Clinical trial results:
Albumin vs. Plasma for PEdiAtric pRiming (APPEAR) trial

Summary

EudraCT number	2014-000177-39
Trial protocol	IT
Global end of trial date	31 January 2018

Results information

Result version number	v1 (current)
This version publication date	19 November 2021
First version publication date	19 November 2021
Summary attachment (see zip file)	Published paper including results of the study (026765911985424 6.pdf)

Trial information

Trial identification

Sponsor protocol code	Linea7-2013/06-APPEAR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02738190
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IRCCS Policlinico San Donato
Sponsor organisation address	Piazza Edmondo Malan 2, San Donato Milanese, Italy, 20097
Public contact	Study Coordinator, IRCCS Policlinico San Donato, 39 0252774754, ekaterina.baryshnikova@gmail.com
Scientific contact	Study Coordinator, IRCCS Policlinico San Donato, 39 0252774754, ekaterina.baryshnikova@gmail.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	31 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the effects of extracorporeal circulation circuit priming containing Albumin 5% versus fresh frozen plasma of hemostasis and coagulation

Protection of trial subjects:

This study was approved by the Local Ethics Committee (San Raffaele Hospital, protocol number 116/int/2017, approved on 12 October 2017), and parents of all patients provided a written informed consent.

Background therapy:

Every subject received our standard surgical care and CPB technique. A total intraoperative dose of 30 mg/kg of tranexamic acid was administered in all patients. CPB was established after a loading dose of 300 IU/kg of unfractioned heparin plus additional doses (80 IU/kg) to reach and maintain a target activated clotting time >= 450 s. The CPB circuit included a hollow-fibre oxygenator, a roller head pump, or a centrifugal pump.
The target patient temperature was chosen based on the type of surgical procedure and cardioplegia protocol. Every volume addition needed during CPB was made giving albumin 5% or RBCs according to our target hematocrit.
Ultrafiltration was a standard of care; conventional or modified ultrafiltration was applied during and after CPB, respectively, according to surgeon's preference. The ultrafiltrated volume was fixed at 30 ml/kg. During ultrafiltration, patients on the late FFP arm had half of the volume replaced with FFP (15 ml/kg). With the same timing, patients in the early FFP group received the same replacement with albumin 5%. Patients in the late FFP arm received an additional dose of 15 ml/kg of FFP during hemostasis and before transfer to the ICU.

Evidence for comparator:

In newborns and small infants undergoing cardiac surgery, red blood cells (RBCs) are usually added to the CPB priming volume to prevent excessive haemodilution. At the same time, maintenance of physiologic colloid oncotic pressure during CPB must be preserved to prevent interstitial fluid accumulation; this is achieved by adding either 5% albumin, fresh frozen plasma (FFP), or colloids to priming. At present, few studies have investigated the superiority of FFP or albumin-based priming solutions in newborns and small infants, and the results are conflicting.
Potential advantages of the use of albumin in the priming solution are avoidance or limitation of exposure to allogeneic blood-derived FFP and prevention of fibrinogen adsorbtion and platelet adhesion to the foreign surfaces of the CPB circuit and oxygenator.
Conversely, FFP-based priming may retain a slightly higher colloid oncotic pressure and prevent haemodilution of soluble coagulation factors and fibrinogen.

Actual start date of recruitment	01 March 2014
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	Italy: 80

Worldwide total number of subjects	80
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	17
Infants and toddlers (28 days-23 months)	63
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was randomized on January 22, 2015, and the last on March 16, 2016.

Pre-assignment

Screening details:

213 patients were considered eligible for the study (considering the elective cardiac surgery requiring CPB, weight < 10 kg, blood priming required). 133 patients were excluded (declined to participate, not meeting inclusion criteria, no staff available). 80 patients were enrolled and randomized.

Pre-assignment period milestones

Number of subjects started	80
Number of subjects completed	80

Period 1

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

Blinding implementation details:

The attending anesthesiologist and the surgical staff were not blinded; conversely, ICU and ward doctors were blinded, as well as the person in charge of database data entry.

Arms

Are arms mutually exclusive?	Yes
Arm title	Late FFP (albumin priming)

Arm description:

Patients in this group receive priming required to start the cardiopulmonary bypass made of albumin 5% and red blood cells. The solution is titrated to reach an on-pump hematocrit of 30%. The volume of RBCs used in the priming solution varied according to the patient's baseline HCT and weight and priming volume.

Arm type	Experimental
Investigational medicinal product name	Albumin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use, Extracorporeal use

Dosage and administration details:

5% albumin solution was used instead of fresh frozen plasma for priming solution preparation, titrated to reach an on-pump hematocrit (HCT) of 30%. In this arm, CPB priming was formulated with albumin 5% and RBCs. The volume of RBCs used varied according to the patient's baseline hematocrit (HCT), weight and priming volume.

Arm title	Early FFP (FFP priming)

Arm description:

Patients in the early FFP group received priming solution made of fresh frozen plasma (FFP) and red blood cells (RBC). The priming was titrated to achieve an on-pump hematocrit (HCT) of 30%. The volume of RBCs used varied according to the patient's baseline HCT, weight, and priming volume.

Arm type	Placebo

Investigational medicinal product name	Fresh Frozen Plasma
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Extracorporeal use, Intravenous use

Dosage and administration details:

Patients in the early FFP arm received a priming solution with FFP plus RBCs. The solution was titrated to reach an "on pump" hematocrit of 30%. The amount of RBCs used for priming varied depending on the patient's baseline hematocrit, weight, and priming volume. The "clear prime volume" (FFP) was obtained as the difference between the circuit priming volume and the calculated amount of RBCs.

Number of subjects in period 1	Late FFP (albumin priming)	Early FFP (FFP priming)
Started	40	40
Completed	40	40

Baseline characteristics

Reporting groups	
Reporting group title	Late FFP (albumin priming)
Reporting group description:	
Patients in this group receive priming required to start the cardiopulmonary bypass made of albumin 5% and red blood cells. The solution is titrated to reach an on-pump hematocrit of 30%. The volume of RBCs used in the priming solution varied according to the patient's baseline HCT and weight and priming volume.	
Reporting group title	Early FFP (FFP priming)
Reporting group description:	
Patients in the early FFP group received priming solution made of fresh frozen plasma (FFP) and red blood cells (RBC). The priming was titrated to achieve an on-pump hematocrit (HCT) of 30%. The volume of RBCs used varied according to the patient's baseline HCT, weight, and priming volume.	

Reporting group values	Late FFP (albumin priming)	Early FFP (FFP priming)	Total
Number of subjects	40	40	80
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: months			
median	4	4	
inter-quartile range (Q1-Q3)	1 to 10	2 to 9.5	-
Gender categorical			
Units: Subjects			
Female	17	17	34
Male	23	23	46

End points

End points reporting groups

Reporting group title	Late FFP (albumin priming)

Reporting group description:

Patients in this group receive priming required to start the cardiopulmonary bypass made of albumin 5% and red blood cells. The solution is titrated to reach an on-pump hematocrit of 30%. The volume of RBCs used in the priming solution varied according to the patient's baseline HCT and weight and priming volume.

Reporting group title	Early FFP (FFP priming)

Reporting group description:

Patients in the early FFP group received priming solution made of fresh frozen plasma (FFP) and red blood cells (RBC). The priming was titrated to achieve an on-pump hematocrit (HCT) of 30%. The volume of RBCs used varied according to the patient's baseline HCT, weight, and priming volume.

Primary: Postoperative bleeding

End point title	Postoperative bleeding

End point description:

Postoperative blood loss from chest drains

End point type	Primary

End point timeframe:

First 24 postoperative hours

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[1]	36[2]		
Units: ml				
arithmetic mean (standard error)	154 (± 101)	117 (± 52)		

Notes:

[1] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

[2] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

Statistical analysis title	Comparison of postoperative bleeding between arms

Statistical analysis description:

Postoperative bleeding from chest drains during the first 24 postoperative hours was significantly (p=0.028) higher in the late FFP arm than in the early FFP arm.

Comparison groups	Late FFP (albumin priming) v Early FFP (FFP priming)

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.028
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Primary: Postoperative bleeding

End point title	Postoperative bleeding

End point description:

Postoperative blood loss standardized for weight

End point type	Primary

End point timeframe:

First 24 postoperative hours

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[3]	36[4]		
Units: ml/kg				
arithmetic mean (standard deviation)	33.1 (± 20.6)	24.1 (± 12.9)		

Notes:

[3] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[4] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

Statistical analysis title	Difference between arms

Statistical analysis description:

Chest drain blood loss in the first 24 postoperative hours was significantly higher in the late FFP group than in the early FFP group.

Comparison groups	Early FFP (FFP priming) v Late FFP (albumin priming)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.028
Method	t-test, 2-sided

Primary: Incidence of severe bleeding

End point title	Incidence of severe bleeding

End point description:

Severe bleeding was arbitrarily defined as a chest drain blood loss > 30 ml/kg (roughly corresponding to the upper tertile of chest blood loss in our historical database).

End point type	Primary

End point timeframe:

First 24 postoperative hours

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[5]	36[6]		
Units: subjects	17	7		

Notes:

[5] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[6] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

Statistical analysis title	Difference in incidence of severe bleeding

Statistical analysis description:

Seventeen patients (46%) in the late FFP group experienced a serious bleed vs. 7 (19.4%) in the early FFP arm.

Comparison groups	Late FFP (albumin priming) v Early FFP (FFP priming)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.016
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	10

Secondary: Transfusion of Platelet Concentrates

End point title	Transfusion of Platelet Concentrates

End point description:

End point type	Secondary

End point timeframe:

First 48 postoperative hours

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[7]	36[8]		
Units: subjects	9	5		

Notes:

[7] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[8] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

No statistical analyses for this end point

Secondary: Fibrinogen concentrate administration

End point title	Fibrinogen concentrate administration

End point description:

End point type	Secondary

End point timeframe:

First 48 postoperative hours

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[9]	36[10]		
Units: subjects	6	6		

Notes:

[9] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[10] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

No statistical analyses for this end point

Secondary: Dose of fibrinogen concentrate administration

End point title	Dose of fibrinogen concentrate administration

End point description:

End point type	Secondary

End point timeframe:

First 48 postoperative hours

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[11]	36[12]		
Units: mg/kg				
arithmetic mean (standard deviation)	7.9 (± 19.3)	6.8 (± 18.8)		

Notes:

[11] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[12] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

No statistical analyses for this end point

Secondary: Mechanical ventilation duration

End point title	Mechanical ventilation duration

End point description:

End point type	Secondary

End point timeframe:

Duration of mechanical ventilation during the ICU stay

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[13]	36[14]		
Units: hours				
median (inter-quartile range (Q1-Q3))	36 (18 to 90)	30 (17 to 72)		

Notes:

[13] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[14] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

No statistical analyses for this end point

Secondary: ICU stay

End point title	ICU stay

End point description:

End point type	Secondary

End point timeframe:

Overall stay in the intensive care unit

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[15]	36[16]		
Units: days				
median (inter-quartile range (Q1-Q3))	5 (3 to 8)	5 (2 to 8)		

Notes:

[15] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[16] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative hospital stay

End point title	Postoperative hospital stay

End point description:

End point type	Secondary

End point timeframe:

Postoperative hospital stay, from the day of surgery to the day of discharge.

End point values	Late FFP (albumin priming)	Early FFP (FFP priming)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[17]	36[18]		
Units: days				
median (inter-quartile range (Q1-Q3))	15 (9 to 21)	14 (7 to 23)		

Notes:

[17] - Three patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.
[18] - Four patients in the group were withdrawn due to the need for extracorporeal membrane oxygenation.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Overall hospital stay	
Adverse event reporting additional description:	
No serious adverse drug reactions (SADRs) nor serious adverse events (SAEs) specifically related to the study procedures have been observed.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

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

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: No non-serious adverse events have been recorded for this trial.

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? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We have no specific limitations and caveats for this summary of the results to notify.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28510741