



Clinical trial results:

The Effects of Isovolumetric and Isoeffective Infusions of Colloid Versus Crystalloid on Renal Blood Flow and Cardiac Output

Summary

EudraCT number	2013-003260-32
Trial protocol	GB
Global end of trial date	12 November 2015

Results information

Result version number	v1 (current)
This version publication date	14 April 2019
First version publication date	14 April 2019

Trial information

Trial identification

Sponsor protocol code	13090
-----------------------	-------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Jubilee Campus, Triumph Road, Nottingham, United Kingdom, NG8 1DH
Public contact	Shone, University of Nottingham, +44 1159315679, dileep.lobo@nottingham.ac.uk
Scientific contact	Angela Shone, Professor Dileep Lobo, +44 115 8467906, sponsor@nottingham.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	12 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2015
Global end of trial reached?	Yes
Global end of trial date	12 November 2015
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 determine the differential impact of isovolumetric and isoeffective infusions of crystalloid and gelatin on blood volume expansion - to test whether an infusion of a gelatin based colloid solution expands blood volume to a greater degree than an isovolumetric infusion of crystalloid, resulting in increased renal blood flow and perfusion, and cardiac output..

Protection of trial subjects:

All interventions carried out on healthy volunteers in the presence of qualified doctors

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2013
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: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period 02.10.2014 to 12.11.2015

Pre-assignment

Screening details:

12 healthy, male volunteers, aged between 18 and 40 and weight between 65 and 80 kg. 2 participants later withdrew and were excluded from the analysis.

Period 1

Period 1 title	Started first infusion
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

A nurse not involved in the study in charge of blinding the investigational products, program the automated infusion pump, set up and start the infusion and remove infusion equipment upon completion of administration.

Infusion bags covered with opaque bags, in a manner making it not possible to recognize the number of bags being infused.

The infusion lines covered to mask the yellowish colour of Gelatine.

The data shown on the screen of the automated infusion pump masked to the investigator

Arms

Are arms mutually exclusive?	No
Arm title	Arm A : reference Sterofundin

Arm description:

Infusion A: received 1500mls of crystalloid (Sterofundin ISO®)

Arm type	Active comparator
Investigational medicinal product name	Sterofundin ISO®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

1500mls of crystalloid (Sterofundin ISO®)

Arm title	Arm B: 4% Gelaspan
------------------	--------------------

Arm description:

0.5 Litres of colloid (4% Gelaspan®)

Arm type	Experimental
Investigational medicinal product name	4% Gelaspan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.5 Litres of colloid (4% Gelaspan®)

Arm title	Arm C: colloid and crystalloid
------------------	--------------------------------

Arm description:

0.5 Litres of colloid plus 1 Litre of crystalloid (0.5 Litres 4% Gelaspan ® and 1 Litre of Sterofundin ISO

®)

Arm type	Experimental
Investigational medicinal product name	Sterofundin ISO®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

1500mls of crystalloid (Sterofundin ISO®)

Investigational medicinal product name	4% Gelaspan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.5 Litres of colloid (4% Gelaspan®)

Number of subjects in period 1	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid
Started	10	10	10
Completed	10	10	10

Period 2

Period 2 title	Received all infusions
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	No
Arm title	Arm A : reference Sterofundin

Arm description:

Infusion A: received 1500mls of crystalloid (Sterofundin ISO®)

Arm type	Active comparator
Investigational medicinal product name	Sterofundin ISO®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

1500mls of crystalloid (Sterofundin ISO®)

Arm title	Arm B: 4% Gelaspan
------------------	--------------------

Arm description:	
0.5 Litres of colloid (4% Gelaspan®)	
Arm type	Experimental
Investigational medicinal product name	4% Gelaspan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
0.5 Litres of colloid (4% Gelaspan®)	
Arm title	Arm C: colloid and crystalloid
Arm description:	
0.5 Litres of colloid plus 1 Litre of crystalloid (0.5 Litres 4% Gelaspan ® and 1 Litre of Sterofundin ISO ®)	
Arm type	Experimental
Investigational medicinal product name	Sterofundin ISO®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details:	
1500mls of crystalloid (Sterofundin ISO®)	
Investigational medicinal product name	4% Gelaspan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
0.5 Litres of colloid (4% Gelaspan®)	

Number of subjects in period 2	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid
Started	10	10	10
Completed	10	10	10

Baseline characteristics

Reporting groups

Reporting group title	Started first infusion
-----------------------	------------------------

Reporting group description:

Number entered first infusion 10

Reporting group values	Started first infusion	Total	
Number of subjects	12	12	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age			
Units: years			
arithmetic mean	23.9		
standard deviation	± 2.8	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	12	12	
Weight			
Units: kg			
arithmetic mean	74.5		
standard deviation	± 5.7	-	
Height			
Units: Metres			
arithmetic mean	1.81		
standard deviation	± 0.1	-	
Body Mass Index			
Units: kg/m squared			
arithmetic mean	22.7		
standard deviation	± 1.6	-	
Haemoglobin			
Units: g/L			
arithmetic mean	150.1		
standard deviation	± 7.6	-	
Haematocrit			
Units: Percent			

arithmetic mean	43.9		
standard deviation	± 1.9	-	
Sodium			
Units: mmol/L			
arithmetic mean	102.9		
standard deviation	± 1.3	-	
Serum bicarbonate			
Units: mmol/L			
arithmetic mean	28.2		
standard deviation	± 2.2	-	
Serum albumin			
Units: g/L			
arithmetic mean	41.2		
standard deviation	± 2.5	-	
Serum osmolality			
Units: mOsm/kg			
arithmetic mean	291		
standard deviation	± 2.5	-	
Creatinine			
Units: umol/L			
arithmetic mean	139.6		
standard deviation	± 37.9	-	
Calculated blood volume			
Units: Litres			
arithmetic mean	5.2		
standard deviation	± 1.6	-	

Subject analysis sets

Subject analysis set title	Infusion A versus Infusion B
Subject analysis set type	Full analysis
Subject analysis set description: Differences between colloid versus crystalloid	
Subject analysis set title	Infusion A versus Infusion C
Subject analysis set type	Full analysis
Subject analysis set description: Difference between colloid versus crystalloid and colloid	
Subject analysis set title	Infusion B versus Infusion C
Subject analysis set type	Full analysis
Subject analysis set description: Difference between crystalloid and colloid/crystalloid	

Reporting group values	Infusion A versus Infusion B	Infusion A versus Infusion C	Infusion B versus Infusion C
Number of subjects	10	10	10
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			

Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	10	10	10
Age continuous			
Age			
Units: years arithmetic mean standard deviation	23.9 ± 2.8	23.9 ± 2.8	23.9 ± 2.8
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	10	10	10
Weight			
Units: kg arithmetic mean standard deviation	 ±	 ±	 ±
Height			
Units: Metres arithmetic mean standard deviation	 ±	 ±	 ±
Body Mass Index			
Units: kg/m squared arithmetic mean standard deviation	 ±	 ±	 ±
Haemoglobin			
Units: g/L arithmetic mean standard deviation	 ±	 ±	 ±
Haematocrit			
Units: Percent arithmetic mean standard deviation	 ±	 ±	 ±
Sodium			
Units: mmol/L arithmetic mean standard deviation	 ±	 ±	 ±
Serum bicarbonate			
Units: mmol/L arithmetic mean standard deviation	 ±	 ±	 ±
Serum albumin			
Units: g/L arithmetic mean standard deviation	 ±	 ±	 ±
Serum osmolality			
Units: mOsm/kg arithmetic mean standard deviation	 ±	 ±	 ±
Creatinine			
Units: umol/L			

arithmetic mean			
standard deviation	±	±	±
Calculated blood volume			
Units: Litres			
arithmetic mean			
standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	Arm A : reference Sterofundin
Reporting group description: Infusion A: received 1500mls of crystalloid (Sterofundin ISO®)	
Reporting group title	Arm B: 4% Gelaspan
Reporting group description: 0.5 Litres of colloid (4% Gelaspan®)	
Reporting group title	Arm C: colloid and crystalloid
Reporting group description: 0.5 Litres of colloid plus 1 Litre of crystalloid (0.5 Litres 4% Gelaspan ® and 1 Litre of Sterofundin ISO ®)	
Reporting group title	Arm A : reference Sterofundin
Reporting group description: Infusion A: received 1500mls of crystalloid (Sterofundin ISO®)	
Reporting group title	Arm B: 4% Gelaspan
Reporting group description: 0.5 Litres of colloid (4% Gelaspan®)	
Reporting group title	Arm C: colloid and crystalloid
Reporting group description: 0.5 Litres of colloid plus 1 Litre of crystalloid (0.5 Litres 4% Gelaspan ® and 1 Litre of Sterofundin ISO ®)	
Subject analysis set title	Infusion A versus Infusion B
Subject analysis set type	Full analysis
Subject analysis set description: Differences between colloid versus crystalloid	
Subject analysis set title	Infusion A versus Infusion C
Subject analysis set type	Full analysis
Subject analysis set description: Difference between colloid versus crystalloid and colloid	
Subject analysis set title	Infusion B versus Infusion C
Subject analysis set type	Full analysis
Subject analysis set description: Difference between crystalloid and colloid/crystalloid	

Primary: Change in blood volume

End point title	Change in blood volume
End point description: Change in blood volume over time. The end point values for each time point have been given in the attached table.	
End point type	Primary
End point timeframe: Blood sampled at baseline and times 30, 60, 90, 120, 180 and 240 minutes	

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: Litres	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: Litres	10	10		

Attachments (see zip file)	Blood volume/Blood volume.pdf
-----------------------------------	-------------------------------

Statistical analyses

Statistical analysis title	Change in blood volume
-----------------------------------	------------------------

Statistical analysis description:

For all secondary endpoints the statistical analyses are presented in the attached tables.

Comparison groups	Infusion A versus Infusion B v Infusion A versus Infusion C v Infusion B versus Infusion C
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	> 0.05 ^[2]
Method	ANOVA

Notes:

[1] - Repeated measures ANOVA Change in blood volume (A v B, B v C, A v C)

[2] - P > 0.05 for all comparisons.

Secondary: Change in weight

End point title	Change in weight
-----------------	------------------

End point description:

Weight change monitored at 0, 90, 120, 180 and 240 minutes after the start of the infusion
The end point values for each time point have been given in the attached table.

End point type	Secondary
----------------	-----------

End point timeframe:

0, 90, 120, 180, and 240 mins

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: Kilograms	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: Kilograms	10	10		

Attachments (see zip file)	Change in weight/Weight.pdf
-----------------------------------	-----------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haematocrit %

End point title	Change in haematocrit %
-----------------	-------------------------

End point description:

The end point values for each time point have been given in the attached table.

End point type	Secondary
----------------	-----------

End point timeframe:

Blood will be sampled at 60, 90, 120, 180 and 240 minutes after the start of the infusion

End point values	Infusion A versus Infusion B	Infusion A versus Infusion C	Infusion B versus Infusion C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	10	10	
Units: percentage	10	10	10	

Attachments (see zip file)	Change in haematocrit/Haematocrit.pdf
-----------------------------------	---------------------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Change in albumin %

End point title	Change in albumin %
End point description: The end point values for each time point have been given in the attached table.	
End point type	Secondary
End point timeframe: Blood sampled at baseline and times 0, 30, 60, 90, 120, 180 and 240 minutes	

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: percentage	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: percentage	10	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum sodium mmol/l

End point title	Serum sodium mmol/l
End point description: The end point values for each time point have been given in the attached table.	
End point type	Secondary
End point timeframe: Blood sampled at baseline and times 30, 60, 90, 120, 180 and 240 minutes	

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: mmol/l	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: mmol/l	10	10		

Attachments (see zip file)	Serum Sodium/Sodium.pdf
-----------------------------------	-------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Aortic flow (ml/s)

End point title	Aortic flow (ml/s)
End point description: The end point values for each time point have been given in the attached table. Comparisons between groups using un-paired t-test, comparison over time using paired t-test.	
End point type	Secondary
End point timeframe: MRI at -15, 7, 26, 54 and 83 minutes	

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: ml/s	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: ml/s	10	10		

Attachments (see zip file)	Aortic flow/Aortic flow.pdf
-----------------------------------	-----------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Serum chloride mmol/l

End point title	Serum chloride mmol/l
-----------------	-----------------------

End point description:

The end point values for each time point have been given in the attached table.

End point type	Secondary
----------------	-----------

End point timeframe:

Blood sampled at baseline and times 30, 60, 90, 120, 180 and 240 minutes

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: mmol/l	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: mmol/l	10	10		

Attachments (see zip file)	Serum Chloride/Chloride.pdf
-----------------------------------	-----------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Renal volume (ml)

End point title	Renal volume (ml)
-----------------	-------------------

End point description:

The end point values for each time point have been given in the attached table. Comparisons between groups using un-paired t-test, comparison over time using paired t-test.

End point type	Secondary
----------------	-----------

End point timeframe:

MRI at -5, 10, 38, 57 and 90 min

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: ml/s	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: ml/s	10	10		

Attachments (see zip file)	Renal volume/Renal volume.pdf
-----------------------------------	-------------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Strong ion differences

End point title	Strong ion differences
End point description: The end point values for each time point have been given in the attached table.	
End point type	Secondary
End point timeframe: Blood sampled at baseline and times 30, 60, 90, 120, 180 and 240 minutes	

End point values	Arm A : reference Sterofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: mmol/l	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: mmol/l	10	10		

Attachments (see zip file)	Strong io difference/SID.pdf
-----------------------------------	------------------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Renal artery blood flow

End point title	Renal artery blood flow
End point description: The end point values for each time point have been given in the attached table. Comparisons between groups using un-paired t-test, comparison over time using paired t-test.	
End point type	Secondary
End point timeframe: MRI at -15, 15, 43, 62 and 95 min	

End point values	Arm A : reference Stereofundin	Arm B: 4% Gelaspan	Arm C: colloid and crystalloid	Infusion A versus Infusion B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	10	10
Units: ml/s	10	10	10	10

End point values	Infusion A versus Infusion C	Infusion B versus Infusion C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: ml/s	10	10		

Attachments (see zip file)	Renal flow/Renal artery flow.pdf
-----------------------------------	----------------------------------

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout trial

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	1.0
--------------------	-----

Reporting groups

Reporting group title	All groups
-----------------------	------------

Reporting group description: -

Serious adverse events	All groups		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All groups		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Excessive sweating			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	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