units: Subjects			
Female	6	7	13
Male	10	8	18
Hydroxycarbamide therapy Units: Subjects			
Yes	8	5	13
No	8	10	18
Administered pre-hospital analgesia Units: Subjects			
Yes	15	14	29
No	1	1	2
History of painful episodes Units: Subjects			
Yes	16	15	31
History of intravenous Morphine administration Units: Subjects			
Yes	10	10	20

No	2	2	4
Uncertain	4	3	7
History of intranasal Fentanyl administration Units: Subjects			
Yes	0	0	0
No	16	15	31
Number of visits to the emergency department in the past year Units: Subjects			
Zero	5	3	8
1-3	11	8	19
4 or more	0	4	4
Sickle Cell Disease Type Units: Subjects			
HbSS	15	14	29
HbSD	1	0	1
HbSC	0	1	1
Pain assessment tool Units: Subjects			
Manchester Pain Tool	13	12	25
Face, Legs, Activity, Cry and Consolability scale	3	3	6
Weight Units: kilogram(s)			
arithmetic mean	40.3	36.2	
standard deviation	± 19.9	± 16.9	-
Pain Score Units: score			
arithmetic mean	8.38	8.2	
standard deviation	± 0.96	± 1.26	-

End points

End points reporting groups

Reporting group title	Intravenous Morphine Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 0.1mg/kg of intravenous Morphine with intranasal placebo	
Reporting group title	Intranasal Fentanyl Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 1.5mcg/kg intranasal Fentanyl and intravenous placebo (water for injection).	
Reporting group title	Intravenous Morphine Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 0.1mg/kg of intravenous Morphine with intranasal placebo	
Reporting group title	Intranasal Fentanyl Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 1.5mcg/kg intranasal Fentanyl and intravenous placebo (water for injection).	

Primary: Pain score at 10 minutes

End point title	Pain score at 10 minutes
End point description:	
End point type	Primary
End point timeframe:	
Pain score will be measured 10 minutes after administration of study medication	

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: score				
arithmetic mean (standard deviation)	4.6 (± 1.55)	6.0 (± 1.75)		

Statistical analyses

Statistical analysis title	Difference in mean pain scores at 10 minutes
Comparison groups	Intravenous Morphine Group v Intranasal Fentanyl Group

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.41
upper limit	-0.39

Secondary: Time to patient-reported first change in pain intensity

End point title	Time to patient-reported first change in pain intensity

End point description:

End point type	Secondary

End point timeframe:

During 120 minutes after intervention

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: minutes				
arithmetic mean (confidence interval 95%)	26.00 (4.49 to 47.50)	8.57 (5.93 to 11.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Required rescue intravenous morphine

End point title	Required rescue intravenous morphine

End point description:

End point type	Secondary

End point timeframe:

During 120 minutes after intervention

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: subjects				
Required analgesia	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to patient-reported first change from severe to mild pain

End point title	Time to patient-reported first change from severe to mild pain

End point description:

End point type	Secondary

End point timeframe:

During 120 minutes after intervention

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	14		
Units: minutes				
arithmetic mean (confidence interval 95%)	67.50 (20.21 to 114.79)	36.78 (14.24 to 59.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to patient-reported first change from severe to no pain

End point title	Time to patient-reported first change from severe to no pain

End point description:

End point type	Secondary

End point timeframe:

During 120 minutes after intervention

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: minutes				
arithmetic mean (confidence interval 95%)	45.00 (-19.54 to 109.54)	47.50 (-29.77 to 124.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Required additional oral analgesic medications (not acetaminophen or ibuprofen)

End point title	Required additional oral analgesic medications (not acetaminophen or ibuprofen)

End point description:

End point type	Secondary

End point timeframe:

During 120 minutes after intervention

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: subjects	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Lowest depth of sedation

End point title	Lowest depth of sedation

End point description:

Lowest depth of sedation as reported by University of Michigan Sedation Scale Scores

End point type	Secondary

End point timeframe:

During 120 minutes after intervention

End point values	Intravenous Morphine Group	Intranasal Fentanyl Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: subjects				
Score 0	7	12		
Score 1	7	3		
Score 2	2	0		
Score 3	0	0		
Score 4	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported for the duration of trial, 120 minutes post administration of study medication	
Assessment type	Systematic

Dictionary used	
Dictionary name	NA
Dictionary version	NA

Reporting groups	
Reporting group title	Intravenous Morphine Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 0.1mg/kg of intravenous Morphine with intranasal placebo	
Reporting group title	Intranasal Fentanyl Group
Reporting group description:	
Trial Subjects were randomly assigned to receive 1.5mcg/kg intranasal Fentanyl and intravenous placebo (water for injection).	

Serious adverse events	Intravenous Morphine Group	Intranasal Fentanyl Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Intravenous Morphine Group	Intranasal Fentanyl Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 16 (31.25%)	1 / 15 (6.67%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	4 / 16 (25.00%)	1 / 15 (6.67%)	
occurrences (all)	4	1	

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