Clinical trial results:
Non-invasive bed-side measurement of systemic endothelial function in patients undergoing abdominal aortic aneurysm repair; modulation by ascorbic acid

Summary

EudraCT number	2006-006887-44
Trial protocol	GB
Global end of trial date	21 September 2013

Results information

Result version number	v1 (current)
This version publication date	23 December 2019
First version publication date	23 December 2019

Trial information

Trial identification

Sponsor protocol code	RGHT000396

Additional study identifiers

ISRCTN number	ISRCTN27369400
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health & Social Care Trust (BHSCT)
Sponsor organisation address	King Edward Building, Royal Hospitals, Grosvenor Road, Belfast, United Kingdom, BT12 6BA
Public contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 976385, d.f.mcauley@qub.ac.uk
Scientific contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 976385, d.f.mcauley@qub.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	05 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2012
Global end of trial reached?	Yes
Global end of trial date	21 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this pilot study is to investigate the acute effects of ascorbic acid supplementation on systemic and pulmonary endothelial function in the immediate post-operative period following AAA repair.

Protection of trial subjects:

A DMEC was appointed which was independent of the study team.
The DMEC functioned primarily as a check for safety, reviewing adverse events. The DMEC reported to the Sponsor via the principal investigator.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	20 December 2007
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: 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 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)	4
From 65 to 84 years	27

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult patients admitted for elective open repair of AAA in the Royal Victoria Hospital, Belfast were screened for eligibility for participation in the study from December 2007 to July 2009.

Pre-assignment

Screening details:

Exclusion criteria were age less than 18 years old, a history of hyperoxaluria or glucose-6-phosphate dehydrogenase deficiency, prior antioxidant therapy, known allergy to ascorbic acid or to anaesthetic agents specified in anaesthetic protocol, participation in another intervention trial within 30 days or a lack of consent.

Period 1

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

Blinding implementation details:

Patients received IV ascorbic acid 2g in 250 ml 0.9% saline or 250 ml 0.9% saline placebo. The randomization assignments were concealed in sealed, tamper-proof envelopes that were opened sequentially by an independent pharmacist. When an eligible subject was recruited, the pharmacist allocated the subject to the designated treatment group, maintaining blinding. Ascorbic acid and 0.9% saline were prepared by the independent pharmacist and had an identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ascorbic acid

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ascorbic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Ascorbic acid 2g in 250 ml 0.9% saline over 15 minutes following induction of anaesthesia.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml 0.9% saline placebo over 15 minutes following induction of anaesthesia.

Number of subjects in period 1	Ascorbic acid	Placebo
Started	13	18
Completed	13	18

Baseline characteristics

Reporting groups	
Reporting group title	Ascorbic acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Ascorbic acid	Placebo	Total
Number of subjects	13	18	31
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)	0	0	0
Adults (18-64 years)	2	2	4
From 65-84 years	11	16	27
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	73.2	70.4	
standard deviation	± 5.9	± 7.4	-
Gender categorical Units: Subjects			
Female	2	1	3
Male	11	17	28
IHD			
ischaemic heart disease			
Units: Subjects			
yes	4	8	12
no	9	10	19
atrial fibrillation Units: Subjects			
yes	2	0	2
no	11	18	29
hypertension Units: Subjects			
yes	12	16	28
no	1	2	3
cerebrovascular disease Units: Subjects			
yes	1	1	2
no	12	17	29
smoking			

Units: Subjects			
yes	5	4	9
no	8	14	22
hypercholesterolaemia Units: Subjects			
yes	6	10	16
no	7	8	15
diabetes Units: Subjects			
yes	0	1	1
no	13	17	30
statin Units: Subjects			
yes	9	12	21
no	4	6	10
ACE inhibitors			
Angiotensin Converting Enzyme inhibitors			
Units: Subjects			
yes	3	5	8
no	10	13	23
betablockers Units: Subjects			
yes	6	7	13
no	7	11	18
diuretics Units: Subjects			
yes	3	2	5
no	10	16	26
anticoagulants Units: Subjects			
yes	5	5	10
no	8	13	21
height Units: metres			
arithmetic mean	1.71	1.71	
standard deviation	± 0.05	± 0.09	-
weight Units: kg			
arithmetic mean	78.2	77.1	
standard deviation	± 7.7	± 11.1	-
body mass index Units: kg/m2			
arithmetic mean	26.8	26.4	
standard deviation	± 2.8	± 3.3	-
respiratory rate Units: min-1			
median	12	14	
inter-quartile range (Q1-Q3)	12 to 15	12 to 15	-
temperature Units: degrees C			
arithmetic mean	36.8	36.6	

standard deviation	± 0.38	± 0.33	-
heart rate			
Units: min-1			
arithmetic mean	60	63	
standard deviation	± 13.7	± 10.3	-
peripheral systolic blood pressure			
Units: mmHg			
arithmetic mean	150.5	145.2	
standard deviation	± 29.6	± 24.9	-
peripheral diastolic blood pressure			
Units: mmHg			
arithmetic mean	76	77	
standard deviation	± 11.7	± 12.4	-
Haemoglobin			
Units: gdl−1			
arithmetic mean	13.7	13.7	
standard deviation	± 1.1	± 1.2	-
leucocyte count			
Units: x109ml−1			
arithmetic mean	7.3	7.3	
standard deviation	± 1.8	± 1.7	-
platelet count			
Units: x109ml−1			
arithmetic mean	211	201	
standard deviation	± 64	± 54	-
Urea			
Units: mmoll−1			
arithmetic mean	6.7	7.8	
standard deviation	± 1.8	± 2.1	-
Creatinine			
Units: µmoll−1			
arithmetic mean	101	96	
standard deviation	± 30	± 31	-
ischaemic time			
Units: minutes			
arithmetic mean	64.6	60.5	
standard deviation	± 17.6	± 16.9	-

End points

End points reporting groups	
Reporting group title	Ascorbic acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: vWF pre-operative	
End point title	vWF pre-operative
End point description: von Willebrand Factor	
End point type	Primary
End point timeframe: pre-operative	

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: % control				
arithmetic mean (standard deviation)	139 (± 60)	141 (± 61)		

Statistical analyses

Statistical analysis title	vWF pre-operative comparison between groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	t-test, 2-sided

Primary: vWF post-operative	
End point title	vWF post-operative
End point description: von Willebrand Factor	
End point type	Primary
End point timeframe: post-operative	

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: % control				
arithmetic mean (standard deviation)	169 (± 65)	158 (± 78)		

Statistical analyses

Statistical analysis title	vWF post-operative comparison between groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	t-test, 2-sided

Secondary: EDV pre-operative	
End point title	EDV pre-operative
End point description: Endothelium-dependent vasodilatation	
End point type	Secondary
End point timeframe: pre-operative	

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: percentage				
median (inter-quartile range (Q1-Q3))	3.0 (1.5 to 5.5)	3.5 (1.8 to 5.3)		

Statistical analyses

Statistical analysis title	EDV pre-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Wilcoxon (Mann-Whitney)

Secondary: EDV post-operative

End point title	EDV post-operative

End point description:

End point type	Secondary

End point timeframe:
post-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: percentage				
median (inter-quartile range (Q1-Q3))	4.0 (2.0 to 6.0)	6.0 (2.5 to 8.5)		

Statistical analyses

Statistical analysis title	EDV post-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Secondary: Vd/Vt pre-operative

End point title	Vd/Vt pre-operative

End point description:
Pulmonary Deadspace Fraction

End point type	Secondary

End point timeframe:
pre-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: ratio				
arithmetic mean (standard deviation)	0.54 (± 0.05)	0.56 (± 0.06)		

Statistical analyses

Statistical analysis title	Vd/Vt pre-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	t-test, 2-sided

Secondary: Vd/Vt post-operative

End point title	Vd/Vt post-operative

End point description:

End point type	Secondary

End point timeframe:
post-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: ratio				
arithmetic mean (standard deviation)	0.54 (± 0.06)	0.56 (± 0.06)		

Statistical analyses

Statistical analysis title	Vd/Vt post-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	t-test, 2-sided

Secondary: Serum hsCRP pre-operative

End point title	Serum hsCRP pre-operative
End point description: C Reactive Protein	
End point type	Secondary
End point timeframe: pre-operative	

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: mgL−1				
median (inter-quartile range (Q1-Q3))	1.83 (1.15 to 4.49)	2.14 (0.97 to 5.75)		

Statistical analyses

Statistical analysis title	Serum hsCRP pre-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Wilcoxon (Mann-Whitney)

Secondary: Serum hsCRP post-operative

End point title	Serum hsCRP post-operative
End point description: C Reactive Protein	
End point type	Secondary
End point timeframe: post-operative	

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: mgL−1				
median (inter-quartile range (Q1-Q3))	1.96 (1.13 to 4.23)	2.85 (1.45 to 4.63)		

Statistical analyses

Statistical analysis title	Serum hsCRP post-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Wilcoxon (Mann-Whitney)

Secondary: Arterial pH pre-operative

End point title	Arterial pH pre-operative

End point description:

End point type	Secondary

End point timeframe:
pre-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: mmHg				
arithmetic mean (standard deviation)	7.40 (± 0.05)	7.38 (± 0.04)		

Statistical analyses

Statistical analysis title	Arterial pH pre-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	t-test, 2-sided

Secondary: Arterial pH post-operative

End point title	Arterial pH post-operative

End point description:

End point type	Secondary

End point timeframe:
post-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: mmHg				
arithmetic mean (standard deviation)	7.29 (± 0.06)	7.32 (± 0.08)		

Statistical analyses

Statistical analysis title	Arterial pH post-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	t-test, 2-sided

Secondary: PaO2:FiO2 ratio pre-operative

End point title	PaO2:FiO2 ratio pre-operative

End point description:

End point type	Secondary

End point timeframe:
pre-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: kPa				
median (inter-quartile range (Q1-Q3))	59.6 (46.5 to 97.7)	59.6 (47.8 to 81.1)		

Statistical analyses

Statistical analysis title	PaO2:FiO2 ratio pre-operative comparison of groups
Comparison groups	Ascorbic acid v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Wilcoxon (Mann-Whitney)

Secondary: PaO2:FiO2 ratio post-operative

End point title	PaO2:FiO2 ratio post-operative

End point description:

End point type	Secondary

End point timeframe:
post-operative

End point values	Ascorbic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: kPa				
median (inter-quartile range (Q1-Q3))	42.5 (32.7 to 51.4)	45.3 (28.3 to 49.4)		

Statistical analyses

Statistical analysis title	PaO2:FiO2 ratio post-operative comparison of group
Comparison groups	Ascorbic acid v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

prior to hospital discharge

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Ascorbic acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

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: All of the adverse event were serious.

Serious adverse events	Ascorbic acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	7 / 18 (38.89%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Patient admitted to ICU from theatre due to excessive blood loss			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Bilateral femoral thromboses in setting of previous thrombotic episode associated with severe PVD			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acutely ischaemic left leg	Additional description: Patient returned to theatre for right femoral artery surgery from recovery ward due to acutely ischaemic left leg. Vascular surgeon had noted severe left femoral arterial disease during AAA repair prior to this.		
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Post operative myocardial infarction and pneumonia requiring admission to critical care	Additional description: Both cardiac and respiratory		
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non ST elevation myocardial infarction	Additional description: Patient with history of ischaemic heart disease diagnosed with post-operative non ST elevation myocardial infarction during planned post-operative HDU stay		
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Persistent lactic acidosis and lower limb weakness and paraesthesia	Additional description: Admitted to HDU postoperatively. Returned to theatre, required laparotomy and Hartmann's procedure for ischaemic sigmoid colon. Admitted to ICU for continued care. These sequelae could all be related to the intra-operative surgical difficulties		
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Patient admitted to ICU on post op Day 2 due to Respiratory failure requiring intubation,ventilation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patient admitted to ICU day 2 post op with respiratory failure secondary to chest sepsis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Patient developed post operative wound infection treated with intravenous antibiotics			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ascorbic acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2008	To allow for ascorbic acid to be provided by an alternative manufacturer

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.

None reported.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26215814