Clinical trial results:
Balanced 6 % HES 130/0.4 vs. balanced crystalloid-based infusion in patients undergoing colorectal surgery

Summary

EudraCT number	2009-017595-25
Trial protocol	DE
Global end of trial date	20 April 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2016
First version publication date	05 May 2016

Trial information

Trial identification

Sponsor protocol code	04-AnIt-09/UKM09_0031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01303250
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University HospitalMuenster
Sponsor organisation address	Albert-Schweitzer-Campus 1, D5, Münster, Germany, 48149
Public contact	Dept. of Anaesthesiology, University Hospital Muenster, +49 25183-47267, wempe-c@anit.uni-muenster.de
Scientific contact	Dept. of Anaesthesiology, University Hospital Muenster, +49 25183-47267, wempe-c@anit.uni-muenster.de

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	01 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2013
Global end of trial reached?	Yes
Global end of trial date	20 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare two goal directed infusion therapies for patients undergoing open colorectal surgery with Volulyte (colloid treatment group) or Jonosteril (crystalloid control group). Comparison between the two groups will be based on the amount of fluids (mL) required to achieve hemodynamic stabilization.

Protection of trial subjects:

At the screening visit the patients who were considered potential candidates for the study were asked to provide a written informed consent. The patients were informed in writing about their right to withdraw from the study at any time without specification of reasons. Written patient information was given to each patient before enrolment. Patients could only participate if their eligibility had been proven.
The study could also be terminated prematurely for medical or ethical reasons following consultation with the investigators.
Patients who were withdrawn due to one or more (serious) AEs were to be treated and followed-up according to established medical practice to evaluate the course of the AE, and to ensure reversibility or stabilisation of the event.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2011
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	Germany: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	20
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from April 2011 (First Patient In) until May 2013 and followed up until May 2013 (Last Patient Out).

Pre-assignment

Screening details:

In total 233 patients were screened.

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Volulyte 6 % Arm

Arm description:

6% Hydroxyethylstarch (HES) 130/0.4 i.v.

Arm type	Experimental
Investigational medicinal product name	Volulyte 6% Solution for Infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The investigational drug Volulyte was administrated on day of surgery.
Intraoperatively fluid administration and optimization based on cardiac output findings during surgery. Postoperative volume requirement and blood loss were compensated with Volulyte. The maximum dosage was 50 mL/kg body weight / day.The maximum dosage was 50 mL/kg body weight / day.

Arm title	Balanced Crystalloid Arm

Arm description:

Balanced Crystalloid

Arm type	Active comparator
Investigational medicinal product name	Jonosteril
Investigational medicinal product code	
Other name	Trade name: Jonosteril® Infusionslösung 500 ml
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The comparator Jonosteril was administrated on day of surgery.
Intraoperatively fluid administration and optimization based on cardiac output findings during surgery. Postoperative volume requirement and blood loss were compensated with Jonosteril. The maximum dosage was 50 mL/kg body weight / day.

Number of subjects in period 1	Volulyte 6 % Arm	Balanced Crystalloid Arm
Started	14	15
Completed	14	15

Baseline characteristics

Reporting groups	
Reporting group title	Volulyte 6 % Arm
Reporting group description:	
6% Hydroxyethylstarch (HES) 130/0.4 i.v.	
Reporting group title	Balanced Crystalloid Arm
Reporting group description:	
Balanced Crystalloid	

Reporting group values	Volulyte 6 % Arm	Balanced Crystalloid Arm	Total
Number of subjects	14	15	29
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)	10	10	20
From 65-84 years	4	5	9
85 years and over	0	0	0
18-64 years	0	0	0
from 65 - 84 years	0	0	0
Age continuous Units: years			
arithmetic mean	52.79	48.93	
standard deviation	± 19.96	± 19.96	-
Gender categorical Units: Subjects			
Female	10	8	18
Male	4	7	11
Height Units: cm			
arithmetic mean	175.4	177.1	
standard deviation	± 9.4	± 8.9	-
Weight Units: kg			
arithmetic mean	85	83.5	
standard deviation	± 20.2	± 14.3	-
Body Mass Index Units: kg/m²			
arithmetic mean	27.4	26.8	
standard deviation	± 5.1	± 5	-

End points

End points reporting groups

Reporting group title	Volulyte 6 % Arm
Reporting group description:	
6% Hydroxyethylstarch (HES) 130/0.4 i.v.	
Reporting group title	Balanced Crystalloid Arm
Reporting group description:	
Balanced Crystalloid	

Primary: Total volume of fluid required intraoperatively

End point title	Total volume of fluid required intraoperatively[1]
End point description:	
End point type	Primary
End point timeframe:	
intraoperatively	

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: The study was terminated. Only 29 patients were randomised and analyzed. Therefore a confirmatoric analysis was not performed.

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: ml				
arithmetic mean (standard deviation)	2188 (± 977)	2414 (± 1110)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total volume of study medication

End point title	Total volume of study medication
End point description:	
End point type	Secondary
End point timeframe:	
Study drug was used intraoperatively and postoperatively on surgery day	

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: ml				
arithmetic mean (standard deviation)	1496 (± 565)	1517 (± 504)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative complications until day 28

End point title	Postoperative complications until day 28

End point description:

End point type	Secondary

End point timeframe:

From day of surgery until day 28 postoperatively

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: number of subjects				
Woundhealing disturbance	6	8		
Dehiscences at the suture	0	1		
Anastomosis insufficiency	1	1		
Renal disease	1	1		
Infections	1	0		
Respiratoric complications	1	0		
Cardiac complications	1	0		
Miscellaneous complications	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative complications until day 90

End point title	Postoperative complications until day 90

End point description:

End point type	Secondary

End point timeframe:

From day of surgery until day 90 postoperatively

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Number of patients				
Wound healing disturbances	1	2		
Miscelleanous disturbances	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurance of PONV (Postoperative Nausea and Vomiting)

End point title	Occurance of PONV (Postoperative Nausea and Vomiting)

End point description:

End point type	Secondary

End point timeframe:

Day of Surgery

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: Number of patients	5	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated length of stay in hospital

End point title	Estimated length of stay in hospital

End point description:

End point type	Secondary

End point timeframe:

From day of surgery until estimated length of stay in hospital

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: days				
median (confidence interval 95%)	10 (8 to 13)	12 (7 to 14)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total volume of fluid balance intraoperatively

End point title	Total volume of fluid balance intraoperatively

End point description:

End point type	Other pre-specified

End point timeframe:

interaoperatively

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: ml				
arithmetic mean (standard deviation)	1399 (± 680)	1732 (± 908)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Difference of BUN

End point title	Difference of BUN

End point description:

Difference of blood urea nitrogen (BUN 1 day after surgery - BUN baseline)

End point type	Other pre-specified

End point timeframe:

1 day after surgery

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mg/100 ml				
arithmetic mean (standard deviation)	2.67 (± 8.02)	2.78 (± 6.67)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: urine production

End point title	urine production

End point description:

End point type	Other pre-specified

End point timeframe:

Day of Surgery

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: Number of patients				
>= 0.5 ml/kg/h (> 6 h)	11	9		
< 0.5 ml/kg/h (> 6h)	0	2		
< 0.5 ml/kg/h (> 12h)	2	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Difference of serum creatinine

End point title	Difference of serum creatinine

End point description:

Difference of serum creatinine (1 day after surgery - baseline)

End point type	Other pre-specified

End point timeframe:

Day of Surgery

End point values	Volulyte 6 % Arm	Balanced Crystalloid Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: mg/100 ml				
arithmetic mean (standard deviation)	-0.06 (± 0.1)	0.03 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event recording was performed throughout the first time of administration of study medication until 8 days after surgery or discharge of hospital (whichever falls earlier)

Adverse event reporting additional description:

Regular assessment by Pharmacovigilance and Safety Assessor

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Volulyte 6 %

Reporting group description: -

Reporting group title	Balanced crystalloid arm

Reporting group description: -

Serious adverse events	Volulyte 6 %	Balanced crystalloid arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 14 (21.43%)	6 / 15 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture related complication			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain in stoma site			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial fibrillation			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			

subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 14 (14.29%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Volulyte 6 %	Balanced crystalloid arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	14 / 15 (93.33%)	
Investigations			
serum creatinine increased			
subjects affected / exposed	2 / 14 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Transaminases increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Anastomotic leak at the gastrointestinal tract			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vomiting in association with a procedure			
subjects affected / exposed	2 / 14 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	2	4	
Nausea in association with a procedure			
subjects affected / exposed	2 / 14 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	2	4	
Wound dehiscence			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
delayed healing			
subjects affected / exposed	2 / 14 (14.29%)	5 / 15 (33.33%)	
occurrences (all)	2	5	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 14 (35.71%)	4 / 15 (26.67%)	
occurrences (all)	5	4	
Gastrointestinal disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Ileus paralytic			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	6 / 14 (42.86%)	7 / 15 (46.67%)	
occurrences (all)	6	7	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	7 / 14 (50.00%)	8 / 15 (53.33%)	
occurrences (all)	7	8	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	3 / 14 (21.43%)	8 / 15 (53.33%)	
occurrences (all)	3	8	
Disorder in emptying the bladder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkaliaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

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? Yes

Date	Interruption	Restart date
25 July 2013	The final decision of the review of hydroxyethyl starch-containing solution shall be awaited.	-

Notes:

Limitations and caveats

None reported