Clinical trial results:
A comparison of crystalloids vs. colloids for intraoperative goal-directed fluid management

Summary

EudraCT number	2005-004602-86
Trial protocol	AT
Global end of trial date	31 December 2016

Results information

Result version number	v1 (current)
This version publication date	26 March 2021
First version publication date	26 March 2021
Summary attachment (see zip file)	Effect of Intraoperative Goal-directed Balanced Crystalloid versus Colloid Administration on Major Postoperative Morbidity (Kabon, Crystaloid-Colloid.pdf)

Trial information

Trial identification

Sponsor protocol code	EK431/2005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00517127
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Barbara Kabon MD, Medical University of Vienna, 0043 1404004102, barbara.kabon@hotmail.com
Scientific contact	Barbara Kabon MD, Medical University of Vienna, 0043 1404004102, barbara.kabon@hotmail.com

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	24 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2016
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To test whether colloid-based goal-directed intraoperative fluid management leads to less perioperative morbidity compared to crystalloid-based goal-directed intraoperative fluid management.

Protection of trial subjects:

Daily blinded follow-up till discharge
30 day follow up
4 interim analysis
Recording of maximal in-hospital Serum Creatinine concentrations and as available within 6 postoperative months

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	03 May 2006
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	Austria: 548
Country: Number of subjects enrolled	United States: 554
Worldwide total number of subjects	1102
EEA total number of subjects	548

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)	752
From 65 to 84 years	350
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment Period: September 2006 bis December 2016,
Recruitment territories: Austria, USA

Pre-assignment

Screening details:

Open or laparoscopic-assisted abdominal surgery expected to last at least 2 h who were age 18 to 80 yr, were American Society of Anesthesiologists (ASA) physical status I–III, body mass index of less than 35 kg/m2.
Exclusion:compromised kidney function or cardiac insufficiency, severe COPD, coagulopathies, oesophageal or aortic abnormalities.

Pre-assignment period milestones

Number of subjects started	1102
Number of subjects completed	1102

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

Blinding implementation details:

Postoperative Follow-up day by day and 30 d postoperative by a blinded Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Crystalloid

Arm description:

goal-directed crystalloid administration

Arm type	Active comparator
Investigational medicinal product name	Lactated Ringer' Solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

250 mL lactated Ringersolution repeatedly according to Esophageal Doppler readings

Arm title	Colloid

Arm description:

goal-directed colloid administration

Arm type	Experimental
Investigational medicinal product name	Voluven
Investigational medicinal product code	B05AA07
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

250 mL Bolus administration according to Esophageal Doppler readings, up to a maximum of 30 mL/kg /d

Number of subjects in period 1	Crystalloid	Colloid
Started	553	549
Analyse	534	523
Completed	534	523
Not completed	19	26
technical problems	3	6
Physician decision	2	3
Surgery not performed	10	10
Adverse event, non-fatal	2	2
organziational problem	2	5

Baseline characteristics

Reporting groups	
Reporting group title	Crystalloid
Reporting group description: goal-directed crystalloid administration	
Reporting group title	Colloid
Reporting group description: goal-directed colloid administration	

Reporting group values	Crystalloid	Colloid	Total
Number of subjects	553	549	1102
Age categorical			
18-80 years			
Units: Subjects			
Adults (18-64 years)	380	372	752
From 65-84 years	173	177	350
Age continuous			
18-80 years			
Units: years			
arithmetic mean	52	52	
standard deviation	± 16	± 16	-
Gender categorical Units: Subjects			
Female	268	242	510
Male	285	307	592

End points

End points reporting groups

Reporting group title	Crystalloid
Reporting group description: goal-directed crystalloid administration	
Reporting group title	Colloid
Reporting group description: goal-directed colloid administration	

Primary: Primary Endpoint

End point title	Primary Endpoint

End point description:

The primary outcome was postoperative morbidity,defined by a composite of major complications.
It included cardiac, pulmonary, infectious, gastrointestinal,renal, and coagulation complication.

End point type	Primary

End point timeframe:

30 postoperative days

End point values	Crystalloid	Colloid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	534	523		
Units: numbers	103	91		

Statistical analyses

Statistical analysis title	Estimated relative risk

Statistical analysis description:

We assessed the treatment effect on the major complications via a common effect “global” relative risk estimated
across six outcomes of interest. In this multivariate analysis,each patient was represented once for each outcome
event.
The within-subject correlation among the outcomes was accounted for using a generalized estimating equation model with an unstructured working correlation matrix.

Comparison groups	Crystalloid v Colloid
Number of subjects included in analysis	1057
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	multivariate analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.23

Notes:

[1] - As a sensitivity analysis we assessed the treatment effect n the collapsed composite of the six major complications,
i.e., any vs. none using a chi-square test.

Secondary: Secondary and Tertiary Outcomes

End point title	Secondary and Tertiary Outcomes

End point description:

We assessed the treatment effect on the collapsed composite of any minor complication and on a collapsed composite of any major complications plus 30-day mortality and 30-day readmission

End point type	Secondary

End point timeframe:

30 postoperative days

End point values	Crystalloid	Colloid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	534	523		
Units: numbers	337	305		

Statistical analyses

Statistical analysis title	Secondary and Tertiary Outcomes

Statistical analysis description:

The minor complication analysis was a per-protocol analysis because more than 10% of patients (n = 145) had at least one minor component missing,making an intention-to-treat analysis with conservative assignment unrealistic.
Duration of hospitalization and readmission were analyzed as time to discharge alive and time to readmission, and the treatment effects were assessed using Cox proportional hazard models.

Comparison groups	Colloid v Crystalloid
Number of subjects included in analysis	1057
Analysis specification	Pre-specified
Analysis type	superiority[2]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	Other: 98.3 %
sides	2-sided
lower limit	0.69
upper limit	1.14

Notes:

[2] - To avoid bias from considering early deaths as short hospitalizations and thus favorable lengths of stay, patients who died in the hospital were assigned the ongest observed hospital stay of any patient and censored at that time (i.e., not discharged alive). Patients who died within 30 days after surgery were censored at the date of death for the time to readmission analysis. Because only 1% of patients died within 30 days, a competing risks analysis was unnecessary.

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Other pre-specified: Safety Outcome

End point title	Safety Outcome

End point description:

We compared colloids and crystalloids groups on the maximum postoperative serum creatinine concentration during hospitalization and within 6 months thereafter with analysis of covariance adjusted for the preoperative
serum creatinine

End point type	Other pre-specified

End point timeframe:

up to 6 month

End point values	Crystalloid	Colloid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	534	523		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))	0.87 (0.73 to 0.94)	0.87 (0.73 to 1.06)		

Statistical analyses

Statistical analysis title	Safety Analysis

Statistical analysis description:

Maximum postoperative serum creatinine concentration during hospitalization and within 6 months thereafter with analysis of covariance adjusted for the preoperative serum creatinine
Because serum creatinine concentrations were not normally distributed, we analyzed them on a log scale, with treatment effect reported as the ratio of geometric means.
We also assessed between-group differences in creatinine changes over time using linear mixed model

Comparison groups	Crystalloid v Colloid
Number of subjects included in analysis	1057
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Ratio geometric means
Parameter estimate	Ratio geometric means
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.02

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
30 postoperative days	
Adverse event reporting additional description:	
Daily follow-up during till discharge and 30 days follow-up call	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
Goal-directed crystalloid administration	
Reporting group title	Arm 2
Reporting group description:	
Goal-directed colloid administration	

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: In this study, these were not defined

Serious adverse events	Arm 1	Arm 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 553 (1.63%)	10 / 549 (1.82%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	3	4	
Vascular disorders			
Bleeding			
subjects affected / exposed	7 / 553 (1.27%)	7 / 549 (1.28%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 3	
pulmonary embolism			
subjects affected / exposed	0 / 553 (0.00%)	1 / 549 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
acute heart failure			
subjects affected / exposed	1 / 553 (0.18%)	0 / 549 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Anastomotic leak			
subjects affected / exposed	1 / 553 (0.18%)	1 / 549 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	0 / 553 (0.00%)	1 / 549 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm 1	Arm 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 553 (0.00%)	0 / 549 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2011	Amendment to the protocol: Changes in conduct of the trial- primary outcome, inclusion criteria Change of the Principal Investigator, Addition of sites
22 December 2014	Amendment to the protocol Changes in conduct of the Trial: IMP maximum dosage reduced Primary outcome extended
16 December 2015	Amendment to the protocol Changes in interpretation of scientific document.... changes of primary outcome parameter Addition of sites

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/30882476