Clinical trial results:
RETIC trial: Reversal of Trauma Induced Coagulopathy by using Coagulation factor concentrates or Fresh frozen Plasma

Summary

EudraCT number	2011-004139-29
Trial protocol	AT
Global end of trial date	20 February 2016

Results information

Result version number	v1 (current)
This version publication date	25 October 2020
First version publication date	25 October 2020

Trial information

Trial identification

Sponsor protocol code	RETIC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01545635
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020
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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 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2016
Global end of trial reached?	Yes
Global end of trial date	20 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the difference in incidence of multi organ failure (MOF) after treatment of trauma induced coagulopathy with Fresh frozen plasma (FFP) or Coagulation factor concentrates (CFC).

Protection of trial subjects:

Fibrinogen administration is calculated and aimed to maintain fibrinogen concentration and polymerization within the lower normal levels of healthy adults. In addition, ROTEM assays are performed following each therapeutic step and enable detection of hypercoagulability.
Several cases of thrombembolismn have been reported after PCC administration. However the majority of data refers to patients receiving huge doses and continuous administration such as needed in patients with haemophilia and antibody formation. The doses used in the present study will be low and are aimed to raise factors levels up to 50% which is the lower normal level. Furthermore patients are closely monitored by ROTEM and a shortened ExTEM CT value should warrant against overdosing. Regarding FXIII concentrate no cases of thrombembolism following FXIII administration have been reported so far. Finally the amount of blood loss (120ml total, about 2% of calculated blood volume in a 70kg patient) due to study related blood sampling should not harm the patient.

Background therapy:

TXA will be administered to all included study patients as a single bolus of 20mg/kg immediately after inclusion. Additional doses will be administered if indicated by ROTEM assays.
Red blood cells will be transfused to maintain haemoglobin between 8-10mg/dl. Autologous salvaged red cells will be re-transfused irrespective of actual hemoglobin levels.
Platelet concentrates (1-2 U PC) will be administered if clot firmness remains poor to maintain platelet count between 50-100 G/L or (ExTEM A10 <35mm) albeit sufficient fibrinogen polymerization (FibTEm A10 >10mm).
Crystalloid fluids and 4% modified gelatin solution should be used preferently to maintain normovolemia in amounts disrected by the treating anaesthesist. Because of the profound effect of HES solutions on haemostasis HES should be avoided and only used if gelatin is contraindicated (known or new allergy). The use of HES will be documented and explained. All patients receive prewarmed iv fluids.
In both groups pH, Ca++, BE and temperature are monitored and corrected as possible (targets pH>7.2, Ca++ >1mmol/L, BE >-4, temperature >35°C).

Evidence for comparator:

We hypothesize that the exclusively use of CFC improves outcome of severely traumatized patients. The administration of CFC should effectively and timely raise coagulation factor levels, thereby limiting coagulopathic bleeding. Because volume expansion and dilution can be avoided with use of CFC the numbers of red cell and platelet transfusion should be reduced. As all types of blood components increase susceptibility to nosocomiale infection and sepsis a reduction in allogeneic transfusions and avoidance of FFP should result in a lower incidence of sepsis and multi organ failure.
To test the hypothesis we will conduct a prospective study in adult patients with major trauma and coagulopathy randomly receiving CFC or FFP for correcting TIC.

Actual start date of recruitment	01 March 2012
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	1
Adults (18-64 years)	88
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult patients (aged 18–80 years) with trauma exhibiting an Injury Severity Score (ISS) greater than 15 and clinical signs or risk of substantial haemorrhage were screened for trauma-induced coagulopathy, which was defined as abnormally low fibrin polymerisation (measured with FibTEM assay) and/or prolonged initiation of coagulation (ExCT).

Pre-assignment

Screening details:

Between March 3, 2012, and Feb 20, 2016, 292 trauma patients with an expected ISS greater than 15 were screened for eligibility, of whom 192 were found ineligible. 100 patients were enrolled and randomly assigned to receive either FFP (n=48) or CFC (n=52).

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Enrolled patients were randomly assigned (1:1) to FFP or CFC. An independent statistician determined random codes using permuted blocks with varying block size and Stata/MP 10.1 for Windows Statistical Software. Randomisation was stratified for presence or absence of brain injury, and patients were stratified into three ISS groups (ISS 16–30, 31–50, or >50).

Arms

Are arms mutually exclusive?	Yes
Arm title	CFC group

Arm description:

We started bleeding management with CFC immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 50 patients completed the treatment period, of which 38 patients received a single dose of CFC, 10 patients recieved a double dose of CFC and 2 patients received a double dose of CFC and in a crossover fashion rescue medication.

Arm type	Experimental
Investigational medicinal product name	Haemocomplettan P
Investigational medicinal product code	
Other name	Blutgerinnungsfaktor 1, Human Fibrinogen
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The used dosage of fibrinogen (50mg/kg), refer to he European Guidelines of trauma management (published 2010, 2013, 2016).

Investigational medicinal product name	Fibrogammin P 250E
Investigational medicinal product code	
Other name	FACTOR XIII
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The FXIII concentrate were administered at 20IU/kg.

Investigational medicinal product name	Beriplex P/N 500 I.E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The 4 factor-PCC and FXIII concentrate were administered at 20IU/kg.

Arm title	FFP group

Arm description:

We started bleeding management with FFP immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 44 patients completed the treatment period, of which 12 patients received a single dose of FFP, 9 patients recieved a double dose of FFP and 23 patients received a double dose of FFP and in a crossover fashion rescue medication.

Arm type	Active comparator
Investigational medicinal product name	Octaplas SD Blutgruppe A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the FFP group, transfusion of FFP (Octapharma, Vienna, Austria) delivered by the local blood bank was done in a single dose of 15 mL/kg of bodyweight.
Octaplas shows activity that is comparable to that of normal fresh-frozen human plasma. The final product contains 45-70 mg/mL of plasma protein.

Number of subjects in period 1	CFC group	FFP group
Started	52	48
Completed	50	44
Not completed	2	4
age < 18 years	1	-
fatal injury	1	3
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	CFC group

Reporting group description:

We started bleeding management with CFC immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 50 patients completed the treatment period, of which 38 patients received a single dose of CFC, 10 patients recieved a double dose of CFC and 2 patients received a double dose of CFC and in a crossover fashion rescue medication.

Reporting group title	FFP group

Reporting group description:

We started bleeding management with FFP immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 44 patients completed the treatment period, of which 12 patients received a single dose of FFP, 9 patients recieved a double dose of FFP and 23 patients received a double dose of FFP and in a crossover fashion rescue medication.

Reporting group values	CFC group	FFP group	Total
Number of subjects	52	48	100
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)	1	0	1
Adults (18-64 years)	45	43	88
From 65-84 years	6	5	11
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.60	42.26	
standard deviation	± 16.724	± 16.748	-
Gender categorical Units: Subjects			
Female	12	13	25
Male	40	35	75

End points

End points reporting groups

Reporting group title	CFC group

Reporting group description:

We started bleeding management with CFC immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 50 patients completed the treatment period, of which 38 patients received a single dose of CFC, 10 patients recieved a double dose of CFC and 2 patients received a double dose of CFC and in a crossover fashion rescue medication.

Reporting group title	FFP group

Reporting group description:

We started bleeding management with FFP immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 44 patients completed the treatment period, of which 12 patients received a single dose of FFP, 9 patients recieved a double dose of FFP and 23 patients received a double dose of FFP and in a crossover fashion rescue medication.

Primary: Multiple organ failure

End point title	Multiple organ failure

End point description:

End point type	Primary

End point timeframe:

Day 0- day 30

End point values	CFC group	FFP group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: MOF				
number (not applicable)	25	29		

Statistical analyses

Statistical analysis title	Multiple organ failure
Comparison groups	CFC group v FFP group

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	4.86

Secondary: Massive transfusions of RBC

End point title	Massive transfusions of RBC

End point description:

As further secondary efficacy endpoint, we also addressed frequency of massive transfusions of RBC during the first 24 h.

End point type	Secondary

End point timeframe:

Day 0

End point values	CFC group	FFP group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Number of patients				
number (not applicable)	6	13		

Statistical analyses

Statistical analysis title	Massive tranfusions of RBC
Comparison groups	CFC group v FFP group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	10.87

Secondary: Frequency of transfusions of platelet concentrates

End point title	Frequency of transfusions of platelet concentrates

End point description:

As further secondary efficacy endpoint, we also addressed frequency of transfusions of platelet concentrates during the first 24 h.

End point type	Secondary

End point timeframe:

Day 0

End point values	CFC group	FFP group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Number of patients				
number (not applicable)	10	21		

Statistical analyses

Statistical analysis title	Frequency of tranfusions of platelet concentrate
Comparison groups	FFP group v CFC group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	10.18

Secondary: Bleeding score of 2 or 3

End point title	Bleeding score of 2 or 3

End point description:

Bleeding score is defined as number fom 0-3, dependent on severity of bleeding. A coagulopathic bleeding score of 2 or 3 after first study drug administration was more frequently observed in the FFP group.

End point type	Secondary

End point timeframe:

Day 0

End point values	CFC group	FFP group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Patients				
number (not applicable)	14	31		

Statistical analyses

Statistical analysis title	Bleeding score of 2 or 3
Comparison groups	CFC group v FFP group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Fisher exact

Statistical analysis title	Bleeding score of 2 or 3 and massive transfusion
Comparison groups	CFC group v FFP group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Fisher exact

Secondary: Rescue therapy

End point title	Rescue therapy

End point description:

20 (87%) of the 23 patients in the FFP group who required rescue medication needed rescue already in the first treatment loop, whereas three other patients in the FFP group and the two patients in the CFC group received rescue therapy in later treatment loops.

End point type	Secondary

End point timeframe:

Day 0

End point values	CFC group	FFP group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Patients				
number (not applicable)	2	23		

Statistical analyses

Statistical analysis title	Rescue medication
Comparison groups	CFC group v FFP group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	25.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.47
upper limit	240.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 0- day 30

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	CFC group

Reporting group description:

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Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 50 patients completed the treatement period, of which 38 patients received a single dose of CFC, 10 patients recieved a double dose of CFC and 2 patients received a double dose of CFC and rescue medication.
In these patients, rescue therapy was initiated, meaning FFP was administered to patients in the CFC group.

Reporting group title	FFP group

Reporting group description:

We started bleeding management with FFP immediately after randomisation and during surgical or radiological interventions, and continued study-specific coagulation management during the first 24 h at the intensive care unit (ICU).
Considering that coagulopathy might reoccur, one or several treatment loops were administered during the entire study period (lasting from admission to the emergency department until 24 h at the ICU).
In total 44 patients completed the treatement period, of which 12 patients received a single dose of FFP, 9 patients recieved a double dose of FFP and 23 patiens received a double dose of FFP and rescue medication.

Serious adverse events	CFC group	FFP group	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 52 (28.85%)	18 / 48 (37.50%)	
number of deaths (all causes)	5	2	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
DVT			
subjects affected / exposed	5 / 52 (9.62%)	8 / 48 (16.67%)	
occurrences causally related to treatment / all	0 / 13	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	3 / 52 (5.77%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	2 / 52 (3.85%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Delir			
subjects affected / exposed	1 / 52 (1.92%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	5 / 52 (9.62%)	7 / 48 (14.58%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CFC group	FFP group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 52 (9.62%)	3 / 48 (6.25%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 52 (1.92%)	1 / 48 (2.08%)	
occurrences (all)	2	2	
Tachycardia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 48 (0.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Dysphagia			
subjects affected / exposed	0 / 52 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Vocal cord paralysis			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 48 (0.00%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1	 0 / 48 (0.00%) 1	
Skin and subcutaneous tissue disorders Exanthema subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 2	 1 / 48 (2.08%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2012	substantial amendments: another trial monitor, another member in study team (a medical doctor for transfusion medicine), definition for platelet transfusion trigger (50.000-100.000)
14 July 2012	Substantial amendment of an inclusion criterium: Limit of FibTEM was changed from <7mm to <9mm

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/28457980