Trauma Hemostasis & Oxygenation Research Symposium

Service de santé des armées

French Dried Plasma Program

update on prehospital and emergency unit use for massive hemorrhage management

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Clamart – France

Bergen

Tuesday 27th June 2017

Conflict of interest

None

Disclaimer

The opinions or assertions contained herein represent FMBI positions on the subject

Characteristics of

French Lyophilized Plasma

FLyP: main characteristics

- Universal blood group compatibility (mixed FFP from less than 11 donors)

- Reconstitution time < 6 min
- 2 years shelf life
- Storage from +4°C up to +25°C
- Inactivated by amotosalen® process
- Leuko-reduced (residual WBCs ≤ 10 000/L)
- All controls are done by bottle and batch production
- Therapeutic plasma monitored by the active French hemovigilance & specific traceability

Regulation – authorization issues

HAS
HAUTE AUTORITÉ DE SANTÉ

TRANSFUSION DE PLASMA THÉRAPEUTIQUE :
PRODUITS, INDICATIONS
ACTUALISATION 2012

ansm

Il existe 4 types de plasma thérapeutique homologue :

- le plasma frais congelé traité par solvant-détergent : PFC-SD ;
- le plasma frais congelé traité par amotosalen : PFC-IA ;
- le plasma frais congelé sécurisé par quarantaine (au moins 60 jours) : PFC-Se ;
- le plasma lyophilisé destiné aux unités militaires déployées en opérations extérieures : PLYO.

Prenant en compte les données d'efficacité et de sécurité (cliniques et toxicologiques) ainsi que le recul d'utilisation, il n'existe pas d'argument pour recommander un plasma par rapport à un autre.

En plus de l'évolution des indications cliniques, les données de la science ont amené de profondes modifications des caractéristiques des différents types de plasmas disponibles : plasmas frais congelés (PFC) en majorité et plasma lyophilisé (PLYO) principalement utilisé en médecine militaire.

Le plasma lyophilisé : PLYO

Le plasma lyophilisé (PLYO), préparé à partir de plasma frais congelé traité par amotosalen, est principalement distribué aux unités médico-chirurgicales militaires déployées en Opérations Extérieures (OPEX) pour répondre aux contraintes logistiques du contexte opérationnel et à la nécessité de disposer, sans délai, de plasma pour le traitement des blessés hémorragiques. En milieu civil, le PLYO pourrait être utilisé par les établissements de santé présentant des difficultés logistiques majeures ne permettant pas d'assurer une chaîne du froid négative ou au cours de situations d'extrême urgence avec nécessité d'un apport de plasma thérapeutique sans délai. Dans cette deuxième indication, le PLYO devrait être utilisé en attendant que le plasma frais congelé soit décongelé et disponible.

Le plasma lyophilisé fait l'objet d'un suivi clinique systématique depuis 2000 et biologique depuis 2010. Aucun effet indésirable grave n'a été signalé, la facilité d'utilisation et la rapidité de reconstitution sont confirmées et l'efficacité clinique est comparable aux autres plasmas thérapeutiques [33,34,35]. Cependant, son utilisation restreinte ne permet pas d'obtenir des données statistiquement exploitables.

Extreme emergency that needs plasma without delay while waiting for thawed fresh frozen plasma

Major logistic problems regarding the negative cold chain capability

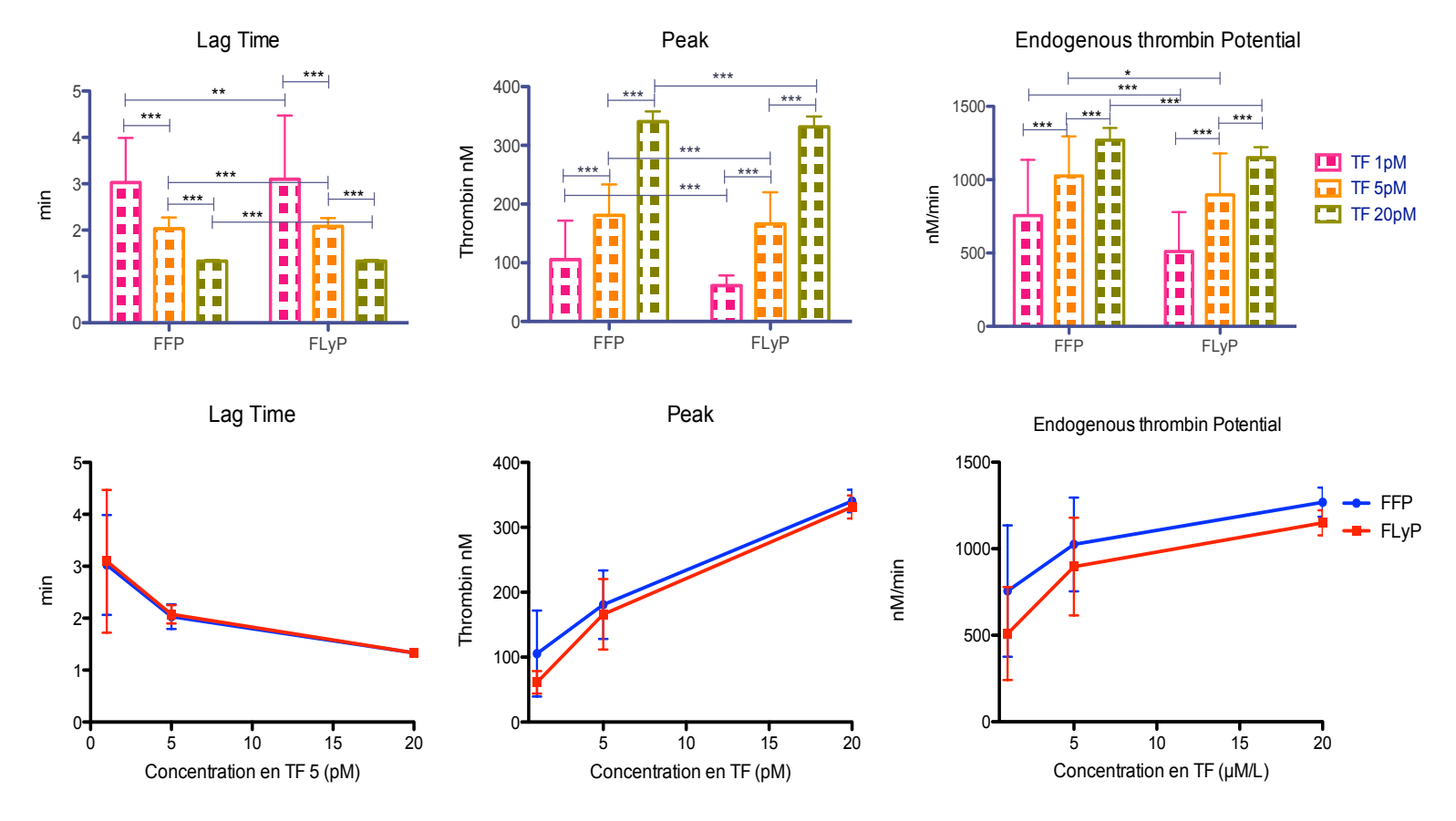
FDP: *in vitro* properties

In vitro properties of FLyP compared with other French plasmas

Parameters	Units	Solvant-Detergnet-FFP	Intercept-FFP	Quarantine -FFP	FLYP	Reference range
Fibrinogen	g/L	2.8	2.7	2.8	2.4	2 - 4
Factor V	IU/mL	0.9	1.0	1.0	0.7	0.7 – 1.2
Factor VIII	IU/mL	0.7	0.8	1.1	0.7	0.5 – 1.5
Factor XI	IU/mL	0.8	0.6	1.0	0.7	0.5 – 1.4
Protein C	IU/mL	1.0	0.9	1.2	0.9	0.7 – 1.2
Protein S	IU/mL	0.6	1.0	1.4	0.9	0.7 – 1.4
Antithrombin	IU/mL	0.9	1.0	1.0	1.0	0.8 – 1.2
α2 antiplasmin	IU/mL	0.2	0.8	1.0	0.9	0.8 – 1.2

ANSM 2012

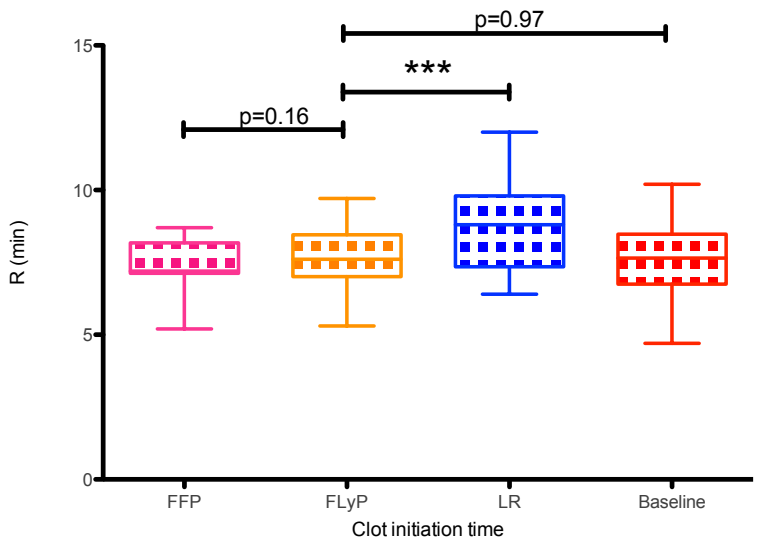
FDP: thrombin generation assays

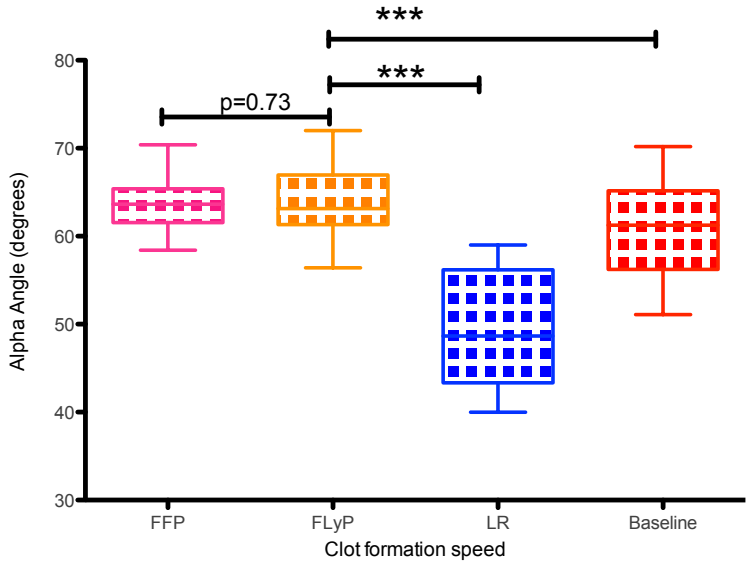


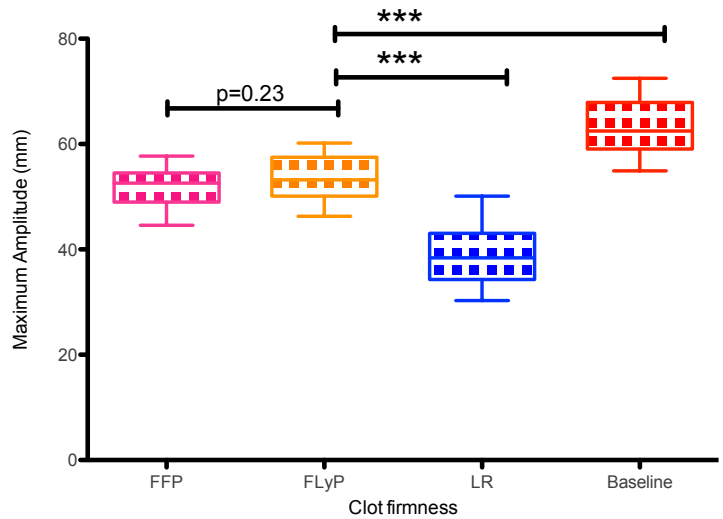
Thrombin generation potential depends on TF concentration used in the assay

Trauma patients exhibit high TF concentrations

FDP: *in vitro* model of fluid resuscitation



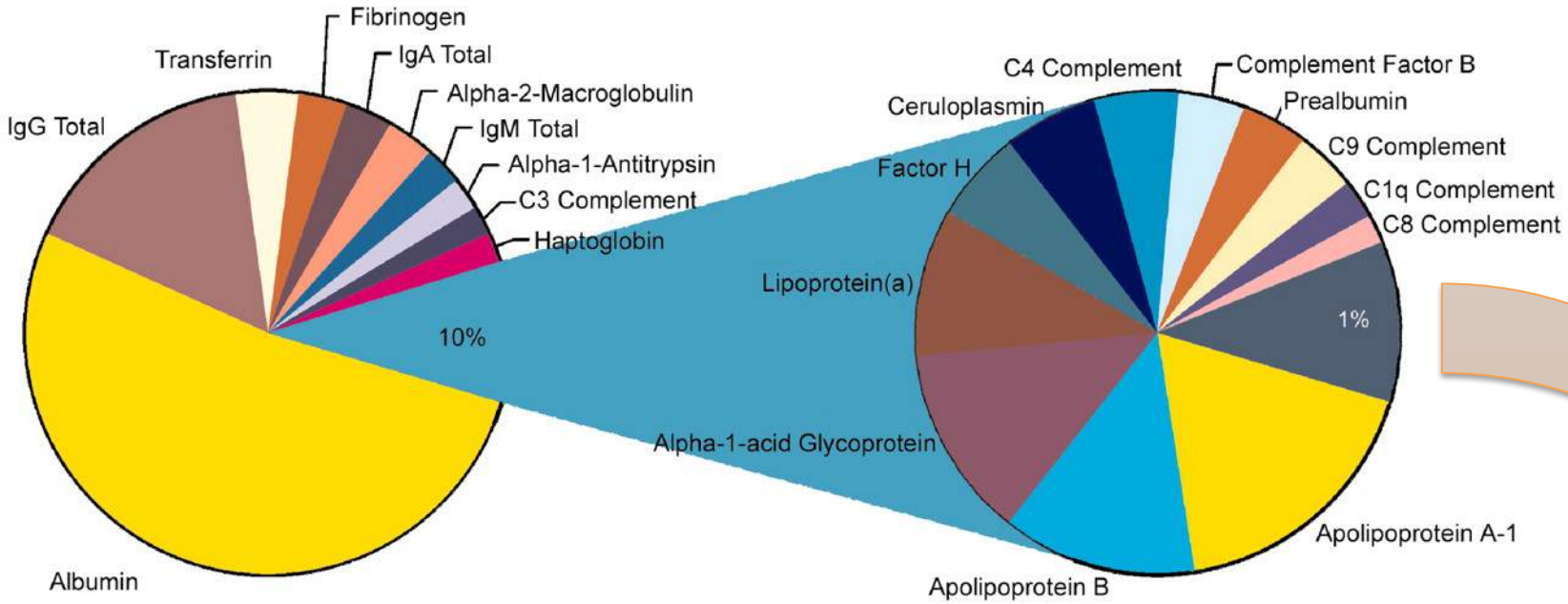


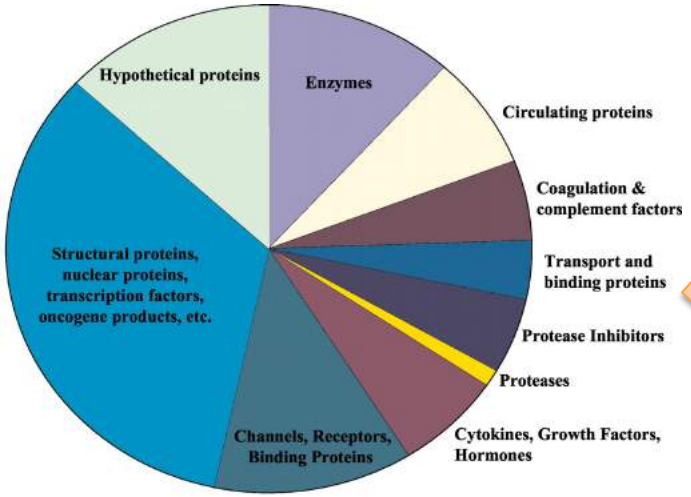


Viscoelastometric assays showed no significant difference due to lyophilization process

But it's only about hemostasis!

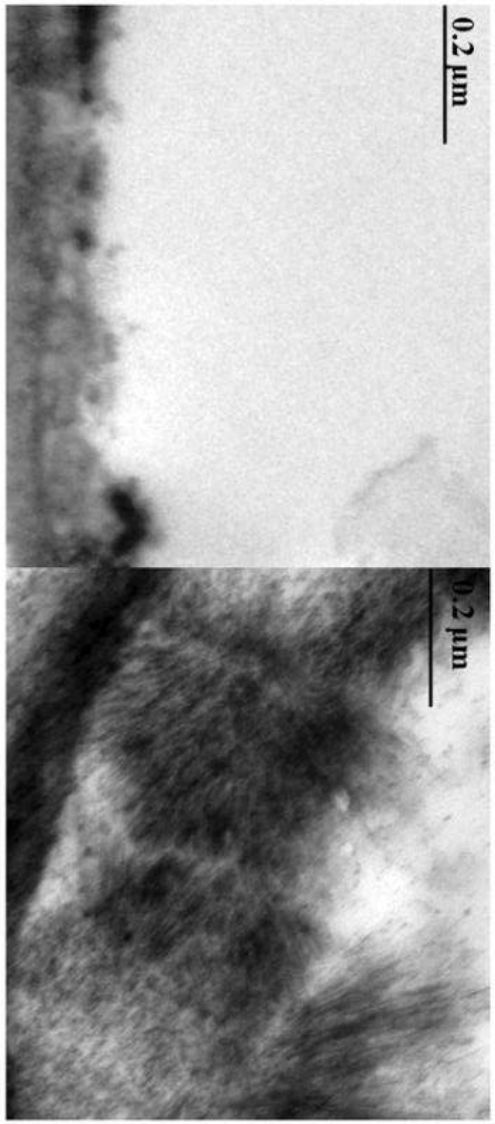
Plasma complexity: « not just to clot »

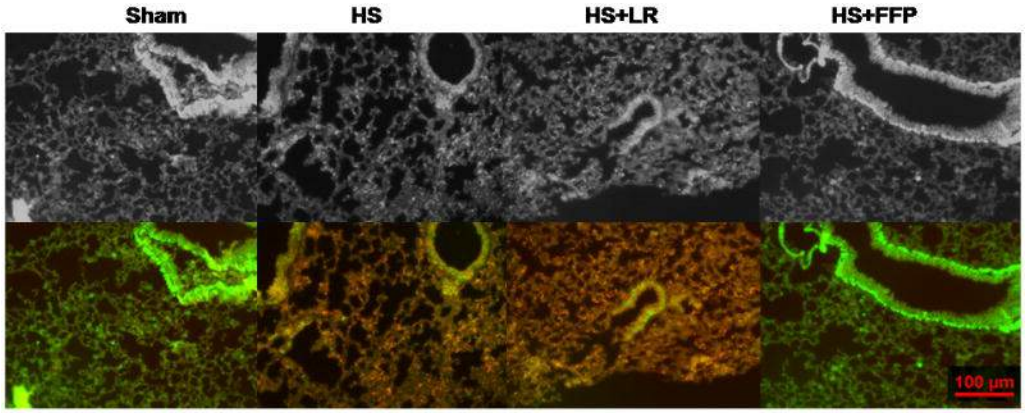




Radhakrishna et al. Mol Cell Proteomics 2003

Post-traumatic endotheliopathy modulation





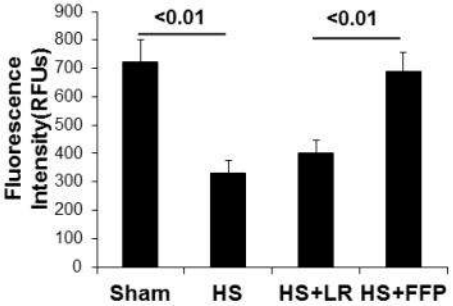


Table 2 Summary of measured glycocalyx components, catecholamines and ECIS resistance

	Healthy controls (N = 5)	Normal COP (N = 11)	Low COP (N = 11)	p-value
Plasma COP (mmHg)	21.2 (19.1, 21.3)	21.6 (16.2, 21.9)	12.4 (10.7, 13.9)[a,b]	<0.001
Chondroitin sulfate (U/L)	22.9 (22.5, 23.3)	32.3 (31.3, 33.7)[a]	32.7 (27.6, 33.9)[a]	0.003
Heparan sulfate (ng/ml)	133.9 (130.5, 138.3)	180.0 (176.4, 185.9)[a]	176.7 (151.5, 185.8)[a]	0.003
Hyaluronic acid (ng/ml)	627.6 (484.1, 753.1)	93.5 (49.0, 885.4)	380.9 (216.6, 682.4)[a,b]	0.035
Syndecan-1 (ng/ml)	31.6 ± 15.3*	34.6 (19.3, 43.1)	221.7 (88.3, 477.4)[a,b]	<0.001
Adrenaline (ng/ml)	72.1 ± 99.2[†]	90.5 (58.7, 226.9)	805.8 (659.3, 4319.3)[a,b]	0.014
Noradrenaline (ng/ml)	282 ± 454.7[†]	739.8 (189.5, 1006.2)	987.1 (352.3, 1187.4)	0.245
TEER (Ωcm^2)	1066.3 (1057.8, 1074.8)	1101.6 (1089.6, 1115.5)	1067.3[b] (1043.7, 1096.4)	0.016
Normalized TEER	1.30 (1.29, 1.31)	1.35 (1.33, 1.38)	1.31 (1.27, 1.33)	0.016

Kozar et al. J Trauma 2015, Rahbar et al. J Transl Med 2015, Peng et al Shock 2013

Evolution in FLyP packaging

Coming soon…

water in plastic bottle

FLyP 270mL

3-year shelf life

e-Formation for FLyP users

Hyper-oncotic reconstitution of FLyP

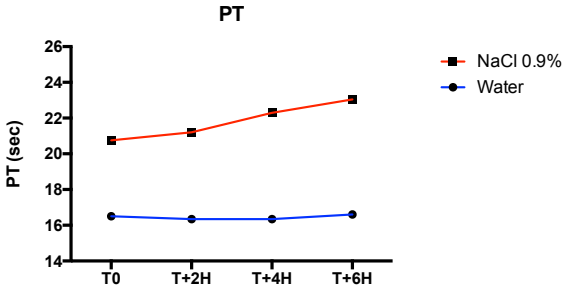
***In vitro* assays** → ***In vivo* assays**

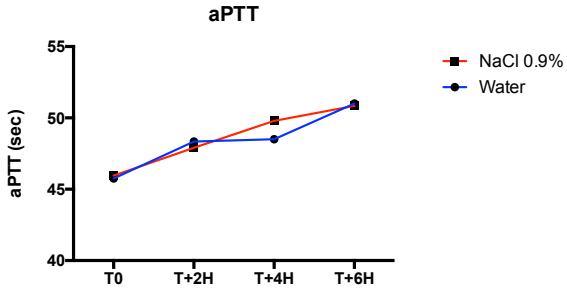
n=6	Hyper-FlyP	Iso-FlyP	p
FV (%)	119 +/- 10	72+/-4	<0.05
FVIII (UI/mL)	1.13 +/- 0.16	0.76 +/- 0.06	
Fg (g/L)	4.36 +/- 0.23	2.49 +/- 0.16	
Reconstitution time (min)	6 +/- 0.5	2.5 +/- 0.3	
Lag Time (min)	1.99 +/- 0.24	1.30 +/- 0.08	<0.01
ETP ($nM.min^{-1}$)	634 +/- 153	1322 +/- 151	
Peak (nM)	178 +/- 46	342 +/- 25	

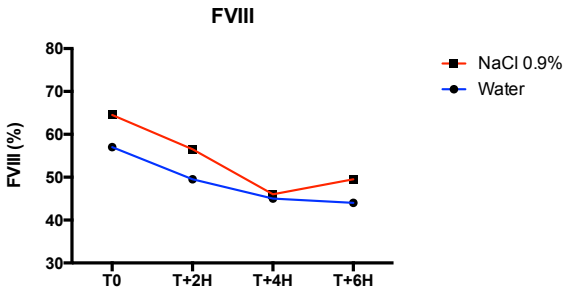
Dilution model and TEG analysis revealed non significant difference between Hyper-FLyP and iso-FLyP

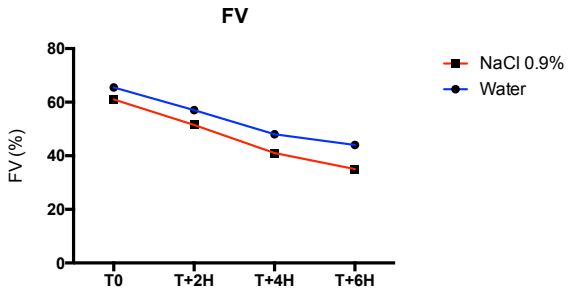
- **Model: pig trauma and hemorrhage**
- **Randomization**
  - **SSH**
  - **iso-pigFLyP**
  - **hyper-pigFlyP L1**
  - **hyper-pigFLyP L2**
- **Primary endpoint**
  - **survival**
- **Secondary endpoint**
  - **biological testing**

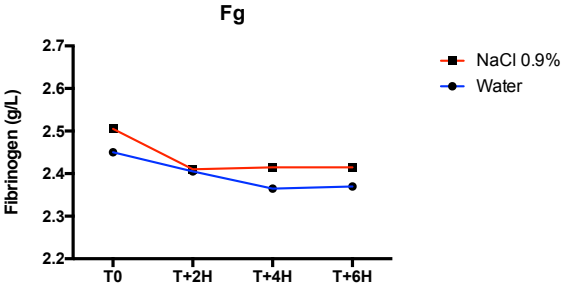
Water vs. NaCl reconstitution of FLyP







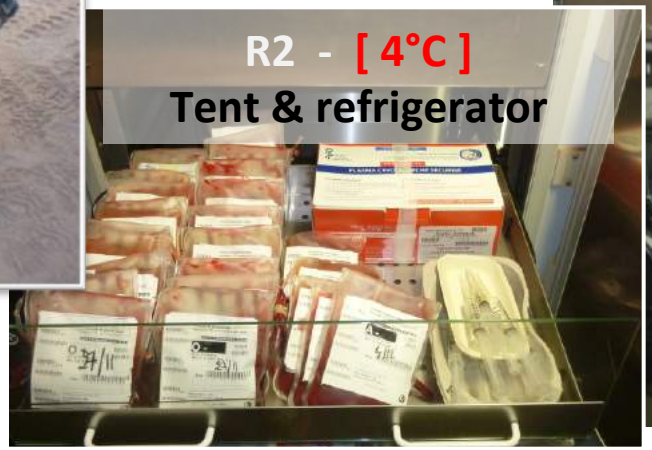




Same batch of FLyP
reconstitution medical water / NaCl 0.9%
hemostasic testing T0, +2H, +4H, +6H
room temperature storage along the protocol

“Live” improvements:

Stability studies in remote conditions



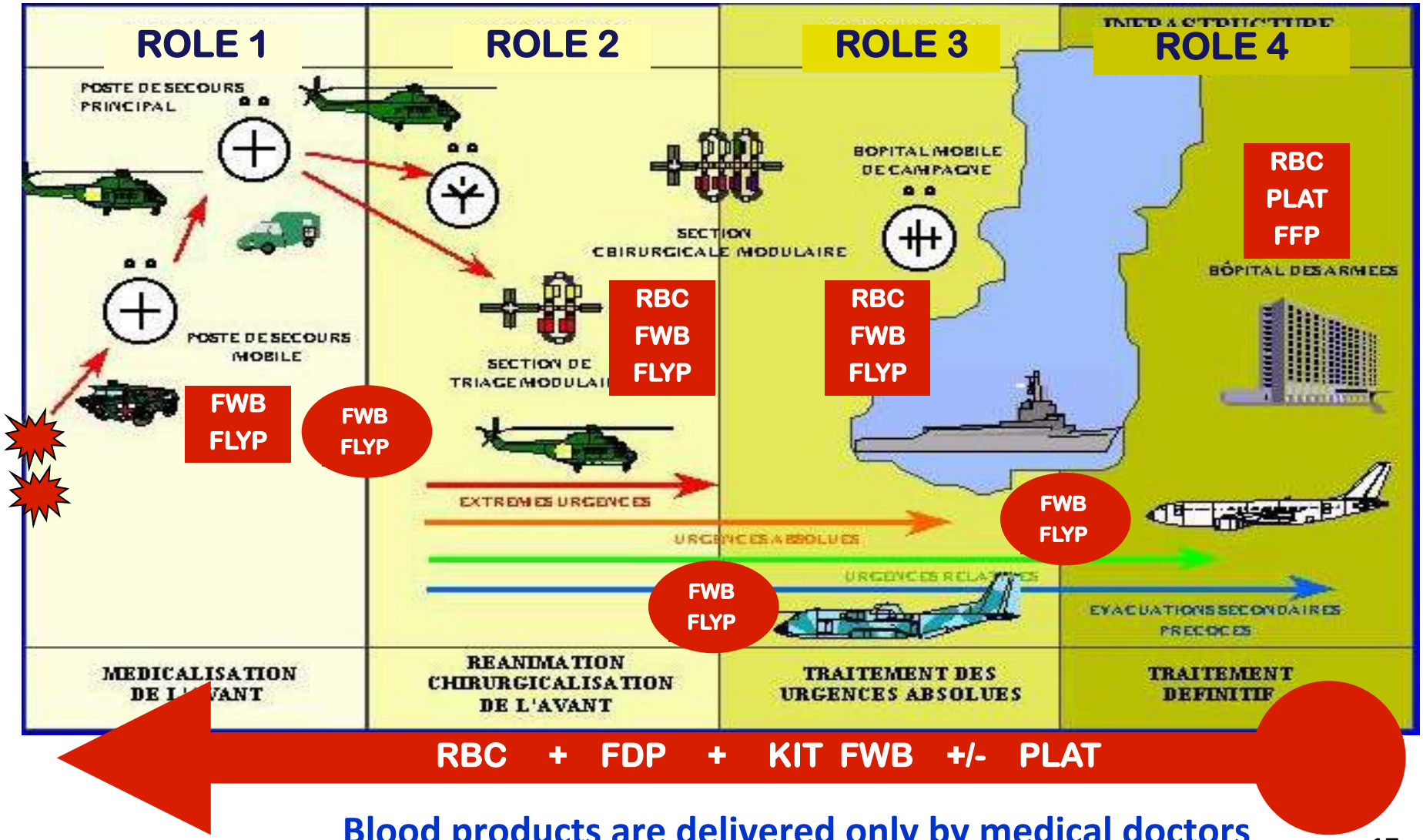
Service de santé des armées

Uses of French Lyophilized Plasma

Bergen

Tuesday 27th June 2017

Use of FLyP in military settings



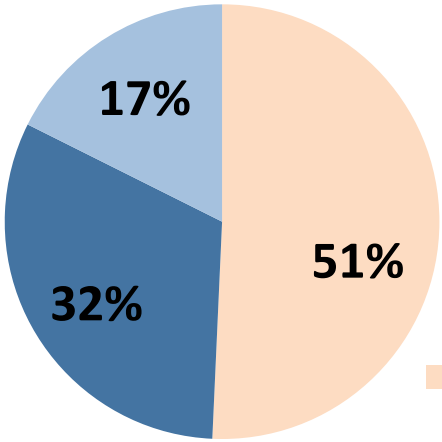
Blood products are delivered only by medical doctors

At the Military Medical Center Percy

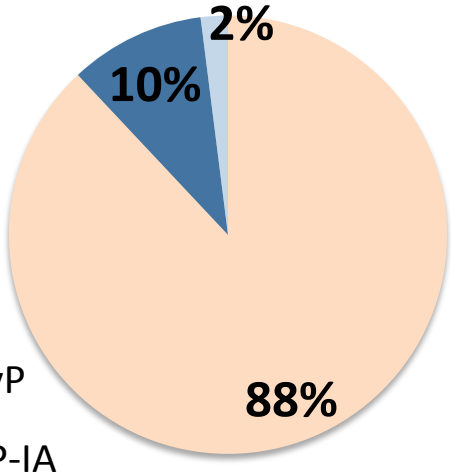
- **400 beds**
  - civilian and military patients
  - Trauma center level 1
  - Burn Unit (20 beds)
  - Hematological Unit (25 beds)

- **18 months (2015 – 2016)**
  - 164 patients
    - M/F ratio: 2.6
    - 57y [15-97]
  - 698 plasma transfused
    - 53% in emergency
    - 50% acute hemorrhage
    - 53min for FFP (fax=> transfusion)

Overall use of Plasma



Plasma type in emergency



FLyP
FFP-IA
FFP-Se

FLyP is delivered in the first MT pack (4+4)

Unpublished data

At the Military Medical Center Toulon

- Retrospective study 2012 – 2015
- Primary objective
  - to compare the time-frame FLyP vs. FFP in trauma patients
- Secondary objective
  - to compare the volume transfused and mortality within 24h
- Inclusion criteria
  - trauma patients who received 2 pRBC in the emergency room

At the Military Medical Center Toulon

- 72 patients included (FLyP: 43, FFP: 29)

- No significant difference
  - age, ISS, Hb, platelet count, ratio, lactate, nb of plasma units transfused within 24h
  - mortality

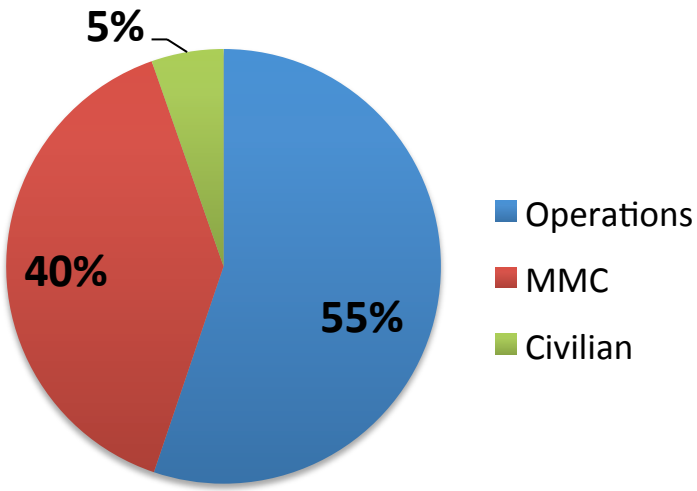
- Significant difference
  - delivery time-frame
  - number of RBC
  - time to reach 1:1 ratio

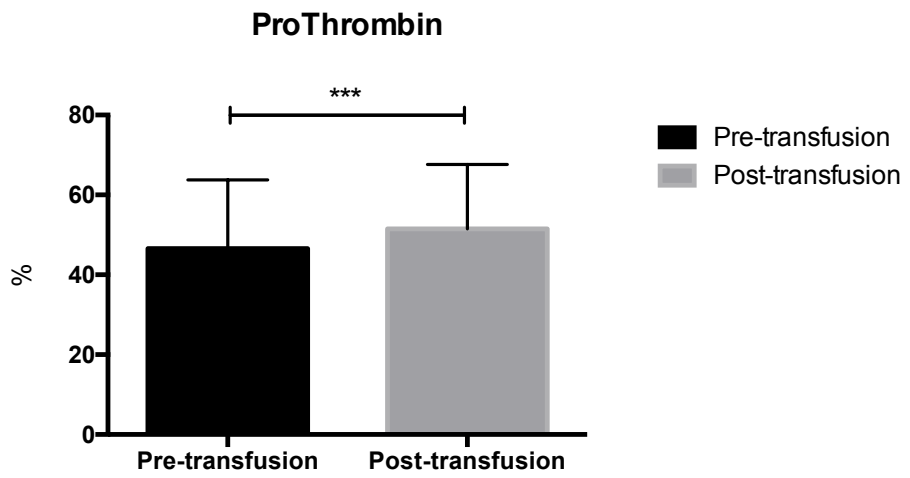
	FLyP (43)	FFP (29)	p
Delivery time-frame (min)	**15** [10-25]	**95** [70-145]	p<0,001
Transfusion > 3 pRBC within 1h (n, %)	19 (44%)	21 (76%)	0,014
pRBC within 24h	4 [2-7]	8 [6-10]	0,004
Mortality within 24h	31%	41 %	0,59

Prunet et al. Submitted

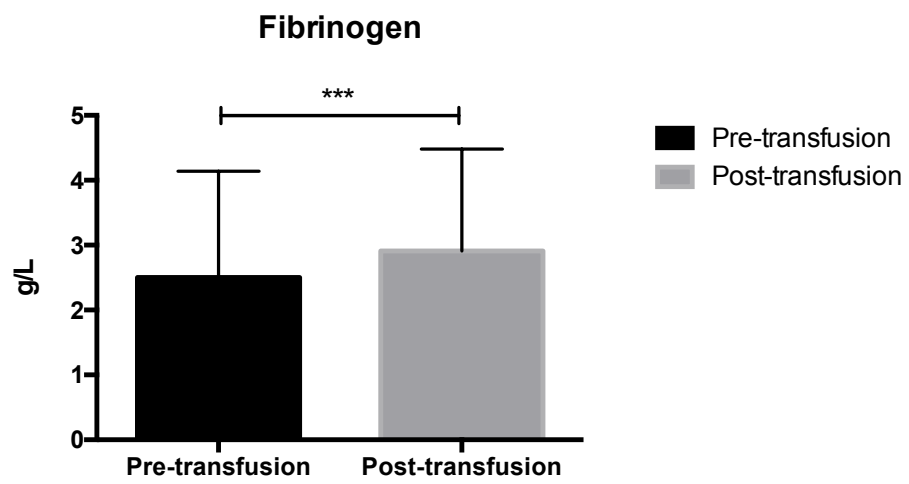
Hemovigilance data 2010 – 2016

- **2956 FLyP transfused**





- **907 patients**
  - 702 male
  - median 40y [1- 95]



- **3 adverse effects**
  - transient erythema
  - uncertain imputability

TRAUCC study: Lille Hospital

Centre Hospitalier Régional Universitaire de Lille

- **Prospective – randomized study**
  - July 2013 – March 2016

- **Primary objective**
  - to determine the most effective plasma, (FFP or FLYP) in the initial management of the coagulopathy in trauma patients

- **Inclusion criteria**
  - severe hemorrhage trauma
  - indication to transfuse 4 pRBC & 4 Plasmas within 6h

TRAUCC study: Lille Hospital

Centre Hospitalier Régional Universitaire de Lille

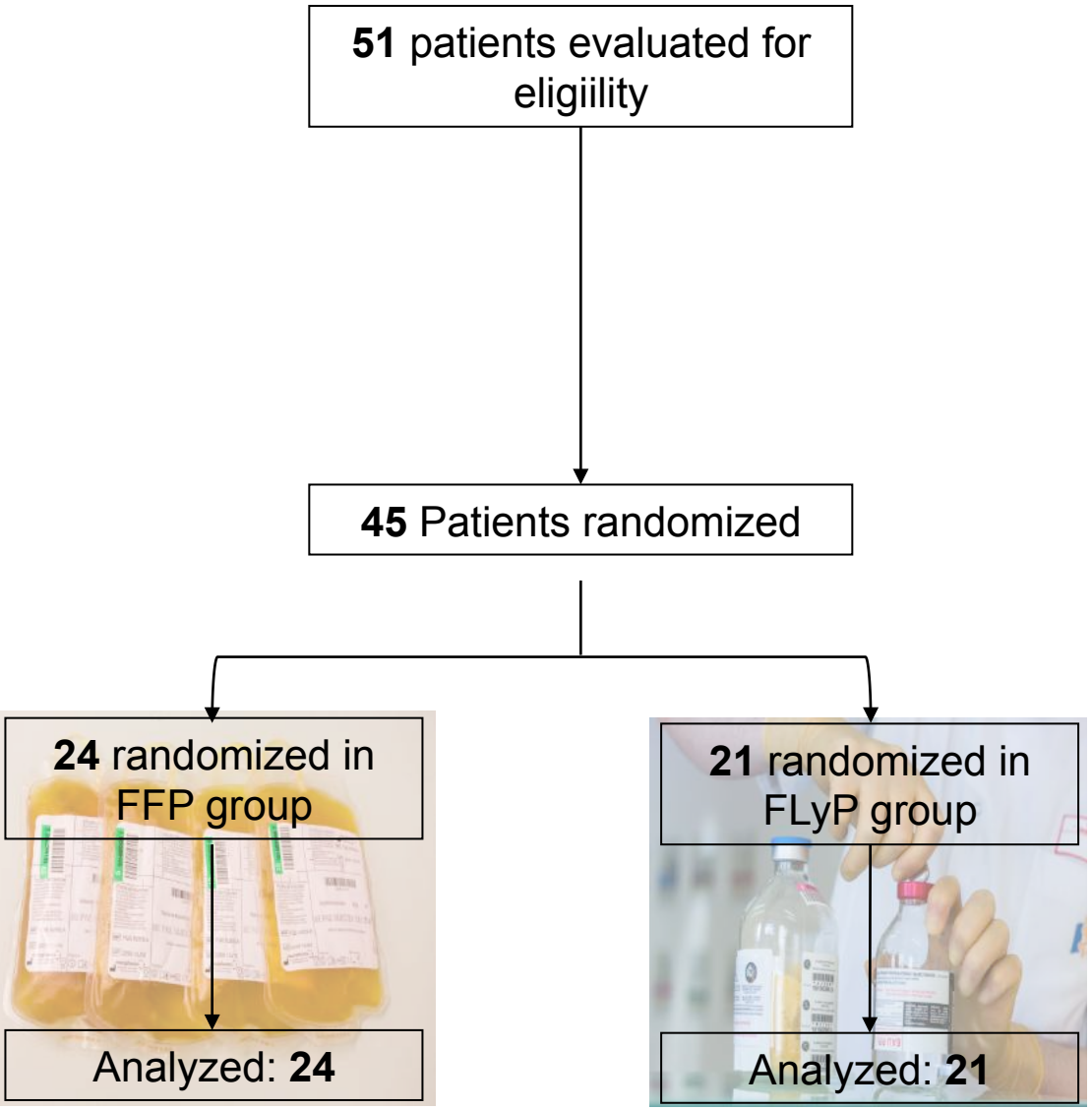
- **Primary endpoint**
  - **variation in fibrinogen level between inclusion and T+45 min**

- **Secondary endpoints**
  - **variations in other parameters:** *PT ratio, aPTT ratio, FII & FV, lactate*
  - **time-frame until transfusion**
  - **fibrinogen concentrate & labile blood products use within 24h**
  - **30-day mortality**

Pr S. Susen and Dr D. Garrigue

TRAUCC study: patients

UNPUBLISHED DATA

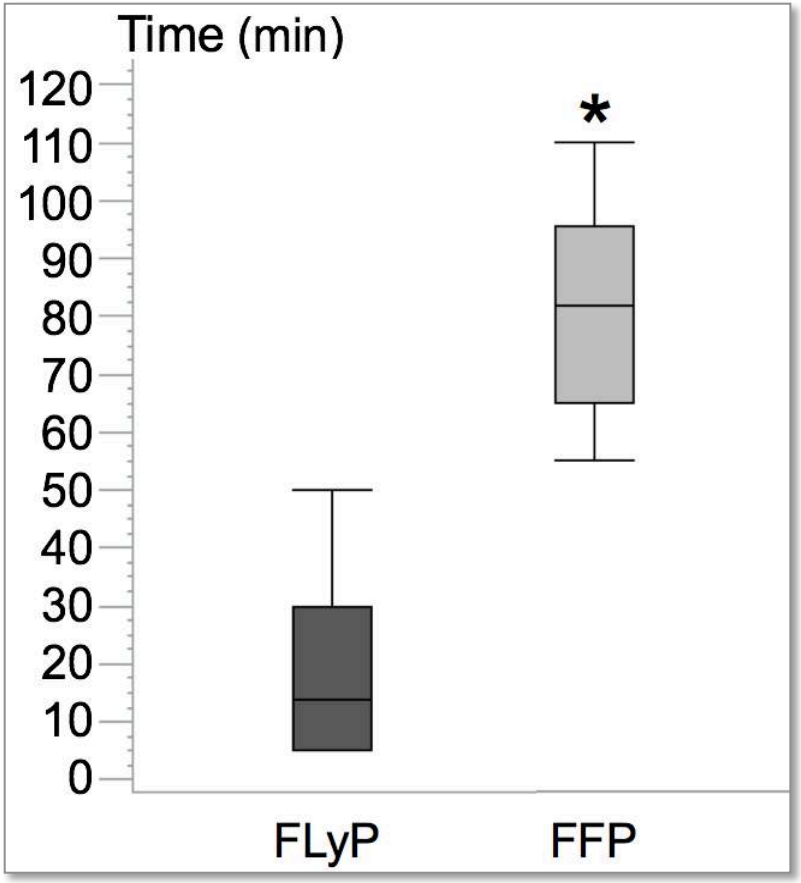


	FLyP (n=21)	FFP (n=24)
Age, years	47.9±17.3	38.0±15.6
Male sex, n (%)	17.0 (81.0)	16.0 (66.7)
Weight, kg	77±12	73±12
Mechanism: blunt trauma, n (%)	17 (81.0)	22.0 (91.7)
Injury Severity Score	24.0±9.7	27.5±11.4
n (%) with score >15	17 (81.0)	21 (87.5)
Glasgow Coma Score, median [IQR]	3 [3-15]	3 [3-13.5]
Systolic Blood Pressure, mmHg	90±23	92±19
n (%) with values <90 mmHg	13 (60.0)	13 (54.2)
Hemoglobin, g/dL	8.8±2.1	7.9±1.6
Platelet count, $x10^3/\mu L$	176±65	170±70
Tranexamic acid, n (%)	17 (81.0)	22 (91.7)

TRAUCC study: results

Centre Hospitalier Régional Universitaire de Lille

UNPUBLISHED DATA



	FLyP n = 21	FFP n = 24	p
From hospital **arrival to transfusion** of the first plasma	**37** [24-82]	**91** [85-106.5]	p<0.01
From randomization to **end of transfusion** of the fourth unit	**45** [45-70]	**100** [85-120]	p<0.01

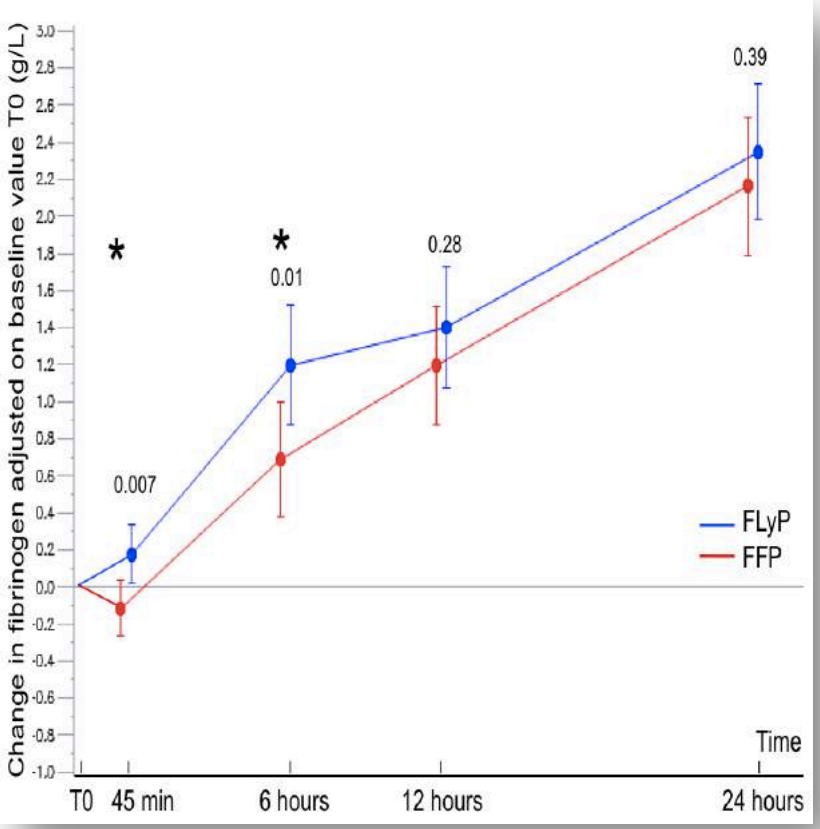
Interval between randomization and transfusion of the 1st plasma

Time-frame of transfusions

TRAUCC study: results

Centre Hospitalier Régional Universitaire de Lille

UNPUBLISHED DATA



		FLyP n=21	FFP n=24	Difference in change from baseline adjusted on baseline value (95% CI)	p
T0	[Fib] g/L	1.41 ±0.94	1.14 ±0.51		
T45		1.56 ±0.81	1.05 ±0.51		0.03
Δ Fib g/L		**0.18 ±0.08**	**-0.12 ±0.07**	**0.29 (0.08 to 0.50)**	**0.007**

Fibrinogen level significantly higher until H6

Fibrinogen increasing significantly higher in FLyP group

TRAUCC study: results

Centre Hospitalier Régional Universitaire de Lille

UNPUBLISHED DATA

24h after randomization	FLyP n=21		FFP n=24		p
	n	median [IQR]	n	median [IQR]	
Fibrinogen concentrates 1.5g doses	21	2 [0 - 3]	24	3 [2 - 4]	0.030
Crystalloids, 500ml doses	19	3 [1 - 4]	22	4 [3 - 5]	0.204
Colloids, 500ml doses	20	1.5 [1 - 2]	23	2 [1 - 4]	0.072
Platelet concentrate units	21	0 [0 - 1]	24	1 [0 - 2]	0.121
Red blood cell units	21	6 [4 - 9]	24	7 [6 - 11.5]	0.109
Plasma units	21	4 [4 - 8]	24	5.5 [4 - 9]	0.239

	FLyP n=21	FFP n=24	p
D30 - Mortality	4 19%	7 29%	0.5

Mortality wasn't an endpoint of the study

TRAUCC study: conclusions

Centre Hospitalier Régional Universitaire de Lille

- **FlyP corrects faster and better the post-traumatic coagulopathy as compared to FFP**

- **FLyP offers**
  - **availability**
  - **pathogen attenuation**
  - **RT-storage**
  - **quick reconstitution**
  - **ABO compatibility**

Larger use in civilian settings

1. **first plasma before thawing**
2. **massive casualties**

PREHO-PLYO Trial

Assessment of pre-hospital FLyP transfusion to prevent/treat coagulopathy associated with haemorrhagic shock

PREHO-PLYO Trial

Service de santé des armées

- **Prospective – randomized trial**

- **Multicenter trial**
  - Paris
  - Lyon
  - Annecy
  - Marseille

- **Primary objective**
  - to show the benefits of early FLyP transfusion in trauma patients
    - In terms of blood product use
    - In terms of survival

PREHO-PLYO Trial

Service de santé des armées

- **Inclusion criteria**
  - Severe haemorrhagic trauma patients
  - [SBP < 90 mmHg and HR > 108] or [SBP < 70 mmHg]

- **Primary study endpoint**
  - Improving PT ratio in the FLyP group
  - or INR (Coaguchek®)

- **Secondary endpoints**
  - Blood product consumption in hospital
  - 24 hours and 28 days survival rate
  - Feasibility & safety criteria: traceability of the FLYP, adverse events reporting & management of the multisite study.

PreHo-Plyo : first impressions (n = 20)

Service de santé des armées

UNPUBLISHED DATA

- **Technical issues**
  - starting point: september 2016
  - inclusions slower than expected (1/month/center)
    - less trauma
    - inclusion criteria restrictives +++
  - coagulation testing failure leading to non inclusion
- **Protocol modifications**
  - 4 additionnal centers included in the study
  - POC devices for coagulation monitoring

- **Results**
  - mortality 20%
  - 2 FLyP/patient +++
  - prehospital time-frame: 60-90min
  - 1 side-effect investigated
  - feeling of efficiency +++

Acknowledgments

- French Military Blood Institute
  - B. Clavier (MD),
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  - AC.Mendes (PharmD)
  - T. Pouget (MD)
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- Medical Military Research Center
  - N. Prat (MD, PhD)

French Dried Plasma Program

update on prehospital and emergency unit use for massive hemorrhage management

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French Military Blood Institute
Clamart – France