



Clinical trial results: Vasopressin vs Noradrenaline as Initial therapy in Septic Shock Summary

EudraCT number	2011-005363-24
Trial protocol	GB
Global end of trial date	03 June 2015

Results information

Result version number	v1 (current)
This version publication date	21 June 2017
First version publication date	21 June 2017

Trial information

Trial identification

Sponsor protocol code	CRO1888
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Additional study identifiers

ISRCTN number	ISRCTN20769191
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
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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	20 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2015
Global end of trial reached?	Yes
Global end of trial date	03 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aims of the trial are

1. To assess if vasopressin reduces kidney dysfunction compared to noradrenaline when used as the initial treatment in the management of septic shock in adult patients.
2. To assess if there is an interaction between vasopressin and steroids in the management of septic shock in adult patients.

Protection of trial subjects:

All patients were treated in an intensive care unit with constant 1:1 nursing care to ensure safety and comfort, and minimise any distress.

Background therapy:

In order to ensure that patients are treated as early as possible we will compare vasopressin to noradrenaline as the first line vasopressor in the management of septic shock, after adequate fluid resuscitation to maintain mean arterial blood pressure has been achieved. As international guidelines only suggest corticosteroids for cases of septic shock that are poorly responsive to fluids and vasopressors, patients will only be prescribed corticosteroids once higher doses of vasopressin or noradrenaline are required.

Other management of septic shock, including use of inotropes (e.g. dobutamine) will be at the treating physician's discretion, based on the international 'Surviving Sepsis' guidelines. All other drugs (other than vasopressors) should be prescribed as clinically indicated. High volume haemofiltration for the management of sepsis (i.e. RRT not to treat kidney failure) should not be used.

Evidence for comparator:

The rationale for the current study is that evidence to date suggests that vasopressin may prevent renal dysfunction in septic shock when used early, and that vasopressin may interact with corticosteroids.

A 2011 Cochrane review concluded "There is not sufficient evidence that any one of the investigated vasopressors is clearly superior over others". There are six randomised controlled trials of vasopressin in adults with septic shock. The majority of these trials were small proof-of-principle studies that used physiological variables as the primary outcome and only 150 patients in total have been studied in five of these trials.

In all studies the use of vasopressin allowed a reduction in the dose of conventional catecholamines required to maintain blood pressure. In one study vasopressin also increased cardiac index, and combined vasopressin and norepinephrine infusion improved gastrointestinal perfusion as assessed by gastric tonometry. Another important finding in one study was that vasopressin infusion doubled urine output and increased creatinine clearance by the end of the 4-hour study period.

For corticosteroids a 2009 Cochrane review reported that prolonged low-dose corticosteroid treatment led to better outcomes (RR 0.84 95%CI 0.72-0.97, $p=0.02$, for 28-day mortality). Another review in 2009 found a similar beneficial effect of low dose steroids. However the decrease in mortality was confined to the more severely ill patients.

A sub-group analysis from the VASST study reported a statistically significant interaction between vasopressin / noradrenaline treatment and corticosteroid treatment (interaction statistic $p=0.008$). The combination of vasopressin and steroids led to a significantly lower mortality compared to noradrenaline plus steroids (35.9% v 44.7% respectively, $p=0.03$) and less organ dysfunction demonstrated by more days alive and free from shock, ventilation and renal failure.

Actual start date of recruitment	09 February 2013
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: 409
Worldwide total number of subjects	409
EEA total number of subjects	409

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)	190
From 65 to 84 years	199
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in multiple general adult ICUs within the UK with a target of recruiting 412 patients to include 400 patients in the final analysis. The first patient was recruited on 09/02/2013 and the last patient was recruited on 06/05/2015, with a maximum follow up of 28 days in ICU.

Pre-assignment

Screening details:

All patients who were clinically judged to have septic shock were screened against the inclusion and exclusion criteria to be eligible for the study. A total of 2237 patients were screened in the study between 05/02/2013 and 07/05/2015

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, Carer, Assessor

Blinding implementation details:

Ampoules of vasopressin, noradrenaline and hydrocortisone phosphate were masked by overlabeling on the body and neck of normal drug ampoules. Matching placebo ampoules (0.9% saline) were manufactured to provide dummies for all active drugs.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vasopressin + hydrocortisone

Arm description:

Vasopressin + hydrocortisone

Arm type	Active comparator
Investigational medicinal product name	Vasopressin
Investigational medicinal product code	ATC code: H01BA01
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received vasopressin titrated up to 0.06 U/min via a central venous catheter to maintain the target mean arterial pressure (MAP). The protocol recommended a MAP of 65 to 75 mm Hg, but this could be altered by the treating physician if clinically indicated.

Investigational medicinal product name	Hydrocortisone Phosphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

50mg given as intravenous bolus once vasopressin dose at 0.06 Units/min. Administered 6hrly

Arm title	Vasopressin + placebo
Arm description: -	
Arm type	Active comparator

Investigational medicinal product name	Vasopressin
Investigational medicinal product code	ATC code: H01BA01
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received vasopressin titrated up to 0.06 U/min via a central venous catheter to maintain the target mean arterial pressure (MAP). The protocol recommended a MAP of 65 to 75 mm Hg, but this could be altered by the treating physician if clinically indicated.

Arm title	Noradrenaline + hydrocortisone
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Hydrocortisone Phosphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

50mg given as intravenous bolus once vasopressin dose at 0.06 Units/min. Administered 6hrly

Investigational medicinal product name	Noradrenaline
Investigational medicinal product code	ATC code: C01CA03
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Noradrenaline titrated up to 12mcg/min via a central venous catheter to maintain the target mean arterial pressure (MAP). The protocol recommended a MAP of 65 to 75 mm Hg, but this could be altered by the treating physician if clinically indicated.

Arm title	Noradrenaline + placebo
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Noradrenaline
Investigational medicinal product code	ATC code: C01CA03
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Noradrenaline titrated up to 12mcg/min via a central venous catheter to maintain the target mean arterial pressure (MAP). The protocol recommended a MAP of 65 to 75 mm Hg, but this could be altered by the treating physician if clinically indicated.

Number of subjects in period 1	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone
Started	101	104	101
Completed	100	104	101
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

Number of subjects in period 1	Noradrenaline + placebo
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Started	103
Completed	103
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	409	409	
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	66		
inter-quartile range (Q1-Q3)	54 to 77	-	
Gender categorical			
Units: Subjects			
Female	171	171	
Male	238	238	
APACHE II score			
Acute Physiology and Chronic Health Evaluation (range 0-72, a higher score corresponds to more severe illness and a higher risk of death)			
Units: None			
median	24		
inter-quartile range (Q1-Q3)	19 to 30	-	

End points

End points reporting groups

Reporting group title	Vasopressin + hydrocortisone
Reporting group description:	
Vasopressin + hydrocortisone	
Reporting group title	Vasopressin + placebo
Reporting group description: -	
Reporting group title	Noradrenaline + hydrocortisone
Reporting group description: -	
Reporting group title	Noradrenaline + placebo
Reporting group description: -	

Primary: Survivors with no renal failure

End point title	Survivors with no renal failure ^[1]
End point description:	
28-day Survivors who never developed kidney failure	
End point type	Primary
End point timeframe:	
Over 28 days in ICU	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was a single primary endpoint, the distribution of renal failure free days (days alive and free of renal failure) between groups. This was tested statistically.

The survivors with no renal failure is simply another way to display this part of the primary endpoint analysis but is not a separate primary outcome and therefore doesn't require a separate statistical test.

End point values	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone	Noradrenaline + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	84	77	80
Units: People				
No Kidney failure	46	48	46	47

Statistical analyses

No statistical analyses for this end point

Primary: Kidney failure free days

End point title	Kidney failure free days ^[2]
End point description:	
In those who had kidney failure, died, or both at any time.	
End point type	Primary
End point timeframe:	
Over 28 days after randomisation	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was a single primary endpoint, the distribution of renal failure free days (days alive and free of renal failure) between groups. This was tested statistically.

The Kidney failure free days is simply another way to display this part of the primary endpoint analysis but is not a separate primary outcome and therefore doesn't require a separate statistical test.

End point values	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone	Noradrenaline + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	56	55	56
Units: Days				
median (inter-quartile range (Q1-Q3))	5 (0 to 23)	12 (1 to 25)	13 (0 to 25)	14 (1 to 24)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of renal replacement therapy

End point title	Rate of renal replacement therapy
End point description:	
End point type	Secondary
End point timeframe:	
Over 28 days in ICU	

End point values	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone	Noradrenaline + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	101	104	101	103
Units: People				
Yes	29	23	32	40

Statistical analyses

No statistical analyses for this end point

Secondary: 28-day mortality rate

End point title	28-day mortality rate
End point description:	
End point type	Secondary

End point timeframe:

28 days

End point values	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone	Noradrenaline + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	104	101	103
Units: People				
Dead	33	30	29	27
Alive	67	74	72	76

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Fatal or life threatening SAEs should be reported on the day that the local site is aware of the event (within 24 hours).

Adverse event reporting additional description:

Clinical outcomes from sepsis are exempt from adverse event reporting, unless the investigator deems the event to be related to the administration of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Vasopressin + hydrocortisone
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Reporting group description:

Vasopressin + hydrocortisone

Reporting group title	Vasopressin + placebo
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Reporting group description: -

Reporting group title	Noradrenaline + hydrocortisone
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Reporting group description: -

Reporting group title	Noradrenaline + placebo
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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: As all patients included in the trial were critically ill by definition then it is very difficult to define what is an adverse event as they will have abnormal blood results and physiological signs as part of their underlying illness.

Therefore the trial focused only on serious adverse events only, as the priority safety analysis.

Serious adverse events	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 101 (8.91%)	13 / 104 (12.50%)	11 / 101 (10.89%)
number of deaths (all causes)	33	30	29
number of deaths resulting from adverse events	4	5	4
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	4 / 101 (3.96%)	7 / 104 (6.73%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	1 / 5	4 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 1
Cerebral ischaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 104 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Arrhythmia	Additional description: Life-threatening arrhythmia		
subjects affected / exposed	2 / 101 (1.98%)	0 / 104 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	4 / 101 (3.96%)	3 / 104 (2.88%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	2 / 4	2 / 3	0 / 2
deaths causally related to treatment / all	2 / 2	1 / 1	0 / 1
Acute left ventricular failure			
subjects affected / exposed	0 / 101 (0.00%)	0 / 104 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Pupil fixed			
subjects affected / exposed	0 / 101 (0.00%)	0 / 104 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mesenteric vascular insufficiency			
subjects affected / exposed	2 / 101 (1.98%)	3 / 104 (2.88%)	4 / 101 (3.96%)
occurrences causally related to treatment / all	1 / 2	1 / 3	4 / 4
deaths causally related to treatment / all	1 / 1	1 / 2	1 / 1
Umbilical hernia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 104 (0.96%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 101 (0.00%)	0 / 104 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	0 / 101 (0.00%)	1 / 104 (0.96%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Secondary transmission			
subjects affected / exposed	1 / 101 (0.99%)	0 / 104 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Noradrenaline + placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 103 (5.83%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	1		
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia	Additional description: Life-threatening arrhythmia		
subjects affected / exposed	4 / 103 (3.88%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute left ventricular failure			

subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Pupil fixed			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Mesenteric vascular insufficiency			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Secondary transmission			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Vasopressin + hydrocortisone	Vasopressin + placebo	Noradrenaline + hydrocortisone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 101 (0.00%)	0 / 104 (0.00%)	0 / 101 (0.00%)

Non-serious adverse events	Noradrenaline + placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 103 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2012	<p>Changes made to the quantity of IMP:</p> <ul style="list-style-type: none">(i) Decreased maximum limit of study drug 1 from 9mls/hr to 4.5ml/s(ii) Increased quantity of study drug 1 in one small ampoule from 1ml to 2ml, increasing the total quantity of study drug 1 from 5mls to 10mls(iii) Reduced the quantity of 5% dextrose from 45mls to 40mls(iv) Infusion of study drug 1 to start at 1ml/hr instead of 2ml/hr <p>Supply of study drug 1 – to be supplied as 3 ampoules/vials (2ml and 2x4ml) to contain Vasopressin (40U)/Noradrenaline (8mg), instead of 2 ampoules/vials (1ml and 4ml) to contain Vasopressin (20U)/Noradrenaline (4mg).</p> <p>Change in the number of vials being supplied for the first 3 days per patient – from 15 vials in each of the 3 packs to 9 vials in each of the 3 packs.</p>
27 October 2014	Change in the manufacturer of placebo to match all IMPs - from Northwick Park Hospital to South Davon Healthcare NHS Foundation Trust.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27483065>