

# X JORNADA MULTIDISCIPLINAR DE ACTUALIZACIÓN EN EL MANEJO DEL SANGRADO



13:15 - 14:15h

## Mesa de debate PRO/CON: administración precoz de fibrinógeno en hemorragia masiva

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Organiza:  
**octapharma**



# Premisa inicial\*

**Este es un ejercicio de divertimento  
intelectual**

**\*No somos *talibanes* con las posturas PRO/CONTRA**



1.- La administración de fibrinógeno se debe hacer antes del diagnóstico de hipofibrinogenemia (antes de la monitorización), solo con la sospecha de ésta.

**PRO: LLAU**

**CON: QUINTANA**

2.- La administración de fibrinógeno en el contexto de una hemorragia masiva debe estar basada en “dosis fijas” y no en dosis ajustadas a la monitorización.

**PRO: QUINTANA**

**CON: LLAU**

3.- La administración de fibrinógeno se debe hacer exclusivamente mediante concentrado de fibrinógeno, no siendo válido el plasma como sustituto para reponer el déficit.

**PRO: QUINTANA**

**CON: LLAU**

4.- La administración de fibrinógeno debe estar acompañada siempre de la administración de CCP.

**PRO: LLAU**

**CON: QUINTANA**

5.- La administración de fibrinógeno exógeno no presenta problemas de tromboembolismo, por lo que es preferible una sobre-administración que una infra-administración.

**PRO: QUINTANA**

**CON: LLAU**



La administración de fibrinógeno se debe hacer antes del diagnóstico de hipofibrinogenemia (antes de la monitorización), solo con la sospecha de ésta

**PRO: JV Llau**

**CON: M Quintana**

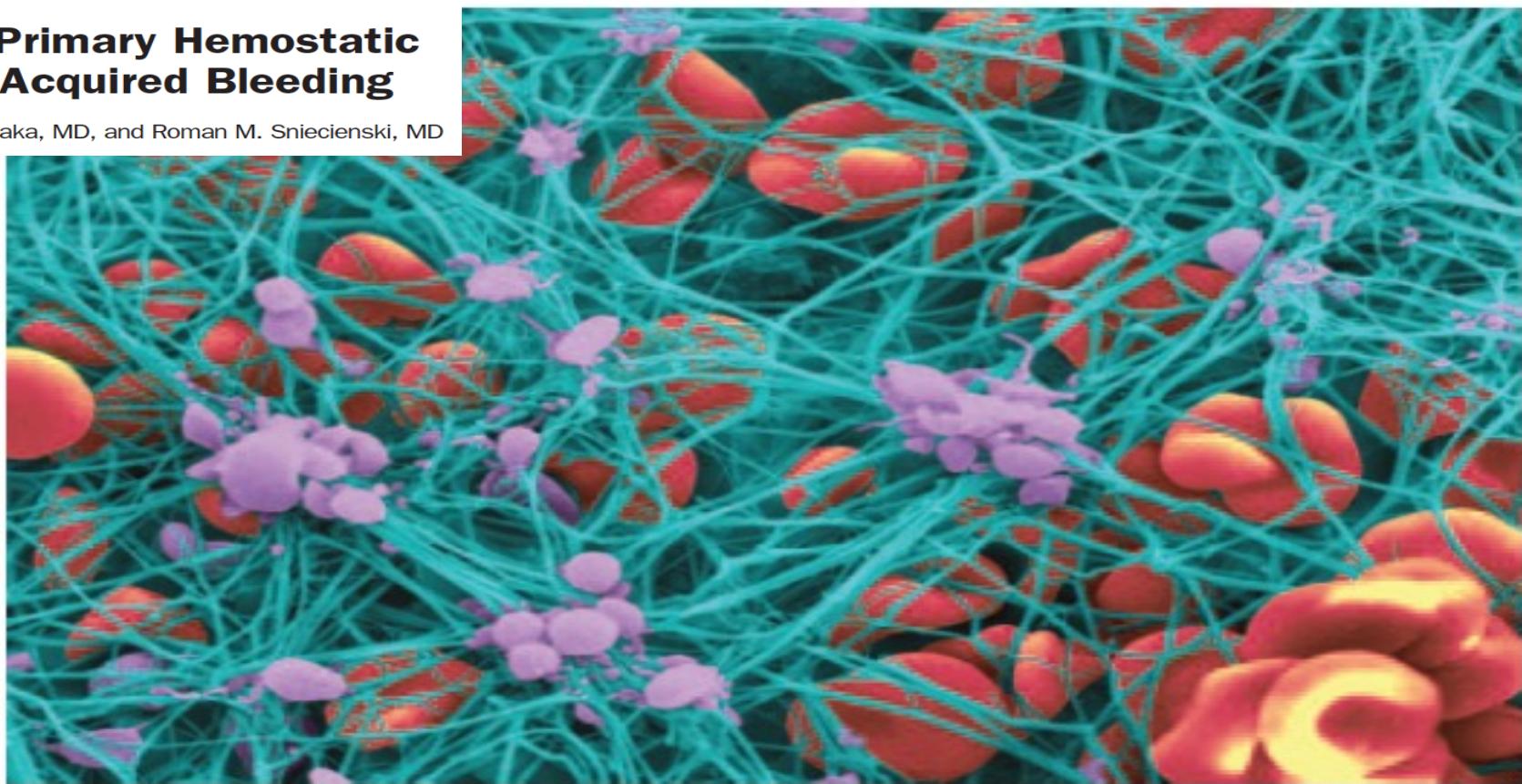
**1.- La administración de fibrinógeno se debe hacer antes del diagnóstico de hipofibrinogenemia (antes de la monitorización), solo con la sospecha de ésta**

CME

## Fibrinogen and Hemostasis: A Primary Hemostatic Target for the Management of Acquired Bleeding

Jerrold H. Levy, MD, FAHA, Fania Szlam, MMSc, Kenichi A. Tanaka, MD, and Roman M. Sniecienski, MD

(Anesth Analg 2012;114:261–74)



**Figure 2.** A fibrin blood clot: the constituent parts of a blood clot are shown (red blood cells, red; fibrin fibers, blue; platelet aggregates, purple). From John W. Weisel, PhD, University of Pennsylvania, with permission.

## Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial

B. Nascimento<sup>1,\*</sup>, J. Callum<sup>1</sup>, H. Tien<sup>1</sup>, H. Peng<sup>2</sup>, S. Rizoli<sup>3</sup>, P. A. Alam<sup>1</sup>, W. Xiong<sup>1</sup>, R. Selby<sup>1</sup>, A-M. Garzon<sup>1</sup>, C. Colavecchi A. Nathens<sup>1</sup>, and A. Beckett<sup>4</sup>

*British Journal of Anaesthesia*, 117 (6): 775–82 (201

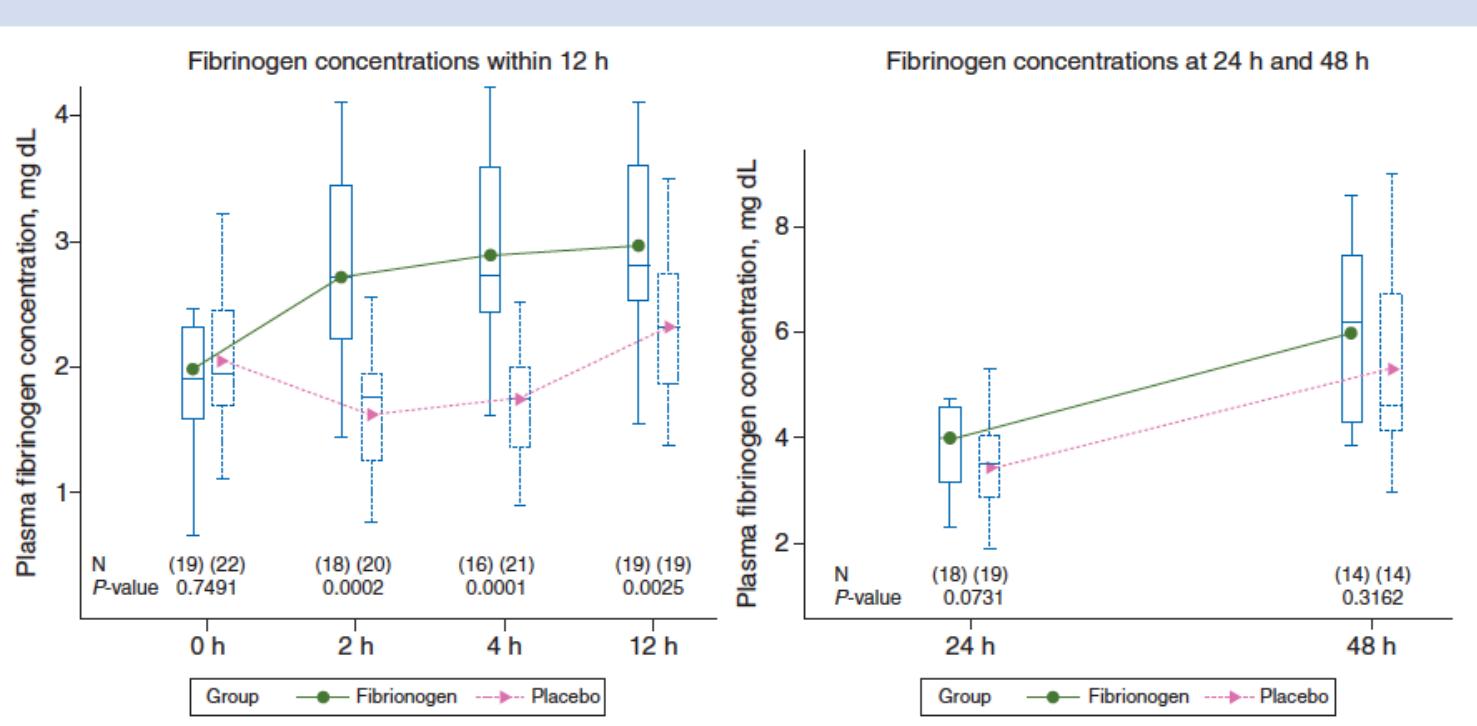
### Abstract

**Background.** Decreased plasma fibrinogen concentrations are associated with increased mortality. In North America and the UK, current guidelines recommend early infusion of fibrinogen concentrate (FC) during acute haemorrhage, which often occurs in trauma patients. The benefit of early FC infusion in trauma remains undetermined. The objective of this trial was to evaluate the safety and feasibility of early infusion of FC in trauma.

**Methods.** Fifty hypotensive (systolic arterial pressure  $\leq 100$  mmHg) patients with major trauma were randomised to either 6 g of FC or placebo, between Oct 2014 and Mar 2015. Safety was assessed by the proportion of patients receiving FC. Plasma fibrinogen concentration was measured, and 28-day mortality was assessed.

**Results.** Overall, 96% (43/45) [95% CI 86–99%] of patients received FC in the fibrinogen group compared with 50% (23/45) in the placebo group, respectively ( $P=1.00$ ). Plasma fibrinogen concentrations increased over time in both groups, with the largest difference at three h (2.9 mg dL $^{-1}$  vs 1.6 mg dL $^{-1}$ ,  $P=0.0002$ ). No thromboembolic complications were similar between groups.

**Conclusions.** Early infusion of FC is feasible and increases plasma fibrinogen concentration during trauma resuscitation. Larger trials are justified.



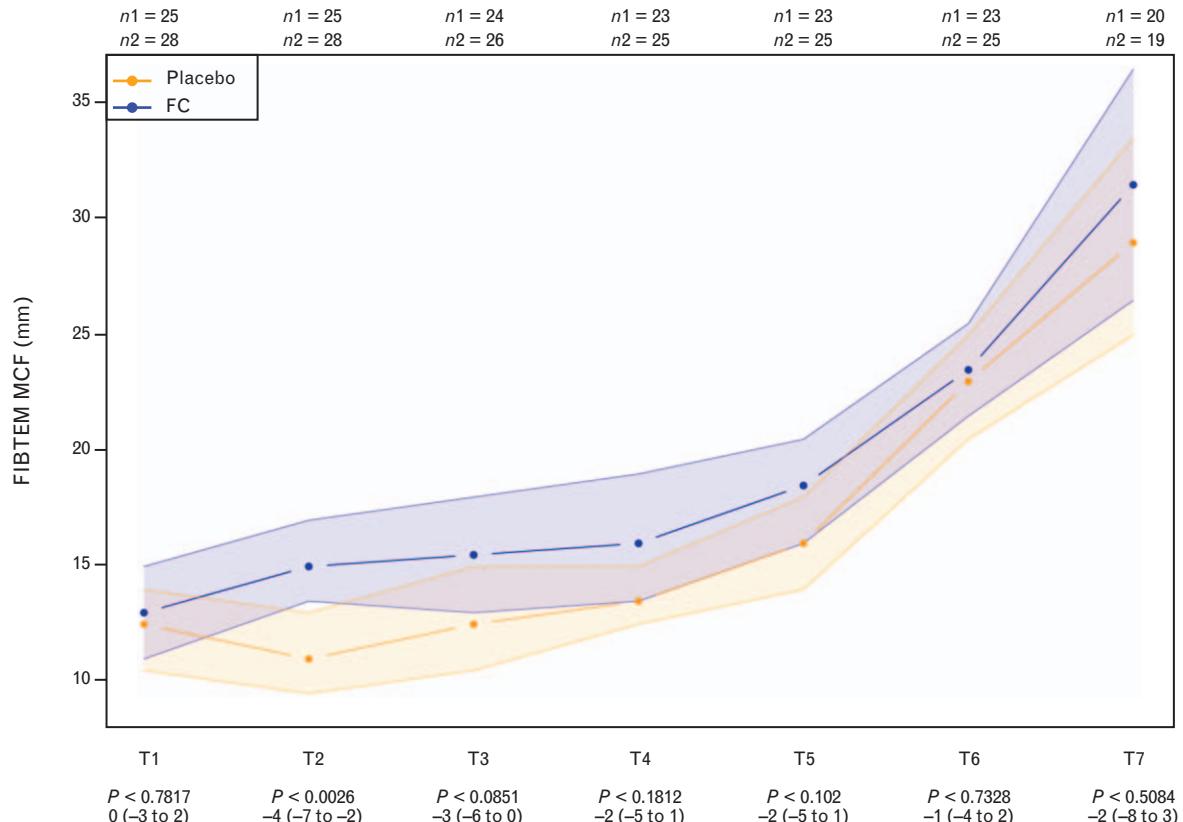
**Fig 2** Plasma Fibrinogen Concentrations throughout 48 h of Hospitalization.  
Data are presented as means (standard deviation) or median (interquartile ranges)  
FC, fibrinogen concentrate

## Efficacy of prehospital administration of fibrinogen concentrate in trauma patients bleed to bleed (FlinTIC)

A multicentre, double-blind, placebo-controlled randomised pilot study

Bernhard Ziegler, Mirjam Bachler, Hubert Haberfellner, Christiane Kainz, Tobias Hell, Marc Kaufmann, Marc Maegele, Uriel Martin, Herbert Schöchl, Bettina Schenk, Markus Thaler, Benjamin Wenzl, Ivana Zykova, Christine Wimmer, Dietmar Fries, the FlinTIC Study Group

**Fig. 3** Changes in FIBTEM maximum clot firmness (FIBTEM MCF) between baseline (T1) and 7 days posttrauma (T7)



Data are presented as median [IQR] (boxes; as well as minimum and maximum plus outliers as dots). P values are given with difference between groups and 95% CI. Horizontal dashed red lines show boundaries of the normal range. FC, Factor Concentrate group; n1, Placebo group; n2, FC group.

**MAIN OUTCOME MEASURES** Primary outcome was the assessment of clot stability as reflected by maximum clot firmness in the FIBTEM assay (FIBTEM MCF) before and after administration of the study drug.

**RESULTS** Median FIBTEM MCF decreased in the placebo group between baseline (before administration of study treatment) and admission to the Emergency Department, from a median of 12.5 [IQR 10.5 to 14] mm to 11 [9.5 to 13] mm ( $P=0.0226$ ), but increased in the FC Group from 13 [11 to 15] mm to 15 [13.5 to 17] mm ( $P=0.0062$ ). The median between-group difference in the change in FIBTEM MCF was 5 [3 to 7] mm ( $P<0.0001$ ). Median fibrinogen plasma concentrations in the fibrinogen concentrate Group were kept above the recommended critical threshold of  $2.0 \text{ g l}^{-1}$  throughout the observation period.

**CONCLUSION** Early fibrinogen concentrate administration is feasible in the complex and time-sensitive environment of pre-hospital trauma care. It protects against early fibrinogen depletion, and promotes rapid blood clot initiation and clot stability.

**TRIAL REGISTRY NUMBERS** EudraCT: 2010-022923-31 and ClinicalTrials.gov: NCT01475344.

Published online 28 October 2020



## PRIMERA PREGUNTA

¿Estamos de acuerdo en administrar ácido tranexámico de inicio en el politrauma con HM? → SÍ  
¿Incluso antes de monitorizar la fibrinólisis? → SÍ

## SEGUNDA PREGUNTA

¿Estamos de acuerdo en que el fibrinógeno se consume en el sangrado masivo? → SÍ  
¿Hay déficit de fibrinógeno en los pacientes con sangrado masivo? → SÍ  
¿Podemos administrarlo incluso antes de su diagnóstico, solo con la sospecha? → SÍ





**1.- La administración de fibrinógeno se debe hacer antes del diagnóstico de hipofibrinogenemia (antes de la monitorización), solo con la sospecha de ésta**

Fisiológicamente

# AGRESIÓN

COAGULOPATÍA INDUCIDA POR LA AGRESIÓN

Activación sistema coagulación

Trombina burst

Fibrinólisis

Inactivación PAI-1

↑ Proteína C activada

Coagulopatía de consumo

HIPERFIBRINOLISIS

DAÑO TISULAR

Medicación

Comorbilidades

INFLAMACIÓN

Lesión endotelial

↑ Permeabilidad

Hipoxia tisular

HEMORRAGIA

Hipovolemia

Pérdida de factores

Pérdida de plaquetas

Acidosis

Hipotermia

Hipocalcemia

Hiper glucemia

RESUCITACIÓN

Hemodilución

Anemia

SHOCK

COAGULOPATÍA

SANGRADO MASIVO

# Fisiopatológicamente en el sangrado



**Defecto en la firmeza del coágulo**

Debido a la deficiencia (cuantitativa) de fibrinógeno y plaquetas



**Defecto en la estabilidad del coágulo**

Debido a la hiperfibrinolisis y a la deficiencia de FXIII.



**Prolongación de la formación del coágulo**

Debido a deficiencia de varios factores por consumo y dilución

# Analíticamente

## 1. Tranexamic acid

Tranexamic acid 1-2 g i.v.

## 2. Fibrinogen first dose



## 3. Prothrombin Complex Concentrate (PCC)

Consider 20–40 IU/kg

## 4. FFP (in case of massive transfusion)

Consider FFP in 1:1 ratio in the case of persistent bleeding after PCC

## 5. Others

Consider Desmopressin: 0.3–0.4 µg/kg in case of suspected blood platelet disorder

Consider repetition of tranexamic acid 1 g / FXIII 2500 IU

rFVIIa: 90 µg/kg initial bolus i.v.

## Periodo de Resucitación Inicial:

Se define como resucitación inicial al periodo comprendido entre la llegada del paciente a Urgencias y la **obtención de los primeros resultados analíticos** (parámetros de coagulación, recuento de Plaquetas, nivel de Fibrinógeno) o de **Tests Viscoelásticos**.

Previo a la recepción de los resultados que muestren el grado de coagulopatía, el tratamiento inicial con Componentes Sanguíneos en un **ratio prefijado** constituye un manejo razonable...

... y una vez se disponga de dichos resultados, la terapia transfusional debería ser **guiada** por ellos.

Some means with which to evaluate trauma-related coagulopathy have been developed [370], however, these largely confirm the main pathophysiological mechanisms described above [371, 372]. While several general pathophysiological mechanisms can be described that result in trauma-related coagulopathy, it is essential to quickly determine the type and degree of coagulopathy in the individual patient in order to determine the most prominent cause or causes to be treated specifically in a goal-directed manner [373].

Early monitoring of coagulation is essential to detect trauma-induced coagulopathy and to define the main causes, including hyperfibrinolysis [13, 25, 179, 183, 374]. Early therapeutic intervention does improve coagulation tests [375], reduce the need for transfusion of RBC, FFP and platelets [12, 376], reduce the incidence of post-traumatic multi-organ failure, shorten length of hospital stay [12] and may improve survival [377, 378]. Interestingly, the success of early algorithm-based and goal-directed coagulation management in reducing transfusions and improving outcome, including mortality, has also been shown in cardiac surgery [202, 379–381]. Therefore, early algorithm-based and goal-directed coagulation management treatment is likely to improve the outcome of severely injured patients [382, 383]. This has indeed been shown in a prospective randomised study [384] and in a large study assessing the introduction of such a concept in two large Italian trauma centres [385]. However, there are also studies in which no survival benefit could be shown [375, 386, 387]; variation in published results may be due to choice of coagulation



**Riesgo de sobremedicación innecesaria.  
No evidencia constatada tipo 1A de su administración empírica.**

**Perdida de tiempo con respecto a otras maniobras de resucitación prioritarias.**



La administración de fibrinógeno en el contexto de una hemorragia masiva debe estar basada en “dosis fijas” y no en dosis ajustadas a la monitorización.

**PRO: M Quintana**

**CON: JV Llau**

**2.- La administración de fibrinógeno en el contexto de una hemorragia masiva debe estar basada en “dosis fijas” y no en dosis ajustadas a la monitorización.**



## Abstract

Fibrinogen is a key coagulation protein that is necessary for the formation of stable clots. Fibrinogen levels have been reported to be one of the first to fall during major haemorrhage reflecting consumption, dilution and fibrinogenolysis. Its role in acquired major haemorrhage, both in relation to the contribution it plays to the coagulopathy of major bleeding that can exacerbate bleeding and how effective fibrinogen supplementation can be at improving clinical outcomes, has received a great deal of attention over the last 10 - 15 years. This commentary focuses on just three of the more recent publications from the last 5 years that provide some of the evidence behind how we can think about fibrinogen as a haemostatic treatment for acquired major haemorrhage and how we can use the laboratory thresholds to guide therapy.

## Journal Pre-proof

Fibrinogen replacement in haemostatic resuscitation: dose, laboratory targets and product choice

Nicola Curry

PII: S0887-7963(21)00037-7  
DOI: <https://doi.org/10.1016/j.trmr.2021.06.005>  
Reference: YTMRV 50663

To appear in: *Transfusion Medicine Reviews*



Please cite this article as: Nicola Curry , Fibrinogen replacement in haemostatic resuscitation: dose, laboratory targets and product choice, *Transfusion Medicine Reviews* (2021), doi: <https://doi.org/10.1016/j.trmr.2021.06.005>

## ROTEM

Rotational Thromboelastography

- FIBRINOGEN

If FIBTEM CA5 < 10mm

Give additional 4g equivalent of fibrinogen  
(as cryoprecipitate or concentrate)

- PLATELETS

If (EXTEM CA5 - FIBTEM CA5) < 30 mm

Give 1 additional pool of platelets

- PLASMA

If EXTEM CA5 ≥ 40 mm AND EXTEM CT > 80s

Give 4 additional units of plasma

- TRANEXAMIC ACID

If EXTEM LI30 < 85%

Give additional 1g tranexemic acid

## TEG

Thromboelastography

- FIBRINOGEN

If FF TEG MA < 20mm

Give additional 4g equivalent of fibrinogen  
(as cryoprecipitate or concentrate)

- PLATELETS

If (rTEG MA - FF TEG MA) < 45 mm

Give 1 additional pool of platelets

- PLASMA

If rTEG MA ≥ 65 mm AND rTEG ACT > 120 s

Give 4 additional units of plasma

- TRANEXAMIC ACID

If rTEG LY30 10%

Give additional 1g tranexemic acid

## CCT

Conventional Coagulation Tests

- FIBRINOGEN

If fibrinogen < 2g/L

Give additional 4g equivalent of fibrinogen  
(as cryoprecipitate or concentrate)

- PLATELETS

If platelets < 100 X 10<sup>9</sup>/L

Give 1 additional pool of platelets

- PLASMA

If EXTEM CA5 ≥ 40 mm AND EXTEM CT > 80 s

Give 4 additional units of plasma

FibAT>5

# Analíticamente

## 1. Tranexamic acid

Tranexamic acid 1–2 g i.v.

## 2. Fibrinogen first dose

Hb (g/dL)	> 12	12–10	10–8	Hb < 8					
BE (mmol/L)	> -6	< -6	> -6	< -6	< -10	> -2	< -6	< -10	
Fib (in g)	--	--	0–1 g	1–2 g	2–3 g	3–4 g	2–3 g	3–4 g	4–6 g

## 3. Prothrombin Complex Concentrate

## Fibrinogen

## 4. FFP (in case of massive transfusion)

Consider FFP in 1:1 ratio in the case of persistent bleeding after PCC

## 5. Others

Consider Desmopressin: 0.3–0.4 µg/kg in case of suspected blood platelet disorder

Consider repetition of tranexamic acid 1 g / FXIII 2500 IU

rFVIIa: 90 µg/kg initial bolus i.v.

signs [110]. Another study showed that fibrinogen levels show strong correlation with rapidly obtainable routine laboratory parameters, such as base excess (BE) and Hb [108]. These two parameters might provide a sensitive and quick tool to identify major trauma patients that are at risk of reaching critically low fibrinogen. Both parameters are now included in the European Guidelines for bleeding following trauma [14]. Initial Hb is used as indicator for severe bleeding, associated with coagulopathy (Grade 1B) and BD measurements to estimate the extent of bleeding (Grade 1B) [14].

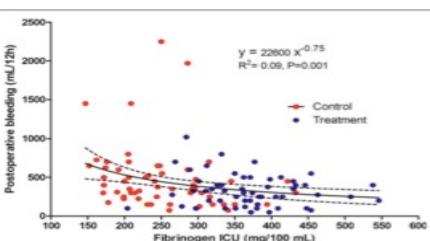
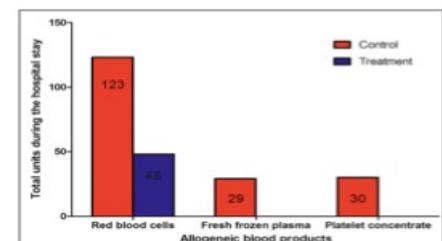
ORIGINAL RESEARCH

Dosis Promedio: 4 gr.



### Randomized, Double-Blinded, Placebo-Controlled Trial of Fibrinogen Concentrate Supplementation After Complex Cardiac Surgery

Marco Ranucci, MD; Ekaterina Baryshnikova, PhD (Biol.); Giulia Beatrice Crapelli, MD; Niels Rahe-Meyer, MD; Lorenzo Menicanti, MD; Alessandro Frigiola, MD; for the Surgical Clinical Outcome REsearch (SCORE) Group\*



PRO

X JORNADA MULTIDISCIPLINAR  
DE ACTUALIZACIÓN EN EL  
MANEJO DEL SANGRADO



Estandarización de la práctica clínica y de los protocolos TM.  
Retraso de pruebas diagnósticas y monitorización.  
*“Mejor que sobre” en las fases iniciales.*



2.- La administración de fibrinógeno en el contexto de una hemorragia masiva debe estar basada en “dosis fijas” y no en dosis ajustadas a la monitorización.

## ■ REVIEW ARTICLE

## Trauma Bleeding Management: The Concept of Goal-Directed Primary Care

Herbert Schöchl, MD,\*† and Christoph J. Schlimp, MD†

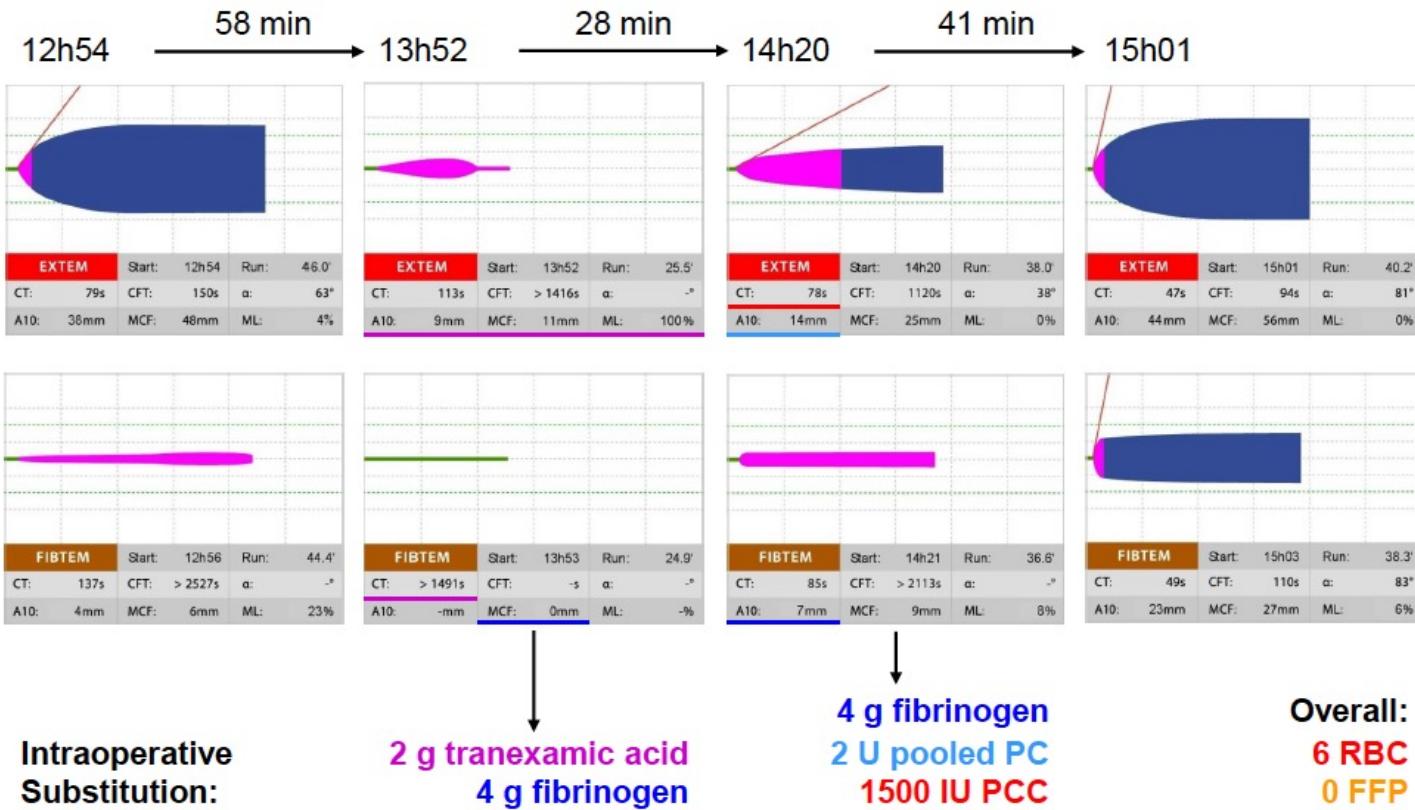
The early and aggressive high-volume administration of fresh frozen plasma, platelet concentrates, and red blood cells (RBCs), using ratio-driven massive transfusion protocols, has been adopted by many for the treatment of trauma-induced coagulopathy and hemorrhagic shock. However, the optimal ratio of RBC: fresh frozen plasma and RBC:platelet concentrate is still under investigation. In some European trauma centers, hemostatic agents such as fibrinogen concentrate, prothrombin complex concentrates, and antifibrinolytics are integral parts of goal-directed massive transfusion protocols. Both a ratio-driven coagulation therapy and a point-of-care-guided coagulation management based on coagulation factor concentrates aim for the same target—the rapid prevention and treatment of shock and coagulopathy to prevent death from traumatic hemorrhage. In this review, we compare the evidence relating to the effectiveness and safety of the ratio-driven and goal-directed approaches to trauma-induced coagulopathy to draw attention to the potential benefits and drawbacks associated with these management strategies. (Anesth Analg 2014;119:1064–73)



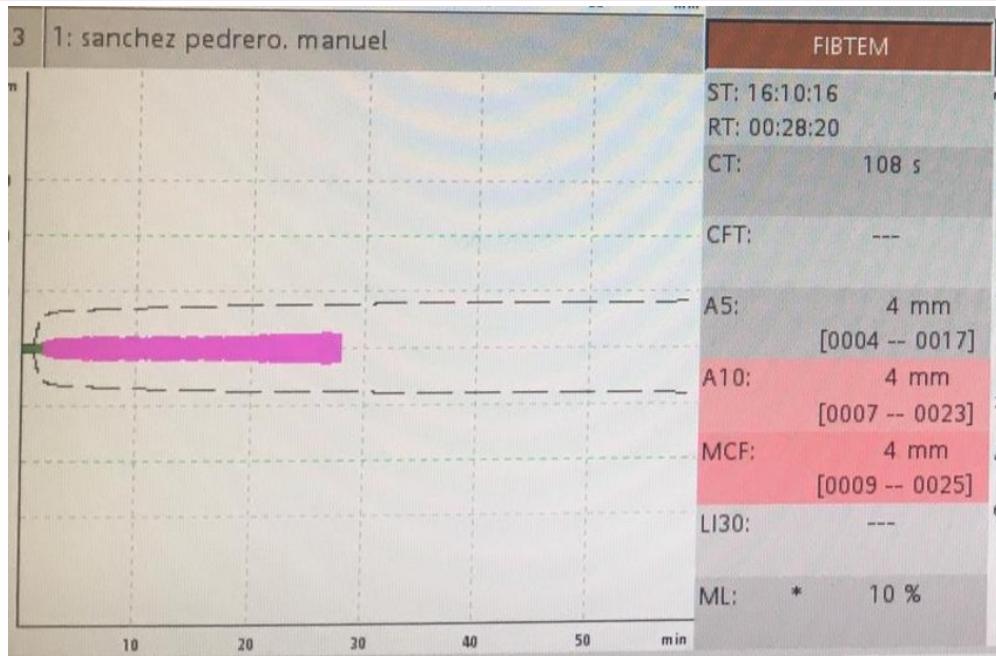
## Dynamics of POC testing and hemostatic intervention in a woman with PPH and hyperfibrinolysis



K. Gorlinger



# CONTRA



¿Creen ustedes que tenemos que administrar la misma dosis independientemente del resultado del FIBTEM en el ROTEM?

No estoy de acuerdo, porque si es así, lo mejor es NO MONITORIZAR, porque vamos a hacer lo mismo independientemente del resultado...





La administración de fibrinógeno se debe hacer  
exclusivamente mediante concentrado de fibrinógeno, no  
siendo válido el plasma para reponer el déficit.

**PRO: M Quintana**

**CON: JV Llau**

**3.- La administración de fibrinógeno se debe hacer exclusivamente mediante concentrado de fibrinógeno, no siendo válido el plasma como sustituto para reponer el déficit.**



## • Plasma fresco congelado 2,5 g/L (0,9-3)



## • Crioprecipitado 14 g/L (3-30)



## • Concentrado de fibrinógeno 15-20 g/L



Guía	Año	Preferencia	Referencia
ESAC	2017	CF	Kozack-Langenecker et al. Eur J Anesthesiol 2017; 34:332-395
(SCGH /Australia)	2017	Crio	SCGH blood transfusion committee. April2017
ACS	2018	CF	ACS. Trauma Quality Improvement Program Massive transfusion in trauma. 2018
BSH	2018	Crio	Green L et al. British Journal of Haematology 2018, 181:54-67 Curry NS et al. British Journal of Haematology 2018; 6, 182:789-806
ASCV	2019	Crio	Raphael J et al. Anesth Analg 2019, 129 (5) 1209-1222
EG Mayor Bleeding	2019	CF	Spahn DR et al. Critical Care 2019, 23:98
EACA	2019	CF	Erdoes G et al. Anaesthesia 2019, 74: 1589-1600

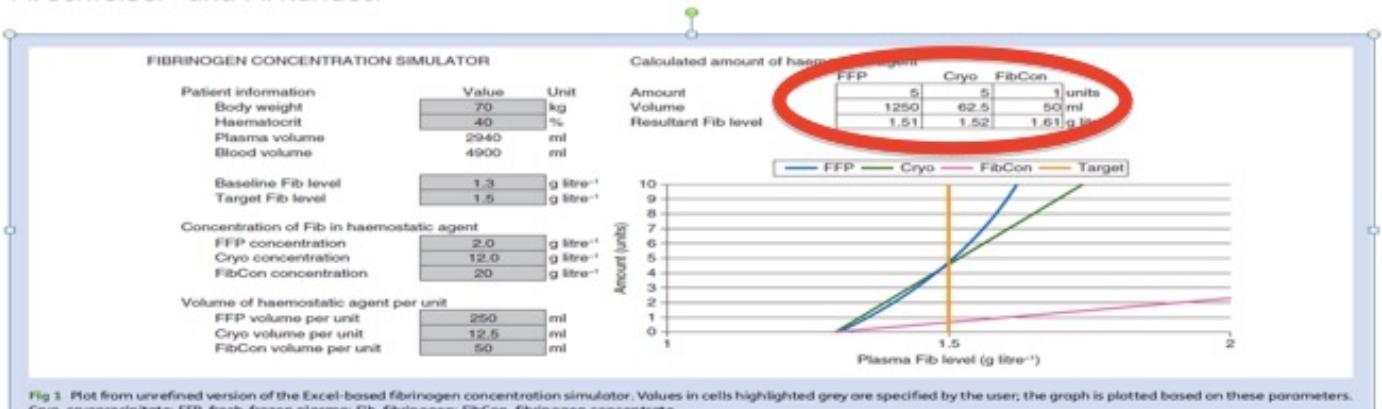
BJA Advance Access published August 9, 2014

British Journal of Anaesthesia Page 1 of 11  
doi:10.1093/bja/aeu086

BJA

## Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate

P. W. Collins<sup>1\*</sup>, C. Solomon<sup>2,3</sup>, K. Sutor<sup>4</sup>, D. Crispin<sup>4</sup>, G. Hochleitner<sup>5</sup>, S. Rizoli<sup>6</sup>, H. Schöchl<sup>7,8</sup>, M. Schreiber<sup>9</sup> and M. Ranucci<sup>10</sup>





Review

## Management of Coagulopathy in Bleeding Patients

Stefan Hofer<sup>1,\*</sup>, Christoph J. Schlimp<sup>2,3</sup>, Sebastian Casu<sup>4</sup> and Elisavet Grouzi<sup>5</sup>

Los niveles de fibrinógeno en sangre varían mucho por lo tanto es difícil alcanzar niveles adecuados empleando PFC por lo que se necesitarán grandes volúmenes del mismo. Esto aumenta el riesgo de generar TACO

Theusinger, O.M.; Baulig,W.; Seifert, B.; Emmert, M.Y.; Spahn, D.R.; Asmis, L.M. Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. *Br. J. Anaesth.* **2011**, *106*, 505–511. [CrossRef]

Tanaka, K.A.; Esper, S.; Bolliger, D. Perioperative factor concentrate therapy. *Br. J. Anaesth.* **2013**, *111* (Suppl. 1), i35–i49

**Un modelo matemático** compara los niveles de fibrinógeno con la cantidad de PFC necesario para aumentar de 0,75 a 1,75 siendo el resultado imposible de realizar ya que el volumen del PFC **aumentaba de manera exponencial** al acercarse a los valores de FIB requeridos.

Collins, P.W.; Solomon, C.; Sutor, K.; Crispin, D.; Hochleitner, G.; Rizoli, S.; Schochl, H.; Schreiber, M.; Ranucci, M. Theoretica modelling of fibrinogen supplementation with therapeutic pl113, 585asma, cryoprecipitate, or fibrinogen concentrate. *Br. J. Anaesth.* **2014**, –595.



Kozek-Langenecker et al. *Critical Care* 2011, 15:R239  
<http://ccforum.com/content/15/5/R239>



RESEARCH

Open Access

## Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review

Sibylle Kozek-Langenecker<sup>1\*</sup>, Benny Sørensen<sup>2,3</sup>, John R Hess<sup>4</sup> and Donat R Spahn<sup>5</sup>

- las guías europeas recomiendan el FIB como primera línea de tratamiento en la hemorragia grave asociada a hipoFIB
- agentes como crioprecipitados, fibrinógeno o complejo protrombínico parecen ser superiores al PFC como primera línea de tratamiento. La comparación directa de FIB fue superior al PFC reduciendo la hemorragia, necesidad de otros hemoderivados y estancia hospitalaria. Un estudio por Khan et al. demostró que pacientes que reciben una trasfusión mixta de PFC y hematíes con suplemento de fibrinógeno de manera tardía o sin fibrinógeno no mostraban mejoría en niveles de lactato o parámetros de ROTEM.

Kozek-Langenecker, S.A.; Ahmed, A.B.; Afshari, A.; Albaladejo, P.; Aldecoa, C.; Barauskas, G.; De Robertis, E.; Faraoni, D.; Filipescu, D.C.; Fries, D.; et al. Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology: First update 2016. *Eur. J. Anaesthesiol.* 2017, 34, 332–395.

Kozek-Langenecker, S.; Sørensen, B.; Hess, J.R.; Spahn, D.R. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: A systematic review. *Crit. Care* 2011, 15, R239.

Khan, S.; Brohi, K.; Chana, M.; Raza, I.; Stanworth, S.; Gaarder, C.; Davenport, R. Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. *J. Trauma Acute Care Surg.* 2014, 76, 561–567.

## Concentrados de Fibrinógeno: ventajas

- Inactivación viral (**mayor seguridad**)
- Bajo riesgo trombótico (**fibrinógeno purificado**)
- Sin riesgo de TRALI o TACO
- Cantidades conocidas de fibrinógeno (**dosificación precisa**)
- Bajo volumen de infusión
- No necesita compatibilidad ABO
- No necesita descongelación (**rápida administración**)
- El PFC aporta poco FI y mucho volumen
- El crioprecipitado aporta poco FI y más factores de la coagulación
- El tiempo es muy importante en el reemplazo de FI
- El concentrado de FNG es el producto de elección para el reemplazo de fibrinógeno

National Advisory Committee | Comité consultatif national sur  
on Blood and Blood Products | le sang et les produits sanguins  
NAC STATEMENT ON FIBRINOGEN CONCENTRATE WORKING GROUP

However, fibrinogen concentrate is pathogen inactivated and has a preferred **safety profile** in terms of transmissible disease risk as compared to frozen plasma and cryoprecipitate. Furthermore, fibrinogen concentrate offers many logistical advantages, including a **more precise fibrinogen dose**, simpler preparation (without need for thawing and with capability for **bedside reconstitution**), and efficiency of administration

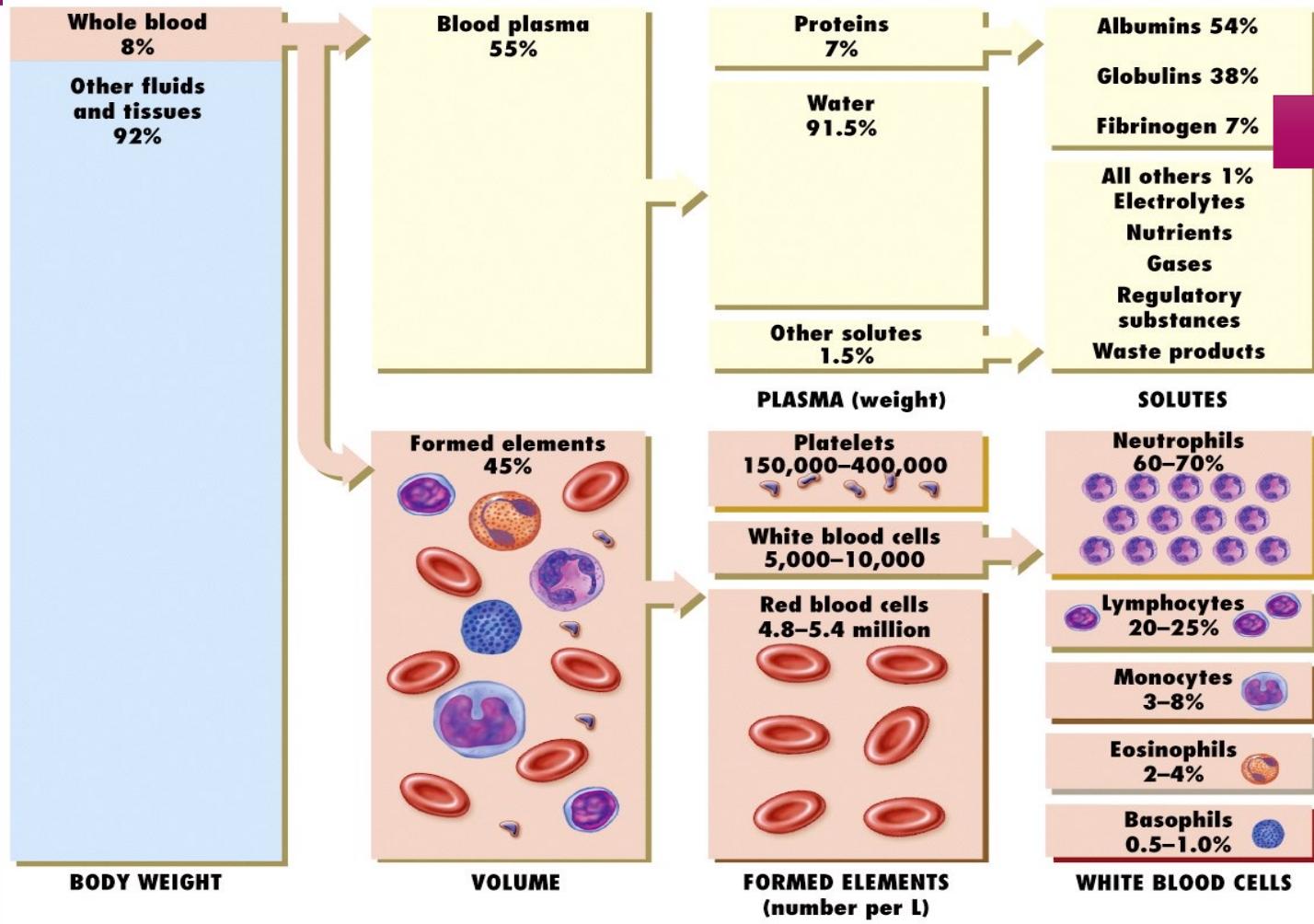


Composición del plasma.  
Disfibrinogenemia.

Viales de contenido estandarizado entre lotes.  
Reposición *real no a ciegas*.



**3.- La administración de fibrinógeno se debe hacer exclusivamente mediante concentrado de fibrinógeno, no siendo válido el plasma como sustituto para reponer el déficit.**



2-4 g/L

0.6-1.2 g/300 mL  
de cada unidad  
de plasma



	Plasma fresco
Factor II	1
Factor VII	1
Factor IX	1
Factor X	1
Proteína C	1
Proteína S	1
Antitrombina	1
Heparina	-
Inactivación viral Eliminación	Azul de metíleno



**Alrededor de 300 UI de  
cada factor de la  
coagulación por cada  
300 mL de plasma**



¿Creen ustedes que NO SE PUEDE reponer en ningún caso FIBRINÓGENO con plasma?

Pues yo no estoy de acuerdo, porque, si bien el plasma puede que no sea la fuente ÓPTIMA de fibrinógeno, desde luego en algunas ocasiones se debe poder recurrir a él





La administración de fibrinógeno debe estar acompañada  
siempre de CCP.

**PRO: JV Llau**

**CON: M Quintana**

**CONTRA**

**X** JORNADA MULTIDISCIPLINAR  
DE ACTUALIZACIÓN EN EL  
MANEJO DEL SANGRADO



**4.- La administración de fibrinógeno debe estar  
acompañada siempre de la administración de CCP...**

	<b>Plasma fresco</b>	<b>Octaplex®</b>	<b>Beriplex®</b>	<b>Prothromplex Inf®</b>
Factor II	1	11-38	20-48	30
Factor VII	1	9-24	10-25	25
Factor IX	1	25	20-31	30
Factor X	1	18-30	22-60	30
Proteína C	1	7-31	15-45	>20
Proteína S	1	7-32	13-26	14-16
Antitrombina	1	–	0,2-1,5	0,75-1,5
Heparina	–	5-12,5	0,4-2,0	<15
Inactivación viral Eliminación	Azul de metileno	Solvente-detergente Nanofiltración	Pasteurización Nanofiltración	Vapor Nanofiltración

Contenido de factores coagulantes y anticoagulantes en el plasma y en los concentrados de complejo protrombínico comercializados en España (datos en UI/ml)

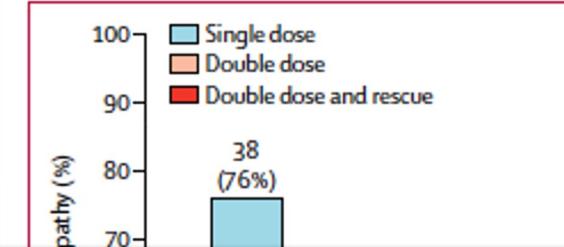


# Reversal of trauma-induced coagulopathy using first-coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

Petra Innerhofer, Dietmar Fries, Markus Mittermayr, Nicole Innerhofer, Daniel von Langen, Tobias Hell, Gottfried Gruber, Stefan S. Barbara Friesenecker, Ingo H. Lorenz, Mathias Ströhle, Verena Rastner, Susanne Trübsbach, Helmut Raab, Benedikt Treml, Dieter W. Benjamin T.

**Findings** Between March 3, 2012, and Feb 20, 2016, 100 out of 292 screened patients were included and randomly allocated to FFP (n=48) and CFC (n=52). Six patients (four in the FFP group and two in the CFC group) discontinued treatment because of overlooked exclusion criteria or a major protocol deviation with loss of follow-up. 44 patients in the FFP group and 50 patients in the CFC group were included in the final interim analysis. The study was terminated early for futility and safety reasons because of the high proportion of patients in the FFP group who required rescue therapy compared with those in the CFC group (23 [52%] in the FFP group vs two [4%] in the CFC group; odds ratio [OR] 25·34 [95% CI 5·47–240·03], p<0·0001) and increased need for massive transfusion (13 [30%] in the FFP group vs six [12%] in the CFC group; OR 3·04 [0·95–10·87], p=0·042) in the FFP group. Multiple organ failure occurred in 29 (66%) patients in the FFP group and in 25 (50%) patients in the CFC group (OR 1·92 [95% CI 0·78–4·86], p=0·15).

**Interpretation** Our results underline the importance of early and effective fibrinogen supplementation for severe clotting failure in multiple trauma. The available sample size in our study appears sufficient to make some conclusions that first-line CFC is superior to FFP.



Considering that coagulopathy might reoccur, one or

were administered during the period from admission to the ICU until 24 h at the ICU) according to randomisation and

use medication.

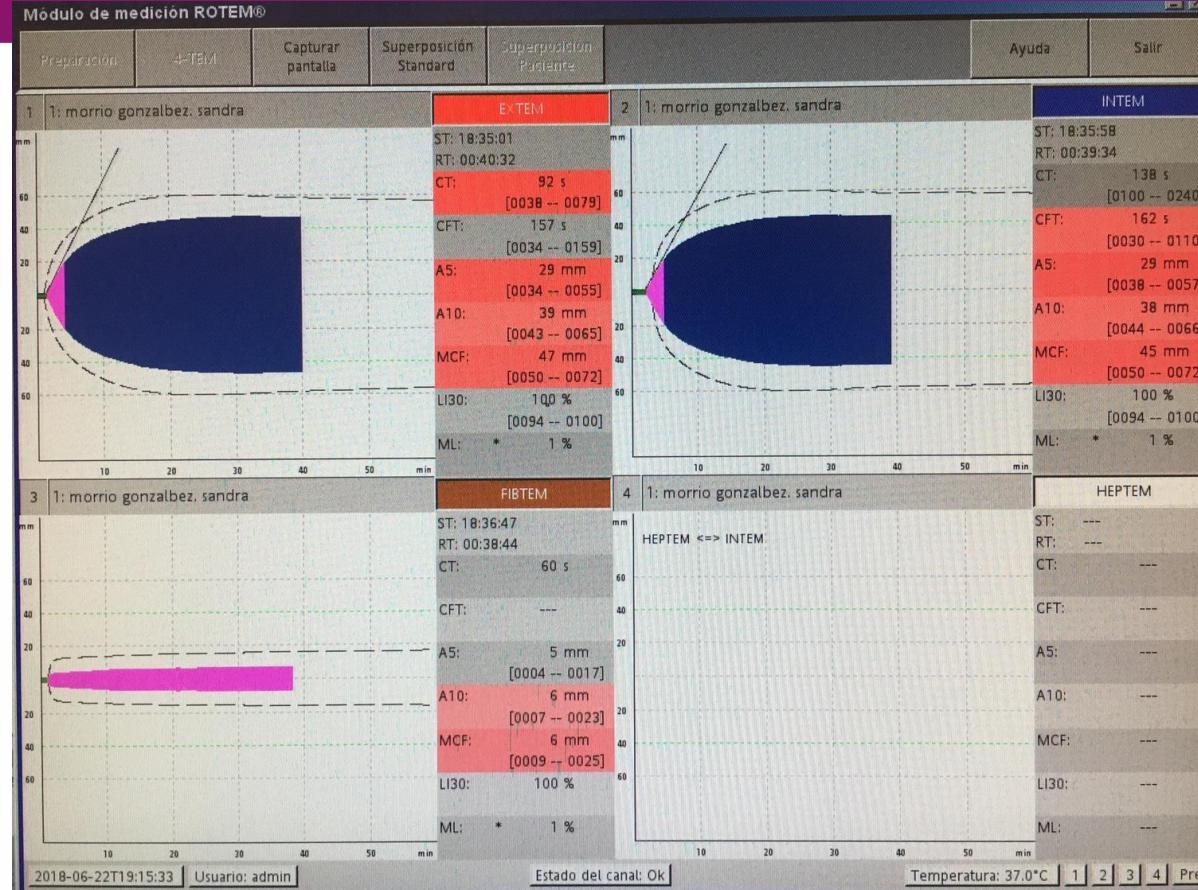
(Octapharma, blood bank was weight. For the

en concentrate  
normal fibrin  
ur-factor PCC

initial thrombin  
in time index  
of bodyweight)

ogen dose and  
hibiting FXIII  
p 1 for details

ite, four-factor produced by CSL



La realidad es que, si bien el fibrinógeno es el primer y principal factor de la coagulación que disminuye en una HM, NO ES EL ÚNICO y su administración debe hacerse en el contexto de un tratamiento multimodal con administración concomitante de los otros factores de coagulación y de plaquetas



**CONTRA**

**X** JORNADA MULTIDISCIPLINAR  
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**MANEJO DEL SANGRADO**



**4.- La administración de fibrinógeno debe estar  
acompañada siempre de la administración de CCP...**

# Sangrado masivo

## Pirámide de tratamiento

Árbol de decisión/manejo

rFVII/XIII

Trombopenia

Plaquetas

Déficit factores

Plasma / CCP

Déficit Fibrinógeno

C. Fibrinógeno

Hiperfibrinolisis

Tranexámico

¿AAS / Anticoagulantes orales / Heparina?

Condiciones básicas

T<sup>a</sup>>34ºC; pH>7.2; Ca<sup>2+</sup>>1 mmol/L; Hb>8 g/L

Perfusión / Oxigenación tisular

Cristaloides / Coloides / Vasoconst / Hematíes

Estanqueidad quirúrgica

(Vendaje compresivo; MAST; compresión pélvica; packing)



## Generación de trombina

## Aceptable fibrinógeno funcional

## Adecuación de cifras/función plaquetaria

## Modulación de la hiperfibrinoisis



Review

Management of Coagulopathy in Bleeding Patients

Stefan Hofer <sup>1,\*</sup>, Christoph J. Schlimp <sup>2,3</sup>, Sebastian Casu <sup>4</sup> and Elisabet Grouzi <sup>5</sup>

La generación de trombina está aumentada en CIS por la desregulación hemostática y los cambios sistémicos inducidos. Durante un sangrado, **los niveles de trombina tienen que considerarse solo después de la corrección de los niveles de fibrinógeno**. Esto se debe al hecho que el goalterapéutico FIBTEMA10 >10-12mm se asocia a menudo a niveles de trombina adecuados.

## 17th ANNUAL NATA SYMPOSIUM on Patient Blood Management, Haemostasis and Thrombosis

- TXA should be used routinely in preventing & treating bleeding
- PCC are the preferred agent to reverse vitamin K antagonists
- There is missing evidence on the use of fibrinogen & PCC in managing bleeding patients as regards:
  - Efficacy
  - Safety
  - Cost effectiveness



Dra. B. Hunt

Provided that fibrinogen levels are normal, we **suggest that PCC or plasma be administered in the bleeding patient based on evidence of delayed coagulation initiation using viscoelastic monitorin (Grade 2C)**



**Terapia guiada : solo repongo lo que necesito reponer,  
Terapia sin guía: riesgo añadido y iatrogenia.  
Siempre no es una respuesta en medicina.**



La administración de fibrinógeno exógeno no presenta problemas de tromboembolismo, por lo que es preferible siempre una sobre-administración que una infra-administración.

**PRO: M Quintana**

**CON: JV Llau**

**5.- La administración de fibrinógeno exógeno no presenta problemas de tromboembolismo, por lo que es preferible una sobre-administración que una infra-administración.**

## 6 ADVERSE REACTIONS

The most serious adverse reactions reported in clinical studies or through postmarketing surveillance following RIASTAP treatment are thromboembolic episodes, including myocardial infarction, pulmonary embolism, deep vein thrombosis, arterial thrombosis, and allergic-anaphylactic reactions.

The most common adverse reactions observed in more than one subject in clinical trials (frequency >1%) were fever and headache.

> *Perfusion*. 2014 Jul;29(4):369-372. doi: 10.1177/0267659113513312. Epub 2013 Nov 20.

### Prophylactic fibrinogen administration during complex congenital cardiac surgery leading to thrombosis of a patient's brachial artery and the cardiopulmonary bypass circuit: a case report

Rdp Stanzel <sup>1</sup>, M Henderson <sup>2</sup>, Sb O'Blenes <sup>3</sup>

#### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The safety and efficacy of fibrinogen concentrate (human) for routine prophylaxis, treatment of bleeding or surgery in subjects with congenital fibrinogen deficiency was evaluated in a retrospective, multicenter trial with a prospective one-year follow-up period. Twenty-two subjects between 2 to 78 years with a mean age of 34 years were enrolled, with treatment recorded during the retrospective period from an age of less than 1 year. Thirteen of the 22 (59.1%) subjects were female, 21 (95.5%) subjects were white, and 1 (4.5%) subject Asian [see *Clinical Studies* (14)].

The adverse reactions reported in the retrospective period were visual impairment, chest discomfort, chest pain, cough, wheezing, flushing, and venous thrombosis of the limb [1 event each] and dyspnea [2 events]. No adverse reactions were found in the prospective period.

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i. Rotational thromboelastography for monitoring fibrinogen deficiency. *Blood Coagulation and*

**Abstract**

**Background:** Congenital fibrinogen deficiency affecting normal blood clotting function, where or frequent bleeding episodes (BEs). Treatment (HFC) can prevent/arrest bleeding. There is pharmacokinetics (PK) and safety of HFC treatment.

**Methods:** Haemostatic efficacy of HFC (Fibryga®)

Received: 26 August 2020 | Revised: 18 November 2020 | Accepted: 25 November 2020  
DOI: 10.1111/hae.14230

ORIGINAL ARTICLE  
Rare bleeding disorders

## Efficacy and safety of fibrinogen concentrate for on-demand treatment of bleeding and surgical prophylaxis in paediatric patients with congenital fibrinogen deficiency

dose of 0.078 mg/kg for BEs, mean ( $\pm$ SD) MCF significantly increased from pre-treatment to 1-hour post-infusion (3.3 mm [ $\pm$ 1.77];  $P = 0.0002$ ), coinciding with haemostatic efficacy. PK parameters were favourable. Two possibly related adverse events occurred, including one serious (portal vein thrombosis). No allergic/hypersensitivity reactions or deaths were observed.

**Conclusion:** HFC treatment for on-demand treatment of BEs and surgical prophylaxis was efficacious for this ultra-rare paediatric population with congenital afibrinogenemia and showed a favourable PK and safety profile.

Thrombosis Research 199 (2021) 110–118  
Contents lists available at ScienceDirect  
**Thrombosis Research**  
journal homepage: [www.elsevier.com/locate/thromres](http://www.elsevier.com/locate/thromres)

Full Length Article  
Pharmacokinetics, surrogate efficacy and safety evaluations of a new human plasma-derived fibrinogen concentrate (FIB Grifols) in adult patients with congenital afibrinogenemia

*Journal of Thrombosis and Haemostasis*, 16: 253–261

DOI: 10.1111/jth.13923

**ORIGINAL ARTICLE**

## Pharmacokinetics, clot strength and safety of a new fibrinogen concentrate: randomized comparison with active control in congenital fibrinogen deficiency

*J Thromb Haemost* 2018; 16: 253–61.

**Essentials**

- Congenital afibrinogenemia causes a potentially life-threatening bleeding and clotting tendency.
- Two human fibrinogen concentrates (HFCs) were compared in a randomized pharmacokinetic study.
- Bioequivalence was not shown for  $AUC_{norm}$ , which was significantly larger for the new HFC.
- Increases in clot strength were comparable, and no thromboses or deaths occurred in the study.

Review > J Crit Care. 2014 Jun;29(3):471.e11-7. doi: 10.1016/j.jcrc.2013.12.011.

Epub 2013 Dec 30.

## Efficacy and safety of fibrinogen concentrate in trauma patients--a systematic review

C Aubron <sup>1</sup>, M C Reade <sup>2</sup>, J F Fraser <sup>3</sup>, D J Cooper <sup>4</sup>

Affiliations + expand

PMID: 24508201 DOI: 10.1016/j.jcrc.2013.12.011

Multicenter Study > J Cardiothorac Vasc Anesth. 2019 Feb;33(2):321-327.

doi: 10.1053/j.jvca.2018.06.001. Epub 2018 Jun 8.

## Safety of Fibrinogen Concentrate and Cryoprecipitate in Cardiovascular Surgery: Multicenter Database Study

Takuma Maeda <sup>1</sup>, Shigeki Miyata <sup>2</sup>, Akihiko Usui <sup>3</sup>, Kimitoshi Nishiwaki <sup>4</sup>, Hitoshi Tanaka <sup>5</sup>, Yutaka Okita <sup>5</sup>, Nobuyuki Katori <sup>6</sup>, Hideyuki Shimizu <sup>7</sup>, Hiroaki Sasaki <sup>8</sup>, Yoshihiko Ohnishi <sup>9</sup>, Yuichi Ueda <sup>10</sup>.



*Int. J. Mol. Sci.* **2021** *22*, 2185.



Article

## Fibrinogen Replacement Therapy for Traumatic Coagulopathy: Does the Fibrinogen Source Matter?

Gael B. Morrow <sup>1,2</sup>, Molly S. A. Carlier <sup>2</sup>, Sruti Dasgupta <sup>2</sup>, Fiona B. Craigen <sup>2</sup>, Nicola J. Mutch <sup>2</sup> and Nicola Curry <sup>1,3,\*</sup>

JAMA | Original Investigation JAMA. 2019;322(20):1966-1976.

## Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery The FIBRES Randomized Clinical Trial

Jeannie Calum, MD; Michael E. Folkert, MD; Gannon C. Scales, MD; Nancy M. Heddle, MS; Mark Crowther, MD; Vivik Rao, MD; Hans-Peter Hocke, PhD; Jo Carroll, BHA; Deep Grewal, MD; Salimpal Brar, MD; Alan Bassler, MD; Hilary Gross, MD; Christopher Hark, MD; Katerina Pavlou, MD; Antoine Rochon, MD; Tait Sha, MD; Lois Shepherd, MD; Summer Syed, MD; Dem Tran, MD; Daniel Wong, MD; Michelle Zeller, MD; Keyvan Karbassi, MD, for the FIBRES Research Group

Table 4. Treatment-Emergent Adverse Events and Other Measured Outcomes at 28-Day Follow-up

Outcome	No. (%) Fibrinogen Concentrate (n = 372)	No. (%) Cryoprecipitate (n = 363)
Any adverse event	248 (66.7)	264 (72.7)
No. of events	623	673
Any serious adverse event	117 (31.5)	126 (34.7)
No. of events	224	264
Thromboembolic adverse events <sup>a</sup>	26 (7.0)	35 (9.6)
No. of events	27	20
Stroke/TIA	17 (4.6)	18 (5.0)
DVT/PE	5 (1.3)	9 (2.5)
Myocardial infarction	3 (0.8)	4 (1.1)
Other vessel thrombosis	0	7 (1.9)
Amaurosis fugax	0	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)	0
Thrombophlebitis	1 (0.3)	0
Acute kidney injury <sup>b</sup>	48 (12.9)	48 (13.2)
Hepatobiliary disorders <sup>c</sup>	32 (8.6)	37 (10.2)
Duration of mechanical ventilation, median (IQR), d	1.3 (0.7-5.0) [n = 337]	1.3 (0.7-4.2) [n = 342]
Duration of intensive care unit stay, median (IQR), d	2.9 (1.4-5.7) [n = 352]	2.8 (1.2-5.6) [n = 345]
Duration of hospitalization, median (IQR), d	8.2 (6.3-13.0) [n = 314]	9.0 (6.3-13.3) [n = 308]

La administración de fibrinógeno exógeno, vía CF, crioprecipitado o PFC, no incrementa el riesgo de eventos trombóticos.

REVIEW FOR CRITICAL CARE MEDICINE  
DOI: 10.1007/s00606-019-04862-w  
CRITICAL CARE  
RESEARCH  
Open Access  
Management of bleeding following major trauma: an updated European guideline

REVIEW FOR CRITICAL CARE MEDICINE  
DOI: 10.1007/s00606-019-04862-w  
CRITICAL CARE  
RESEARCH  
Open Access  
Management of bleeding and coagulopathy following major trauma: an updated European guideline

The issue of whether the administration of fibrinogen via factor concentrate, cryoprecipitate or FFP is associated with an increased risk of hospital-acquired venous thromboembolism has never been addressed. However, fibrino-

It is not known whether the administration of fibrinogen via factor concentrate, cryoprecipitate or FFP is associated with a post-traumatic venous thrombotic risk.

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No hay estudios *potentes* que lo evidencie  
Lo reportado son casos puntuales y en pacientes  
pediátricos con afibrinogenemia congénita

**5.- La administración de fibrinógeno exógeno no presenta problemas de tromboembolismo, por lo que es preferible una sobre-administración que una infra-administración.**

# CONTRA

X JORNADA MULTIDISCIPLINAR  
DE ACTUALIZACIÓN EN EL  
**MANEJO DEL SANGRADO**





## Premisa final

**Todo es relativo, aproximado y  
provisional**

**\*Con los medios disponibles..... pero con el conocimiento  
adecuado!!!!!!**

**X** JORNADA MULTIDISCIPLINAR  
DE ACTUALIZACIÓN EN EL  
**MANEJO DEL SANGRADO**



**Muchas gracias**

Organiza:  
**octapharma**