MANEJO DEL SANGRADO MASIVO EN EL SIGLO XXI

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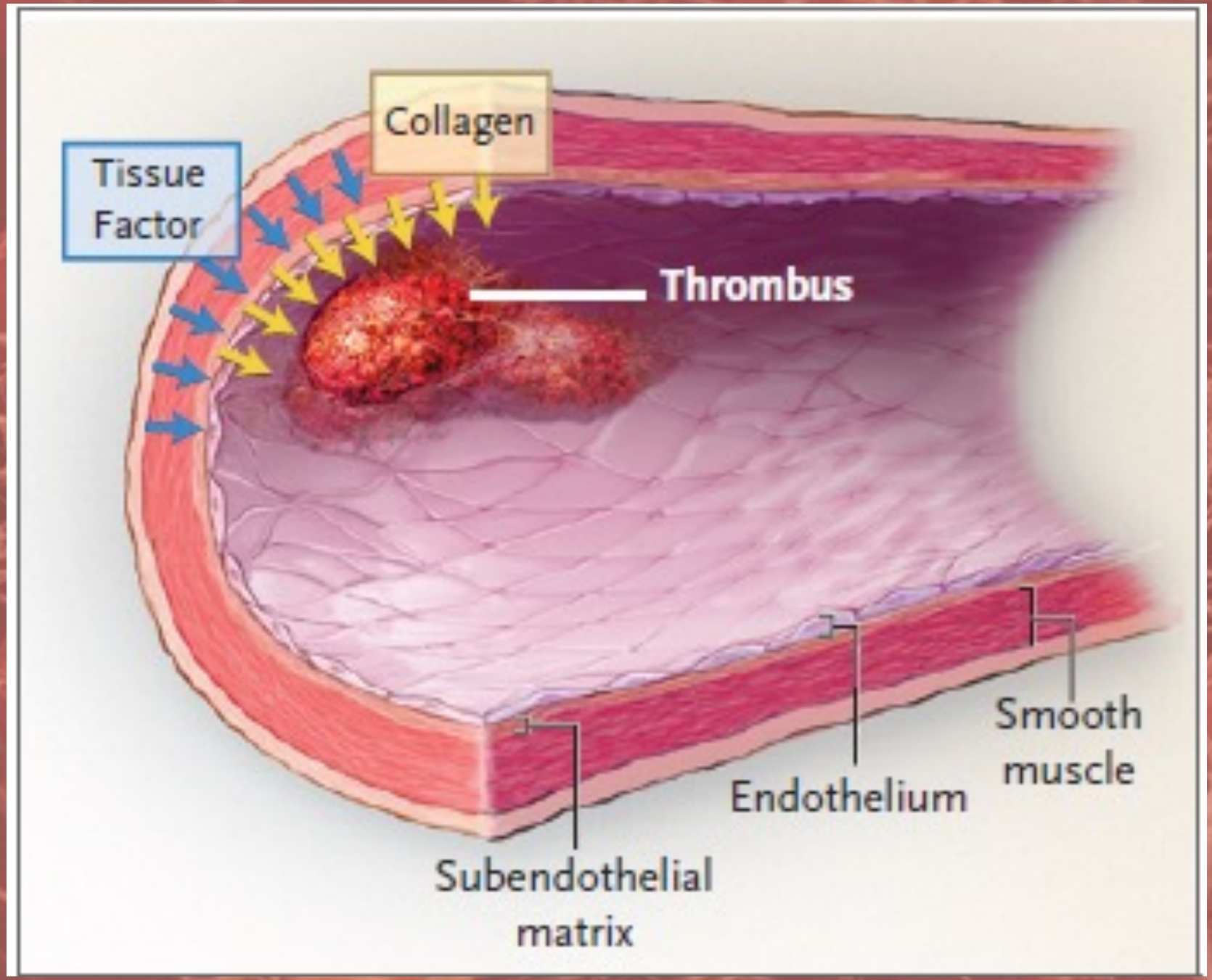
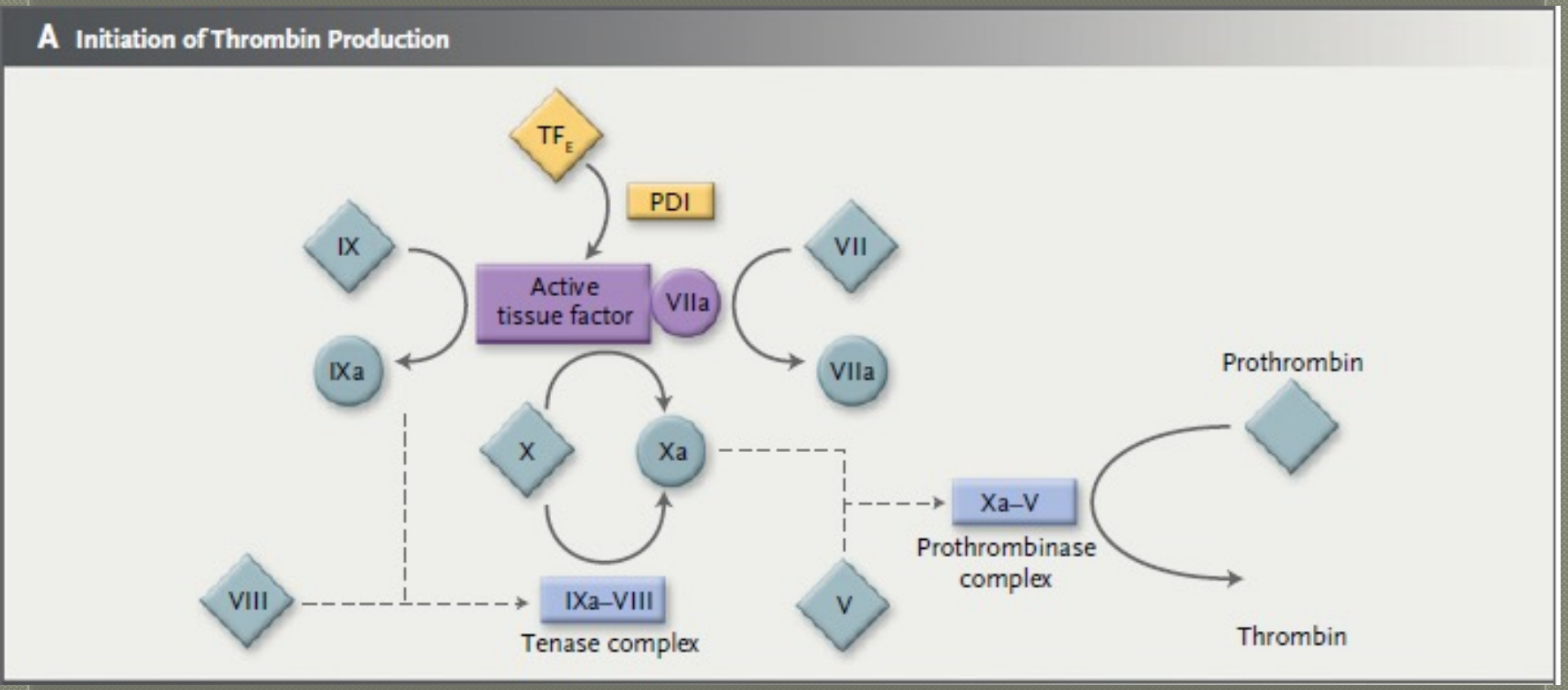
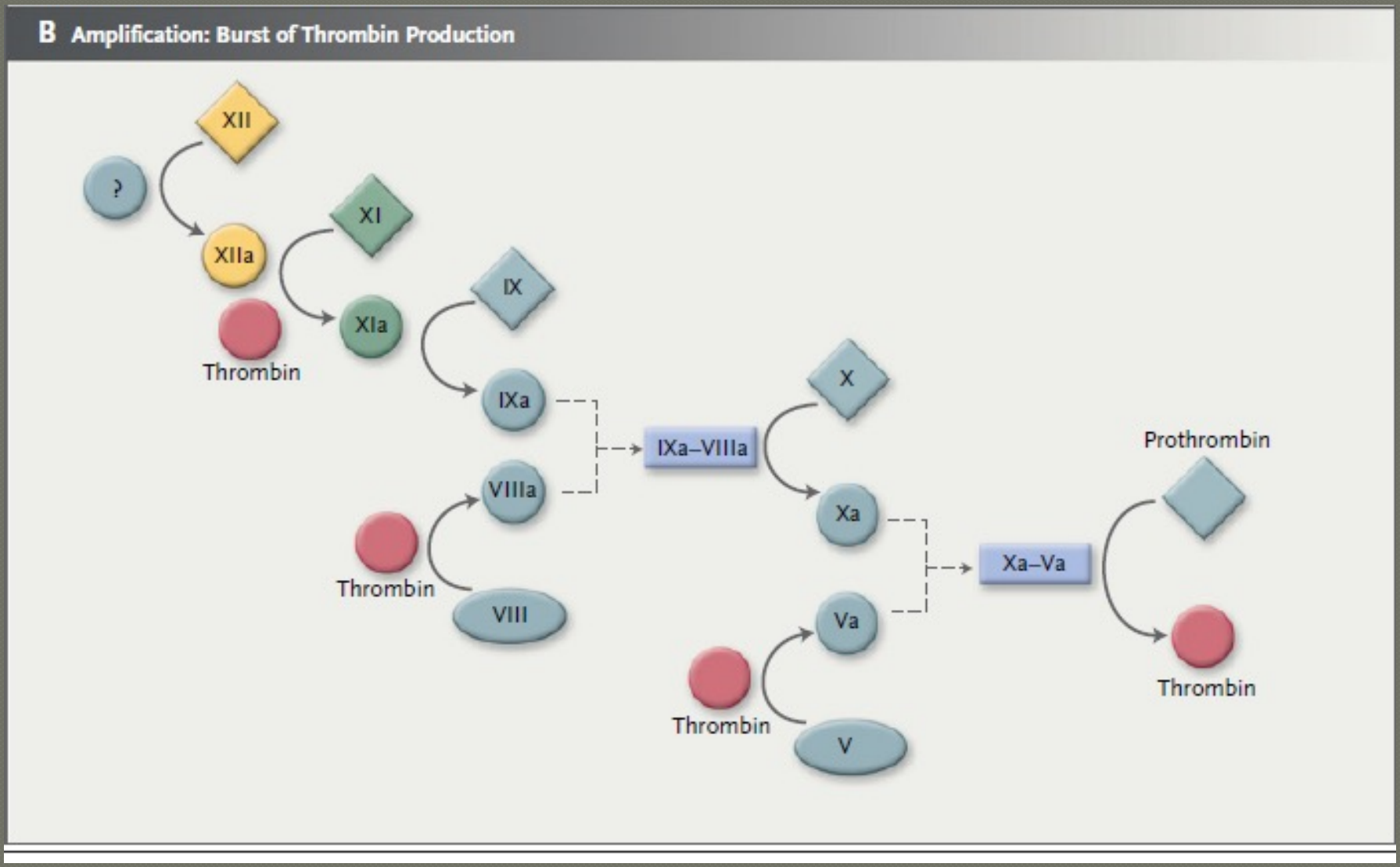
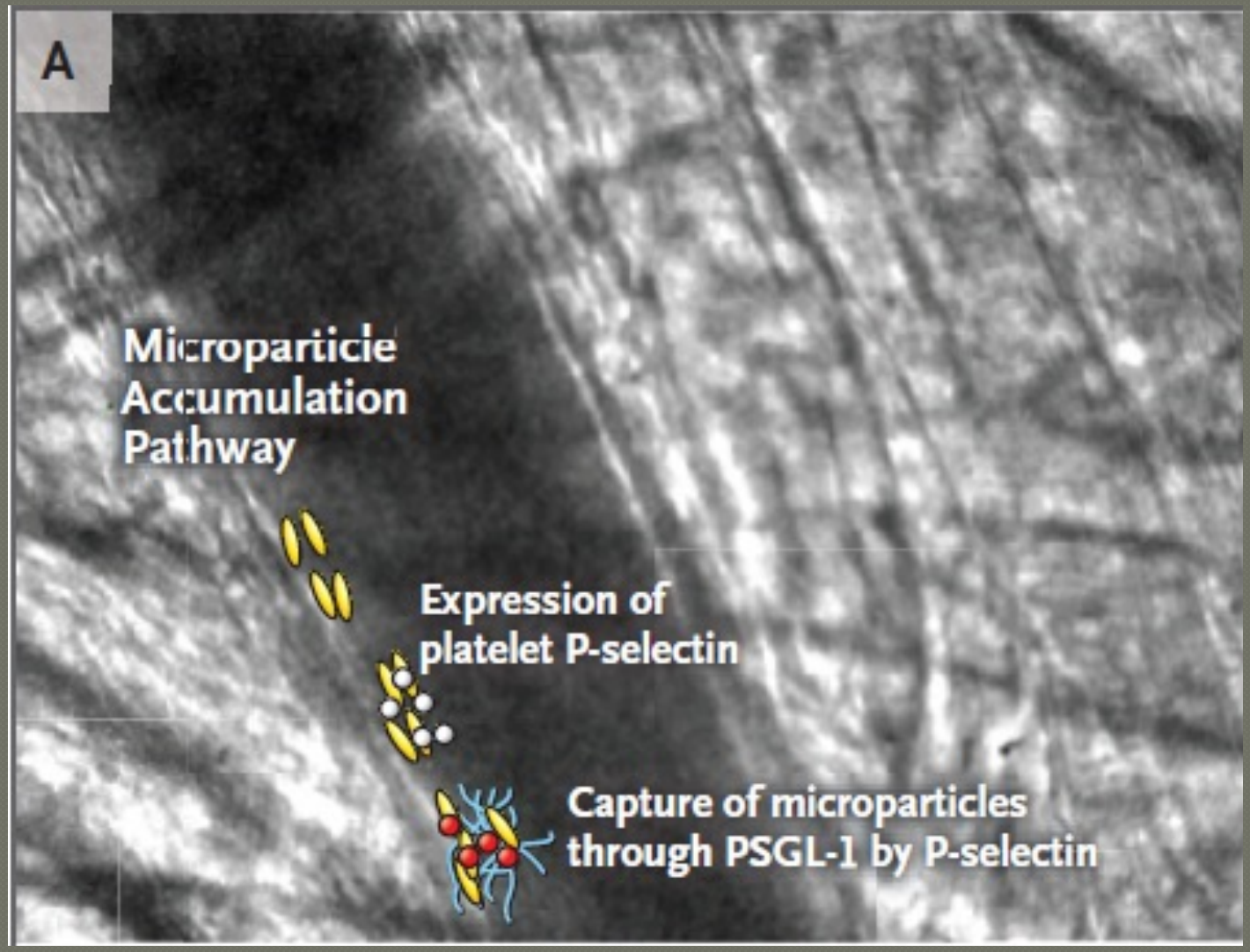
LIMA PERU
2015

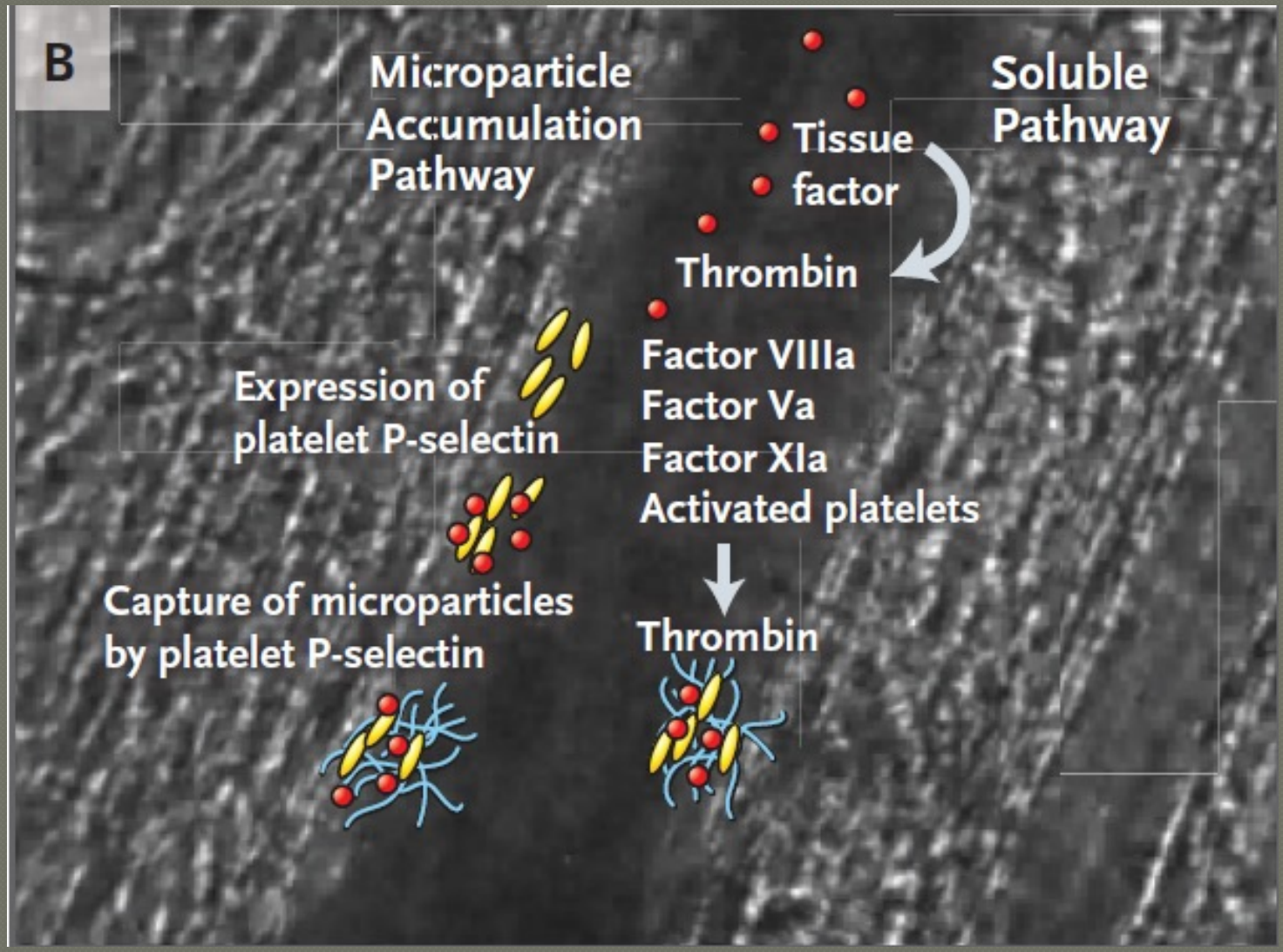

HOSPITAL EDGARDO REBAGLIATI MARTINS
EsSalud


Collagen
Tissue Factor
Thrombus
Smooth muscle
Endothelium
Subendothelial matrix


A Initiation of Thrombin Production
TF
E
PDI
IX
Active tissue factor
VIIa
VII
IXa
VIIa
Prothrombin
X
Xa
Xa–V
Prothrombinase complex
VIII
IXa–VIII
Tenase complex
V
Thrombin


B Amplification: Burst of Thrombin Production
XII
?
XIIa
XI
XIa
IX
IXa
Thrombin
VIIIa
Thrombin
VIII
IXa–VIIIa
X
Xa
Xa–Va
Prothrombin
Thrombin
Va
Thrombin
V


A
Microparticle
Accumulation
Pathway
Expression of
platelet P-selectin
Capture of microparticles
through PSGL-1 by P-selectin


B
Microparticle Accumulation Pathway
Soluble Pathway
Tissue factor
Thrombin
Factor VIIIa
Factor Va
Factor XIa
Activated platelets
Expression of platelet P-selectin
Capture of microparticles by platelet P-selectin
Thrombin

	Clase I	Clase II	Clase III	Clase IV
Pérdidas				
- Porcentaje %	<15	15-30	30-40	>40
- Volumen (ml)	750	800-1500	1500-2000	>2000
Presión sistólica	No cambia	Normal	Reducida	Muy baja
Frecuencia card.	Tq ligera	100-120	120 (filiforme)	>120
Relleno capilar	Normal	lento (>2s)	lento (>2s)	Indetectable
Frecuencia respir	Normal	Normal	>20/min	>20/min
Diuresis/hora	>30	20-30	10-20	0-10
Extremidades	normal	Pálidas	Pálidas	Pálidas, frías
Conciencia	Alerta	Ansioso	Ansioso/sueño	Sueño/Inconsciente

Tabla 1. Clasificación de la Hemorragia aguda.

DEFINICION HEMORRAGIA MASIVA

- Pérdida de la volemia sanguínea en un intervalo de 24 horas. 7% de peso ideal en adultos, 8-9% de peso en niños.
- Transfusión de más de 10 U , PG en 24 horas.
- Pérdida y reemplazo de más del 50% del volumen sanguíneo en un periodo de 3 horas y/o pérdidas de 4 PG en menos de 1 hora.

DEFINICION

- Pérdida de sangre a una velocidad de más de 150 ml / min.
- Pérdida de 1.5 ml/kg/min durante un periodo de más de 20 min.
- La pérdida de sangre es tan rápida y grave que el soporte de hemoderivados y con volumen excede los mecanismos compensatorios del organismo.

EPIDEMIOLOGÍA

- Politraumatismo 30%
- Hemorragias Gastrointestinales 30%
- Cirugía cardiovascular. 12%
- Enfermedades Neoplásicas. 9%
- Urgencias Obstétricas.
- Sobreanticoagulación
- Cirugía de Urgencia
- Cirugia electiva. <1%
  - Transplante hepático.
  - Artroplastías.
  - Prostatectomía.

Brockamp et al. Critical Care 2012, 16:R129
http://ccforum.com/content/16/4/R129

CRITICAL CARE

RESEARCH Open Access

Predicting on-going hemorrhage and transfusion requirement after severe trauma: a validation of six scoring systems and algorithms on the

Table 1 Parameters of compared scores.

Score Civilian or Military Database Number of patients	TASH [22,28] Civilian 4527		Rainer (PWH) [19] Civilian 1891		Vandromme [21] Civilian 514		ABC [18] Civilian 596		Schreiber [20] Military 558		Larson [29] Military 1124	
Variable	Value	Pts	Value	Pts	Value	Pts	Value	Pts	Value	Pts	Value	Pts
Gender	male	1										
Pelvic fracture (AIS 5 ≥ 5)	clinically unstable	6	displaced (AIS 5 ≥ 4)	1								
Femur fracture (AIS 5 ≥ 3)	open and/or dislocated	3										
Free IF (FAST) (AIS 4 ≥ 3)	present	3	or CT-positive	2			positive	1				
Heart rate (bpm)	> 120	2	≥ 120	1	> 105	1	≥ 120	1			> 110	1
Systolic blood presure (mmHg)	< 100	4	≤ 90	3	< 110	1	≤ 90	1			< 110	1
	< 120	1										
	< 7	8	≤ 7	10	≤ 11	1			≤ 11	1	< 11	1
	< 9	6	7.1 to 10	1								
Hemoglobin (g/dl)	< 10	4										
	< 11	3										
	< 12	2										
	< -10	4	BD > 5	1							≤ -6	1
Base excess (mmol/L)	< -6	3										
	< -2	1										
Mechanism of injury							penetrating	1	penetrating	1		
INR					> 1.5	1			> 1.5	1		
GCS			≤ 8	1								
Lactate					≥ 5	1						

TASH score

Variable	Value		Points
Haemoglobin (g/dl)	< 7	8	6
	< 9	6	
	<10	4	
	< 11	3	
	< 12	2	
Base excess (mmol/l)	< –10	4	3
	< –6	3	
	< –2	1	
Blood pressure$_{systol}$ (mmHg)	< 100	4	4
	< 120	1	
Heart rate (bpm)	> 120	2	2
Free intraabdominal fluid (e.g. FAST)		3	3
Extremities			
> Clinically instabile pelvic fracture		6	
> Clinically femur fracture/open/dislocated		3	3
Male		1	
		Total	**21**

MT predicted: 75%

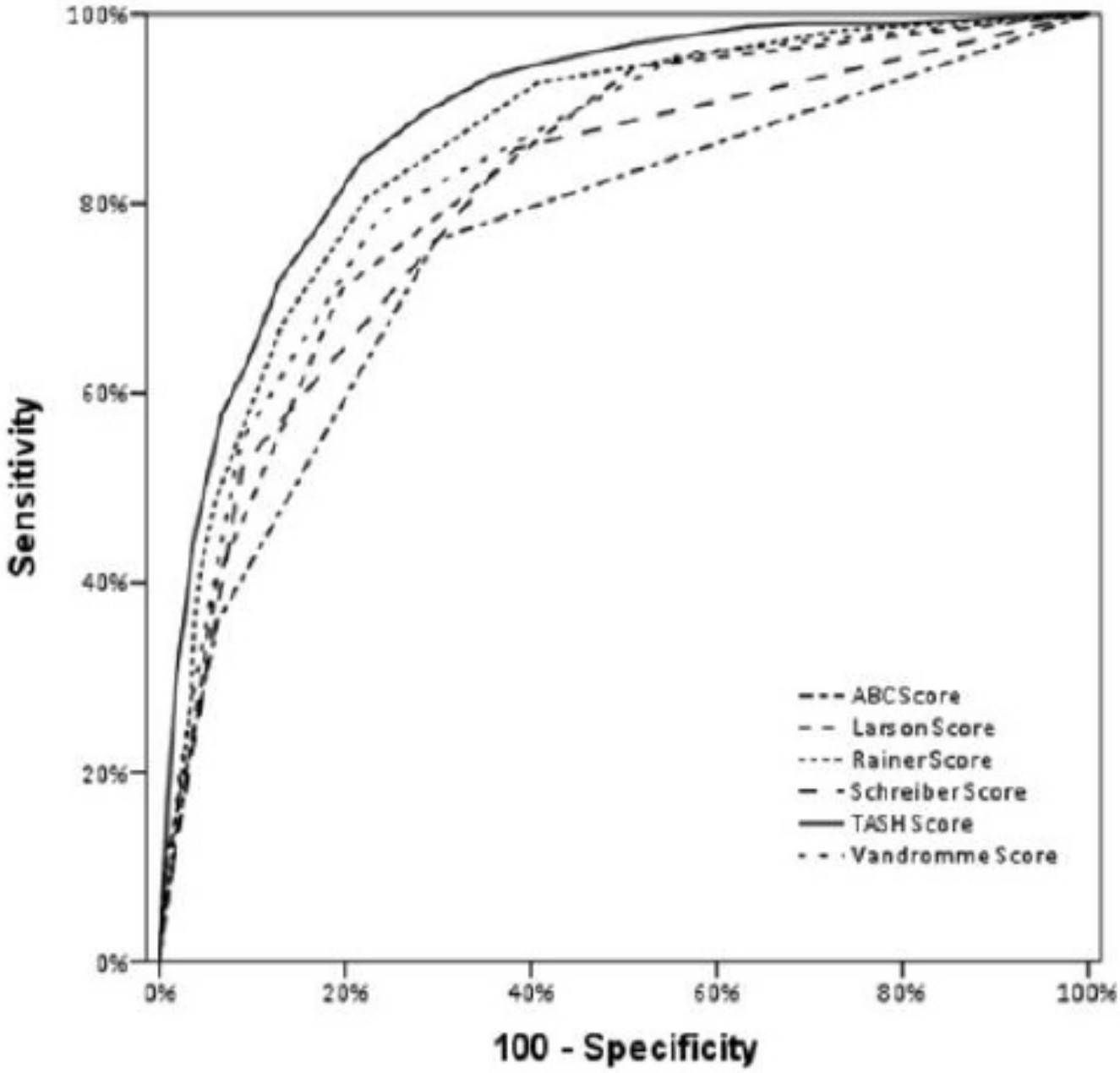
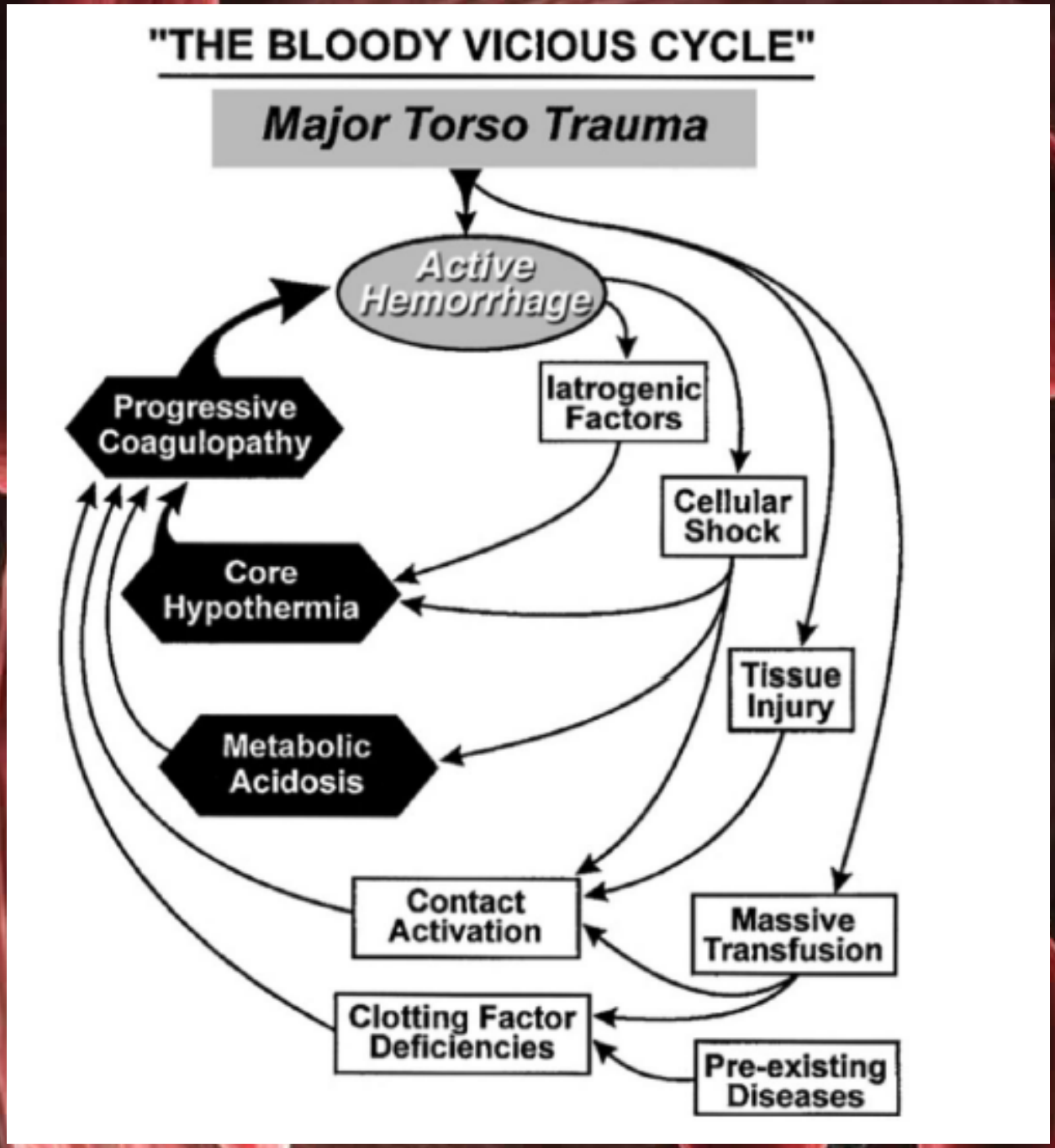


Figure 1 Validation of six scoring systems and algorithms on one dataset (n = 5,147) of severely injured patients extracted from the TraumaRegister DGU® database. The TASH-Score was internally re-validated while all other scores were externally validated. The two weighted scores (TASH and PWH/Rainer) performed superior over the others.


"THE BLOODY VICIOUS CYCLE"
Major Torso Trauma
Active Hemorrhage
Iatrogenic Factors
Progressive Coagulopathy
Cellular Shock
Core Hypothermia
Tissue Injury
Metabolic Acidosis
Contact Activation
Massive Transfusion
Clotting Factor Deficiencies
Pre-existing Diseases

ENFOQUE SISTEMICO DE HM

TRAUMA

OBSTETRICIA

CTCV

LESIÓN ANATOMICA

MEDIDAS QUIRÚRGICAS

RESUSCITACIÓN CON FLUIDOS

ENFOQUE SISTEMICO DE HM

PERDIDA DE SANGRE

PERDIDA Y CONSUMO DE FACT DE COAG

HEMODILUCIÓN

COAGULOPATÍA ADQUIRIDA

HIPOVOLEMIA PERSISTENTE

ACIDOSIS

DISFUNCIÓN DE LOS FACTORES DE COAGULACION

DISFUNCIÓN PLAQUETARIA

HEMORRAGIA MASIVA

ENFOQUE SISTEMICO DE HM

Gando and Otomo *Critical Care* (2015) 19:72
DOI 10.1186/s13054-015-0735-x

CRITICAL CARE

REVIEW Open Access

Local hemostasis, immunothrombosis, and systemic disseminated intravascular coagulation in trauma and traumatic shock

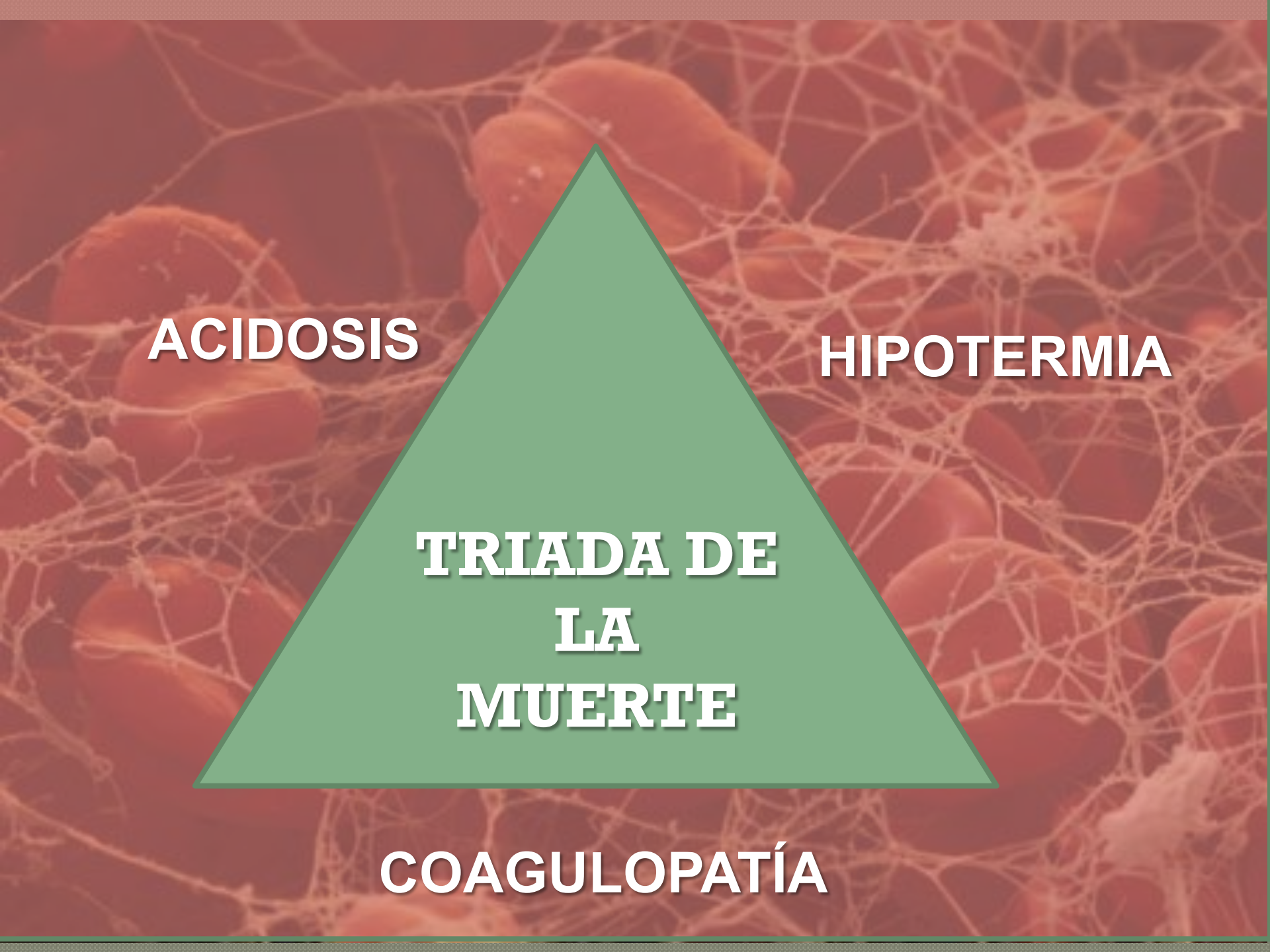
Satoshi Gando[1*] and Yasuhiro Otomo[2]

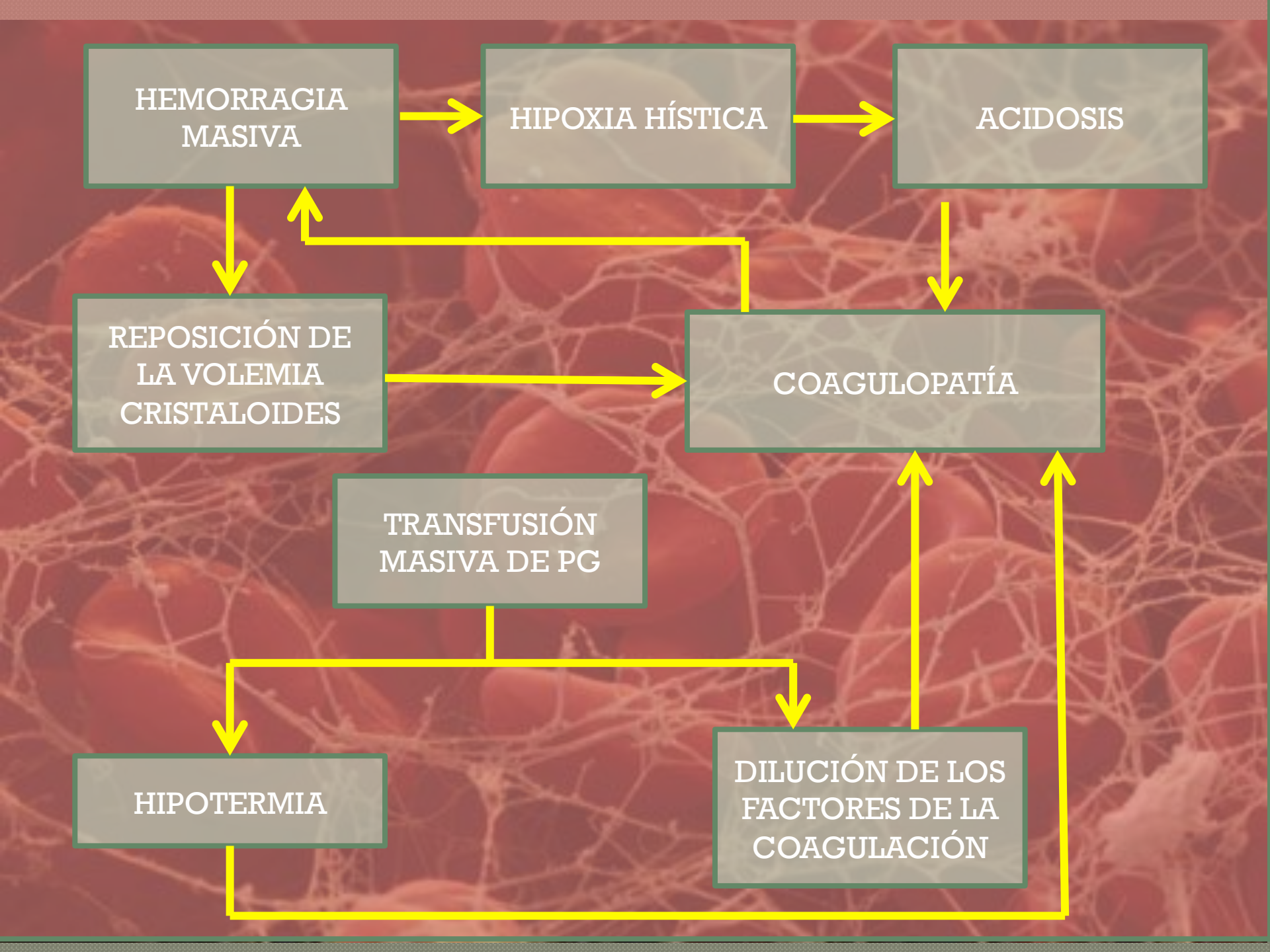
Abstract

Knowing the pathophysiology of trauma-induced coagulopathy is important for the management of severely injured trauma patients. The aims of this review are to provide a summary of the recent advances in our understanding of thrombosis and hemostasis following trauma and to discuss the pathogenesis of disseminated intravascular coagulation (DIC) at an early stage of trauma. Local hemostasis and thrombosis respectively act to induce physiological wound healing of injuries and innate immune responses to damaged-self following trauma. However, if overwhelmed by systemic inflammation caused by extensive tissue damage and tissue hypoperfusion, both of these processes foster systemic DIC associated with pathological fibrin(ogen)olysis. This is called DIC with the fibrinolytic phenotype, which is characterized by the activation of coagulation, consumption coagulopathy, insufficient control of coagulation, and increased fibrin(ogen)olysis. Irrespective of microvascular thrombosis, the condition shows systemic thrombin generation as well as its activation in the circulation and extensive damage to the microvasculature endothelium. DIC with the fibrinolytic phenotype gives rise to oozing-type non-surgical bleeding and greatly affects the prognosis of trauma patients. The coexistences of hypothermia, acidosis, and dilution aggravate DIC and lead to so-called trauma-induced coagulopathy.

He that would know what shall be must consider what has been.
The Analects of Confucius.

HEMORRAGIA MASIVA


ACIDOSIS
HIPOTERMIA
TRIADA DE LA MUERTE
COAGULOPATÍA


HEMORRAGIA MASIVA
HIPOXIA HÍSTICA
ACIDOSIS
REPOSICIÓN DE LA VOLEMIA CRISTALOIDES
COAGULOPATÍA
TRANSFUSIÓN MASIVA DE PG
HIPOTERMIA
DILUCIÓN DE LOS FACTORES DE LA COAGULACIÓN

CONTROL DE DAÑOS

GROUND CERO

PREHOSPITALARIA
SALA DE EMERGENCIA

FASE I

CIRUGIA

FASE II

UCI
REANIMACION

FASE III

REINTERVENCIÓN
TRATAMIENTO
DEFINITIVO

COAGULOPATIA AGUDA DEL TRAUMA (ACT)

28-60 % se presenta en fase temprana, asociada a INJURIA TISULAR Y SHOCK
POBRE PRONOSTICO

Incrementa la mortalidad.
Mayor requerimiento de transfusiones
Mayor estancia Uci y Hospitalaria

Journal of Intensive Care Medicine
28(1) 46-57

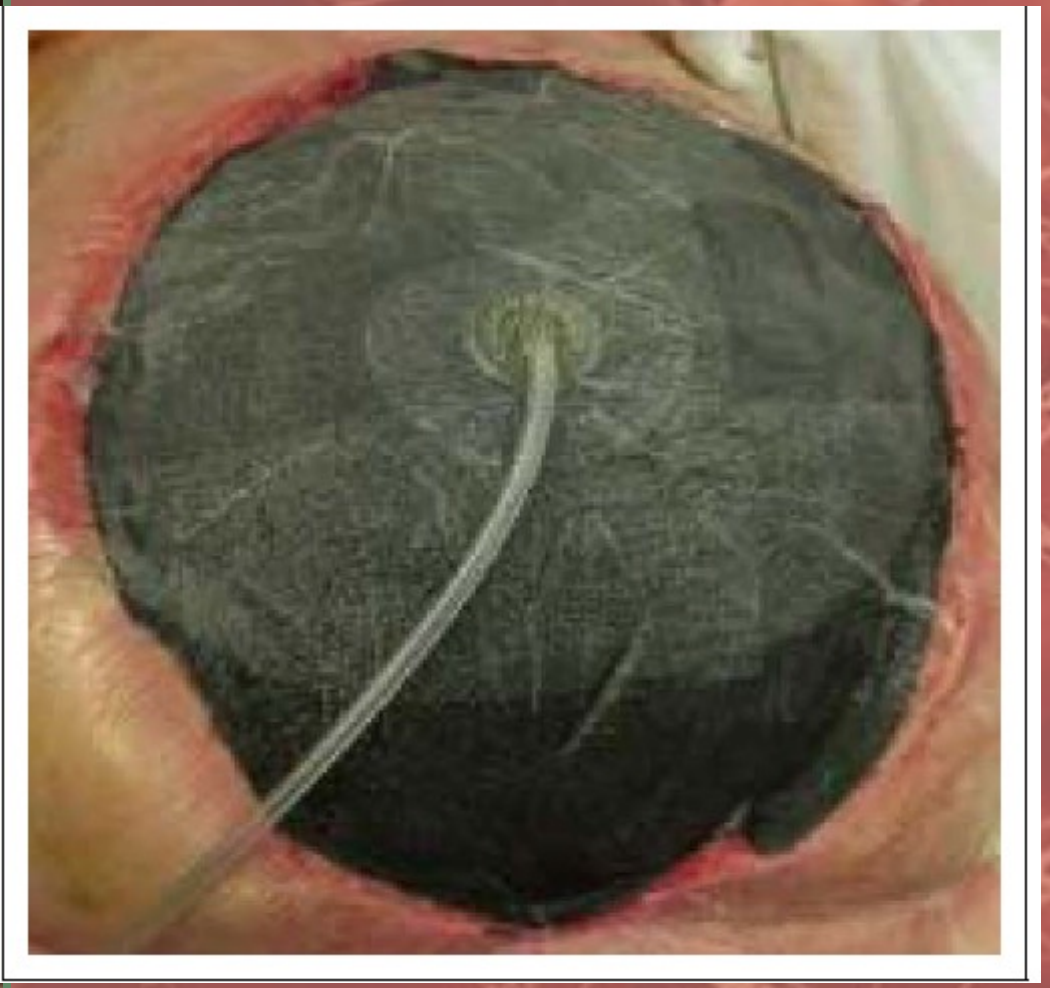
DOI: 10.1177/0885066611403273
http://jicm.sagepub.com
SAGE

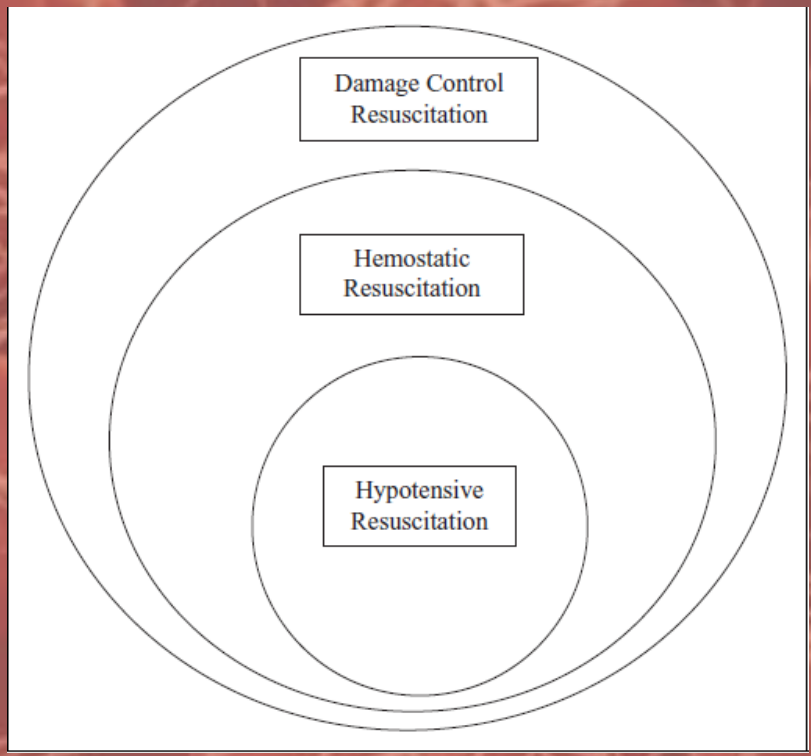
Update and New Developments in the Management of the Exsanguinating Patient

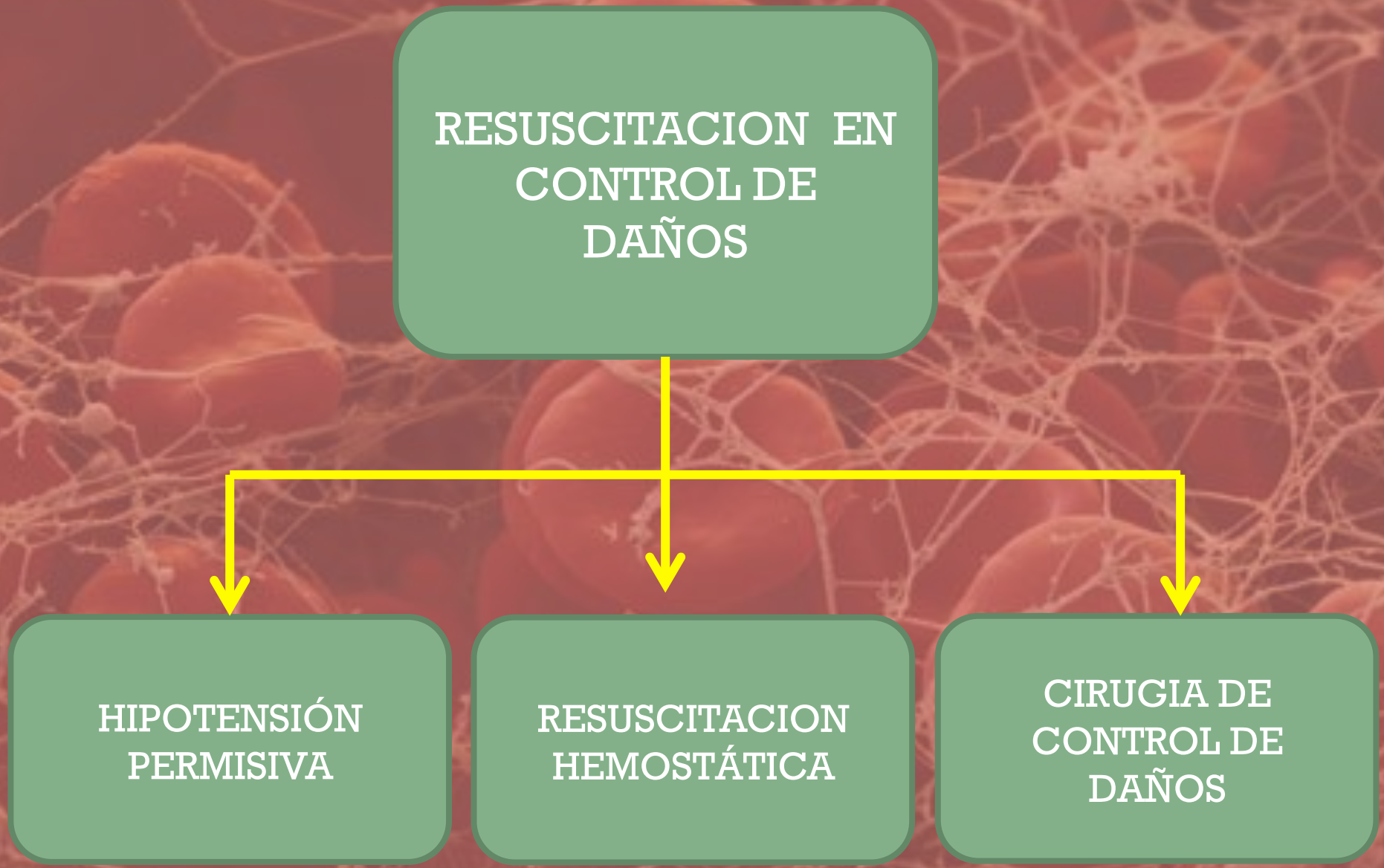
Gordon M. Riha, MD[1] and Martin A. Schreiber, MD[1]

Abstract

Definitive management of the exsanguinating patient continues to challenge providers in multiple specialties. Significant hemorrhage may be encountered in a variety of patient care circumstances. Over the past two decades, the vast majority of data and evidence regarding transfusion in the exsanguinating patient has been based upon the trauma literature, and a large amount of recent research has investigated this subject area. In addition to the care of trauma patients, the data which have emerged can also be extrapolated to the treatment of nontrauma patients undergoing transfusion for major hemorrhage. The concept of massive transfusion is an evolving paradigm, and numerous investigations have challenged old principles while creating new controversies. The current review will examine the latest developments in the management of patients with profound hemorrhage. The challenges of dealing with the "lethal triad" will be discussed, as will the various aspects of damage control and hemostatic resuscitation. The latest literature and controversy regarding massive transfusions and massive transfusion protocols will be elucidated with inclusion of data from recent military experiences. Finally, adjuncts including the most recent advances in hemorrhage control, identification of early predictors for massive transfusion, and utilization of pharmacologic and complementary factor agent therapy will be discussed.




Damage Control Resuscitation
Hemostatic Resuscitation
Hypotensive Resuscitation


RESUSCITACION EN CONTROL DE DAÑOS
HIPOTENSIÓN PERMISIVA
RESUSCITACION HEMOSTÁTICA
CIRUGIA DE CONTROL DE DAÑOS

FISIOPATOLOGÍA

- HEMODILUCIÓN
- HIPOTERMIA
- ACIDOSIS
- DISFUNCIÓN PLAQUETARIA
- ANEMIA
- ALTERACIONES METABÓLICAS Ca+
- HIPERFIBRINOLISIS
- COAGULOPATIA DE CONSUMO.

Pérdidas de volumen sanguíneo y estado de la hemostasia en la Hemorragia masiva

vol sang Pérdido	% vol sangre intercambiado.	% resid de FC	TP/TPTA	FIBRI NOG 1 gr/lt	PLAQ $x10^9$
Una volemia	70%	30%	<1.5%	> 1.0	>100
Dos volemias	85%	15%	>1.5%	< 1.0	< 50
Tres volemias	>95%	5%	> 1.8%	< 0.5	< 50

ACIDOSIS

- Asociada a la hipoperfusión tisular
- Efectos cardiovasculares, arritmias hipotensión, baja respuesta a las catecolaminas.
- Ph menos de 7.0 hay una disminución del 90% de la actividad del factor VIIa y la generación de trombina y agregación plaquetaria.

HIPOTERMIA

- Aumento del riesgo de hemorragia incontrolable.
- Disfunción plaquetaria.
- Efecto más modesto sobre la coagulación con una reducción del 10% de la actividad de los fact de coagulación por cada grado de descenso. Se suelen subestimar los efectos por que los laboratorios hacen los cálculos a 37°

Greuters et al. Critical Care 2011, 15:R2
http://ccforum.com/content/15/1/R2

CRITICAL CARE

RESEARCH Open Access

Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury

Sjoerd Greuters[1*], Annelies van den Berg[1], Gaby Franschman[1], Victor A Viersen[1], Albertus Beishuizen[2], Saskia M Peerdeman[3], Christa Boer[1], ALARM-BLEEDING investigators

Stanworth *et al. Critical Care* 2010, **14**:R239
http://ccforum.com/content/14/6/R239

CRITICAL CARE

RESEARCH Open Access

Reappraising the concept of massive transfusion in trauma

Simon J Stanworth[1*], Timothy P Morris[2], Christine Gaarder[3], J Carel Goslings[4], Marc Maegele[5], Mitchell J Cohen[6], Thomas C König[7], Ross A Davenport[7], Jean-Francois Pittet[8], Pär I Johansson[9], Shubha Allard[10], Tony Johnson[2,11], Karim Brohi[7]

Rossaint *et al. Critical Care* 2010, **14**:R52
http://ccforum.com/content/14/2/R52

CRITICAL CARE

RESEARCH Open Access

Management of bleeding following major trauma: an updated European guideline

Rolf Rossaint[1], Bertil Bouillon[2], Vladimir Cerny[3], Timothy J Coats[4], Jacques Duranteau[5], Enrique Fernández-Mondéjar[6], Beverley J Hunt[7], Radko Komadina[8], Giuseppe Nardi[9], Edmund Neugebauer[10], Yves Ozier[11], Louis Riddez[12], Arthur Schultz[13], Philip F Stahel[14], Jean-Louis Vincent[15], Donat R Spahn[16*]

Abstract

Introduction: Evidence-based recommendations are needed to guide the acute management of the bleeding trauma patient, which when implemented may improve patient outcomes.

Methods: The multidisciplinary Task Force for Advanced Bleeding Care in Trauma was formed in 2005 with the aim of developing a guideline for the management of bleeding following severe injury. This document presents an updated version of the guideline published by the group in 2007. Recommendations were formulated using a nominal group process, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence and based on a systematic review of published literature.

Results: Key changes encompassed in this version of the guideline include new recommendations on coagulation support and monitoring and the appropriate use of local haemostatic measures, tourniquets, calcium and desmopressin in the bleeding trauma patient. The remaining recommendations have been reevaluated and graded based on literature published since the last edition of the guideline. Consideration was also given to changes in clinical practice that have taken place during this time period as a result of both new evidence and changes in the general availability of relevant agents and technologies.

Conclusions: This guideline provides an evidence-based multidisciplinary approach to the management of critically injured bleeding trauma patients.

I. Initial resuscitation and prevention of further bleeding

- TRATAMIENTO QX
- USO DE TORNIQUETES
- EVALUACION INICIAL MECANISMO
- VENTILACION MECANICA
- INTERVENCIÓN INMEDIATA
- INVESTIGACION FUENTE DE SANGRADO NO INDENTIFICADA

Fibrinogen and cryoprecipitate

Recommendation 26 We recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by thrombelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5 to 2.0 g/l (Grade 1C). We suggest an initial fibrinogen concentrate dose of 3 to 4 g or 50 mg/kg of cryoprecipitate, which is approximately equivalent to 15 to 20 units in a 70 kg adult. Repeat doses may be guided by thrombelastometric monitoring and laboratory assessment of fibrinogen levels (Grade 2C).

Rationale The formation of fibrin is a key step in blood coagulation [222,279], and hypofibrinogenemia is a usual component of complex coagulopathies associated with massive bleeding. Coagulopathic civilian trauma patients had a fibrinogen concentration of 0.9 g/l (interquartile ratio (IQR) 0.5 to 1.5 g/l) in conjunction with a maximum clot firmness of 6 mm (IQR 0 to 9 mm) using thrombelastometry, whereas only 2.5% of healthy volunteers had a maximum clot firmness of 7 mm or less [10]. In trauma patients, a maximum clot firmness of 7 mm was associated with a fibrinogen level of approximately 2 g/l [10]. During massive blood loss replacement, fibrinogen may be the first coagulation factor to decrease critically [280].

During postpartum haemorrhage, fibrinogen plasma concentration is the only coagulation parameter independently associated with progress toward severe bleeding, with a level less than 2 g/l having a positive predictive value of 100% [281]. Blood loss and blood transfusion needs were also found to inversely correlate with preoperative fibrinogen levels in coronary artery bypass graft surgery [282].

During serious perioperative bleeding, fibrinogen treatment (2 g, range 1 to 5 g) was associated with a reduction in allogeneic blood product transfusion [283]. The fibrinogen concentration before treatment was 1.4 g/l (IQR 1.0 to 1.8 g/l) rising to 2.4 g/l (IQR 2.1 to 2.6 g/l) after fibrinogen substitution [283]. An observational study suggests that fibrinogen substitution can improve survival in combat-related trauma [284]. An RCT in patients undergoing radical cystectomy with excessive blood loss has shown that postoperative blood

Prothrombin complex concentrate

Recommendation 29 We recommend the use of prothrombin complex concentrate for the emergency reversal of vitamin K-dependent oral anticoagulants (Grade 1B).

Rationale Despite the increasing off-license use of PCC, there are no studies to support its use other than in haemophilia [321-323] or for the rapid reversal of the effect of oral vitamin K antagonsists [324-326]. With an ageing population, more trauma patients are likely to be taking vitamin K antagonists, therefore every trauma unit should have an established management policy for these patients. The comparison between outcomes other than speed of reversal of anticoagulation between FFP and PCC has not been established; several clinical trials are in progress, although none relates specifically to trauma patients. Despite some clinical recommendations [327], no clinical studies have been performed to determine whether administration of PCC is efficacious and safe in managing bleeding in trauma patients who are not on vitamin K antagonists, although a swine model suggests that there may be some advantages [328].

Because the use of PCC carries the theoretical increased risks of both venous and arterial thrombosis

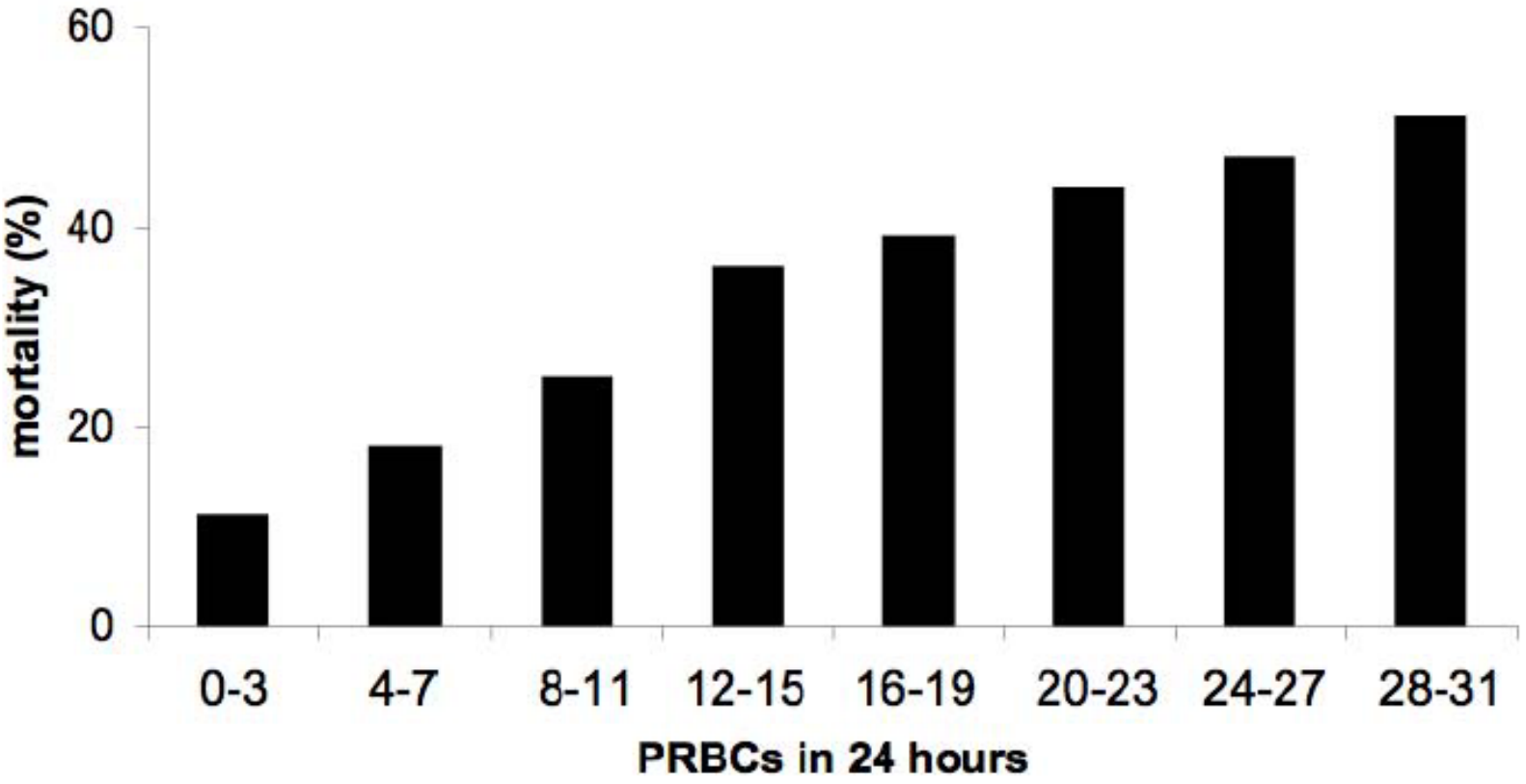


Figure 1 Transfusion-related mortality. Mortality by packed red blood cells (PRBCs) administered during the first 24 hours of admission.

MANEJO Y GENERALIDADES

- Resucitación y volemia
- Personal y recursos. (banco de sangre)
- Monitoreo y pruebas de laboratorio. TEG
- Hemoderivados : PG, PFC, FIBRI, CRIOP.
- Concentrado de complejo Protrombínico.
- Factores de coagulación aislados.
- Plaquetas.
- Agentes hemostáticos (desmopresina, antifibrinolíticos, ádhesivos hísticos.

ALGORITMOS Y PROTOCOLOS

- Diseño de protocolos multidisciplinario.
- Participación del Médico tratante , el anestesiólogo, hematólogo.
- Se valorara luego de estabilización su traslado a la UCI , radiología intervencionista o al quirófano.

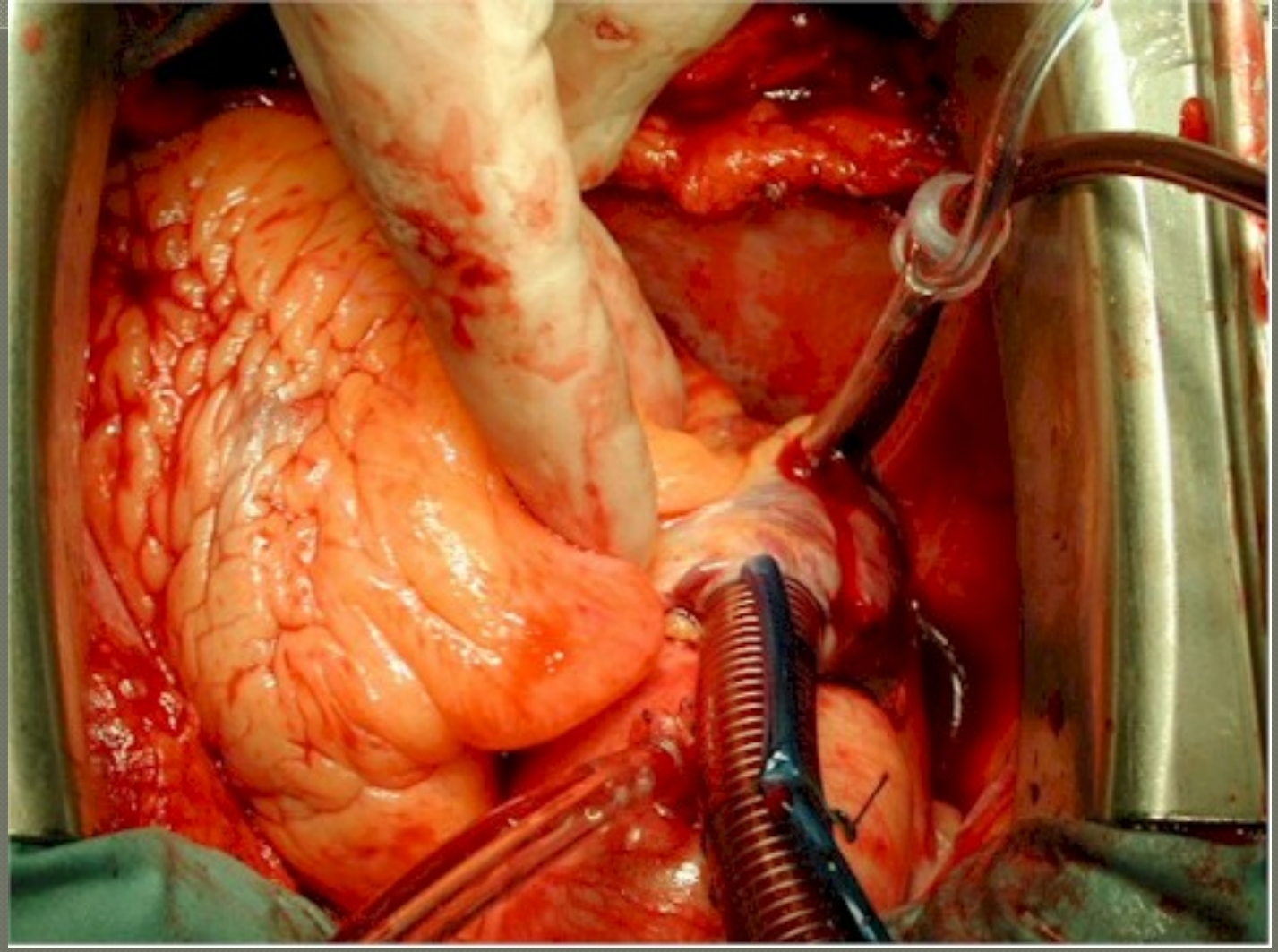
REVIEW

Constant challenges and evolution of US military transfusion medicine and blood operations in combat

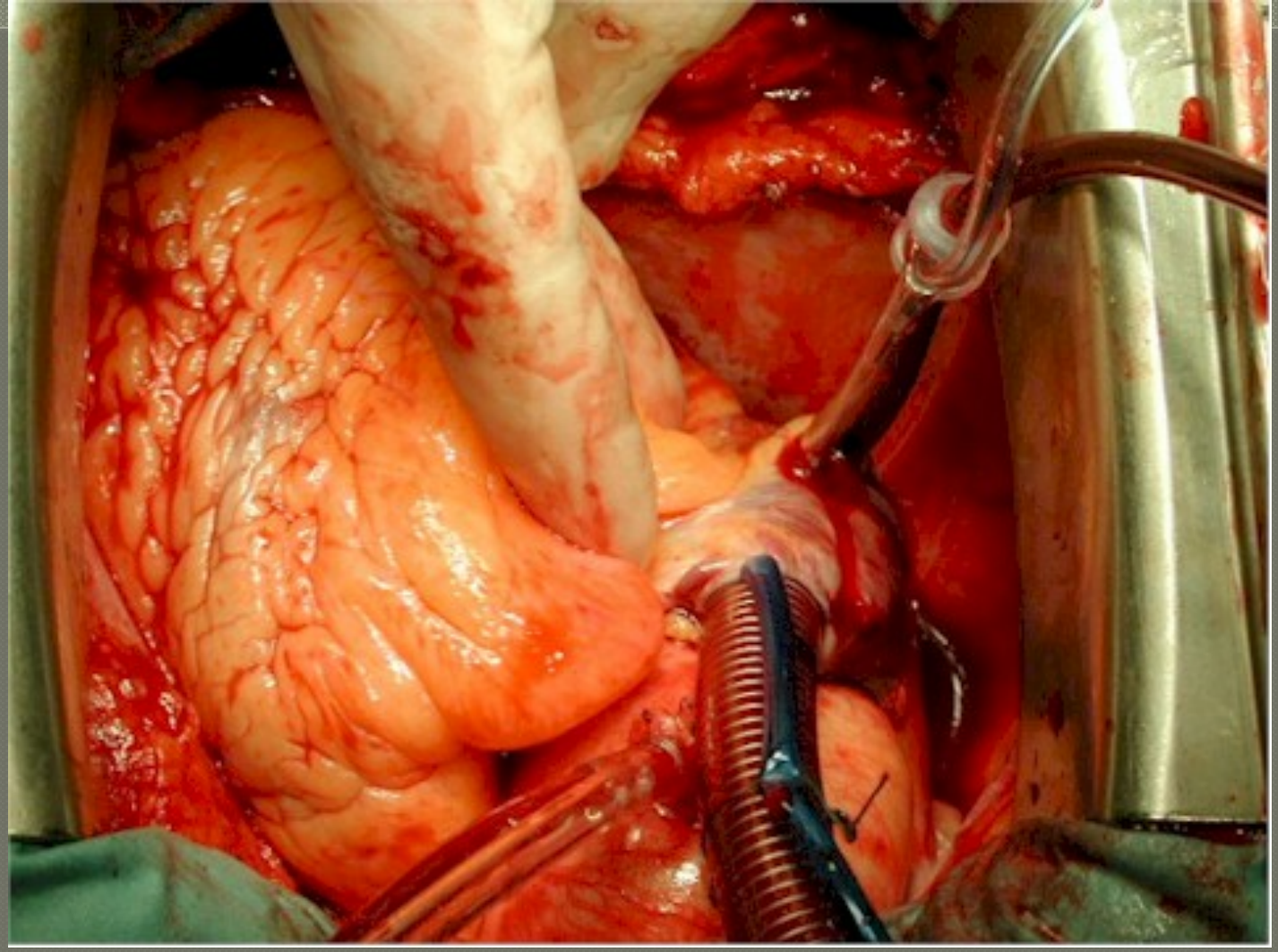
Philip C. Spinella, James Dunne, Greg J. Beilman, Robert J. O'Connell, Matthew A. Borgman, Andrew P. Cap, and Francisco Rentas

From the United States Army Institute of Surgical Research, Ft Sam Houston, Texas; the Department of Pediatrics, Washington University in St Louis, St Louis, Missouri; Blood Systems Research Institute, San Francisco, California; the Department of Surgery, Bethesda Naval Medical Center, Bethesda, Maryland; the Department of Surgery, University of Minnesota, Minneapolis, Minnesota; the Walter Reed Army Institute of Research, Silver Spring, Maryland; the Brooke Army Medical Center, San Antonio, Texas; and the Armed Services Blood Program Office, Falls Church, Virginia.

1. Para el correcto desarrollo de la cirugía sobre el corazón es preciso conseguir un estado en el que este se halle vacío, parado y protegido contra la isquemia. Esto se consigue mediante la técnica conocida como Circulación Extracorpórea. En la foto, se observa una máquina de Circulación Extracorpórea ("máquina de

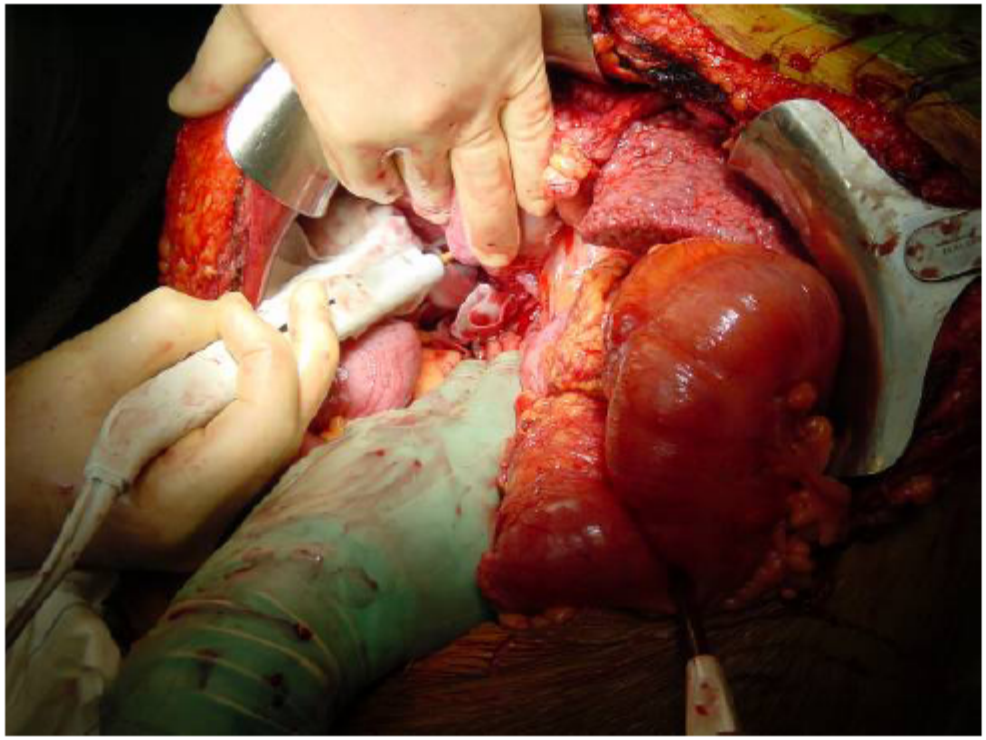


8. Además de la vía anterógrada, se puede inyectar cardioplejia por haciendo un recorrido inverso al de la circulación fisiológica (desde las venas coronarias hacia los capilares) insertando otra cánula en el seno coronario. Este tipo de protección cardiaca se conoce como cardioplejia retrógrada y es especialmente útil en los casos con patología coronaria, que no permite que la cardioplejia anterógrada se distribuya adecuadamente por la circulación rdiaca.



8. Además de la vía anterógrada, se puede inyectar cardioplejia por haciendo un recorrido inverso al de la circulación fisiológica (desde las venas coronarias hacia los capilares) insertando otra cánula en el seno coronario. Este tipo de protección cardiaca se conoce como cardioplejia retrógrada y es especialmente útil en los casos con patología coronaria, que no permite que la cardioplejia anterógrada se distribuya adecuadamente por la circulación rdiaca.

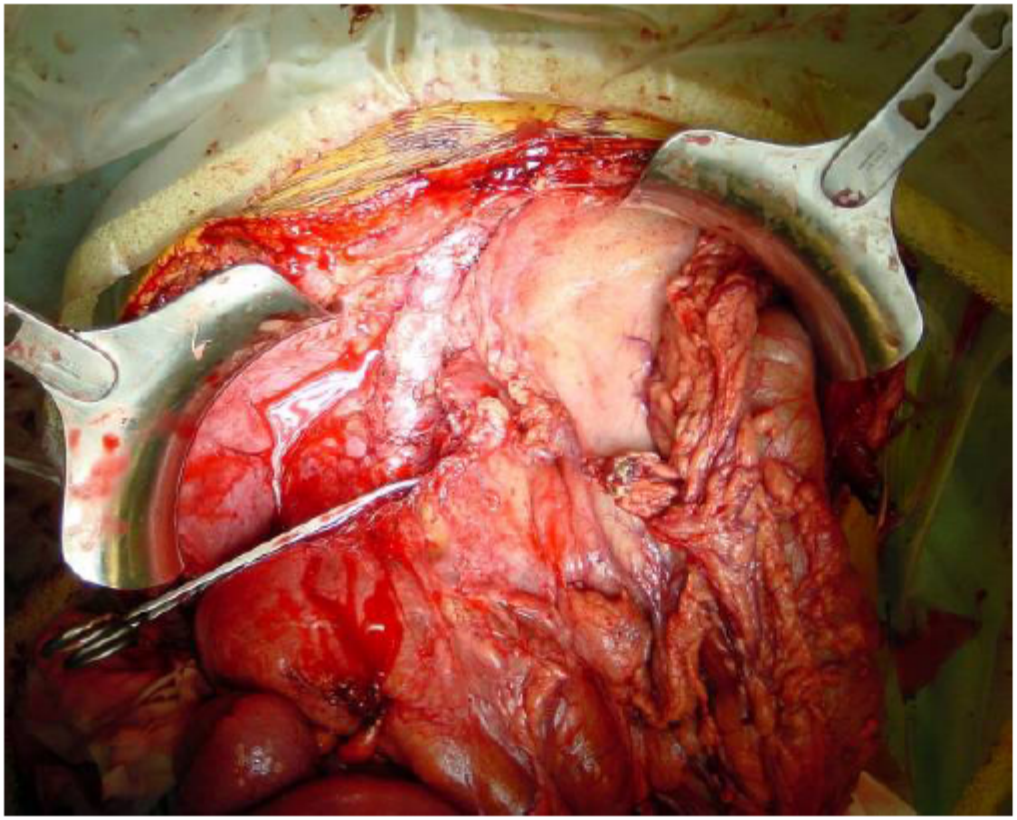
Preanhepatic Phase



- **Bleeding due to**
  - Preoperative coagulopathy
  - Amount of surgical dissection
  - Fibrinolysis
    - 10-20% of pts

Kang YG *et al. Anesthesiology* 1987; 66: 766

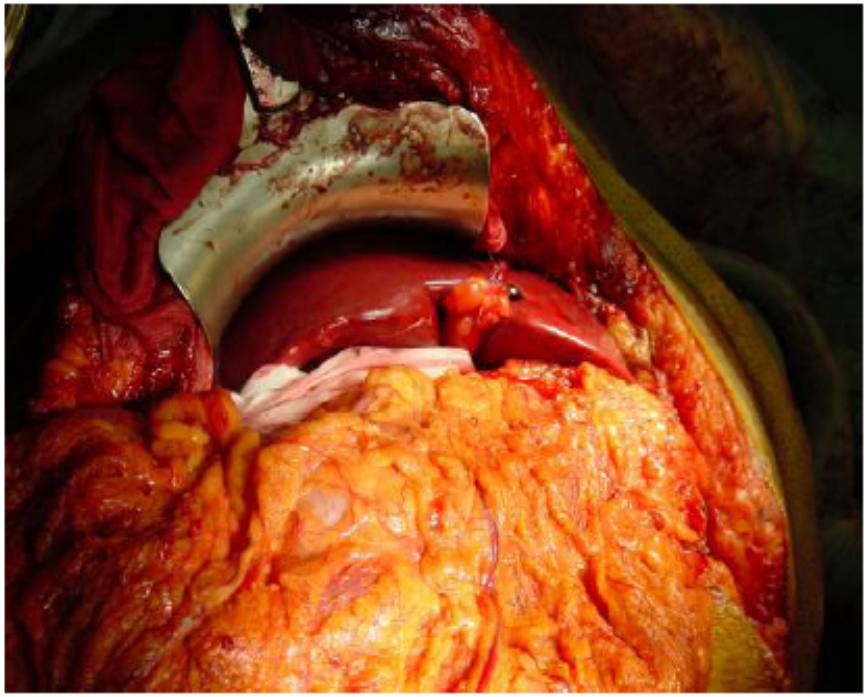
Anhepatic Phase



- **Bleeding due to**
  - Fibrinolysis
  - DIC

Porte RJ *et al. Transplantation* 1989; 47: 978; Porte RJ *Semin Thromb Hemost* 1993; 19: 191

Postanhepatic Phase



- **Bleeding due to**
  - Fibrinolysis
  - Thrombocytopenia
  - Heparin-like substances
  - Hypothermia

Porte RJ *et al. Transplantation* 1989; 47: 978;
Himmelreich G *et al. Semin Thromb Hemost* 1993; 19: 209;
Kettner SC *et al. Anesth Analg* 1998; 86: 691

ENFOQUE SISTEMICO DE HM

TRAUMA

CTCV

OBSTETRICIA

FLUIDOS

CIRCUITO DE CIRCULACION EXTRACORPOREA

DILUCIÓN DE FACTORES

CONSUMO DE FACTORES

BOMBA CARDIOPULMONAR

ENFOQUE SISTEMICO DE HM

POSTCIRCULACION EXTRACORPOREA

FIBRINOGENO disminuye 38%

TROMBINA 7%

PLAQUETAS 27%

ACTIVACION DE CASCADA INFLAMATORIA

ENFOQUE SISTEMICO DE HM

TRAUMA

CTCV

OBSTETRICIA

FLUIDOS

CONSUMO DE FACTORES

DISMINUCION DE FIBRINOGENO

CID

ENFOQUE SISTEMICO DE HM

(Rev. Esp. Anestesiol. Reanim. 2009; 56: 139-146) ORIGINAL

Hemorragia obstétrica: estudio observacional sobre 21.726 partos en 28 meses

E. Guasch[a,1], E. Alsina[b,1], J. Díez[b,2], R. Ruiz[c,3], F. Gilsanz[d,1]

[1]Servicio de Anestesiología y Reanimación. [2]Unidad de Investigación. Hospital Universitario La Paz. Madrid. [3]Hospital de Sanchinarro. Madrid.

OBJETIVO: Describir el manejo de las pacientes que sufrieron una hemorragia obstétrica grave.

MATERIAL Y MÉTODOS: Estudio observacional prospectivo desde julio de 2005 a noviembre de 2007 en mujeres que precisaron ingreso en la Unidad de Reanimación de un hospital terciario de referencia, por hemorragia obstétrica. Se analizó la incidencia, prevalencia, morbi-mortalidad y factores de riesgo asociados.

EN HM

RESULTADOS: Hubo 21.726 partos (124 de ellos con hemorragia grave). La *odds ratio* para la aparición de hemorragia obstétrica fue 4,54 para el parto instrumental y 2,86 para la cesárea. Los factores de riesgo identificados en la población evaluada fueron embarazo múltiple y muerte fetal anteparto. Una paciente falleció debido a una coagulación intravascular diseminada. La causa principal de hemorragia fue la atonía uterina en el 45,2%, seguida por los desgarros vaginales (26,6%). En el tratamiento de 96,8% de pacientes se usó concentrado de hematíes, fibrinógeno en el 49,2%, complejo protrombínico en el 7,25% y factor VII activado en el 3,2%. Se realizó embolización arterial selectiva en el 10,5% de los casos (tasa de éxito del 84,6%). Fue necesaria la histerectomía en el 13,7% de pacientes. Las principales complicaciones fueron: ventilación mecánica postoperatoria (11,3%), isquemia miocárdica (4%), edema pulmonar (4,8%), fallo renal agudo (8,9%), fibrilación ventricular (0,8%) y muerte (0,8%).

CONCLUSIÓN: La incidencia de hemorragia grave en las pacientes atendidas en nuestro hospital es baja, como lo es la tasa de mortalidad. El uso de fibrinógeno es frecuente y dio buenos resultados. La embolización angiográfica es muy efectiva, aunque finalmente el porcentaje de histerectomías es elevado aún. Los embarazos múltiples y los fetos muertos anteparto son factores de riesgo asociados.

ETIOLOGIA DE LAS HEMORRAGIAS POSTPARTO PRIMARIO TEMPRANO 4 T

T	Cause	Risk factors
Tone	Uterine atony *(the most frequent cause)*	Multifoetal gestation Foetal macrosomia Multiple leiomyomata Previous uterine atony
Tissue	Retained placenta	Extreme preterm gestation
	Placenta praevia	
	Placenta accreta/percreta	Previous uterine scar
Trauma	Lower genital tract lacerations	Forceps delivery
	Uterine rupture	Previous uterine scar
Thrombin	Coagulation disorders	Pre-existing, HELLP

British Journal of Anaesthesia **109** (6): 851–63 (2012)
Advance Access publication 16 October 2012 · doi:10.1093/bja/aes361

BJA

Haemostatic monitoring during postpartum haemorrhage and implications for management

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[2] Department of Anaesthesia, University Hospital of Wales, Cardiff, UK
[3] Department of Haematology, School of Medicine, Cardiff University, Cardiff, UK

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Summary. Postpartum haemorrhage (PPH) is a major risk factor for maternal morbidity and mortality. PPH has numerous causative factors, which makes its occurrence and severity difficult to predict. Underlying haemostatic imbalances such as consumptive and dilutional coagulopathies may develop during PPH, and can exacerbate bleeding and lead to progression to severe PPH. Monitoring coagulation status in patients with PPH may be crucial for effective haemostatic management, goal-directed therapy, and improved outcomes. However, current PPH management guidelines do not account for the altered baseline coagulation status observed in pregnant patients, and the appropriate transfusion triggers to use in PPH are unknown, due to a lack of high-quality studies specific to this area. In this review, we consider the evidence for the use of standard laboratory-based coagulation tests and point-of-care viscoelastic coagulation monitoring in PPH. Many laboratory-based tests are unsuitable for emergency use due to their long turnaround times, so have limited value for the management of PPH. Emerging evidence suggests that viscoelastic monitoring, using thrombelastography- or thromboelastometry-based tests, may be useful for rapid assessment and for guiding haemostatic therapy during PPH. However, further studies are needed to define the ranges of reference values that should be considered 'normal' in this setting. Improving awareness of the correct application and interpretation of viscoelastic coagulation monitoring techniques may be critical in realizing their emergency diagnostic potential.

Keywords: blood coagulation tests; point-of-care systems; postpartum haemorrhage; thrombelastography

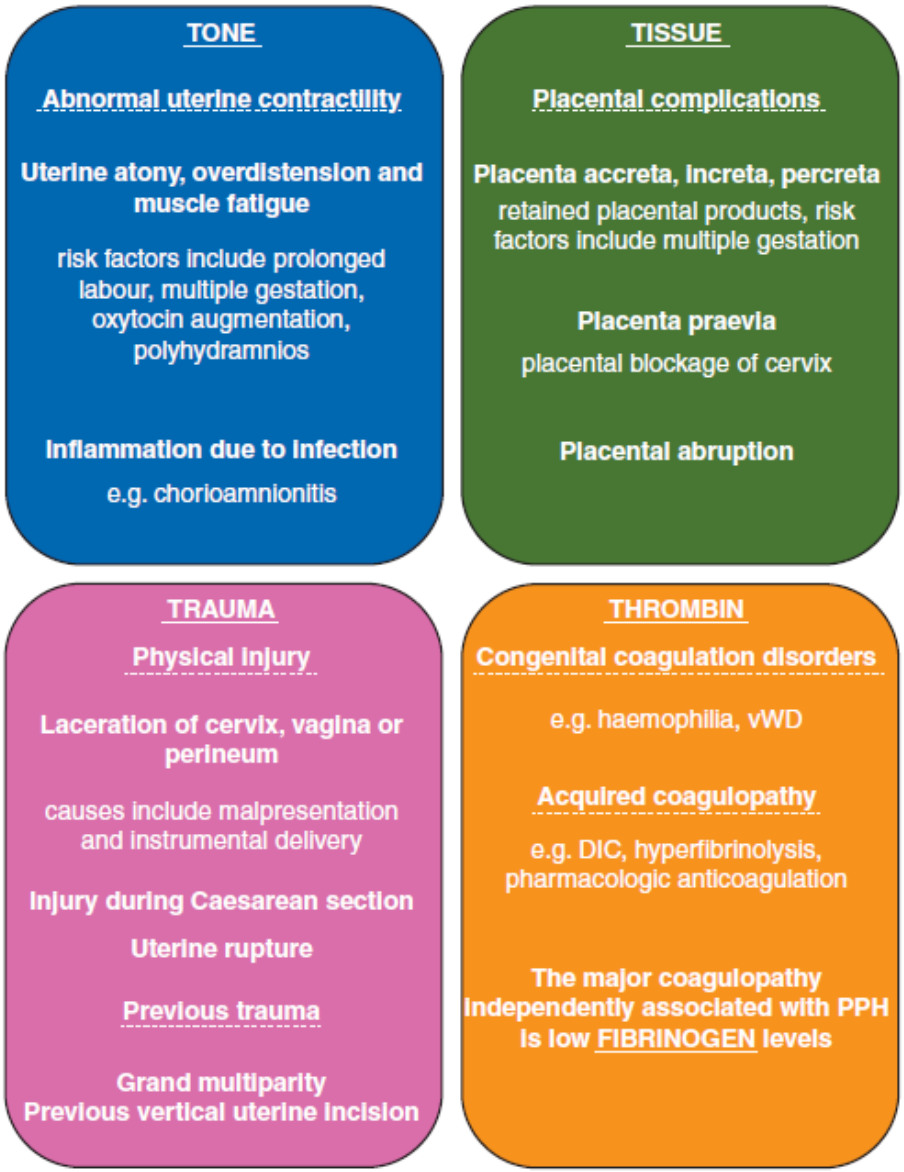


Fig 1 Major risk factors associated with PPH. Conditions are classified according to pathophysiology. DIC, disseminated intravascular coagulation; vWD, von Willebrand's disease; PPH, postpartum haemorrhage.

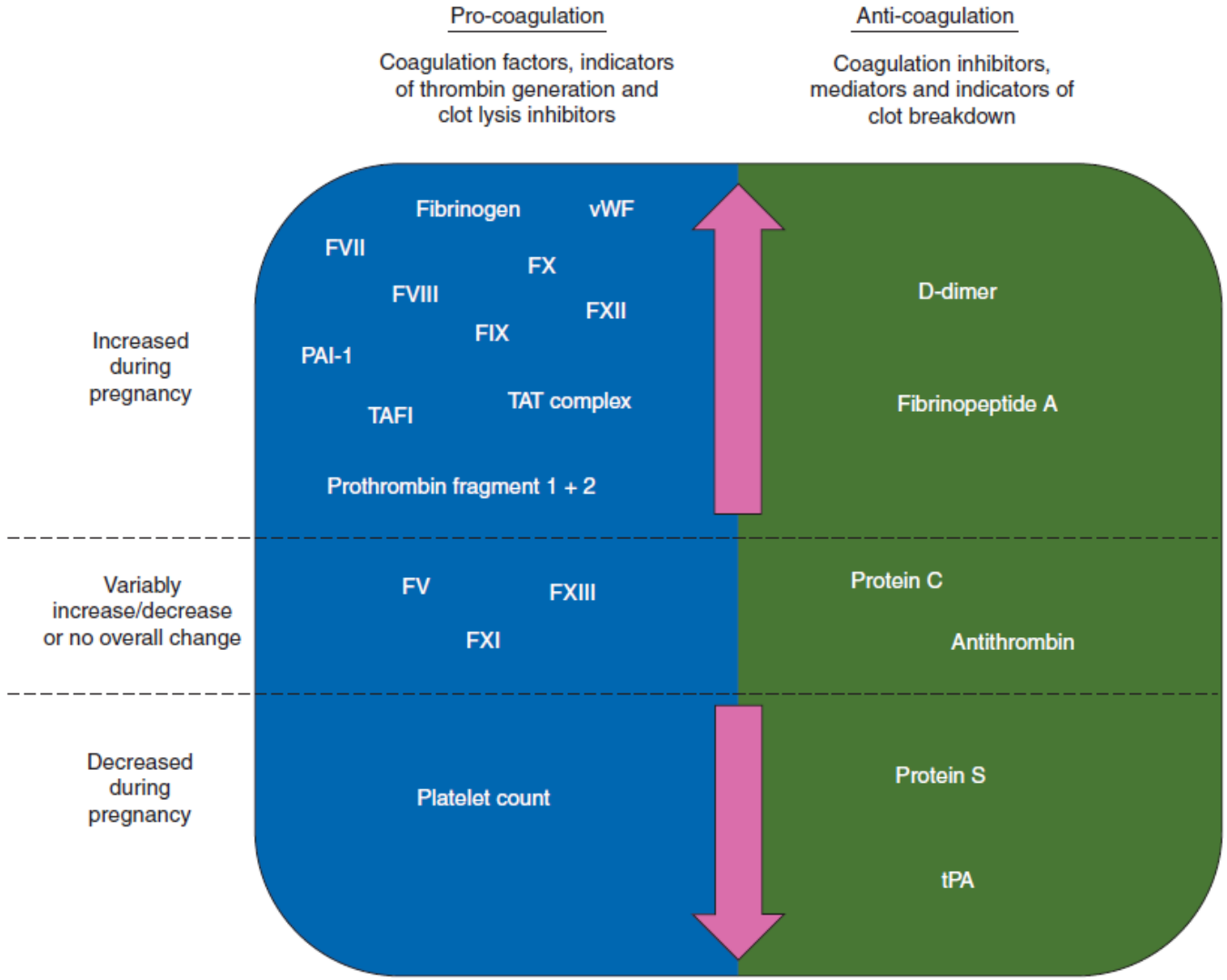
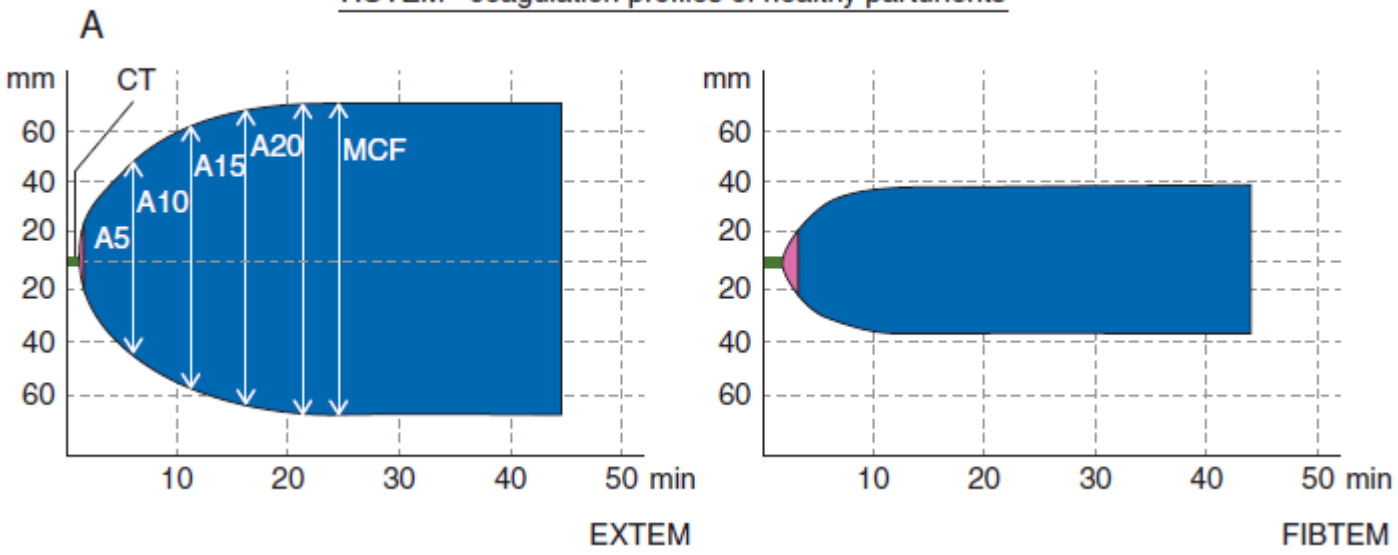
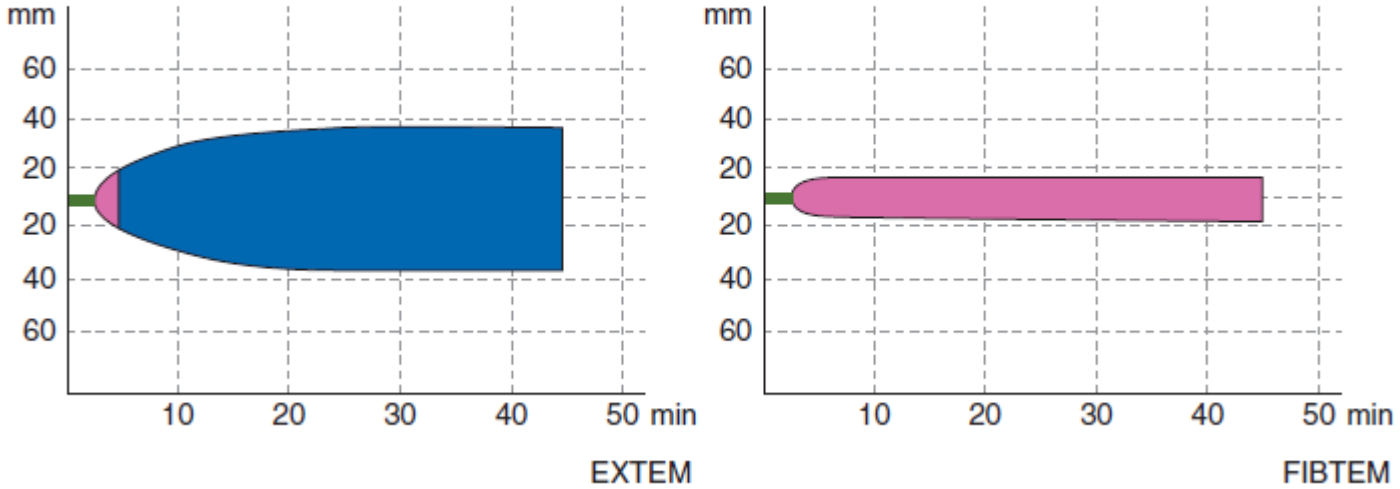


Fig 2 Changes in haemostatic variables observed during normal, healthy pregnancy. The overall increase in pro-coagulant factors results in a typically hypercoagulable state which increases throughout pregnancy. Increases and decreases are relative to non-pregnancy. Positioning of factors is not indicative of the precise level of increase or decrease. FV, Factor V; FVII, Factor VII; FVIII, Factor VIII; FIX, Factor IX; FX, Factor X; FXI, Factor XI; FXII, Factor XII; FXIII, Factor XIII; PAI-1, plasminogen activator inhibitor 1; TAFI, thrombin activatible fibrinolysis inhibitor; TAT complex, thrombin–antithrombin complex; vWF, von Willebrand factor.

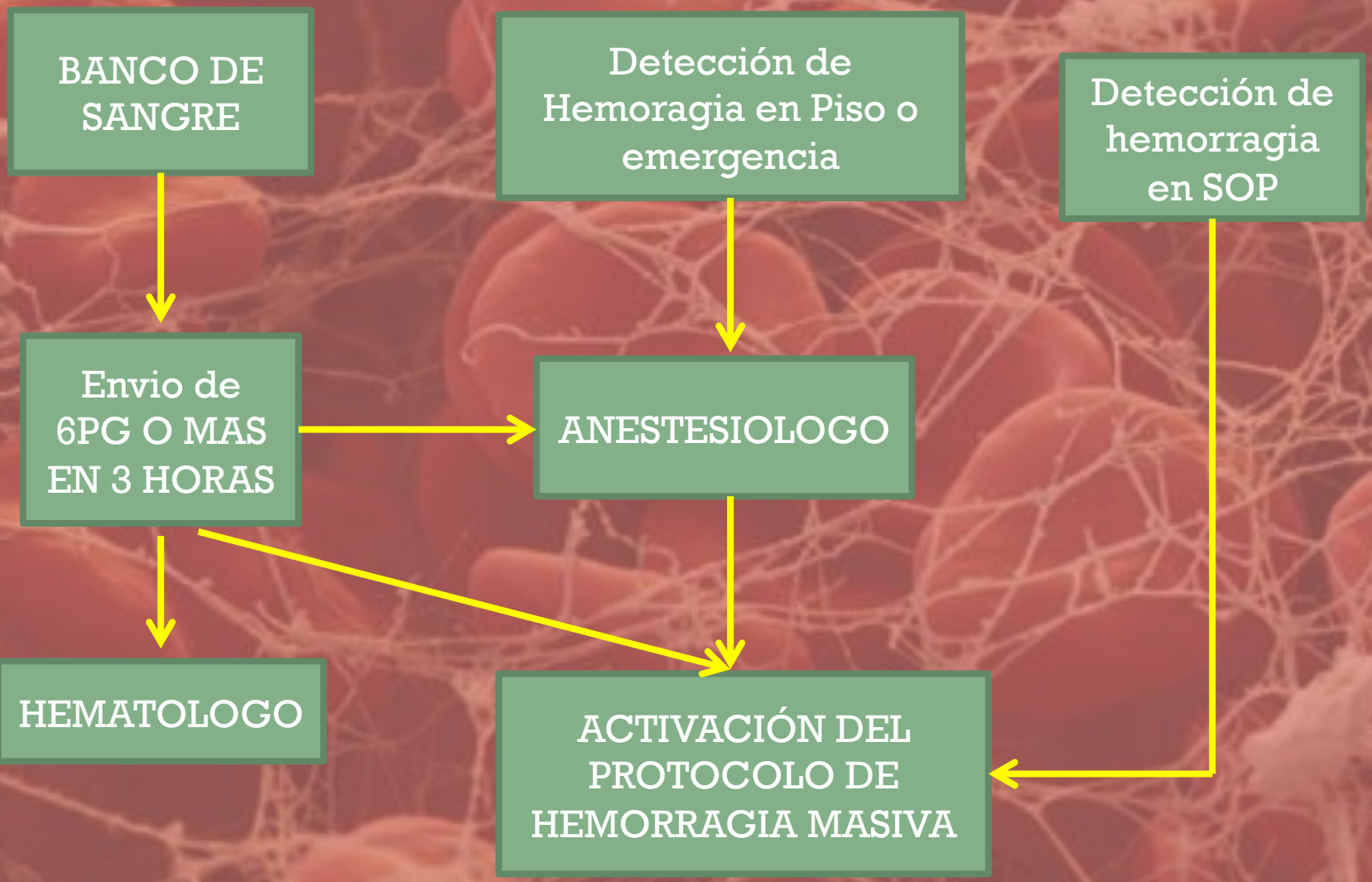
ROTEM® coagulation profiles of healthy parturients



ROTEM® coagulation profiles showing obstetric coagulopathy, e.g. during PPH



ALGORITMOS Y PROTOCOLOS



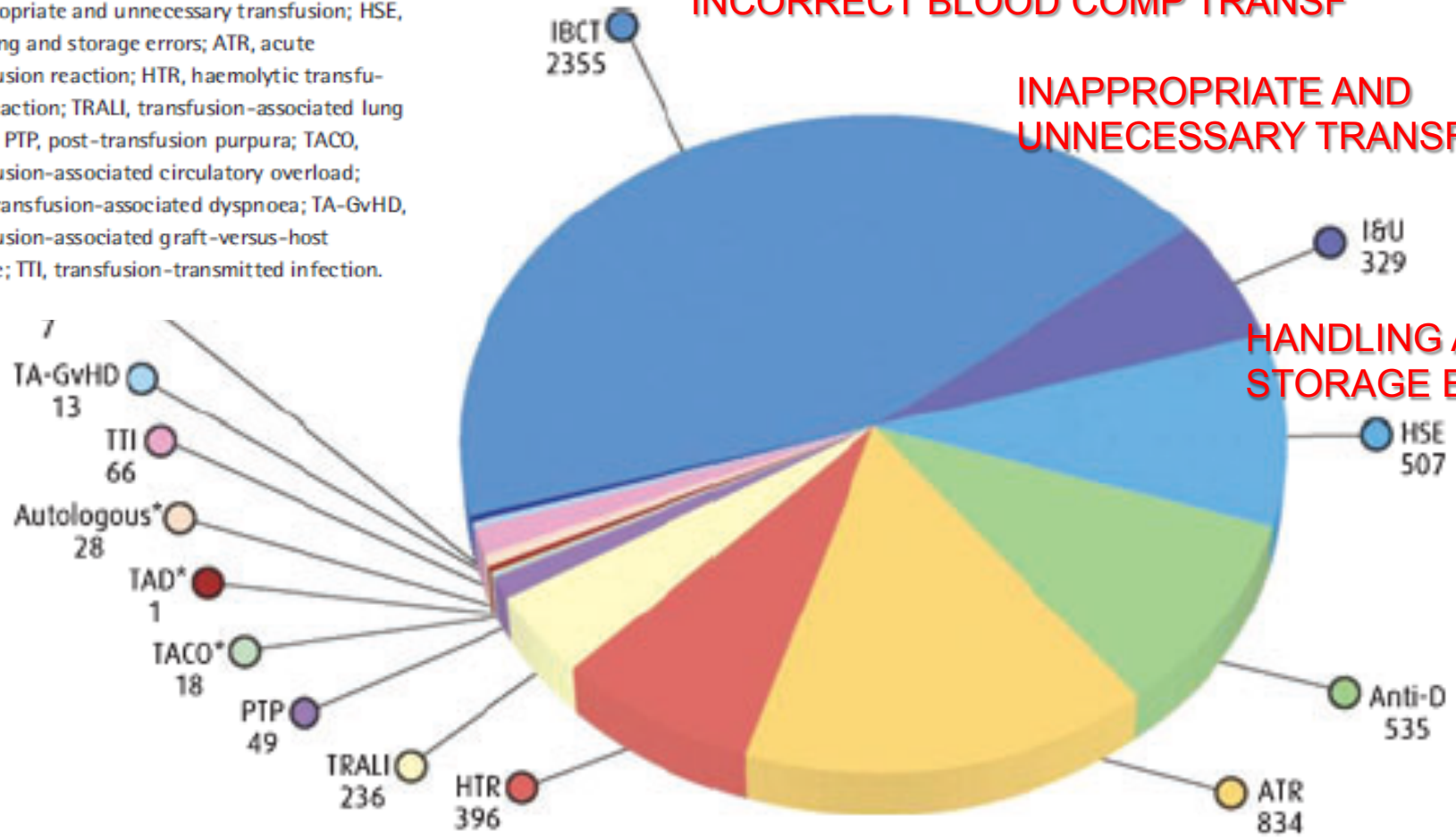
HIPOTERMIA prevención o remisión

- Calentamiento activo prehospitalario con gasas y con mantas.
- Calentadores de fluidos de alta capacidad.
- Salas calentadas de recepción de pacientes con politraumatizado.
- Mantas de aire caliente.
- Oxigeno humedificado caliente.
- Exposición quirúrgica limitada
- Lavado peritoneal o pleural
- Dispositivo de calentamiento extracorpóreo o intravasculares.

Aspectos importantes del Protocolo

- Iniciar coordinación con Hematólogo y Cirujano y anestesiólogo de guardia.
- Resucitación inicial y manejo inicial.
- Reemplazo de volumen y hemoterapia
  - Cristaloides , coloides .
  - Calentador de alto flujo (hemocare).
  - Por cada litro 2PG , + 500 ml PFC. Fibrinógeno.
  - Antifibrinolíticos, Complejo Protrombinico/ factor VIIa.
  - Uso de recuperador sanguineo en SOP.

Fig. 1 Serious Hazards of Transfusion cumulative data from the UK between 1996 and 2008 (5734 incidents reported) [5] IBCT, incorrect blood component transfused; I&U, inappropriate and unnecessary transfusion; HSE, handling and storage errors; ATR, acute transfusion reaction; HTR, haemolytic transfusion reaction; TRALI, transfusion-associated lung injury; PTP, post-transfusion purpura; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnoea; TA-GvHD, transfusion-associated graft-versus-host disease; TTI, transfusion-transmitted infection.



INCORRECT BLOOD COMP TRANSF

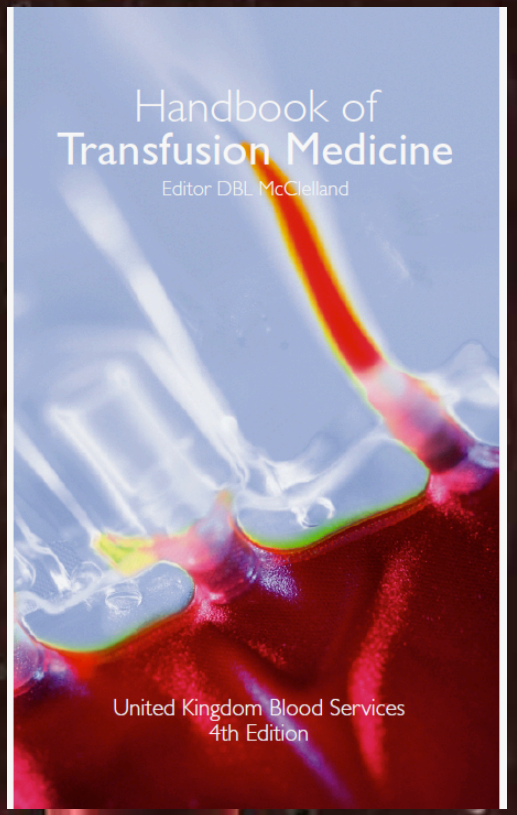
INAPPROPRIATE AND UNNECESSARY TRANSFUSION

HANDLING AND STORAGE ERRORS

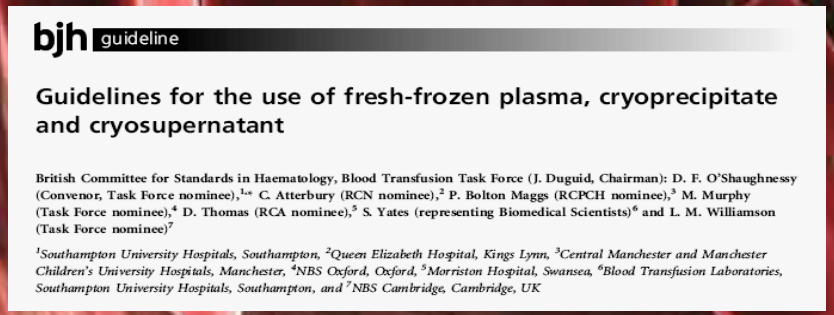
ACUTE TRANSFUSION REACTION

PLASMA FRESCO CONGELADO

SIEMPRE QUE NO EXISTA UNA INDICACION FORMAL O CONDICIONADA, SE DEBE CONSIDERAR QUE LA ADMINISTRACIÓN DE PLASMA FRESCO ESTA CONTRAINDICADA POR LOS RIESGOS ASOCIADOS Y ANTE LA NECESIDAD DEL USO RACIONAL DE UN PRODUCTO DE ORIGEN HUMANO DE DISPONIBILIDAD MUY LIMITADA.



2007

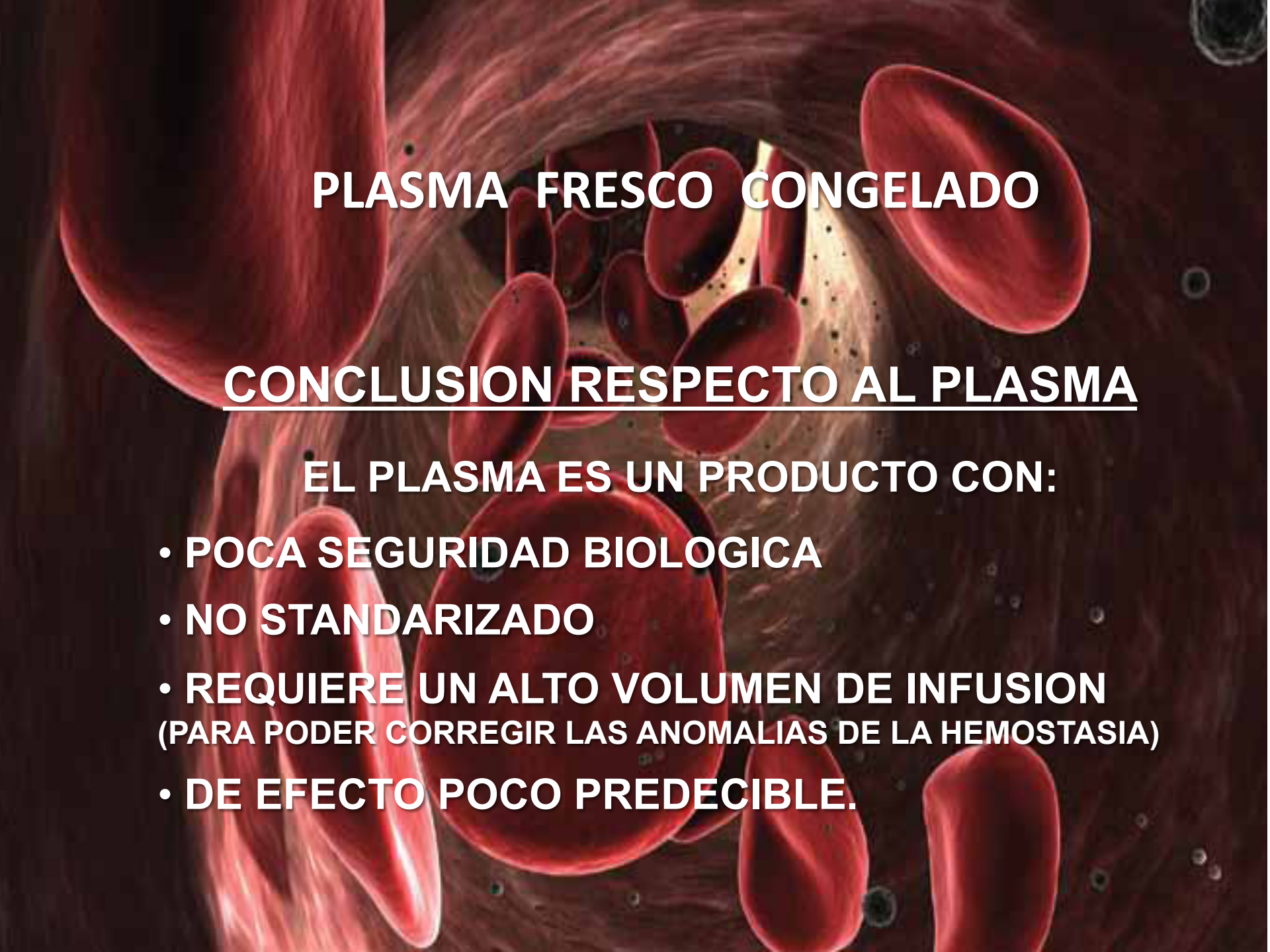


bjh guideline

Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant

British Committee for Standards in Haematology, Blood Transfusion Task Force (J. Duguid, Chairman): D. F. O'Shaughnessy (Convenor, Task Force nominee),[1,*] C. Atterbury (RCN nominee),[2] P. Bolton Maggs (RCPCH nominee),[3] M. Murphy (Task Force nominee),[4] D. Thomas (RCA nominee),[5] S. Yates (representing Biomedical Scientists)[6] and L. M. Williamson (Task Force nominee)[7]

[1]Southampton University Hospitals, Southampton, [2]Queen Elizabeth Hospital, Kings Lynn, [3]Central Manchester and Manchester Children's University Hospitals, Manchester, [4]NBS Oxford, Oxford, [5]Morriston Hospital, Swansea, [6]Blood Transfusion Laboratories, Southampton University Hospitals, Southampton, and [7]NBS Cambridge, Cambridge, UK



PLASMA FRESCO CONGELADO

CONCLUSION RESPECTO AL PLASMA

EL PLASMA ES UN PRODUCTO CON:

- POCA SEGURIDAD BIOLOGICA
- NO STANDARIZADO
- REQUIERE UN ALTO VOLUMEN DE INFUSION
(PARA PODER CORREGIR LAS ANOMALIAS DE LA HEMOSTASIA)
- DE EFECTO POCO PREDECIBLE.

Identificar y tratar la causa

- CONTROL LOCAL DE LA HEMORRAGIA : COMPRESIÓN.
- VALORAR POSIBILIDAD DE CONTROL VIA RADIOLOGIA INTERVENCIONISTA, CIRUGIA DE CONTROL DE DAÑOS.
- EN SOP VALORAR CLAMP VASCULAR O ENPAQUETAMIENTO.
- Gasometria venosa y arterial cada 15 min
- Perfil de coagulación cada 30 min Dimero D
- Mantener calentamiento activo.
- Comunicación permanente con el hematólogo.

OTRAS ESTRATEGIAS PARA EL CONTROL DE SANGRADO

- USO DE CONCENTRADOS DE FIBRINÓGENO
- USO DE CONCENTRADOS DE COMPLEJO PROTROMBINICO
- DESMOPRESINA
- ACIDO TRANEXAMICO
- FACTOR VII RECOMBINANTE HUMANO

CONCENTRADO DE FIBRINOGENO PLASMATICO HUMANO

FIBRINOGENO HUMANO PASTEURIZADO
POOL DE DONANTES
SOMETIDO A INACTIVACION VIRAL DOBLE
CONCENTRACION DE 900 A 1300 mg/ gr producto

FACTORES DE SEGURIDAD:

NO REACCIONES LOCALES
NO FENOMENOS TROMBOEMBÓLICOS
Vg HAEMOCOMPLETTAN

CONCENTRADO DE FIBRINOGENO PLASMATICO HUMANO

INDICACIONES:

HIPOFIBRINOGENEMIA CONGENITA

HIPOFIBRINOGENEMIA ADQUIRIDA

Secundaria a transfusión masiva

Niveles de 0.5 -1 gr/lt con hemorragia activa

Incremento de niveles de fib 0.9 a 2.04 gr por cada mg/kg dosis monitorear respuesta.

Dosis según etiología 30-100 mg/kg (2-4 gr)

Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

BioMed Central

Review

Open Access

Fibrinogen metabolic responses to trauma

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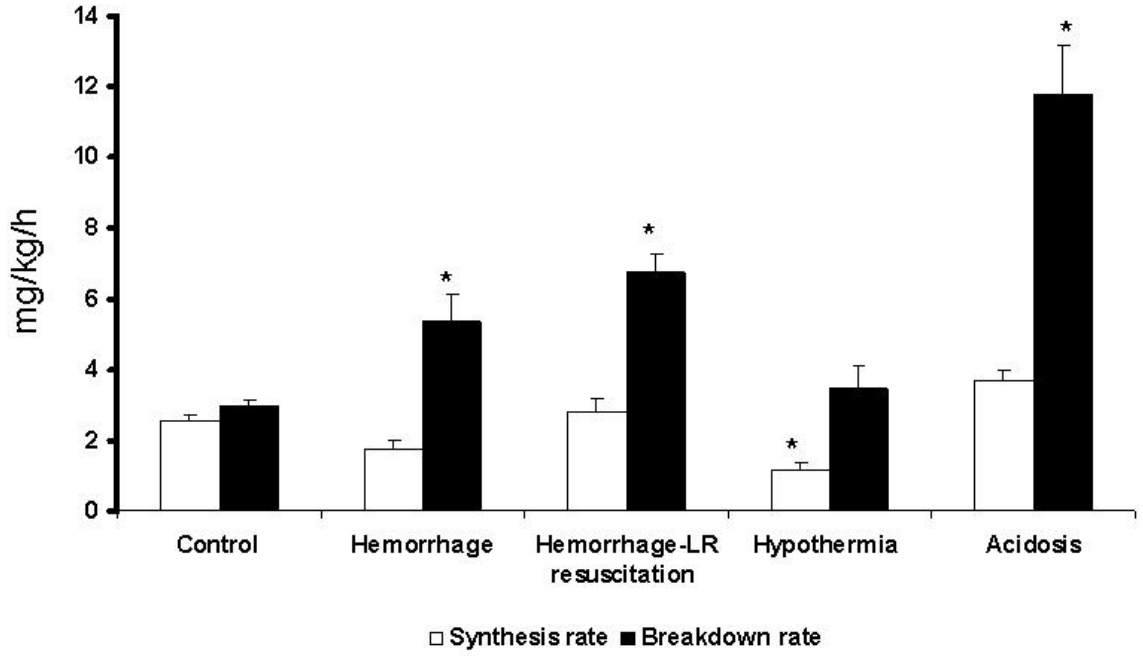
Fibrinogen availability = [[Fibrinogen] × total plasma volume] + [synthesis rate × time] - [breakdown rate × time]



Farm Hosp. 2012;36(6):209-235

Farmacia HOSPITALARIA
ÓRGANO OFICIAL DE EXPRESIÓN CIENTÍFICA DE LA SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA

ARTICULO ESPECIAL

2013: Documento «Sevilla» de Consenso sobre Alternativas a la Transfusión de Sangre Alogénica

Actualización del Documento «Sevilla»

S. R. Leal-Noval[1,3*], M. Muñoz[2,3], M. Asuero[3], E. Contreras[3], J. A. García-Erce[3], J. V. Llau[3], V. Moral[3], J. A. Páramo[3] y M. Quintana[3]

[1]Coordinador General. [2]Vicecoordinador General. [3]Coordinador de bloque temático.

1. *Paciente sangrante con traumatismo grave*

Recomendamos el uso de TEG para guiar la reposición de factores de coagulación y reducir la tasa transfusional. ***1C***

Los pacientes con traumatismos sangrantes pueden presentar alteraciones tempranas (en los 30 minutos que siguen al traumatismo) de la coagulación, incluyendo hipocoagulabilidad, hipercoagulabilidad y/o hiperfibrinolisis[62,63]. Al menos una veintena de estudios han documentado que el uso de TEG permite un más eficiente manejo de la coagulación y puede reducir la tasa transfusional[62,64].

2. *Paciente sangrante quirúrgico*

Recomendamos el uso de TEG para guiar la reposición de factores de coagulación y reducir la tasa transfusional. ***1C***

Un estudio retrospectivo que incluyó más de 3.000 pacientes intervenidos de cirugía cardiaca, documento

que la TEG disminuye significativamente las tasas transfusional y de fenómenos tromboembólicos[65]. Estudios retrospectivos que incluyeron un bajo número de pacientes intervenidos de cirugía vascular, hepática y obstétrica, concluyeron que la TEG reduce la tasa transfusional y permite el tratamiento precoz de las alteraciones de la coagulación[66,67].

3. *Seguridad*

El TEG no tiene riesgos para el paciente. No obstante, no valora la función plaquetaria, por lo que los pacientes con disfunción plaquetaria deben de valorarse con otras tecnologías[63].

1. *Pacientes en tratamiento con Antagonistas de la Vitamina K (AVK) con hemorragia activa o que precisen de un procedimiento quirúrgico urgente o emergente*

Sugerimos la administración de CCP para disminuir el sangrado y/o la tasa transfusional. ***2A***

La normalización del INR (*International Normalized Ratio*) se alcanza en virtualmente todos los pacientes, entre 10 y 30 minutos tras la administración de CCP[69,70,71]. Cuando el objetivo de administrar CCP es evitar el sangrado en pacientes que van a ser sometidos a cirugía u otros procedimientos invasivos, o disminuir la hemorragia en pacientes con sangrado activo, la mayoría de los estudios documentan disminución o cese del sangrado[72]. Las guías clínicas sugieren el uso de CCP de «4 factores» en pacientes sangrantes en tratamiento con AVK, independientemente del valor de INR[73]. En pacientes quirúrgicos, el CCP puede ser preferible al rFVIIa y/o plasma

2. *Pacientes en tratamiento con AVK y hemorragia intracraneal*

Recomendamos la administración de CCP para disminuir el sangrado. ***1C***

La hemorragia intracraneal (HIC) es el evento más grave asociado con la anticoagulación con AVK. El riesgo de HIC se duplica por cada punto de incremento de INR. La velocidad del crecimiento del hematoma y las secuelas neurológicas y la mortalidad son más elevadas en la HIC asociada a la ingesta de AVK que con otros tipos de HIC[75,76,77,78]. La mortalidad en las primeras 24 horas puede llegar al 33%[79,80]. En pacientes tratados con CCP, la corrección del INR y el control del sangrado se alcanzan de forma más eficaz que en aquéllos tratados con PFC[81,82]. Sin embargo, la mortalidad y las secuelas, permanecen invariablemente altas independientemente del tratamiento elegido[79,80].

Sangrado en paciente politraumatizado. Generalmente los pacientes con hemorragia masiva son transfundidos con un mayor número de unidades de concentrado de hematíes que de PFC (ratios 3:1 o superior). Datos recientes documentan que la mortalidad mejora si la ratio se eleva a 1:1:1 (cantidades equiparables de hematíes, plasma y plaquetas) en pacientes traumatizados con hemorragia crítica en el contexto militar, sugiriendo la necesidad de aportar grandes cantidades de factores de coagulación, desde el inicio de la hemorragia[83], aunque existe controversia al respecto[84]. El CCP podría aportar grandes cantidades de factores de forma más rápida y precoz, disminuyendo los requerimientos transfusionales[85].

Sangrado en paciente quirúrgico. La administración de CCP se asocia a disminución de los requerimientos transfusionales en el periodo perioperatorio[86], sobre todo en pacientes sometidos a cirugía cardiaca[65].

Insuficiencia hepática aguda. Un solo estudio observacional sugiere que el CCP podría ser útil en el tratamiento del sangrado o en la profilaxis del mismo en pacientes con déficits de factores hepato-dependientes secundario a insuficiencia hepática aguda[87].

CURRENT OPINION

Perioperatively acquired disorders of coagulation

Oliver Grottke[a], *Dietmar Fries*[b], *and Bartolomeu Nascimento*[c]

Purpose of review

To provide an overview of acquired coagulopathies that can occur in various perioperative clinical settings. Also described are coagulation disturbances linked to antithrombotic medications and currently available strategies to reverse their antithrombotic effects in situations of severe hemorrhage.

Recent findings

Recent studies highlight the link between low fibrinogen and decreased fibrin polymerization in the development of acquired coagulopathy. Particularly, fibrin(ogen) deficits are observable after cardiopulmonary bypass in cardiac surgery, on arrival at the emergency room in trauma patients, and with ongoing bleeding after child birth. Regarding antithrombotic therapy, although new oral anticoagulants offer the possibility of efficacy and relative safety compared with vitamin K antagonists, reversal of their anticoagulant effect with nonspecific agents, including prothrombin complex concentrate, has provided conflicting results. Specific antidotes, currently being developed, are not yet licensed for clinical use, but initial results are promising.

Summary

Targeted hemostatic therapy aims to correct coagulopathies in specific clinical settings, and reduce the need for allogeneic transfusions, thus preventing massive transfusion and its deleterious outcomes. Although there are specific guidelines for reversing anticoagulation in patients treated with antiplatelet agents or warfarin, there is currently little evidence to advocate comprehensive recommendations to treat drug-induced coagulopathy associated with new oral anticoagulants.

Keywords

anticoagulants, coagulopathy, hemorrhage, reversal

KEY POINTS

- Low fibrinogen and decreased quality of fibrin polymerization are important components of acquired coagulopathy in a number of clinical settings.
- Decreased fibrinogen concentration, as opposed to impaired thrombin generation, seems to be the key factor limiting sufficient hemostasis in cardiac surgery, trauma and postpartum-associated coagulopathy.
- Platelets inhibitors are increasingly used for antithrombotic therapy; owing to the lack of specific reversal strategies and antidotes, platelet transfusion remains the most effective therapeutic option in massively bleeding patients receiving antiplatelet therapy.
- In line with the results of several large phase III randomized controlled trials, correct prescription of NOAC therapy and consideration of contraindications (e.g. renal insufficiency), including adaptation of dosing and adherence to medication, should result in an overall low risk of bleeding complications.
- The clinical use of NOACs is currently challenging, there is an absence of specific antidotes to reverse their anticoagulant effect in situations of severe bleeding and the use of nonspecific agents (e.g. PCC, activated PCC) has not yet been fully investigated.

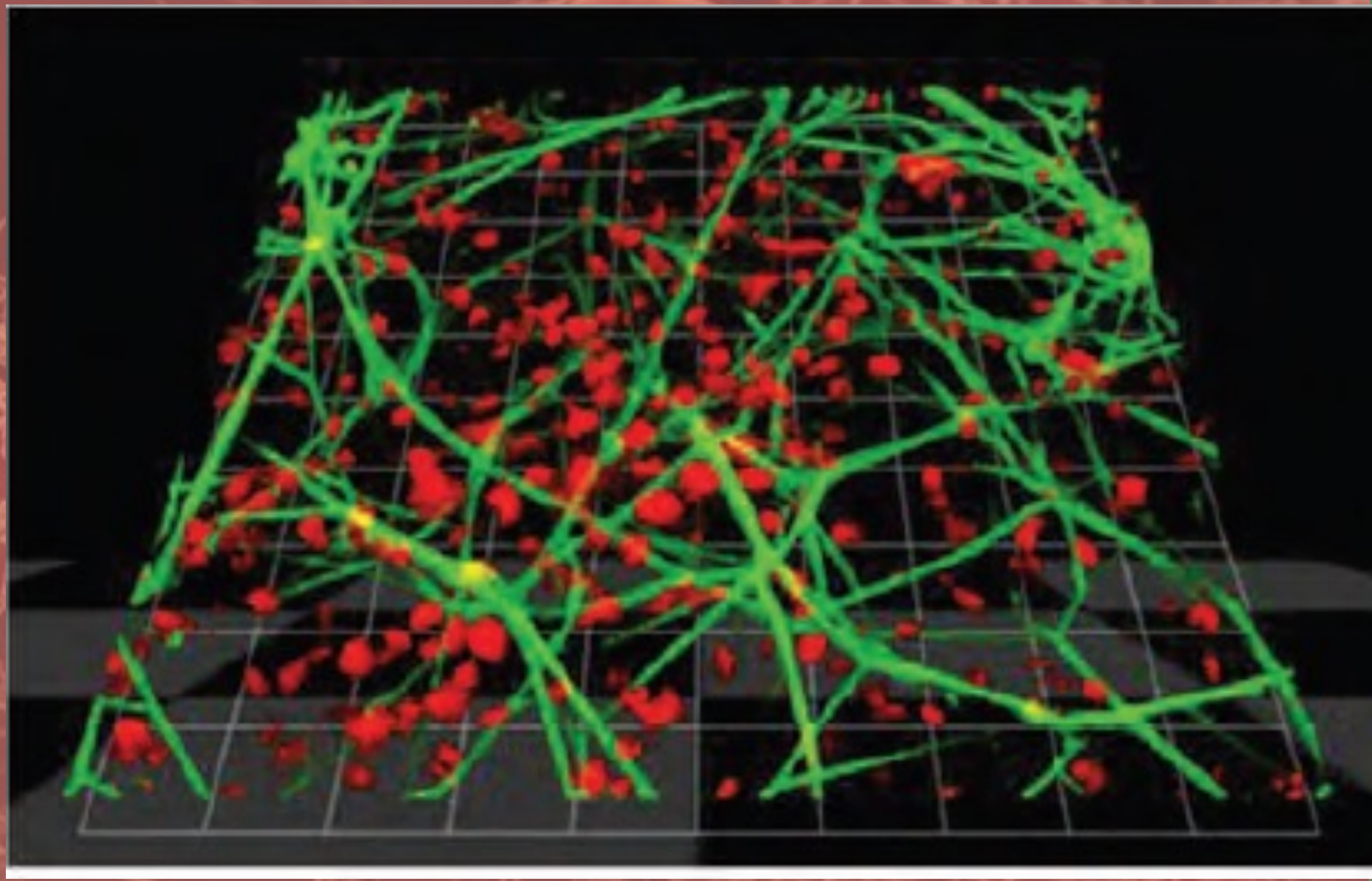


Table 1. Overview of recent studies highlighting methods to control bleeding and correct fibrin-based clot strength in various clinical settings

Study	Design	Treatment (no. of patients)	Major findings
Cardiovascular surgery			
Rahe-Meyer *et al.* [8▪]	RCT	Fibrinogen concentrate ($n=29$)	Fibrinogen concentrate controls coagulopathic bleeding during aortic surgery more effectively than placebo or a standardized treatment algorithm (4 units FFP or 2 units apheresis platelets)
		FFP/PLT ($n=32$)	Fibrinogen concentrate also provides a more rapid and at least as effective control of intraoperative bleeding compared with standardized treatment (post-hoc analysis of data [18])
			Plasma fibrinogen and FIBTEM MCF were corrected by fibrinogen concentrate or fibrinogen concentrate + FFP
			Fibrinogen concentrate raises plasma fibrinogen more effectively than FFP, as it allows targeting of a high normal level
			The increases were short-lived; plasma fibrinogen and FIBTEM MCF were comparable in all groups by 24 h postsurgery
Tanaka *et al.* [15]	Prospective, randomized open-label study	Fibrinogen concentrate ($n=10$)	Despite moderately decreased thrombin generation, bleeding was reduced with a single dose of 4-g fibrinogen concentrate to reach a target fibrinogen level of 2 g/l
		PLT ($n=10$)	
Trauma			
Khan *et al.* [19]	Prospective cohort study	4 U PRBCs up to 12 U	Hemostatic resuscitation does not correct hypoperfusion or coagulopathy during the acute phase of trauma hemorrhage
Innerhofer *et al.* [20]	Post hoc analysis of data from a prospective study	Coagulation factor concentrates (fibrinogen concentrate and/or PCC; $n=66$)	Coagulation factor concentrates alone corrected coagulopathy in patients with severe blunt trauma
		Coagulation factor concentrates (fibrinogen concentrate and/or PCC) + FFP ($n=78$)	
Postpartum hemorrhage			
Collins *et al.* [21▪]	Prospective, observational study	$n=356$	Fibrin-based clot formation is a rapidly available early biomarker for progression of postpartum hemorrhage
Mallaiah *et al.* [10▪]	Prospective two-phase study	Phase 1: $n=42$	Fibrinogen concentrate allows prompt correction of coagulation deficits associated with major obstetric hemorrhage
		Phase 2: $n=51$	

CCP'S 2ª GENERACION

PRODUCTOS CON BALANCE HEMOSTATICO

CONTENIDO FISIOLÓGICO Y EQUILIBRADO DE LOS FACTORES DE COAGULACIÓN Y DE LOS INHIBIDORES.

- **FII, FVII, FIX y FX RATIO IDEAL 1:1:1:1**
- **NIVELES TERAPÉUTICOS DE PROT. C y PROT. S**
- **TRAZAS DE AT-III, COMBINADO CON HEPARINA**
- **ACTIVIDAD PROTEOLITICA BAJA**

PRODUCTO POTENTE CON NULA TENDENCIA TROMBOGENICA

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Octaplex is presented as a powder and solvent for solution for injection containing human prothrombin complex. Octaplex nominally contains:

Name of ingredient	Octaplex Quantity per vial (20ml)	Octaplex Quantity per ml reconstituted solution
Total protein:	260 - 820 mg	13 - 41 mg/ml
Active substances		
Human coagulation factor II	220 - 760 IU	11 - 38 IU/ ml
Human coagulation factor VII	180 - 480 IU	9 - 24 IU/ ml
Human coagulation factor IX	500 IU	25 IU/ ml
Human coagulation factor X	360 - 600 IU	18 - 30 IU/ ml
Further active ingredients		
Protein C	140 - 620 IU	7 - 31 IU/ ml
Protein S	140 - 640 IU	7 - 32 IU/ ml

Factor IX specific activity is ≥ 0.6 IU/ mg proteins.

Kerebel *et al. Critical Care* 2013, **17**:R4
http://ccforum.com/content/17/1/R4

CRITICAL CARE

RESEARCH Open Access

A French multicenter randomised trial comparing two dose-regimens of prothrombin complex concentrates in urgent anticoagulation reversal

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Abstract

Introduction: Prothrombin complex concentrates (PCC) are haemostatic blood preparations indicated for urgent anticoagulation reversal, though the optimal dose for effective reversal is still under debate. The latest generation of PCCs include four coagulation factors, the so-called 4-factor PCC. The aim of this study was to compare the efficacy and safety of two doses, 25 and 40 IU/kg, of 4-factor PCC in vitamin K antagonist (VKA) associated intracranial haemorrhage.

Methods: We performed a phase III, prospective, randomised, open-label study including patients with objectively diagnosed VKA-associated intracranial haemorrhage between November 2008 and April 2011 in 22 centres in France. Patients were randomised to receive 25 or 40 IU/kg of 4-factor PCC. The primary endpoint was the international normalised ratio (INR) 10 minutes after the end of 4-factor PCC infusion. Secondary endpoints were changes in coagulation factors, global clinical outcomes and incidence of adverse events (AEs).

Results: A total of 59 patients were randomised: 29 in the 25 IU/kg and 30 in the 40 IU/kg group. Baseline demographics and clinical characteristics were comparable between the groups. The mean INR was significantly reduced to 1.2 - and ≤1.5 in all patients of both groups - 10 minutes after 4-factor PCC infusion. The INR in the 40 IU/kg group was significantly lower than in the 25 IU/kg group 10 minutes ($P = 0.001$), 1 hour ($P = 0.001$) and 3 hours ($P = 0.02$) after infusion. The 40 IU/kg dose was also effective in replacing coagulation factors such as PT ($P = 0.038$), FII ($P = 0.001$), FX ($P < 0.001$), protein C ($P = 0.002$) and protein S (0.043), 10 minutes after infusion. However, no differences were found in haematoma volume or global clinical outcomes between the groups. Incidence of death and thrombotic events was similar between the groups.

Conclusions: Rapid infusion of both doses of 4-factor PCC achieved an INR of 1.5 or less in all patients with a lower INR observed in the 40 IU/kg group. No safety concerns were raised by the 40 IU/kg dose. Further trials are needed to evaluate the impact of the high dose of 4-factor PCC on functional outcomes and mortality.

Trial registration: Eudra CT number 2007-000602-73.

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

Sørensen *et al. Critical Care* 2011, **15**:201
http://ccforum.com/content/15/1/201

CRITICAL CARE

REVIEW

Clinical review: Prothrombin complex concentrates - evaluation of safety and thrombogenicity

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EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

Table 1. Composition of PCCs in the World Federation of Hemophilia register of clotting factor concentrates

		International units relative to factor IX					
Brand name	**Manufacturer**	**Factor II**	**Factor VII**	**Factor IX**	**Factor X**	**Viral inactivation**	**Additional information**
Bebulin VH	Baxter BioScience, Austria	120	(13)	100	100	Vapour heat, 60°C for 10 hours at 190 mbar, then 80°C for 1 hour at 375 mbar	Heparin added
Beriplex P/N	CSL Behring, Germany	128	68	100	152	Pasteurisation at 60°C for 10 hours, and nanofiltration	Protein C; antithrombin, heparin and albumin added
Cofact	Sanquin, the Netherlands	56-140	28-80	100	56-140	Solvent/detergent and 15 nm nanofiltration	Antithrombin added
KASKADIL	LFB, France	148	40	100	160	Solvent/detergent	Heparin added
Octaplex	Octapharma, Austria and France	44-152	36-96	100	50	Solvent/detergent and nanofiltration	Heparin added; low activated factor VII content
Profilnine SD	Grifols, USA	148	(11)	100	64	Solvent/detergent	–
Prothrombinex VF	CSL Bioplasma, Australia	100	(–)	100	100	Dry heat, 80°C for 72 hours and nanofiltration	–
Prothromplex T	Baxter BioScience, Austria	100	85	100	100	Vapour heat, 60°C for 10 hours at 190 mbar, then 80°C for 1 hour at 375 mbar	Antithrombin and heparin added
UMAN Complex D.I.	Kedrion, Italy	100	(–)	100	80	Solvent/detergent and dry heat, 100°C for 30 minutes	Antithrombin and heparin added

Table 2. Studies reporting thrombogenic complications associated with the use of PCCs

Publication	Study type	PCC indication	Number of patients	Number of thrombotic complications	Nature of complications	Notes
Lusher [11]	Physician survey and registry	Haemophilia	Not available (150 physicians surveyed)	72 (reported over a 4-year period)	Various (for example, deep venous thrombosis of the leg, pulmonary embolus, DIC)	Increased risk among patients receiving large, repeated doses of PCC
Lankiewicz and colleagues [15]	Retrospective review	Warfarin reversal	58	4	Deep vein thrombosis ($n = 2$), non-ST elevation myocardial infarction ($n = 2$)	Thrombotic complications were not attributable to PCC therapy
van Aart and colleagues [16]	Prospective, randomised controlled trial	Oral anticoagulation reversal (acenocoumarol or phenprocoumon)	93	2	Thrombotic stroke ($n = 2$)	Both patients were elderly and had atrial fibrillation; one had vascular disease and the other had a large haematoma
Preston and colleagues [17]	Prospective, uncontrolled trial	Warfarin reversal	42	1	Thrombotic stroke	Stroke occurred following leg amputation, 48 hours after PCC treatment. Patient had peripheral vascular disease
Pabinger-Fasching and colleagues [18,55]	Prospective, uncontrolled trial	Oral anticoagulation reversal (vitamin K antagonists)	43	1	Suspected pulmonary embolism (fatal)	Patient had risk of thrombosis due to metastatic gastrointestinal cancer and atrial fibrillation
Bagot and colleagues [19]	Case report	Warfarin reversal	1	1	Myocardial infarction (fatal)	No definite causal link with PCC administration; patient may have had DIC related to abdominal sepsis
Warren and Simon [20]	Case report	Warfarin reversal	1	1	Intracardial thrombosis (fatal)	Patient had a history of ischaemic stroke and deep venous thrombosis; general disturbance of coagulation
Kohler and colleagues [22]	Case reports ($n = 5$)	Perioperative setting, acquired deficiencies of coagulation factors	5	5	Thrombotic events (fatal)	All patients received an old PCC that was withdrawn in 1994; all patients had underlying diseases predisposing them to thrombosis or DIC

DIC, disseminated intravascular coagulation; PCC, prothrombin complex concentrate.

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

Table 3. Pharmacovigilance data for some of the commercially available PCCs

Brand name (manufacturer)	Dates of survey	Amount produced to date	Estimated number of applications	Number of cases of proven infection transmission	Number of cases of HIT type II	Number of cases of proven thromboembolism
Beriplex P/N (CSL Behring, Germany)	1996 to 2004	>400 million units	>200,000 (average dose 2,000 units)	0	0	0 (two cases were reported but PCC not established as the cause)
Cofact (Sanquin, The Netherlands)	1997 to 2006	~97 million units	~64,000 to 82,500 (average dose 20 to 50 ml)	0	0	0
Uman Complex D.I. (Kedrion, Italy)	2005 to 2007	~31.5 million units	~16,000 (average dose 2,000 units)	0	0	0

MENOS INFECCIONES POTENCIALMENTE GRAVES

Pharmacovigilance data for some of the commercially available prothrombin complex concentrates (PCCs) listed in the World Federation of Hemophilia register of clotting factor concentrates, excluding those for national markets only [54]. HIT, heparin-induced thrombocytopaenia.

Research

Open Access

Management of bleeding following major trauma: a European guideline

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Table 1

Grading of recommendations after Guyatt *et al.* [8]

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A			
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or *vice versa*	Randomised controlled trials (RCTs) without important limitations or overwhelming evidence from observational studies	Strong recommendations, can apply to most patients in most circumstances without reservation
1B			
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or *vice versa*	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendations, can apply to most patients in most circumstances without reservation
1C			
Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or *vice versa*	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A			
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B			
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C			
Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion

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METODOS

- Datasets from severely injured and bleeding patients with established coagulopathy upon emergency room (ER) arrival from two retrospective trauma databases, (i) TR-DGU (Germany) and (ii) Innsbruck Trauma Databank/ ITB (Austria), that had received two different strategies of coagulopathy management during initial resuscitation, (i) fresh frozen plasma (FFP) without coagulation factor concentrates, and (ii) coagulation factor concentrates (fibrinogen and/ or prothrombin complex concentrates) without FFP, were compared for morbidity, mortality and transfusion requirements using a matched-pair analysis approach.

RESULTADOS

- There were no major differences in basic characteristics and physiological variables upon ER admission between the two cohorts that were matched. ITB patients had received substantially less packed red blood cell (pRBC) concentrates within the first 6h after admission (median 1.0 ($IQR_{25–75}$ 0–3) vs 7.5 ($IQR_{25–75}$ 4–12) units; $p<0.005$) and the first 24h as compared to TR-DGU patients (median 3 ($IQR_{25–75}$ 0–5) vs 12.5 (8–20) units; $p<0.005$). Overall mortality was comparable between both groups whilst the frequency for multi organ failure was significantly lower within the group that had received coagulation factor concentrates exclusively and no FFP during initial resuscitation ($n=3$ vs $n=15$; $p=0.015$). This translated into trends towards reduced days on ventilator whilst on ICU and shorter overall in-hospital length of stays (LOS).

ORIGINAL ARTICLE

The early use of fibrinogen, prothrombin complex concentrate, and recombinant-activated factor VIIa in massive bleeding

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doi: 10.1111/trf.12041

TRANSFUSION 2013;53:91S-95S.

BACKGROUND: Coagulopathy related to massive bleeding has a multifactorial aetiology. Coagulopathy is related to shock and blood loss including consumption of clotting factors and platelets and hemodilution. Additionally hyperfibrinolysis, hypothermia, acidosis, and metabolic changes affect the coagulation system. The aim of any hemostatic therapy is to control bleeding and minimize blood loss and transfusion requirements. Transfusion of allogeneic blood products as well as the presence of coagulopathy cause increased morbidity and mortality.

STUDY DESIGN AND METHODS: This paper presents a short review on new treatment strategies of coagulopathy, related to massive blood loss.

RESULTS: Paradigms are actively changing and there is still shortage of data. However, there is increasing experience and evidence that "target controlled algorithms" using point-of-care monitoring devices and coagulation factor concentrates are more effective compared to transfusion of fresh frozen plasma, independently of the individual clinical situation.

CONCLUSION: Future treatment of coagulopathy associated with massive bleeding can be based on an individualized point-of-care guided rational use of coagulation factor concentrates such as fibrinogen, prothrombin complex concentrate, and recombinant factor VIIa. The timely and rational use of coagulation factor concentrates may be more efficacious and safer than ratio-driven use of transfusion packages of allogeneic blood products.

PROTHROMBIN COMPLEX CONCENTRATE (PCC)

PCC has been used for many years for the treatment of congenital coagulation disorders and is recommended for reversing oral anticoagulation. PCCs contain coagulation factors II, VII, IX, and X. There are differences among products in the concentrations of these factors and other constituents including heparin, protein C, and protein S. Reduced thrombin formation and an associated need for PCC must be expected if the activity of the procoagulants, and prothrombin especially, is <30%. This generally only occurs with blood losses >150%-200% of the estimated blood volume. Critical levels can be detected with the use of standard coagulation tests (prothrombin time < 30%) or thrombelastography and/or ROTEM.[23,24] A liberal administration practice of PCC might be associated with an increased risk for thromboembolic complications as shown in two animal trials.[25,26] Until now, the efficacy of PCC in massive bleeding has not been proven in any prospective controlled study. The author wants to caution an uncritical application of PCC in clinical practice.

FIBRINOGEN CONCENTRATE

In severe traumatized and massively bleeding patients, fibrinogen usually reaches critical levels at an early stage. Clinical data from gynecology,[8] neurology,[9] and cardiac surgery[10] show that the perioperative and postoperative hemorrhagic tendency is increased when fibrinogen levels are below 150-200 mg/dL. Data on the efficacy of fibrinogen concentrates in acquired fibrinogen deficiency are limited. In vitro studies and experimental investigations, as well as reports from postmarketing surveillance and retrospective data analyses,[11-17] have shown consistently that fibrinogen can increase clot firmness and improves survival of severely injured massively bleeding patients or soldiers.[18] Four small prospective clinical studies examined the use of fibrinogen concentrate (thrombelastometry [ROTEM, TEM Innovation, Munich, Germany], assisted in two studies). In all four studies, coagulation was optimized, perioperative bleeding was reduced by 32%, and transfusion requirement was significantly reduced.[19-22]

Nienaber and colleagues compared the datasets from severely injured and bleeding patients from the German Trauma Data Registry and the Innsbruck Trauma Databank (Austria) in a matched pair analysis. The German patients received FFP without coagulation factor concentrates, while the patients from Innsbruck received solely coagulation factor concentrates (fibrinogen and/or PCCs) guided by thrombelastometry without transfusion of any FFP. The patients from Innsbruck had received substantially less red blood cells as compared with the German patients ($p < 0.005$). The frequency for multiorgan failure was significantly lower within the group that had received exclusively coagulation factor concentrates ($p = 0.015$).[24] The same results were found in a retrospective analysis comparing retrospective data from the Salzburg Trauma Center, Austria with data from the German Trauma Register. A thrombelastometry-guided coagulation management with the use of clotting factor concentrates depending on the individual needs resulted in a decreased rate of allogeneic transfusion.[23,37]

In summary, massive transfusion protocols are unlikely to be suitable for all kinds of bleeding. Nevertheless, prospective randomized controlled trials are necessary to prove this hypothesis and to confirm the currently available data. Right now, one prospective randomized controlled double blinded study investigates the efficacy of early administration of fibrinogen concentrate in severe traumatized patients on the scene, while another prospective randomized controlled trial compares the use of FFP with coagulation factor concentrates in severly injured patients in the emergency room (for further information: http://www.clotwork.at).

Schöchl *et al. Critical Care* 2010, **14**:R55
http://ccforum.com/content/14/2/R55

CRITICAL CARE

RESEARCH Open Access

Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM®)-guided administration of fibrinogen concentrate and prothrombin complex concentrate

Herbert Schöchl[1,2], Ulrike Nienaber[3], Georg Hofer[1], Wolfgang Voelckel[1], Csilla Jambor[4], Gisela Scharbert[5], Sibylle Kozek-Langenecker[5] and Cristina Solomon*[6]

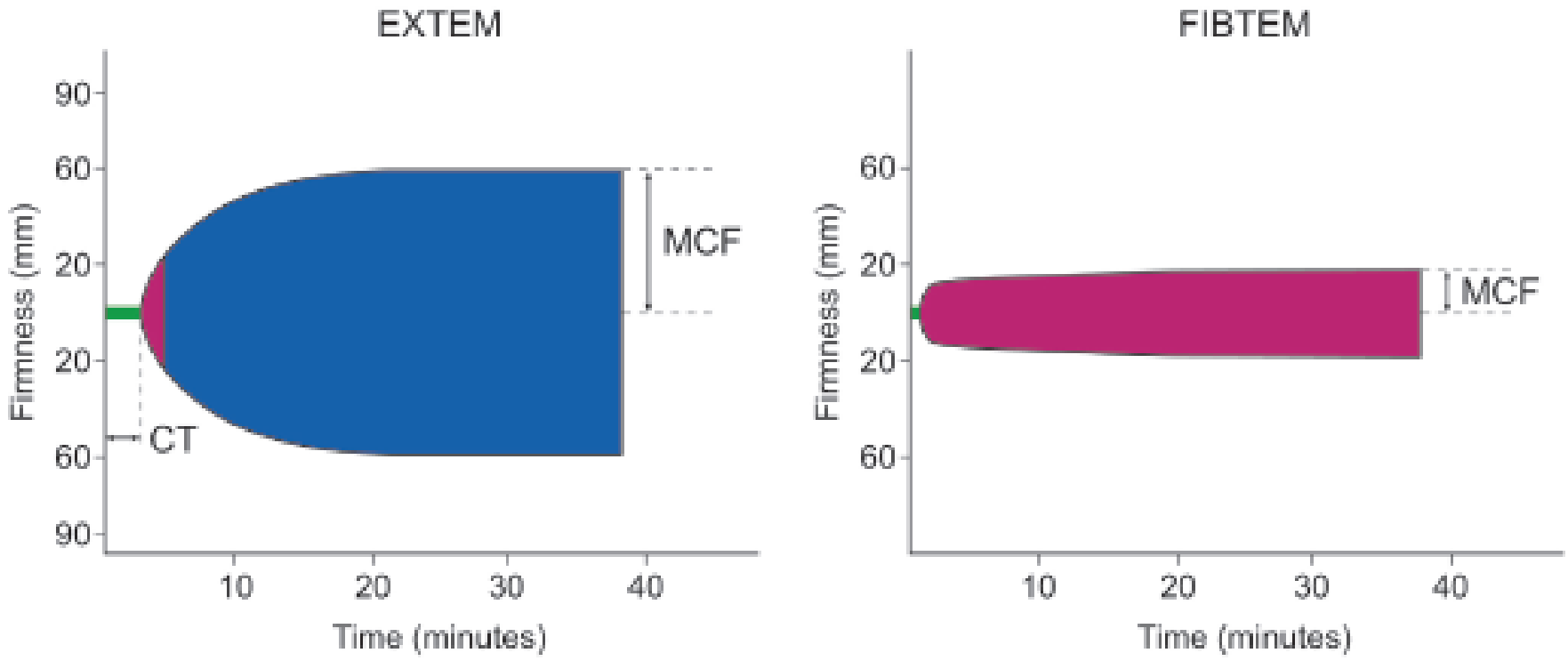


Figure 1 The ROTEM® analyses: EXTEM® test (extrinsically activated test) and FibTEM® test (fibrin clot obtained by platelet inhibition with cytochalasin D). The clotting time (CT (seconds)) represents the time from the start of the test until a clot firmness of 2 mm is detected; maximum clot firmness (MCF (mm)) represents the total amplitude of the clot.

Table 1: Demographic and clinical data

	All patients	Survivors	Non-survivors
N	131	99 (76%)	32 (24%)
Age (years)	46 ± 18	44 ± 17	52 ± 20*
Male (n [%])	96 (73%)	72 (73%)	24 (75%)
Weight (kg)	79 ± 14	79 ± 15	78 ± 11
BMI (kg/m^2)	26 ± 6	26 ± 6	27 ± 6
GCS	11 ± 4	11 ± 4	8 ± 4*
ISS	38 ± 15	36 ± 15	44 ± 15*
RTS	6.2 ± 1.5	6.5 ± 1.3	5.1 ± 1.5*
TRISS	66 ± 31	74 ± 27	46 ± 31*
RISC	71 ± 27	79 ± 22	47 ± 29*

Data are presented as mean ± standard deviation, or as absolute and relative frequency. * $P < 0.05$, significant difference between survivors and non-survivors. BMI, body mass index; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; n, number of patients; RISC, Revised Injury Severity Classification Score; RTS, Revised Trauma Score; TRISS, Trauma Injury Severity Score.

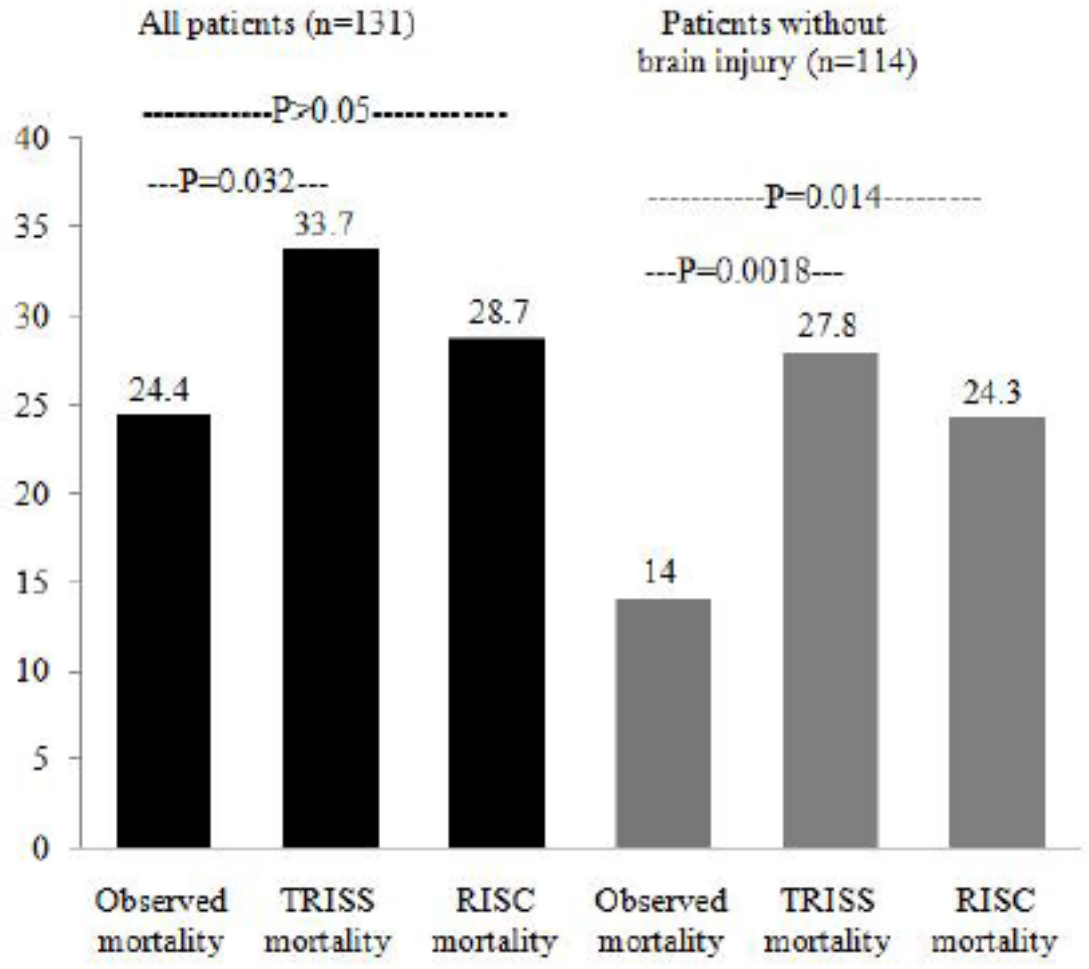


Figure 2 Comparison of the observed mortality with the mortality predicted by the trauma injury severity score (TRISS) and by the revised injury severity classification (RISC) score. A sub-analysis that excluded patients who died of untreatable brain oedema caused by severe brain injury was also performed.

Table 3: Standard laboratory parameters

	Admission to the ER	Arrival at the ICU	24 hours after admission to the ER
Haemoglobin (13.5 to 17 g/dL)	9.6 ± 2.8	9.6 ± 2.1	9.2 ± 1.5
Haematocrit (40 to 50%)	28 ± 8	28 ± 6	27 ± 4
Platelet count (150 to 350 *1000/µL)	166 ± 64	90 ± 49	79 ± 37
PT (11 to 13.5 seconds)	20.3 ± 8.3	22.6 ± 9.9	18.8 ± 3.2
aPTT (26 to 35 seconds)	53 ± 48	69 ± 47	49 ± 21
Fibrinogen (200 to 450 mg/dL)	126 ± 65	150 ± 50	228 ± 71

aPTT, activated partial thromboplastin time; ER, emergency room; PT, prothrombin time. Data are presented as mean ± standard deviation; normal range is indicated in parentheses.

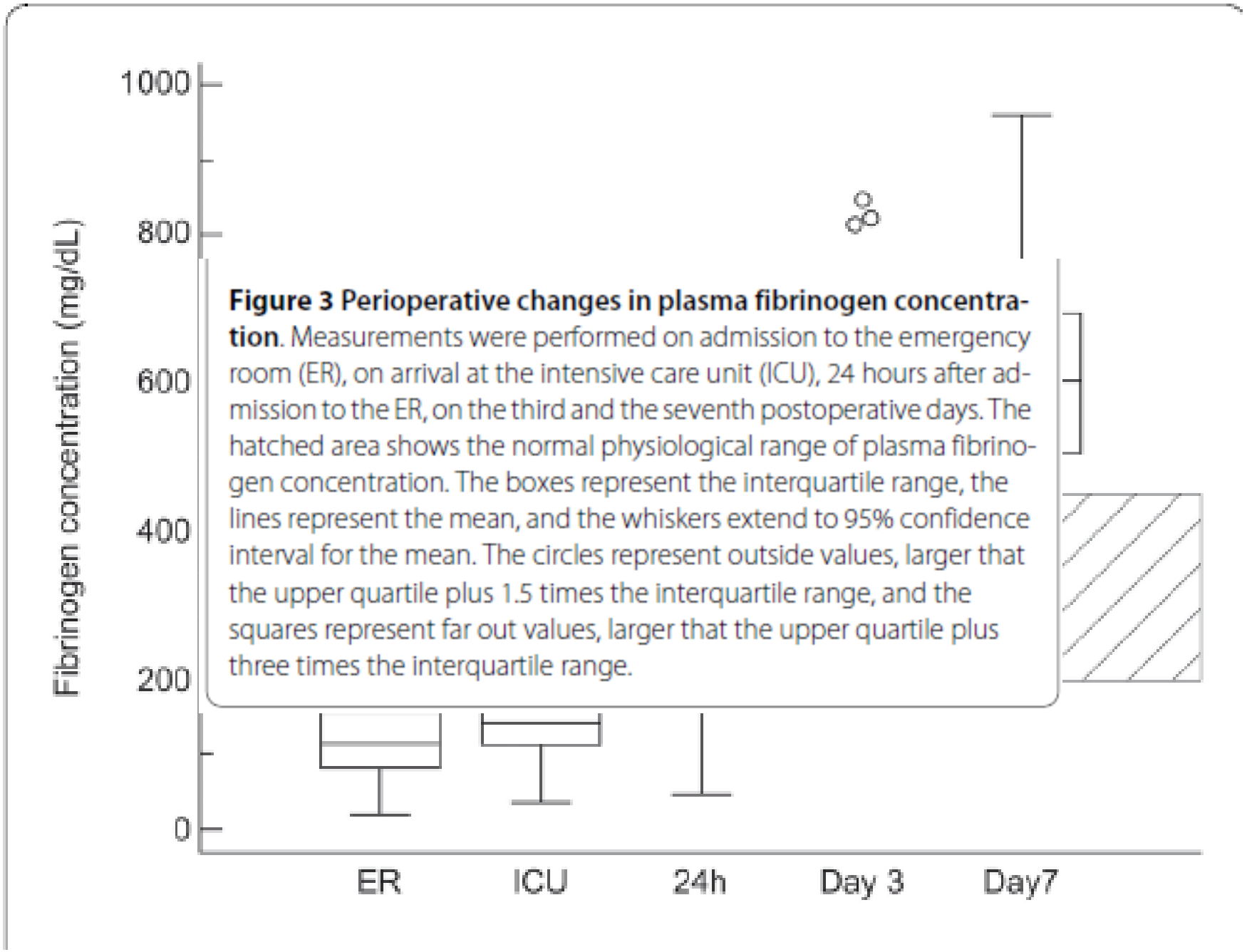


Figure 3 Perioperative changes in plasma fibrinogen concentration. Measurements were performed on admission to the emergency room (ER), on arrival at the intensive care unit (ICU), 24 hours after admission to the ER, on the third and the seventh postoperative days. The hatched area shows the normal physiological range of plasma fibrinogen concentration. The boxes represent the interquartile range, the lines represent the mean, and the whiskers extend to 95% confidence interval for the mean. The circles represent outside values, larger that the upper quartile plus 1.5 times the interquartile range, and the squares represent far out values, larger that the upper quartile plus three times the interquartile range.

Table 4: Haemostatic therapy and RBC transfusion

	Total administered until arrival at ICU		Total administered during 24 hours after admission to the ER	
	Number of patients treated	Dose	Number of patients treated	Dose
Fibrinogen concentrate (g)	123	6 (4, 9)	128	7 (5, 11)
PCC (U)	83	1800 (1650, 3100)	101	2400 (1800, 3600)
FFP (U)	6	10 (7, 10)	12	10 (9.75, 11.25)
PC (U)	22	2 (1, 2)	29	2 (2, 3)
RBC (U)	125	6 (4, 10)	131	10 (6, 13)

Data are presented as median (25th percentile, 75th percentile). Total number of patients = 131. ER, emergency room; FFP, fresh frozen plasma; PC, platelet concentrate; PCC, prothrombin complex concentrate; RBC, red blood cell concentrate.

Table 5: Timing of the administration of coagulation factor concentrates

Time of administration	Number of patients
<1 hour after arrival in ER	68
1-2 hours after arrival in ER	34
2-6 hours after arrival in ER	24
6-24 hours after arrival in ER	5

ER, emergency room.

Key messages

- The present study describes goal-directed haemostatic therapy of haemorrhage in severe trauma patients, in whom the administration of coagulation factor concentrates was tailored to correct the haemostatic defects identified by thromboelastometric analyses.
- The results show that coagulation factor concentrates (fibrinogen concentrate as first-line haemostatic therapy and additional PCC) can be used successfully in trauma patients with severe bleeding.
- Thromboelastometry (ROTEM) allowed rapid and reliable diagnosis of the underlying coagulopathy and guided the haemostatic therapy.
- Observed mortality appeared lower than the mortality predicted by the TRISS and by the RISC score.
- This treatment strategy may reduce allogeneic blood product transfusion, and prospective, randomized studies appear warranted.

Manejo de la hemorragia en la cirugía cardiotorácica.

. J Cardiothorac Vasc Anesth agosto 2013, 27 (Suppl 4): S20-34. doi: 10.1053/j.jvca.2013.05.014

- Görlinger K , Shore-Lesserson L , Dirkmann D , Hanke AA , Rahe-Meyer N , Tanaka KA .
- **Fuente**
- Departamento de Anestesiología y Medicina Intensiva del Hospital Universitario de Essen, la Universidad de Duisburg-Essen, Essen, Alemania. klaus@goerlinger.net

- El sangrado es un problema importante en la cirugía cardiotorácica, y aproximadamente el 20% de todos los productos de la sangre se transfunde en esta configuración clínica en todo el mundo. Las prácticas de transfusión, sin embargo, son muy variables entre los diferentes hospitales y más de 25% de las transfusiones de sangre alogénica se han considerado inadecuados. Por otra parte, tanto el sangrado y la transfusión de sangre alogénica se asocia con una mayor morbilidad, la mortalidad y los costos hospitalarios. En las últimas décadas, se han hecho varios intentos para encontrar un agente hemostático universal a asegurar la hemostasia durante y después de la cirugía cardiotorácica. La mayoría de los fármacos estudiados en este contexto ya sea han fracasado para reducir el sangrado y los requerimientos de transfusión o se han asociado con eventos adversos graves, tales como insuficiencia renal aguda o trombótico / eventos tromboembólicos y, en algunos casos, el aumento de la mortalidad

- Por lo tanto, un tratamiento hemostático dirigido a un objetivo individualizado ("enfoque theranostic") parece ser más apropiada para detener el sangrado en este complejo entorno clínico. El uso del punto-de-cuidado (POC) y transfusión de algoritmos de gestión de coagulación guiado por pruebas viscoelásticas tales como tromboelastometria / tromboelastografía en combinación con las pruebas de la función plaquetaria tales como POC toda impedancia agregometría sangre, y basado en la terapia de primera línea con el fibrinógeno y protrombina complejo concentrado se han asociado con menores necesidades de transfusión de sangre alogénica, la reducción de la incidencia de eventos adversos trombóticos / tromboembólicos y la relacionada con la transfusión, y mejores resultados en la cirugía cardíaca. Este artículo revisa la literatura actual se trata de la gestión de la hemorragia en la cirugía cardiotorácica en base a diagnósticos POC y con concentrados de factor de coagulación específico y su impacto en las necesidades de transfusión y los resultados de los pacientes.

Protrombina complejo concentrado en la reducción de la pérdida de sangre durante el trasplante ortotópico de hígado: Proton-trial.

BMC Surg. 2013 01 de julio, 13:22. doi: 10.1186/1471-2482-13-22

- Arshad F , Ickx B , van Beem RT , Polak W , Grüne F , Nevens F , Ilmakunnas M , Koivusalo AM , Isoniemi H , Strengers PF , Groen H , Hendriks HG , Lisman T , J Pirenne , Porte RJ .
- **Fuente**
- Departamento de Cirugía Hepatobiliar y Trasplante Hepático, University Medical Center Groningen, Universidad de Groningen, Groningen, Países Bajos

Abstracto

ANTECEDENTES:

- En los pacientes con cirrosis, la síntesis de factores de coagulación puede ser deficiente, reflejada por una prolongada protrombina tiempo. Aunque los factores anticoagulantes disminuyen también, la pérdida de sangre durante el trasplante ortotópico de hígado todavía puede ser excesivo. La pérdida de sangre durante el trasplante hepático ortotópico es administrado actualmente por la transfusión de concentrados de glóbulos rojos, concentrados de plaquetas, plasma fresco congelado, y el fibrinógeno concentrado . La transfusión de estos productos puede, paradójicamente, provocar un aumento de la tendencia a la hemorragia por hipertensión portal agravado. El efecto hemostático de estos productos, por lo que puede ser eclipsado por complicaciones hemorrágicas debido al volumen de contraste overload.In a estos productos de transfusión, la protrombina complejo concentrado es un bajo volumen altamente purificado concentrado , que contiene los cuatro factores de la coagulación dependientes de la vitamina K.

- Estudios anteriores han sugerido que la administración de la protrombina complejo concentrado es un método eficaz para normalizar una prolongada protrombina tiempo en pacientes con cirrosis hepática. Nuestro objetivo es investigar si la administración preoperatoria de protrombina complejo concentrado en los pacientes sometidos a trasplante hepático por cirrosis hepática en fase terminal, es un método seguro y eficaz para reducir la pérdida de sangre perioperatoria y la necesidad de transfusión.

Metodos y diseño

- Se trata de un estudio doble ciego, multicéntrico, los pacientes trial.Cirrhotic aleatorios controlados con placebo con un INR prolongado (≥ 1,5) sometidos a trasplante hepático se asignaron al azar entre el placebo o la protrombina complejo concentrado de administración antes de la cirugía. Se registraron los datos demográficos, quirúrgicos y de transfusión. El resultado primario de este estudio es las necesidades de transfusión de glóbulos rojos

- Los pacientes con cirrosis avanzada que han reducido los niveles plasmáticos de las dos proteínas de la coagulación pro-y anticoagulantes. protrombina complejo concentrado es un producto de bajo volumen de plasma que contiene tanto procoagulante y proteínas anticoagulantes y la transfusión no afectará el estado del volumen antes del procedimiento quirúrgico. Nuestra hipótesis es que la administración deprotrombina complejo concentrado dará lugar a una reducción de la pérdida de sangre perioperatoria y las necesidades de transfusión.Teóricamente, la administración de protrombina complejo concentrado puede estar asociada con un mayor riesgo de complicaciones tromboembólicas. Por lo tanto, las complicaciones tromboembólicas son un importante criterio de valoración secundario y la ocurrencia de este tipo de complicación se controlarse estrechamente durante el estudio.

- Transfusión. 2013 Jan; 53 Suppl 1:91 S-95S. doi: 10.1111/trf.12041.
- **El uso temprano de fibrinógeno, protrombina complejo concentrado , y el factor VIIa activado recombinante en la hemorragia masiva.**
- Papas D .
- **Fuente**
- Departamento de la Medicina General y Cirugía Crítica, Universidad Médica de Innsbruck, Innsbruck, Austria. dietmar.fries @ i-med.ac.a

- **Abstracto**
- **ANTECEDENTES:**
- La coagulopatía relacionada con la hemorragia masiva tiene una etiología multifactorial. La coagulopatía se relaciona a los golpes y la pérdida de sangre incluyendo el consumo de factores de coagulación y las plaquetas y hemodilución. Además hiperfibrinolisis, hipotermia, acidosis, y los cambios metabólicos afectan el sistema de coagulación. El objetivo de cualquier terapia es hemostático para controlar el sangrado y reducir al mínimo la pérdida de sangre y las necesidades de transfusión. La transfusión de productos sanguíneos alogénicos así como la presencia de coagulopatía causa aumento de la morbilidad y la mortalidad

- **MATERIALES Y MÉTODOS:**
- En este trabajo se presenta una breve reseña sobre las nuevas estrategias de tratamiento de la coagulopatía, relacionados con la pérdida masiva de sangre.
- **RESULTADOS:**
- Los paradigmas están cambiando activamente y todavía hay escasez de datos. Sin embargo, cada vez hay más pruebas de que la experiencia y "objetivo" algoritmos controlados utilizando dispositivos de control de punto de cuidado y concentrados de factor de coagulación son más eficaces en comparación con la transfusión de plasma fresco congelado, independientemente de la situación clínica individua

- **CONCLUSIÓN:**
- El tratamiento futuro de la coagulopatía asociada con hemorragia masiva puede estar basado en un punto de atención guiada uso racional individualizado de concentrados de factor de coagulación tales como el fibrinógeno, protrombina complejo concentrado , y factor VIIa recombinante. El uso oportuno y racional de los concentrados de factor de coagulación puede ser más eficaz y más seguro que el uso de la relación impulsada por paquetes de productos de transfusión de sangre alogénica.
-

El uso exclusivo de los concentrados de factor de coagulación permite la reversión de la coagulopatía y disminuye las tasas de transfusión en pacientes con trauma mayor

- Innerhofer P , Westermann I , H Tauber , Breitkopf R , patatas D , Kastenberger T , El Attal R , Strasak A , Mittermayr M .
- **Fuente** Injury. 2013 Feb;44(2):209-16. doi: 10.1016/j.injury.2012.08.047. Epub 2012 Sep 20
- Clínica de Medicina Anestesiología y Cuidados Intensivos, Universidad Médica de Innsbruck, Innsbruck, Austria

Abstracto

Fondo

FFP y factor de coagulación concentrados se utilizan para corregir la coagulopatía inducida por trauma (TIC). Sin embargo, los datos sobre los perfiles de coagulación que investigan los efectos de la terapia son escasos.

Métodos

Se trata de un análisis de 144 pacientes con trauma mayor roma ((ISS) ≥ 15), que fueron incluidos en un estudio de cohorte prospectivo de las características y el tratamiento de las TIC. Los pacientes que recibieron concentrado de fibrinógeno y / o concentrado de complejo de protrombina solo (Grupo CF) se compararon con aquellos, además, que reciben transfusiones de FFP (FFP Grupo).

Resultados

Sesenta y seis pacientes recibieron exclusivamente CF, mientras que 78 pacientes recibieron, además, FFP. En general, los pacientes eran comparables en cuanto a edad, género y ISS (CF Grupo, ISS 37 (29, 50); FFP Grupo ISS 38 (33, 55), $p = 0,28$). Los pacientes tratados sólo con FQ mostraron suficiente hemostasia y recibieron significativamente menos unidades de glóbulos rojos (RBC) y plaquetas que aquellos que también recibe FFP [(RBC 2 (0, 4) U vs 9 (5, 12) U; plaquetas 0 (0, 0) U vs 1 (0, 2) U, $p < 0,001$)]. Además, un menor número de pacientes en el Grupo CF desarrollaron fallo multiorgánico (MOF) (18,2% frente a 37,2%, $p = 0,01$) o sepsis (16,9% frente a 35,9%, $p = 0,014$) que en el Grupo FFP.Propensión puntaje de coincidencia ($n = 28$ pares) que se utiliza para reducir el impacto de la selección del tratamiento confirmó que la administración adicional de FFP no mostró ningún beneficio en la restauración de la hemostasia, pero se asoció con un número significativamente más altas tasas de transfusión de glóbulos rojos y plaqueta

Conclusión

- El uso de la FQ solo corrigió eficazmente coagulopatía en pacientes con traumatismo cerrado grave y de forma concomitante disminución de la exposición a la transfusión alogénica, que puede traducirse en un mejor resultado.

Estudio piloto 03 :: RETIC

- **Re** versal de **T** rauma **I** nduced **C** oagulopathy con concentrados de factores de la coagulación o de plasma fresco congelado. *prospectivo, abierto, de grupos paralelos, ensayo clínico, aleatorizado, monocéntrica*

- **OBJETIVO Y PUNTO FINAL**
  Objetivo principal
  El objetivo del estudio es evaluar la diferencia en la incidencia de insuficiencia orgánica múltiple (MOF) después del tratamiento de las TIC con plasma fresco congelado (PFC) o concentrados (CFC), factor de coagulación.
- **Objetivo primario**
  El objetivo primario del estudio es la diferencia en la incidencia de MOF entre la CFC y los grupos de FFP.
- **INFORMACIÓN GENERAL**
  Estudio Inicio: Marzo 2012
- Fin del estudio: marzo 2014
-

Estudio piloto 03 :: RETIC

- **Número de pacientes**
  200 (2x100) pacientes evaluables**Duración de la participación del paciente**
  • Tratamiento de Urgencias (ED) hasta las 24h en la UCI
  • Período de seguimiento "Control Médico": hasta el día 30 después de la admisión
- **Investigación Medicamento:**
  factor de coagulación concentrados (CFC):
  . • concentrado de fibrinógeno, Haemocomplettan ® P 1g, CSL Behring, Marburg, Alemania (1,0 g por cada 50 ml)
  • concentrado de complejo de protrombina (PCC), Beriplex ® P / N 500, CSL . Behring, Marburg, Alemania
  • concentrado de FXIII: Fibrogammin ® P 250 E y P 1250 E, CSL Behring, Marburg, Alemania Fresh Frozen Plasma: • Octaplas SD sangre tipo 0, A, B y AB ® Octapharma Pharmazeutika, Wien Número de pacientes 200 (2x100) pacientes evaluables duración de la participación del paciente • Tratamiento: Departamento de Emergencia (ED) hasta 24 horas en la UCI • Período de seguimiento "Control Médico": hasta el día 30 después de la admisión

Estudio piloto 03 :: RETIC

- **CRITERIOS DE INCLUSIÓN PRINCIPALES**
  I.1. Hombres y mujeres sujetos ≥ 18 años y <80 años,
  I.2. Trauma mayor (ISS> 15),
  I.3. Los signos clínicos de sangrado en curso o los pacientes que están en riesgo de hemorragia significativa evaluados y juzgados por el equipo de la disfunción eréctil en cargo de paciente
  I.4. La presencia de coagulopatía se define mediante ensayos Rotem el siguiente,
  - Los pacientes con disminución concomitante polimerización de fibrinógeno, medida con ROTEM ® FibTEM A10 <7 mm después de 10 min
  - Los pacientes con disminución de los niveles de factor de coagulación concomitantes, medida con ROTEM ® Extem CT> 90 seg

Estudio piloto 03 :: RETIC

- **CRITERIOS DE EXCLUSIÓN PRINCIPALES**
  E.1. Lesión letal
  E.2. CPR en la escena,
  E.3. Lesión cerebral aislada, quemaduras
  E.4. Lesiones Avalancha
  E.5. La administración de factor de coagulación o FFP se concentra antes de ED admisión
  E.6. Retrasada (> 6 horas después del trauma) la admisión a ED
  E.7. Uso de los anticoagulantes orales, o inhibidores de la agregación de plaquetas dentro de 5 días antes de la lesión conocido
  E.8. Antecedentes de reacciones alérgicas graves a los productos de plasma
  E.9. Historia conocida de alteración hemostática congénita, deficiencia de IgA o Proteína C
  E.10. Los pacientes con antecedentes de eventos tromboembólicos (infarto de miocardio, angina de pecho inestable, apoplejía trombosis venosa profunda, embolia pulmonar) o trombocitopenia inducida por heparina (TIH) tipo 2 en el previo 12 meses
  E.11. Los pacientes con un peso corporal <45 kg y> 150 kg
  E.12. Los pacientes que son conocidos por estar embarazada

Estudio piloto 03 :: RETIC

- **Plan de investigación**
  los pacientes traumatizados graves (ISS> 15), ingresados en urgencias del Hospital Universitario de Innsbruck, con sangrado evidente y / o que están en riesgo de hemorragia significativa se proyectará mediante ensayos Rotem durante el tratamiento de la disfunción eréctil y las intervenciones quirúrgicas / radiológicos posteriores por tener coagulopatía (T0) .
  Si un paciente cumple con los criterios de inclusión (T1) y es reclutado para el estudio (criterios de inclusión y exclusión: véase más arriba), un primer estudio muestra de sangre relacionada (40 ml) se sortearán, y los datos recogidos.
  Posteriormente, a 100 pacientes se serán aleatorizados para recibir concentrado de fibrinógeno y / o concentrado de complejo de protrombina y / o FXIII concentrar para la reversión de la coagulopatía, mientras que las otras 100 pacientes recibirán FFP 15ml/kg BW, respectivamente.
  El estudio de gestión de la coagulación específica utilizando CFC o FFP comienza con la asignación al azar (T1) y se continuó durante las primeras 24 horas en la UCI (unidad de cuidados intensivos T24). Dependiendo de las necesidades individuales de un solo paciente (T1) o varios episodios de tratamiento (T2-Txy) ocurrirá. administración del fármaco de estudio está dirigido a corregir cada solo episodio de sangrado que ocurre coagulopathic según la evaluación de FibTEM y Extem.

Estudio piloto 03 :: RETIC

- Tanto en los grupos ROTEM (Extem, FibTEM) se llevará a cabo 20 minutos después de la administración del fármaco de estudio para asegurar la inversión suficiente de coagulopatía. Si persiste la coagulopatía, la dosis del fármaco del estudio se repetirá y eficacia comprobado posteriormente.
  El fracaso del tratamiento se registrará si el sangrado persiste y parámetros Rotem no mejoran después de dos veces las dosis del fármaco del estudio. En estos casos, se administrará tratamiento de rescate hemostático. CFC (concentrado de fibrinógeno y / o PCC, y / o concentrado de FXIII) será administrado a los pacientes asignados al azar para recibir FFP y FFP se administrarán a los pacientes del grupo de CFC.
  Al momento del ingreso en la UCI (unidad de cuidados intensivos T0), 24 horas (T24 UCI) y 48 horas (T48 UCI) después siga estudiando muestras de sangre relacionados se dibujan.
  Las indicaciones de la transfusión de glóbulos rojos o plaquetas, la administración de antifibrinolíticos, el tratamiento de sustitución de la acidosis, la hipotermia, la hipocalcemia y el volumen son similares para ambos grupos y el tratamiento se realizaron de acuerdo a la rutina clínica.
  Además de la gestión de coagulación durante el tratamiento de la disfunción erécti

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Anne Holbrook, MD, PharmD; Sam Schulman, MD, PhD; Daniel M. Witt, PharmD, FCCP; Per Olav Vandvik, MD, PhD; Jason Fish, MD, MSHS; Michael J. Kovacs, MD; Peter J. Svensson, MD, PhD; David L. Veenstra, PharmD, PhD; Mark Crowther, MD; and Gordon H. Guyatt, MD

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

Background: **High-quality anticoagulation management is required to keep these narrow therapeutic index medications as effective and safe as possible. This article focuses on the common important management questions for which, at a minimum, low-quality published evidence is available to guide best practices.**

Methods: **The methods of this guideline follow those described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**

Results: **Most practical clinical questions regarding the management of anticoagulation, both oral and parenteral, have not been adequately addressed by randomized trials. We found sufficient evidence for summaries of recommendations for 23 questions, of which only two are strong rather than weak recommendations. Strong recommendations include targeting an international normalized ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy (Grade 1B) and not routinely using pharmacogenetic testing for guiding doses of vitamin K antagonist (Grade 1B). Weak recommendations deal with such issues as loading doses, initiation overlap, monitoring frequency, vitamin K supplementation, patient self-management, weight and renal function adjustment of doses, dosing decision support, drug interactions to avoid, and prevention and management of bleeding complications. We also address anticoagulation management services and intensive patient education.**

Conclusions: **We offer guidance for many common anticoagulation-related management problems. Most anticoagulation management questions have not been adequately studied.**

CHEST 2012; 141(2)(Suppl):e152S–e184S

Abbreviations: AMS = anticoagulation management service; aPTT = activated partial thromboplastin time; COX = cyclooxygenase; FFP = fresh frozen plasma; HR = hazard ratio; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NSAID = nonsteroidal antiinflammatory drug; PCC = prothrombin complex concentrate; PE = pulmonary embolism; POC = point-of-care; PSM = patient self-management; PST = patient self-testing; RCT = randomized controlled trial; RR = risk ratio; SC = subcutaneous; TTR = time in therapeutic range; UFH = unfractionated heparin; VKA = vitamin K antagonist

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

Recommendations

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor PCC rather than with plasma (Grade 2C).

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

EL COMPLEJO PROTROMBINICO

OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

VENTAJAS DEL COMPLEJO PROTROMBINICO

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

PLASMA FRESCO CONGELADO

- DEBE SER GRUPO SANGUINEO ESPECIFICO
- TIEMPO DE DESCONGELADO
- VOLUMENES ALTOS
- CONTENIDO VARIABLE DE FACTORES
- EFECTOS NO PREDECIBLES
- NO INACTIVACION VIRAL
- RIESGO DE TRALI

COMPLEJO PROTROMBINICO

- NO REQUIERE ESPECIFICIDAD DE GRUPO SANGUINEO
- TEMPERATURA AMBIENTE
- VOLUMENES PEQUEÑOS
- CONTENIDO ESTANDARIZADO DE LOS FACTORES
- EFECTO PREDECIBLE
- INACTIVACION VIRAL
- NO HAY RIESGO DE TRALI

EL COMPLEJO PROTROMBINICO
OBTENIENDO EL EQUILIBRIO DE LA COAGULACION

TERAPIA CON EL COMPLEJO DE PROTROMBINA

PRESENTACION : 1 FRASCO VIAL CON 500 UI CCP

TIEMPO DE ACCION : 10’

NO EXCEDER DE 3000 UI EN LA 1º APLICACIÓN

VELOCIDAD DE INFUSION: 3 mL / 1’ (75 UI/1’)

CONTROL DE EFECTO: TIEMPO DE PROTROMBINA

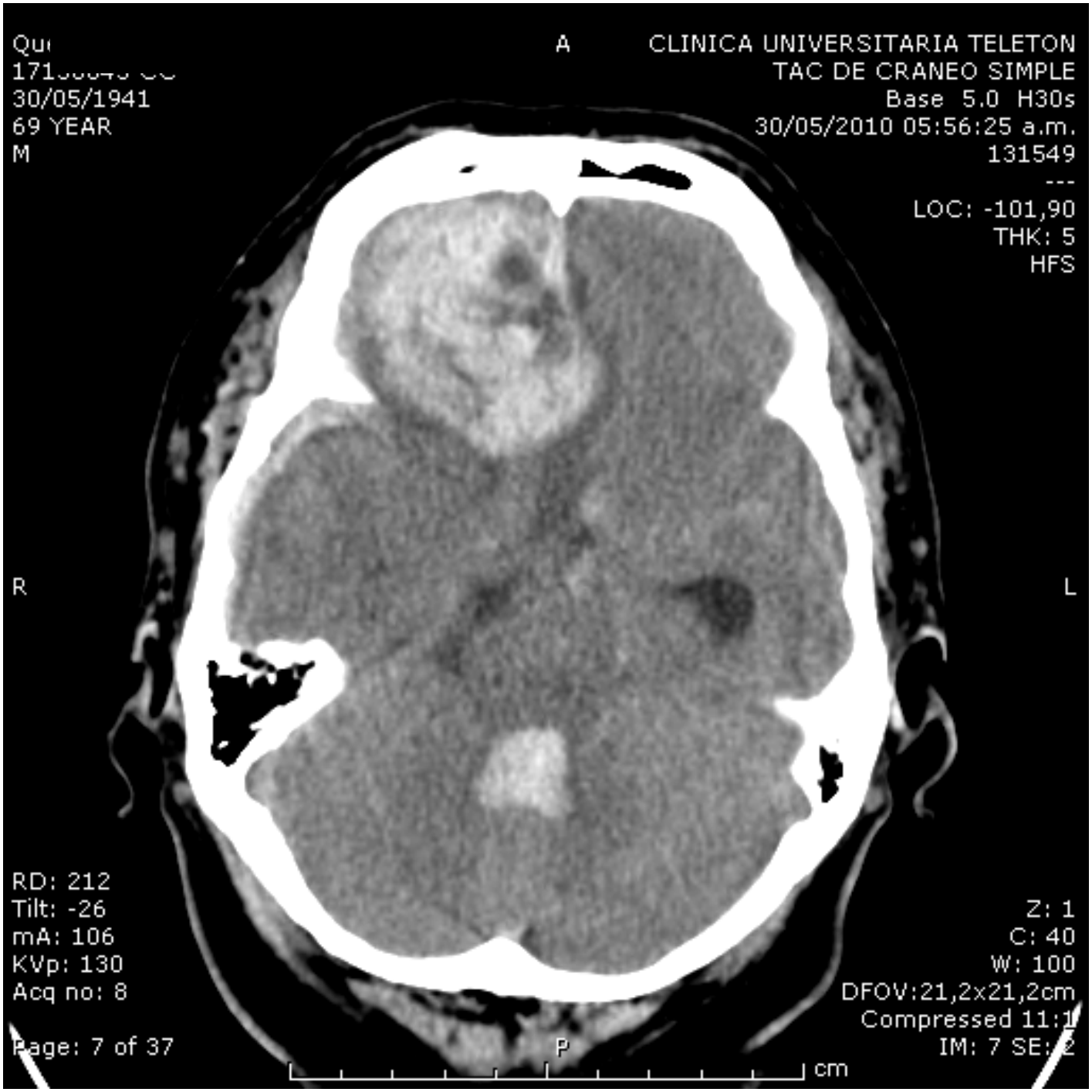
RAPIDA REVERSION DE LA TERAPIA ANTICOAGULANTE ORAL

- PARA MUCHOS PACIENTES, LA TERAPIA CON ANTICOAGULANTES ORALES, ES UN TRATAMIENTO VITAL.
- EL RANGO TERAPEUTICO ES ESTRECHO [INR 2.0 – 3.5].
- LA DOSIFICACIÓN ES DIFICIL, LOS PACIENTES CON FACILIDAD PUEDEN ESTAR CON NIVEL SUBOPTIMOS O EXCESIVOS DE ANTICOAGULACION.

Cálculo y recomendación de dosis

INR > 5.0 - 30 UI / Kg
INR < 5.0 - 15 UI / Kg
(Vitamina K - terapéutica adyuvante)

El British Committee for Standards in Haematology, Transfusion task force y el American College of Chest physicians, recomiendan la utilización de CCP como primera elección para la urgente reversión de ACO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CME Available

Topical Review

Section Editors: Marc Fisher, MD, and Kennedy Lees, MD

Options to Restrict Hematoma Expansion After Spontaneous Intracerebral Hemorrhage

Thorsten Steiner, MD, PhD, MME; Julian Bösel, MD

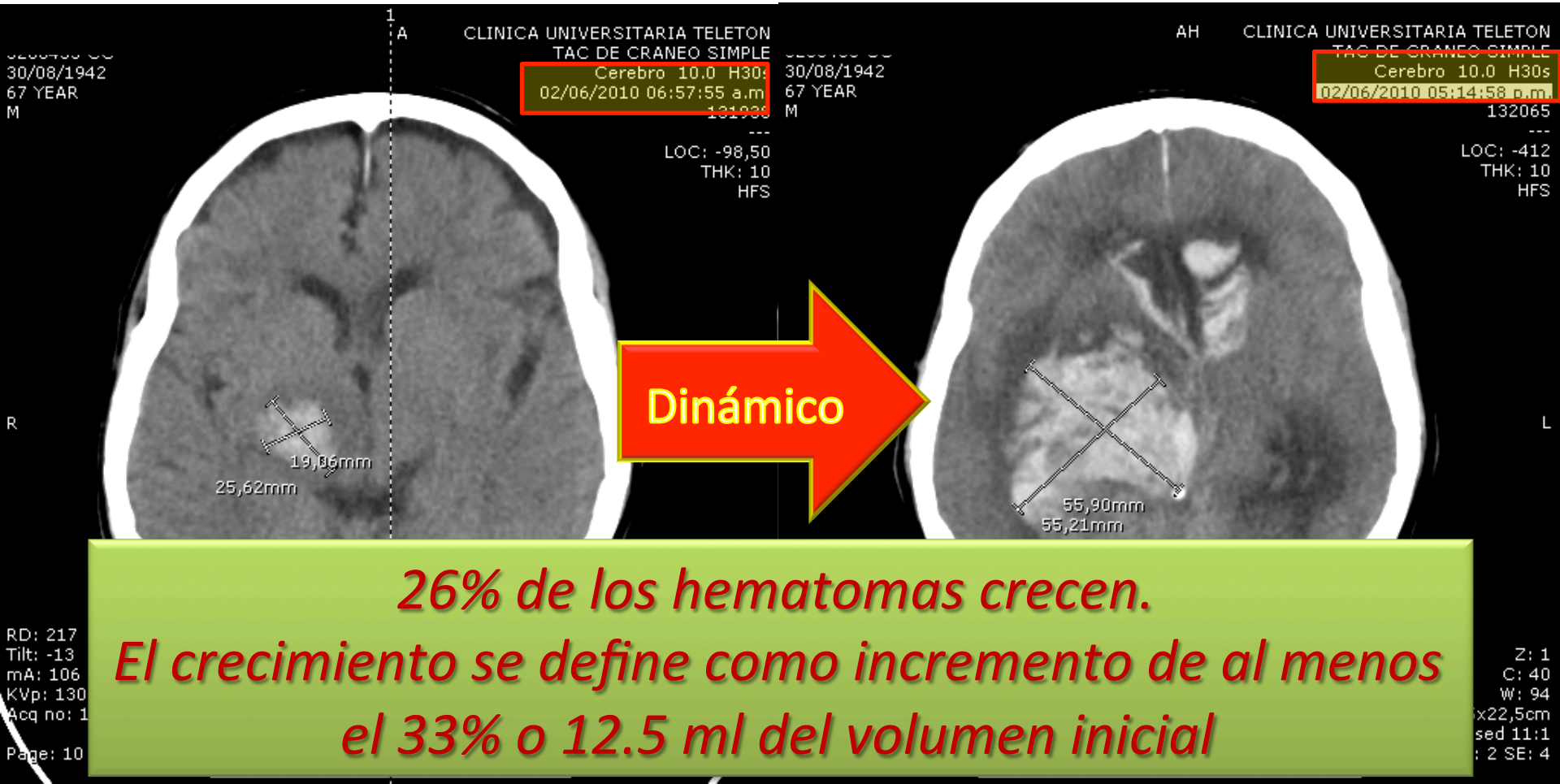
(*Stroke*. 2010;41:402-409.)

- Control de la HTA
- Control de la Anticoagulación

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

(*Stroke*. 2010;41:2108-2129.)



26% de los hematomas crecen.
El crecimiento se define como incremento de al menos el 33% o 12.5 ml del volumen inicial

LONDON'S AIR AMBULANCE

Pre-Hospital Care Standard Operating Procedure

Use of Human Prothrombin Complex (Octaplex®)

REVIEW:	July 2012
APPROVAL/ ADOPTED:	
DISTRIBUTION:	
RELATED DOCUMENTS:	SOP Daily Routine Crew Training Series – Octaplex Octaplex – resource file
THIS DOCUMENT REFERS TO:	

Aims:

1. Describe the rationale for the pre-hospital administration of Octaplex.
2. Describe the steps to be followed in order to correctly administer Octaplex.
3. Illustrate the correct dosing regime for Octaplex to be administered by LAA crews.
4. Describe the administrative processes associated with the pre-hospital use of Octaplex.

Background:

Warfarin is an oral medication that inhibits Vitamin K participation in the synthesis of clotting factors. There are a number of reasons that a patient may be taking Warfarin, including recurrent deep vein thrombosis or pulmonary embolism, the presence of mechanical heart valves or chronic atrial fibrillation. The Vitamin K-dependent clotting factors are Factors II, VII, IX and X. Once synthesised, these clotting factors are present in blood, ready to be used in the clotting cascade for up to 72 hours. Warfarin inhibits the production of these factors. Octaplex is a human prothrombin complex derived from human donor plasma and contains all of the Vitamin K-dependent clotting factors. Octaplex is licensed for the emergency reversal of warfarin.

Warfarinised patients who sustain a head injury or suffer a spontaneous intra-cerebral bleed are at increased risk of developing surgically significant intracranial haematoma. This group of patients may deteriorate more rapidly than those patients with normal clotting. Emergency reversal of Warfarin can prevent or slow the expansion of intracranial haematoma and may reduce the risk of catastrophic clinical deterioration occurring prior to definitive neurosurgical care. Prothrombin complex concentrates rapidly correct coagulopathy in patients who are taking Warfarin and should be given to selected patients at the earliest opportunity.

Pre-hospital physicians have the opportunity to deliver this intervention at a much earlier stage than is currently achievable even with a pre-alert to the hospital. Early reversal not only potentially limits the expansion of the haematoma but may also reduce the time to neurosurgical intervention.

Equipment:

London's Air Ambulance medical teams carry Octaplex in the aircraft and on all rapid response vehicles. This drug is stored in a red insulated bag.

Octaplex insulated bag contains:

6 boxes of Octaplex (3000iu total)
Coaguchek XS plus device (fully charged unit)
Testing strips and lancets
Aide-memoire for reconstitution
3 x green patient wristbands and security devices
3 x Octaplex stickers

Octaplex can be replaced from the supply in the fridge or be obtained from pharmacy.

Policy:

Indications for use

- Confirmed or strongly suspected to be taking Warfarin

  AND
- Clinical suspicion of intracranial haemorrhage

  AND
- INR confirmed to be greater than 2 on near-patient testing

Patients with an INR of less than 2, but who otherwise meet the criteria for administration should also be discussed with the duty consultant in pre-hospital care.

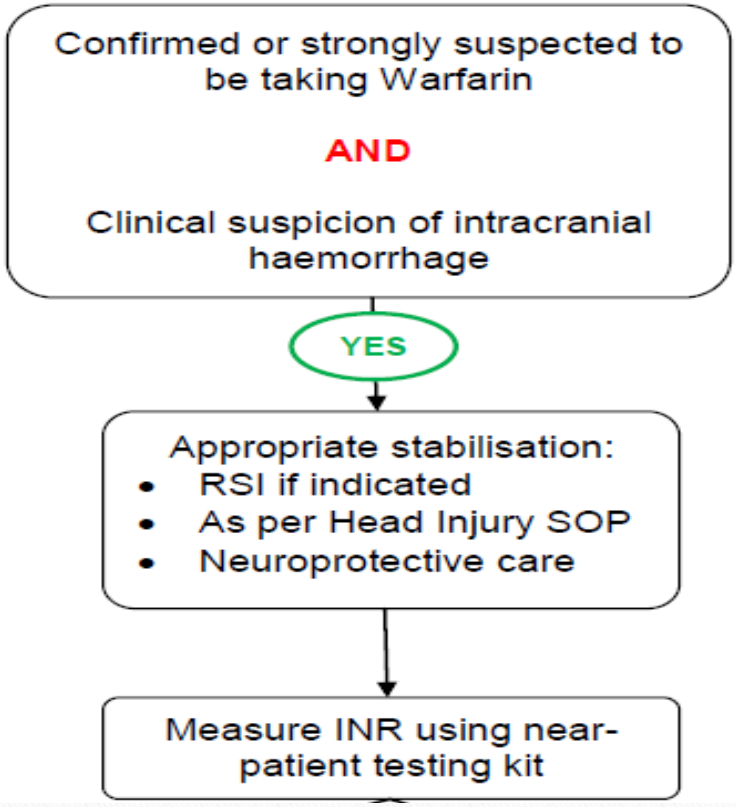
Administration of Octaplex

Dose and reconstitution

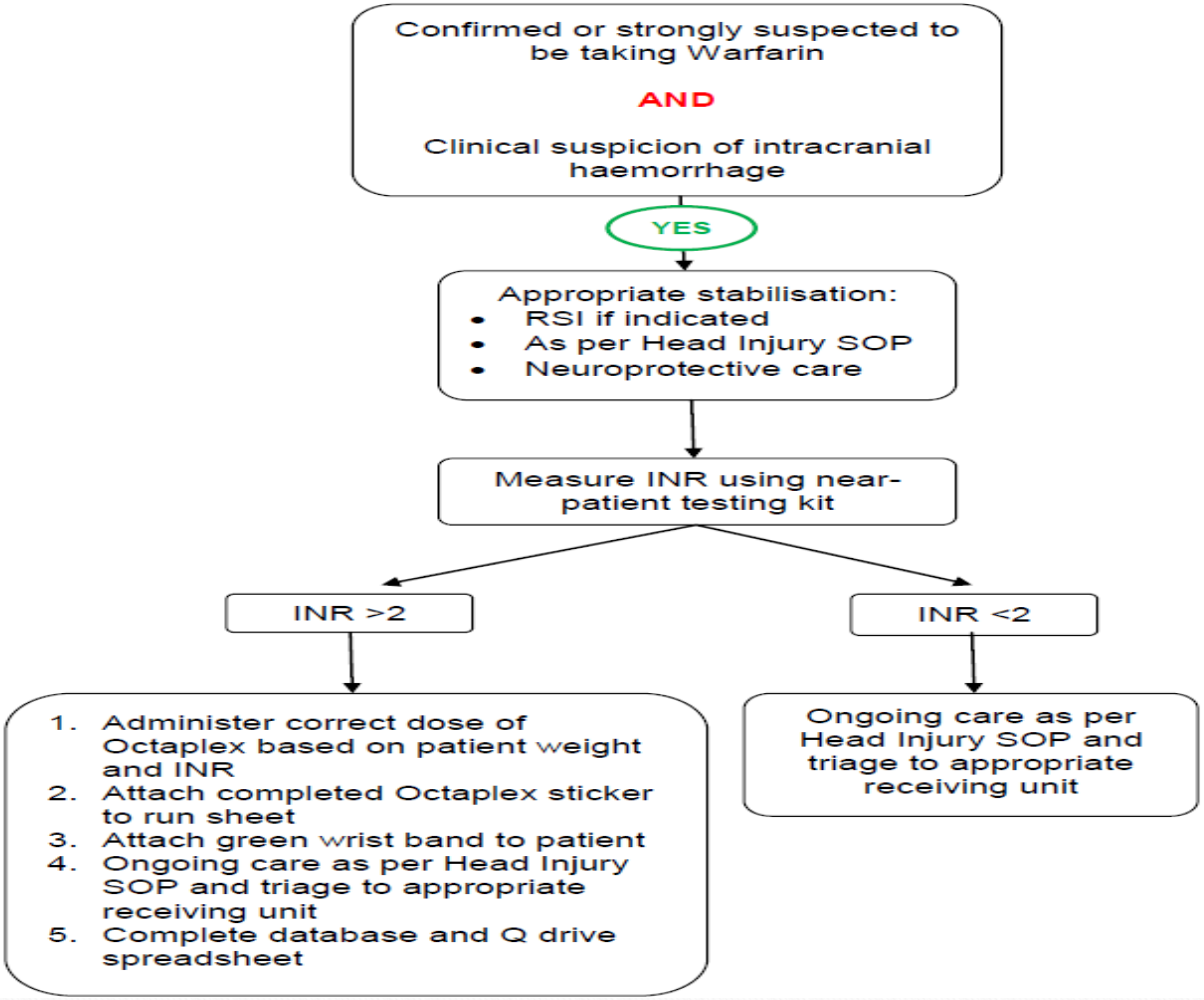
The dose is based on the patient's weight and the measured INR. Octaplex is given immediately after reconstitution as a slow intravenous bolus over 15-30 minutes. The maximum dose is 120mls of reconstituted solution (6 vials). The dose in **mls of reconstituted** solution is given in the table below.

Octaplex dosing chart			
Weight / INR	**2 – 2.5**	**2.6 – 3.5**	**>3.5**
40kg	40mls	60mls	80mls
45kg	40mls	60mls	100mls
50kg	60mls	80mls	100mls
55kg	60mls	80mls	**120mls**
60kg	60mls	100mls	**120mls**
65kg	60mls	100mls	**120mls**
70kg	80mls	100mls	**120mls**
75kg	80mls	**120mls**	**120mls**
80kg	80mls	**120mls**	**120mls**
85kg	80mls	**120mls**	**120mls**
90kg	100mls	**120mls**	**120mls**
95kg	100mls	**120mls**	**120mls**
100kg	100mls	**120mls**	**120mls**

Algorithm for pre-hospital Octaplex administration



Algorithm for pre-hospital Octaplex administration



Babilonia and Trujillo *Thrombosis Journal* 2014, **12**:8
http://www.thrombosisjournal.com/content/12/1/8

THROMBOSIS JOURNAL

REVIEW Open Access

The role of prothrombin complex concentrates in reversal of target specific anticoagulants

Katrina Babilonia[1*] and Toby Trujillo[2]

Abstract

Over the past several years a new era for patients requiring anticoagulation has arrived. The approval of new target specific oral anticoagulants offers practitioners several advantages over traditionally used vitamin K antagonist agents including predictable pharmacokinetics, rapid onset of action, comparable efficacy and safety, all without the need for routine monitoring. Despite these benefits, hemorrhagic complicates are inevitable with any anticoagulation treatment. One of the major disadvantages of the new oral anticoagulants is lack of specific antidotes or reversal agents for patients with serious bleeding or need for urgent surgery. As use of the new target specific oral anticoagulants continues to increase, practitioners will need to understand both the pharmacodynamics and pharmacokinetic properties of the agents, as well as, the available literature with use of non-specific therapies to reverse anticoagulation. Four factor prothrombin complex concentrates have been available for several years in Europe, and recently became available in the United States with approval of Kcentra. These products have shown efficacy in reversing anticoagulation from vitamin K antagonists, however their usefulness with the new target specific oral anticoagulants is poorly understood. This article will review the properties of dabigatran, rivaroxaban and apixaban, as well as the limited literature available on the effectiveness of prothrombin complex concentrates in reversal of their anticoagulant effects. Additional studies are needed to more accurately define the role of prothrombin complex concentrates in patients with life threatening bleeding or who require emergent surgery, as current data is both limited and conflicting.

Table 2 TSOAC Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban
Target	Factor IIa	Factor Xa	Factor Xa
Dosage Form	capsule	tablet	tablet
Bioavailability	6%	60-80%	50-85%
Time to Peak	1-2 hours	2-4 hours	1-3 hours
Metabolism	Conjugation; No CYP involvement	Oxidation via CYP3A4	Oxidation via CYP3A4
Renal Excretion	80%	33%	25%
Substrate of p- glycoprotein?	Yes	Yes	Yes
FDA approved dosing for stroke prevention in a- fib	150 mg twice daily for	20 mg by mouth once daily for patients CrCL > 50 ml/min	5 mg by mouth twice daily
	patients CrCL > 30 ml/min	15 mg by mouth once daily	2.5 mg by mouth twice daily for patients with 2 or more of the following: Age > 80, weight < 60 kg or Serum Cr > 1.5
	75 mg by mouth twice daily for CrCL 15–30 ml/min	for patients with CrCL 15-50 ml/min	
FDA approved dosing for VTE prevention in hip	N/A	10 mg once daily for patients with CrCL > 30 ml/min	N/A
and knee			
replacement			
FDA approved	N/A	15 mg by mouth twice daily	N/A
dosing for {1) treatment of acute DVT or PE, or {2) long term prevention of		for 21 days, then 20 mg once daily for patients with CrCL > 30 ml/min	
recurrent DVTfPE		20 mg once daily for patients with CrCL > 30 ml/min	

Table 4 Prothrombin complex concentrates composition[a]

Prothrombin complex concentrate	Factor levels (IU/ml)				Protein levels (IU/ml)			Other	
	II	VII	IX	X	C	S	Z	ATIII	Heparin
3 Factor									
Bebulin	24-37	< 5	24-37	24-37	NA	NA	NO	None	< 0.15/IU FIX
Profilnine	NMT 150/ U/100 Factor IX U	NMT 35/ U/100 Factor IX U	100 unit	NMT 100/ U/100 Factor IX U	NA	NA	NA	None	None
4 Factor									
Beriplex	20-48	10-25	20-31	22-60	22-31	17-19	Yes	Yes	Yes
Cofact	30	13	23	26	4	21	Yes	Yes	None
Kcentra	19-40	10-25	20-31	25-51	21-41	12-23	No	Yes	Yes
Octaplex	31	16	22	24	12	24	Yes	No	Yes
Activated PCC									
FEIBA*	1.3 IU/IU	0.9 IU/IU	1.4 IU/IU	1.1 IU/IU	1.1 IU/IU	NA	NA	No	No

[a]All concentrations are approximate and vary from one lot to another.
NMT = not more than, IU = international units.
*IU/IU = IU/FEIBA unit.

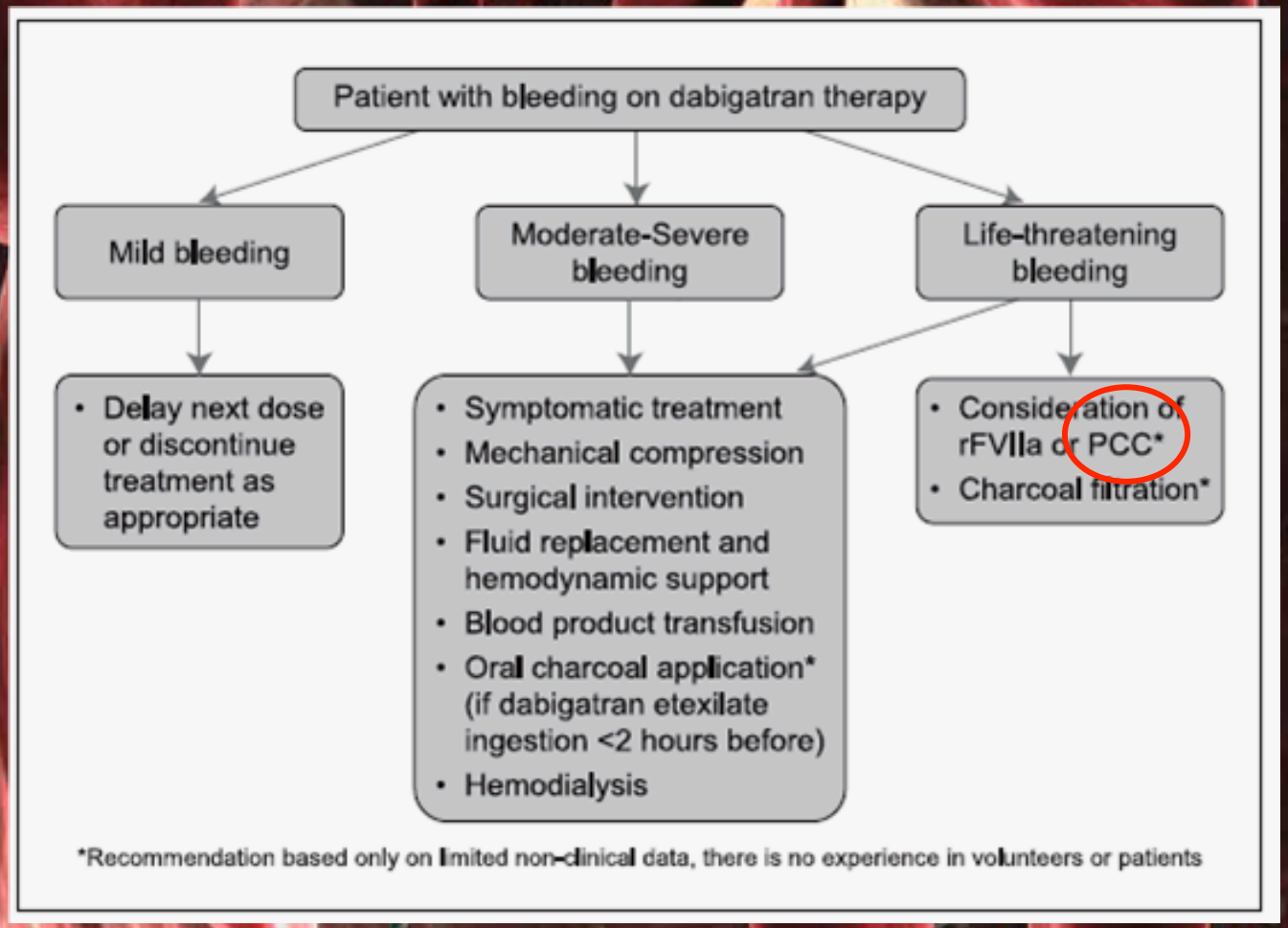
CONCENTRADO COMPLEJO PROTROMBINICO

- Solución esteril liofilizada
- Contiene F II, FVII, FIX, FX.
- Contiene cantidades relevantes de FVII.
- Usado en EEUU, CANADA pare revertir los antagonistas de Vit K.
- Cada vial puede ser reconstituida con 20 ml de agua estéril con 500 UI.
- Puede ser infundidos a 6-10 ml/min

CONCENTRADO COMPLEJO PROTROMBINICO

- 3000 UI -120 ml pueden ser administrados en 20 minutos.
- Los factores II, VII, IX y X se incrementan en 40-80%. Sin disminuir plaquetas ni hematocrito.
- Estudios comparativos de PFC vs PCC Son estudios retrospectivos muestras pequeñas.

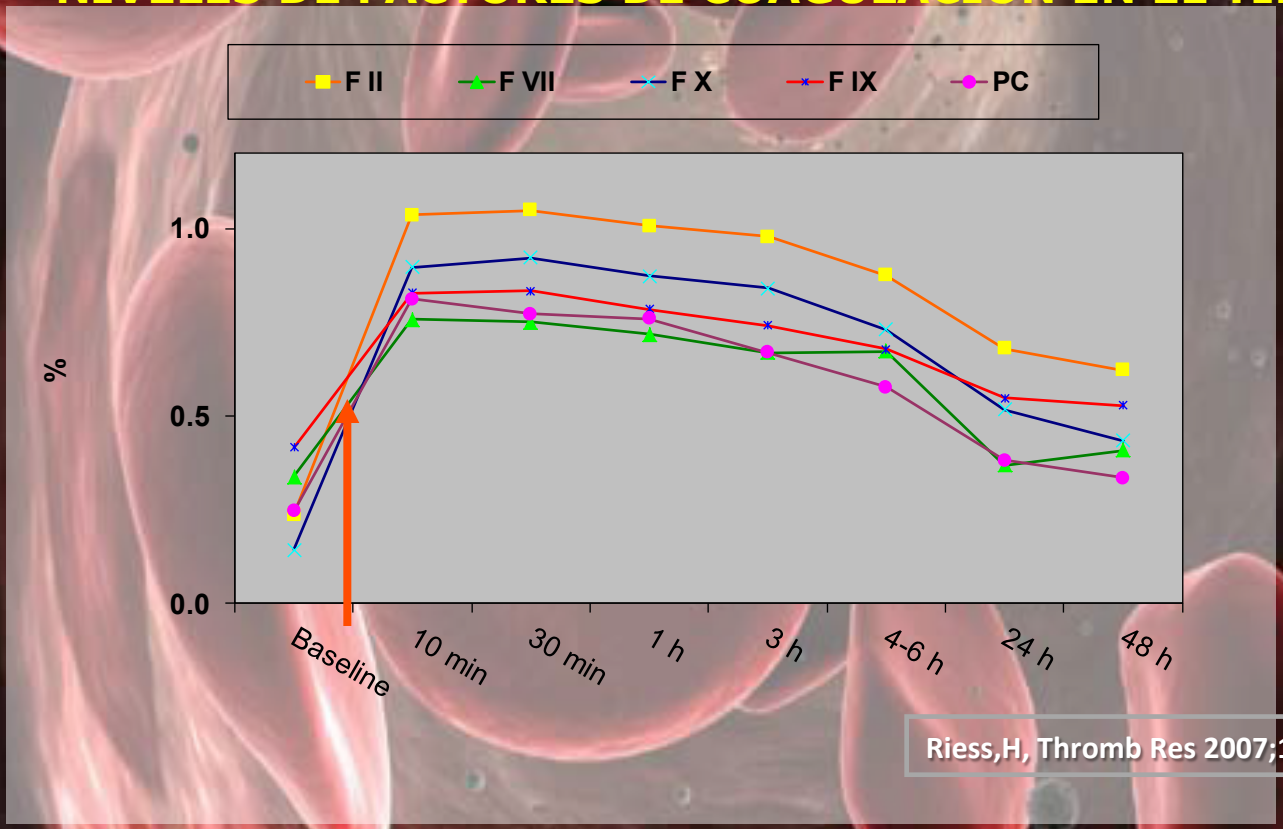
MANEJO DE COMPLICACIONES HEMORRAGICAS CON COMPLEJO PROTROMBINICO



Thrombosis and Haemostasis 103.6/2010

RAPIDA REVERSION DE LA TERAPIA ANTICOAGULANTE ORAL

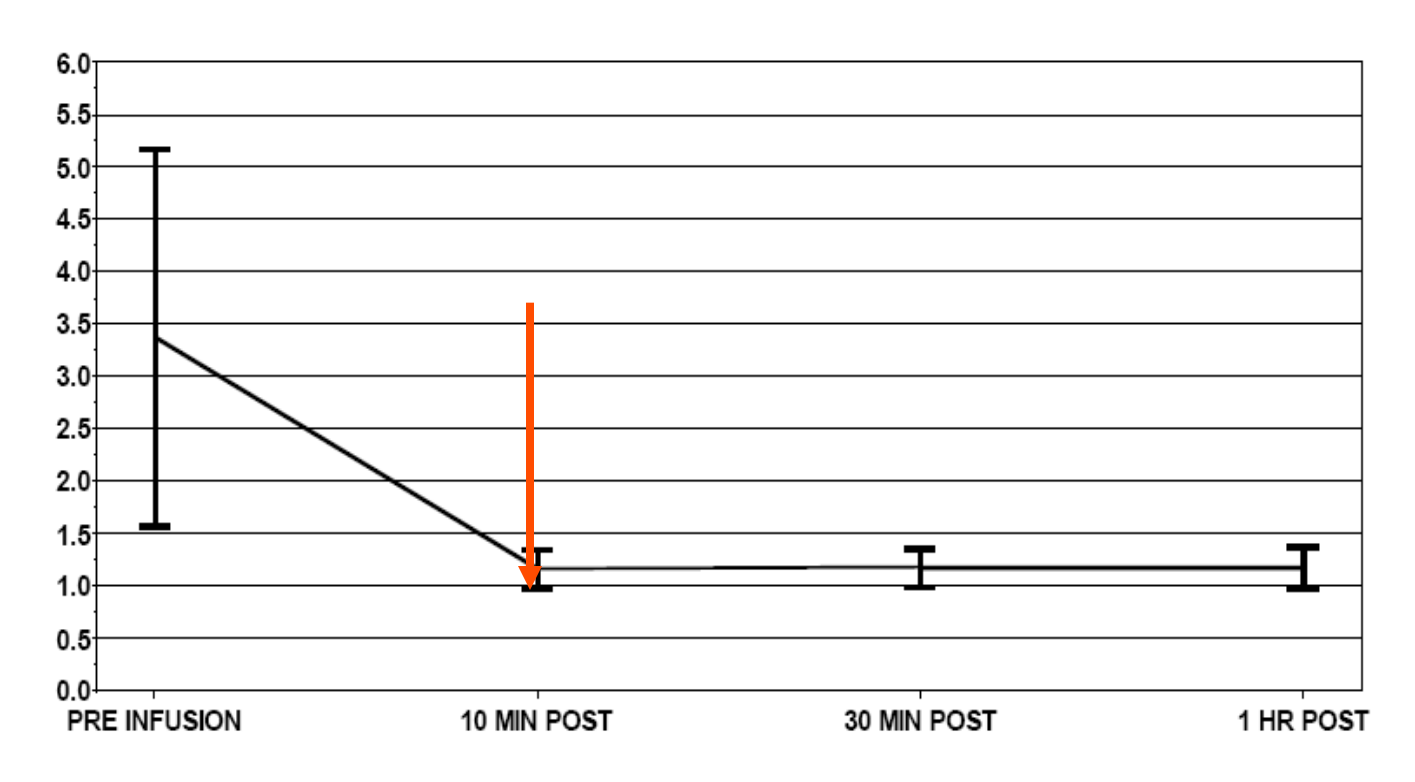
PROTOCOLO LEX-203 / RESULTADOS DE LOS NIVELES DE FACTORES DE COAGULACION EN EL TIEMPO.



Riess,H, Thromb Res 2007;121:9-16

MANEJO DE COMPLICACIONES HEMORRAGICAS CON COMPLEJO PROTROMBINICO

PROTOCOLO LEX-203 / RESULTADOS DE CORRECCION DEL INR CON LA TERAPIA CON CONCENTRADOS DE COMPLEJO DE PROTROMBINA



Riess,H, Thromb Res 2007;121:9-16

Schöchl et al. Critical Care 2011, 15:R83
http://ccforum.com/content/15/2/R83

CRITICAL CARE

RESEARCH Open Access

Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy

Herbert Schöchl[1,2], Ulrike Nienaber[3], Marc Maegele[4], Gerald Hochleitner[5], Florian Primavesi[2], Beatrice Steitz[6], Christian Arndt[7], Alexander Hanke[8], Wolfgang Voelckel[2] and Cristina Solomon[6*]

Abstract

Introduction: Thromboelastometry (TEM)-guided haemostatic therapy with fibrinogen concentrate and prothrombin complex concentrate (PCC) in trauma patients may reduce the need for transfusion of red blood cells (RBC) or platelet concentrate, compared with fresh frozen plasma (FFP)-based haemostatic therapy.

Methods: This retrospective analysis compared patients from the Salzburg Trauma Centre (Salzburg, Austria) treated with fibrinogen concentrate and/or PCC, but no FFP (fibrinogen-PCC group, $n = 80$), and patients from the TraumaRegister DGU receiving ≥ 2 units of FFP, but no fibrinogen concentrate/PCC (FFP group, $n = 601$). Inclusion criteria were: age 18-70 years, base deficit at admission ≥2 mmol/L, injury severity score (ISS) ≥16, abbreviated injury scale for thorax and/or abdomen and/or extremity ≥3, and for head/neck < 5.

Results: For haemostatic therapy in the emergency room and during surgery, the FFP group (ISS 35.5 ± 10.5) received a median of 6 units of FFP (range: 2, 51), while the fibrinogen-PCC group (ISS 35.2 ± 12.5) received medians of 6 g of fibrinogen concentrate (range: 0, 15) and 1200 U of PCC (range: 0, 6600). RBC transfusion was avoided in 29% of patients in the fibrinogen-PCC group compared with only 3% in the FFP group ($P < 0.001$). Transfusion of platelet concentrate was avoided in 91% of patients in the fibrinogen-PCC group, compared with 56% in the FFP group ($P < 0.001$). Mortality was comparable between groups: 7.5% in the fibrinogen-PCC group and 10.0% in the FFP group ($P = 0.69$).

Conclusions: TEM-guided haemostatic therapy with fibrinogen concentrate and PCC reduced the exposure of trauma patients to allogeneic blood products.

Table 1 Inclusion criteria

	Fibrinogen-PCC group (Salzburg Trauma Centre)	FFP group (TR-DGU)
Type of therapy	ROTEM-guided administration of coagulation factor concentrates	According to local protocols
ISS	≥ 16	
AIS thorax, abdomen, extremities	At least in one region, one injury with severity degree ≥3, $AIS_{head/neck} < 5$	
Age (years)	18-70	
Base deficit at admission	≥2 mmol/L	
FFP administered	No FFP	≥2 units FFP
Fibrinogen/PCC administered	≥1 g fibrinogen; ≥ 500 U PCC	No fibrinogen or PCC
Investigated time period	2005-2009	2005-2008
Patients included in database	353	21263
Patients fulfilling inclusion criteria	80	601

AIS, abbreviated injury scale; FFP, fresh frozen plasma; ISS, injury severity score; n, number of patients; PCC, prothrombin complex concentrate; ROTEM, thromboelastometry; TR-DGU, trauma registry of the German Society for Trauma Surgery.

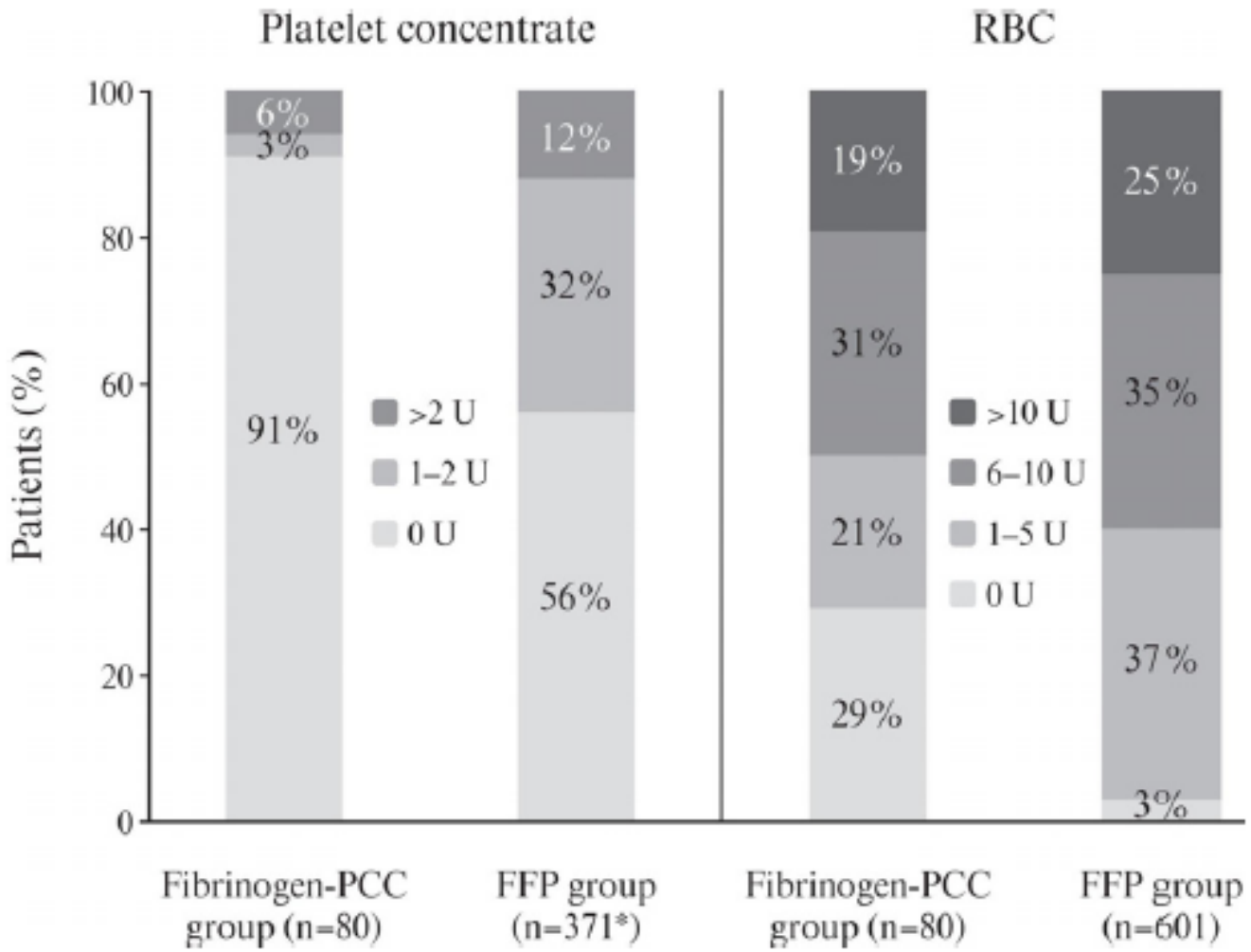


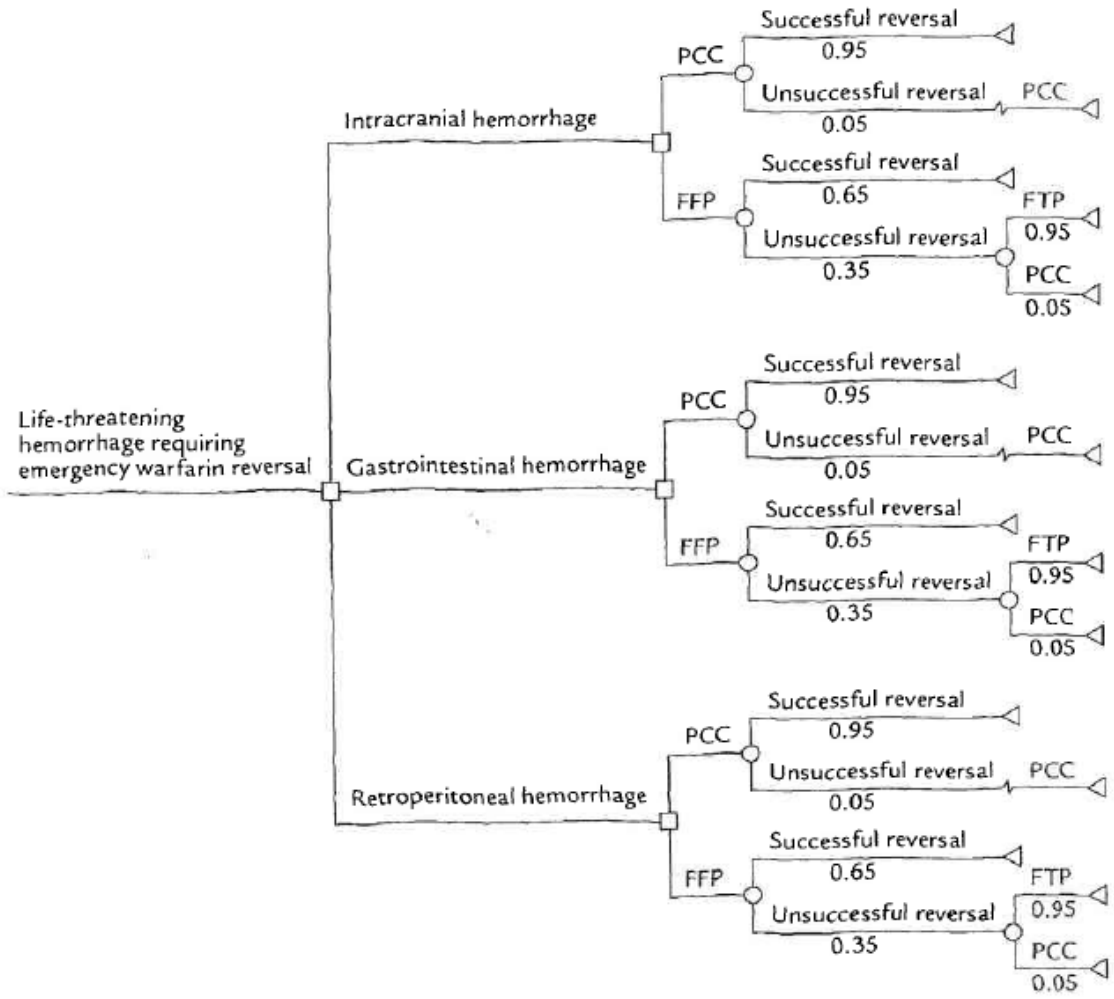
Figure 1 Platelet concentrate and red blood cell (RBC) transfusion in the emergency room and during surgery.
*Platelet concentrate transfusion only reported for 371 of 601 patients from the trauma registry of the German Society for Trauma Surgery (TR-DGU). FFP, fresh frozen plasma; PCC, prothrombin complex concentrate.

Clinical Therapeutics/Volume 32, Number 14, 2010

Modeling the Cost-Effectiveness of Prothrombin Complex Concentrate Compared With Fresh Frozen Plasma in Emergency Warfarin Reversal in the United Kingdom

Julian F. Guest, PhD[1,2]; Henry G. Watson, MD[3]; and Sameer Limaye, MBChB, MRCP[4]

[1]Catalyst Health Economics Consultants, Northwood, Middlesex, United Kingdom; [2]Postgraduate Medical School, Surrey University, Guildford, United Kingdom; [3]Department of Haematology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, United Kingdom; and [4]York Teaching Hospital NHS Foundation Trust, York, United Kingdom


Life-threatening hemorrhage requiring emergency warfarin reversal
Intracranial hemorrhage
Gastrointestinal hemorrhage
Retroperitoneal hemorrhage
PCC
FFP
Successful reversal
0.95
Unsuccessful reversal
0.05
PCC
Successful reversal
0.65
Unsuccessful reversal
0.35
FTP
0.95
PCC
0.05

ORIGINAL

Estudio de coste-efectividad del empleo de concentrado de complejo protrombínico en urgencias para evitar las complicaciones de la sobredosificación de anticoagulantes

MANUEL QUINTANA DÍAZ[1], ALBERTO M. BOROBIA[1], SANTIAGO PÉREZ CACHAFEIRO[2], CILIA RODRÍGUEZ[3], JOSÉ ANTONIO GARCÍA ERCE[4]

[1]Servicio de Urgencias, Hospital Universitario La Paz de Madrid, España. [2]I+D+i, Complejo Hospitalario de Pontevedra, España. [3]Grupo de Investigación USEES-URG, España. [4]Servicio de Hematología, Hospital San Jorge de Huesca, España.

PCCs in Cardiac Surgery and Liver Transplantation

Symposium: The Use of PCCs in non-Warfarin Patients
ESICM 2010 - October 11th, Barcelona, Spain

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University Hospital Essen
Germany
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Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature*

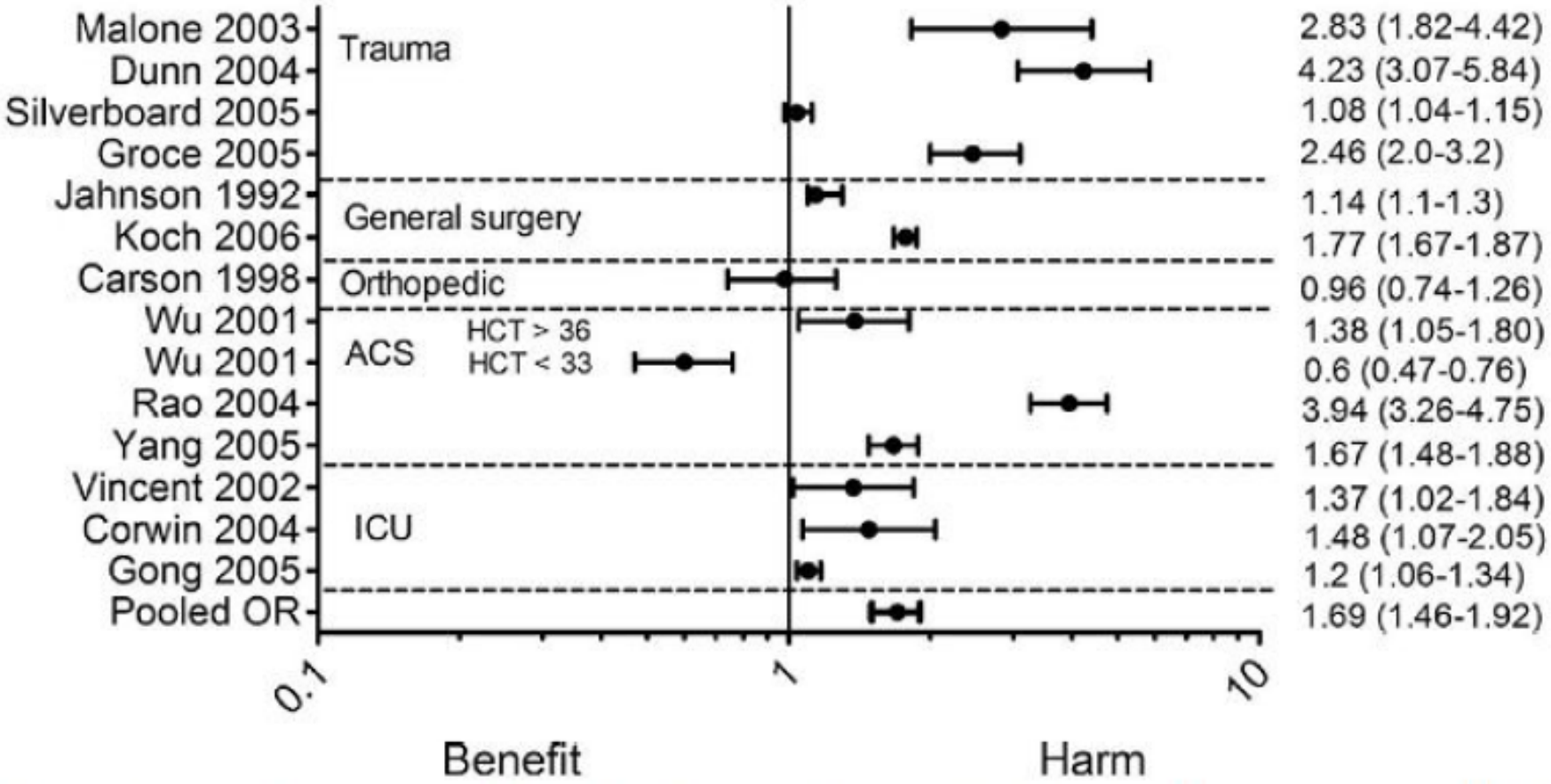


Figure 2. Association between blood transfusion and the risk of death (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ACS*, abdominal compartment syndrome; *ICU*, intensive care unit.

Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature*

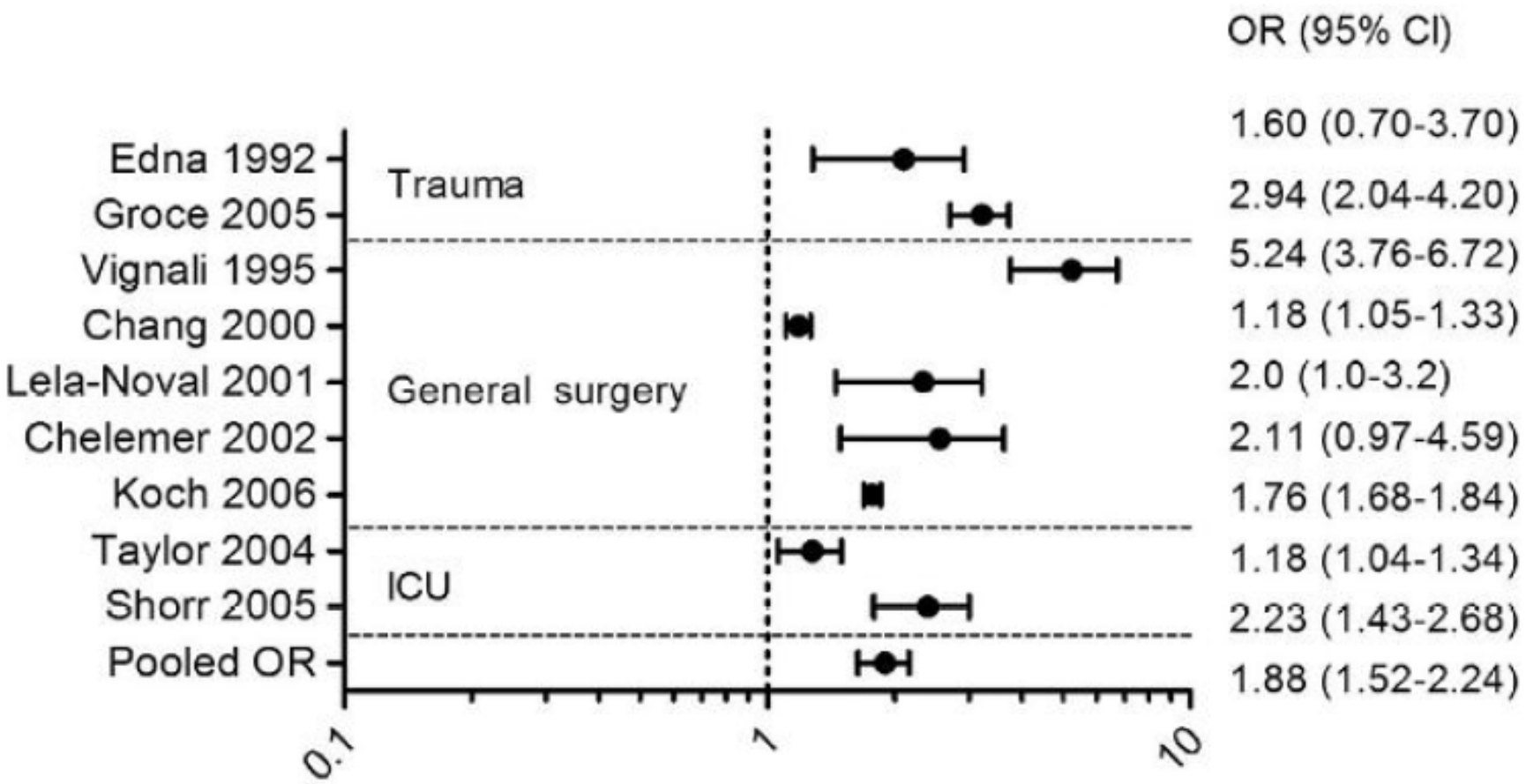


Figure 3. Association between blood transfusion and the risk of infectious complications (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ICU*, intensive care unit.

Crit Care Med 2008 Vol. 36, No. 4

Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection

Babak Sarani, MD, FACS; W. Jonathan Dunkman, BA; Laura Dean; Seema Sonnad, PhD; Jeffrey I. Rohrbach, RN, MSN; Vicente H. Gracias, MD, FACS

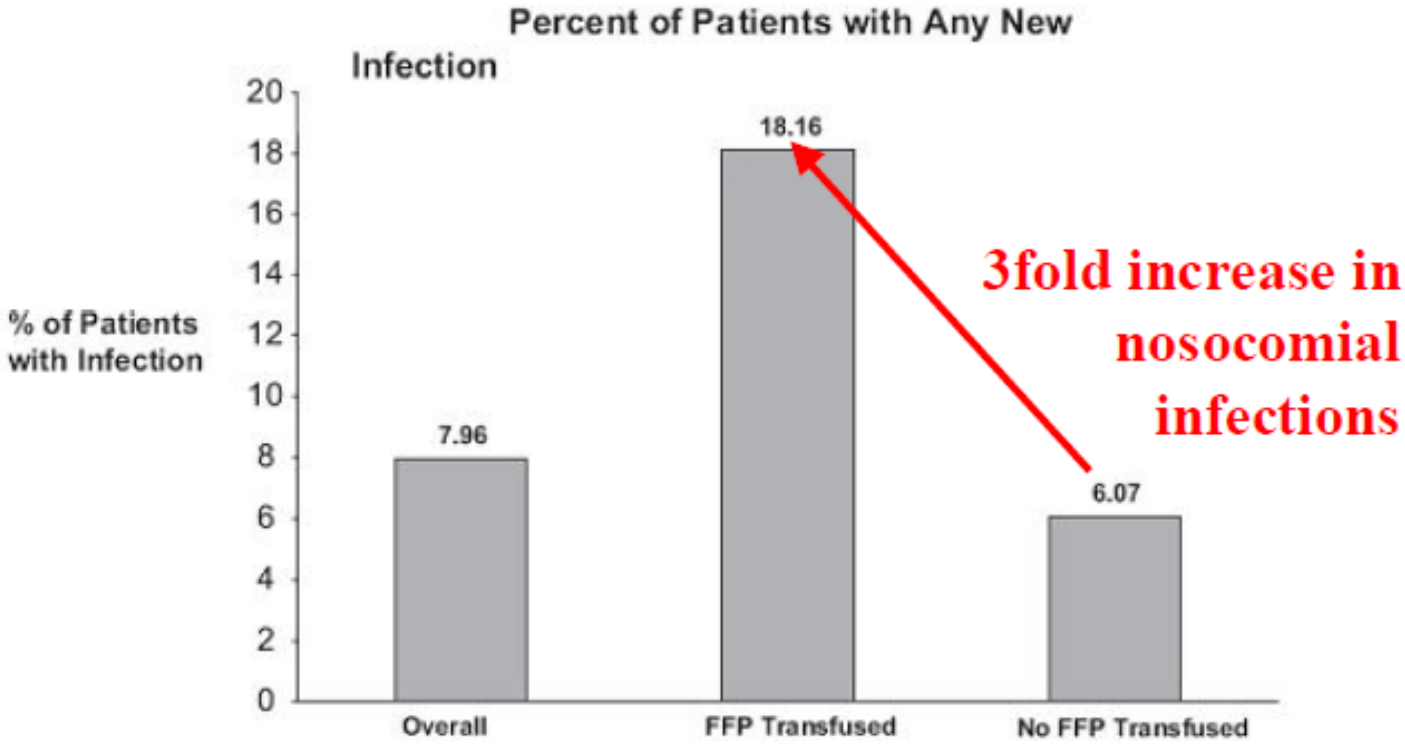


Figure 1. Patients who received fresh frozen plasma (*FFP*) were significantly more likely to develop an infection than those who did not receive FFP in a univariate model ($p < .01$).

Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature*

Paul E. Marik, MD, FACP, FCCM, FCCP; Howard L. Corwin, MD, FACP, FCCM, FCCP

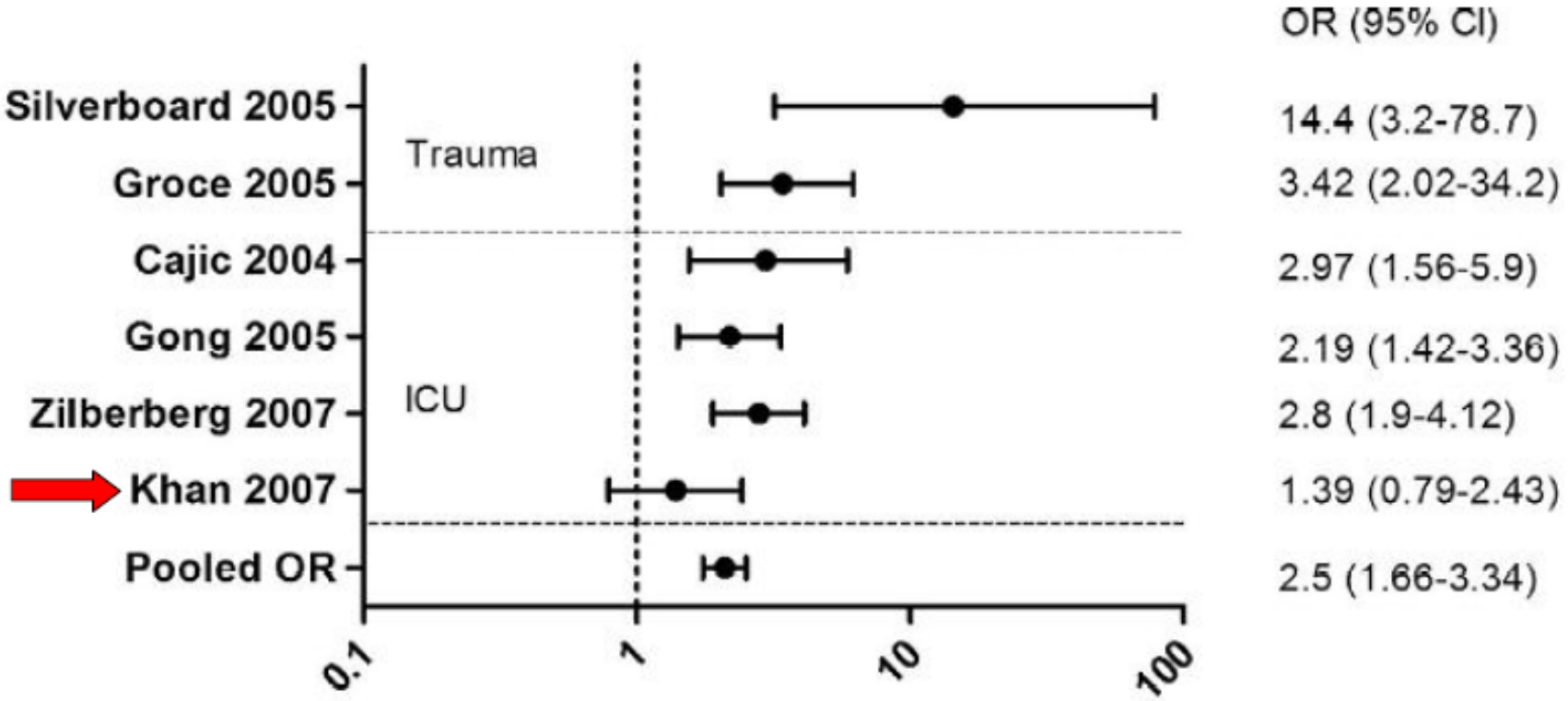
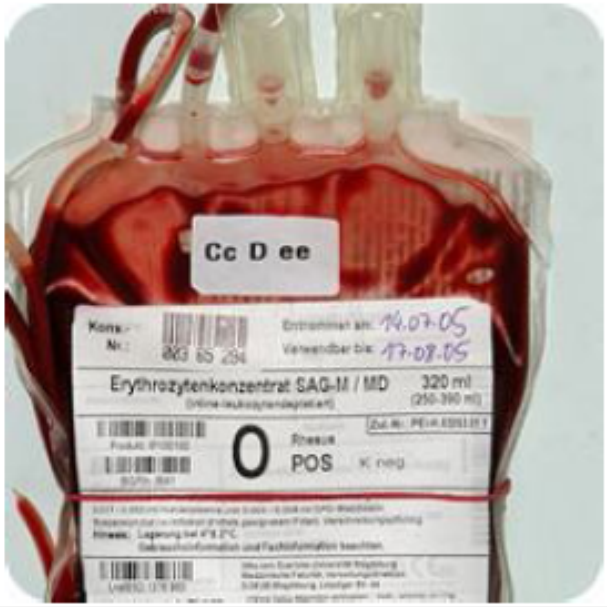
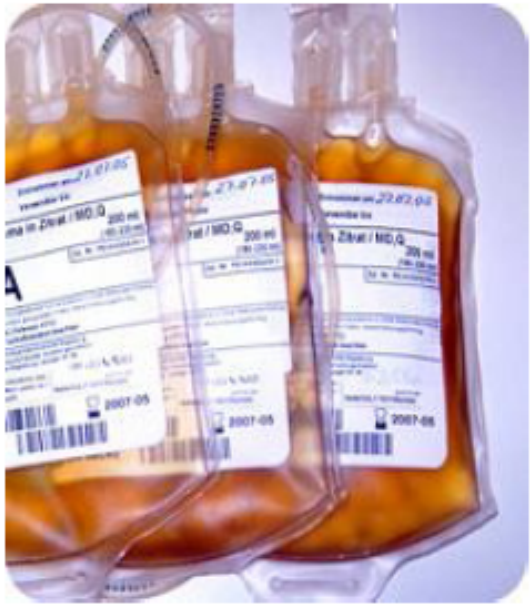


Figure 4. Association between blood transfusion and the risk of developing adult respiratory distress syndrome (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ICU*, intensive care unit.

Risks of blood transfusion



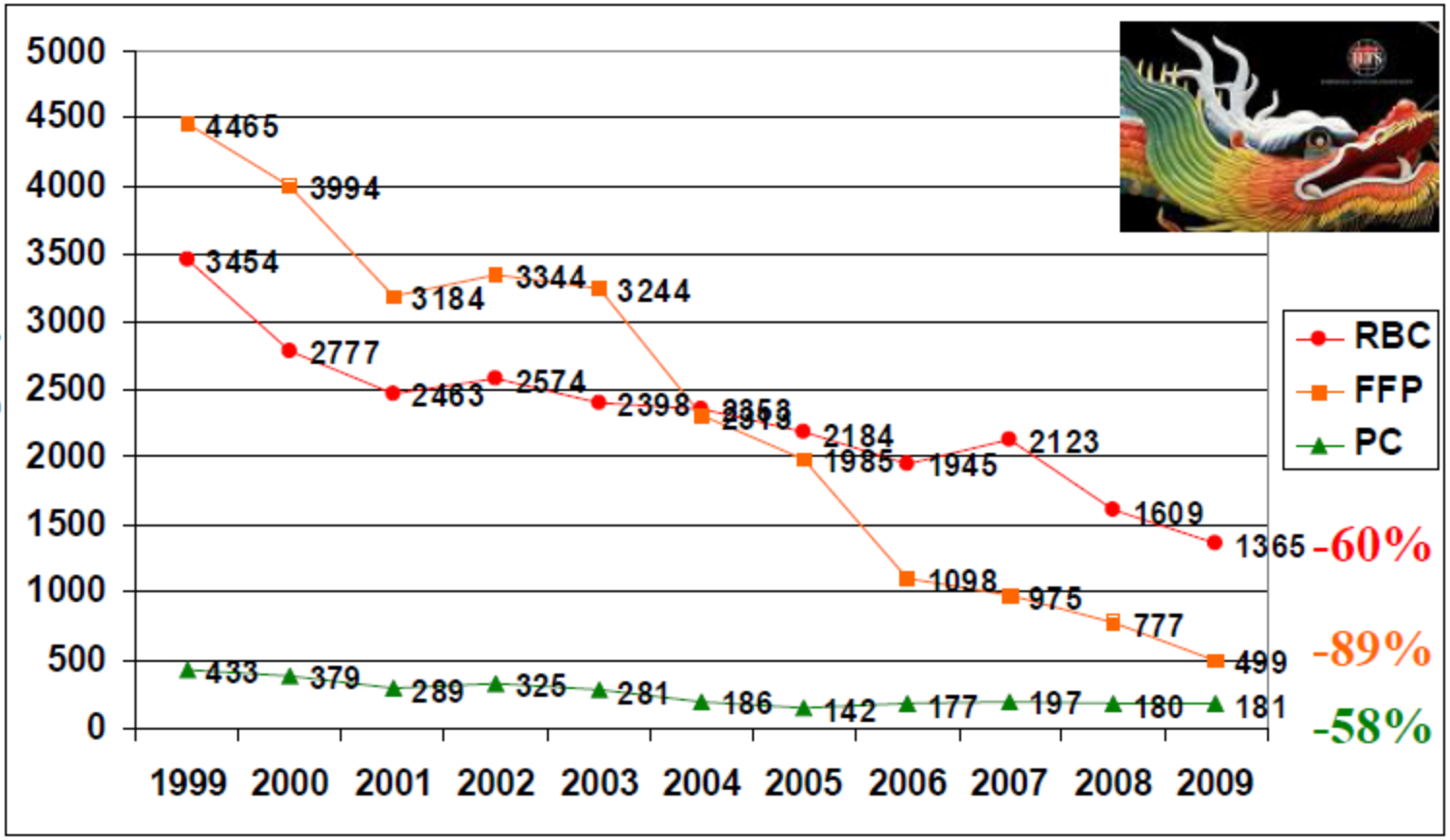
Blood transfusion increases mortality



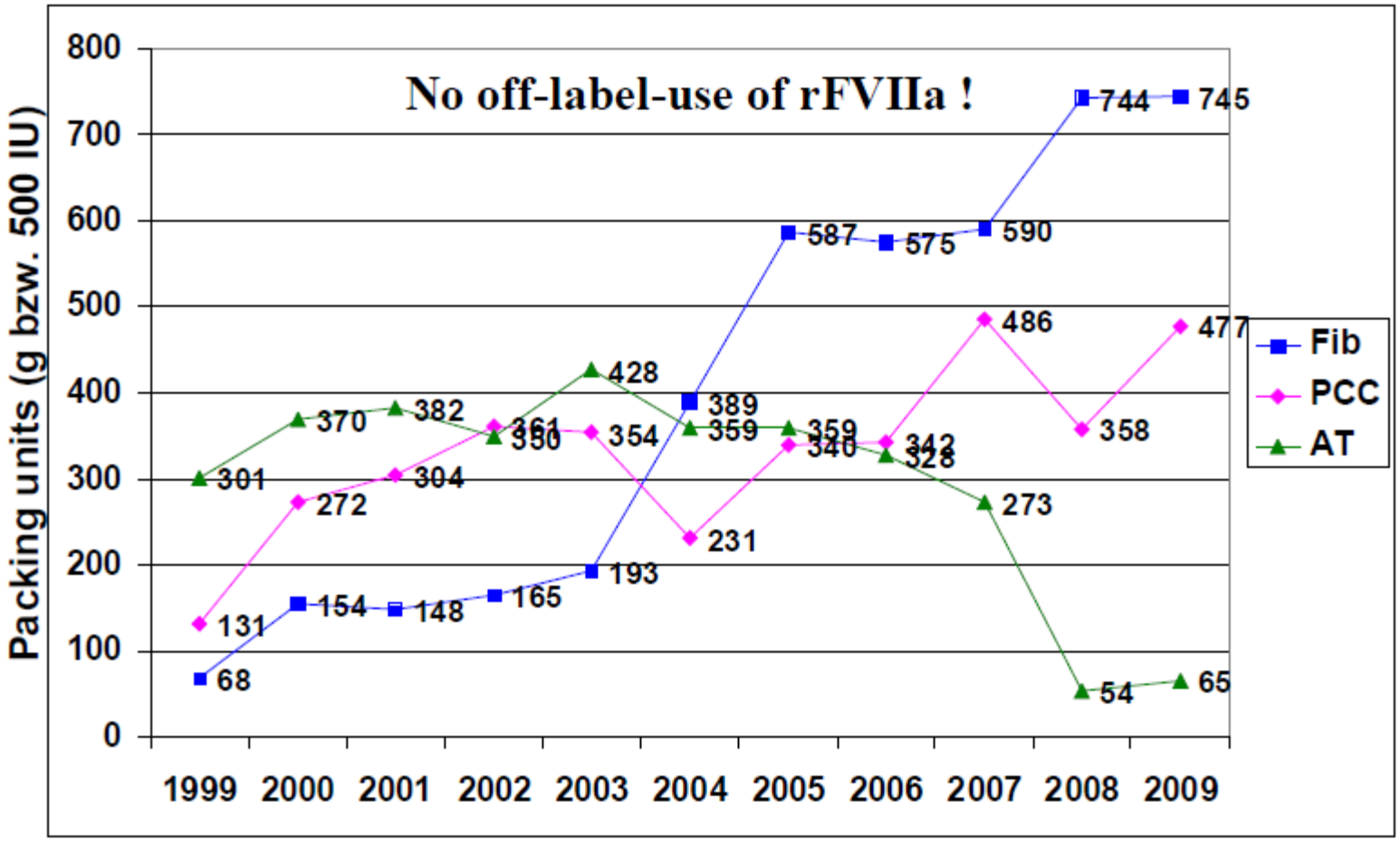
FFP transfusion induces ALI

Platelet transfusion causes ALI and sepsis

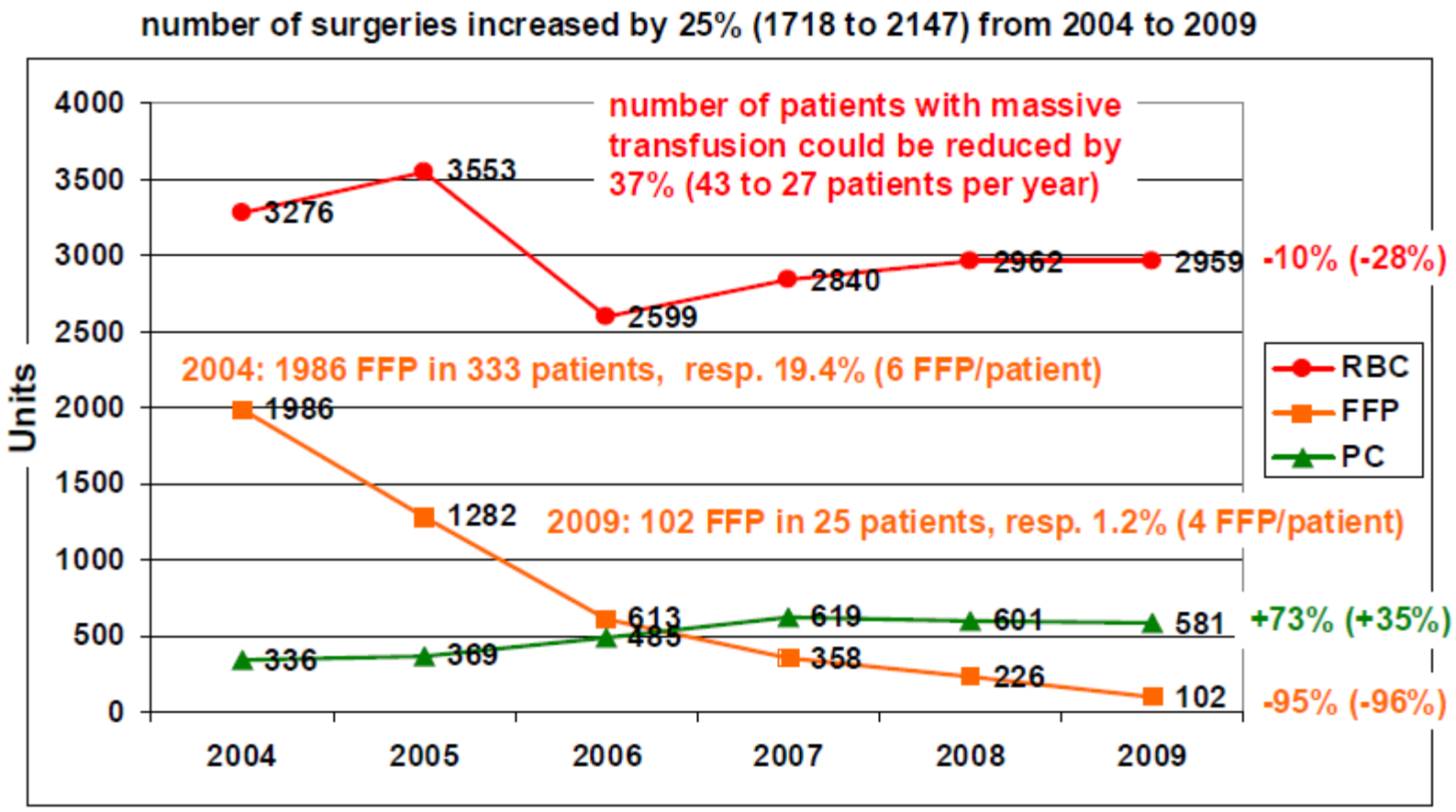
Intraoperative usage of blood products per year in visceral surgery and liver transplantation at University Hospital Essen, Germany



Intraoperative usage of coagulation factor concentrates per year in visceral surgery and liver transplantation at University Hospital Essen, Germany

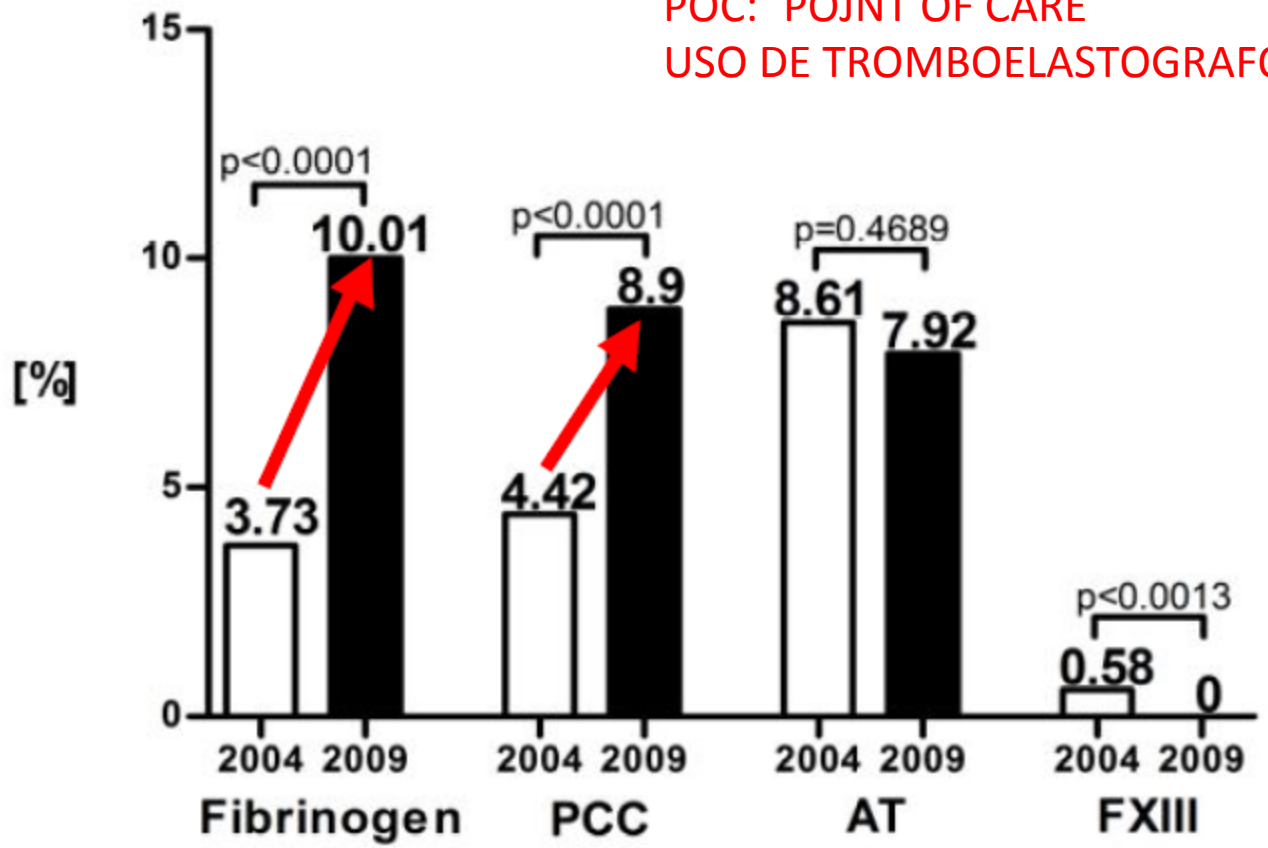


Thoracic and cardiovascular surgery: Reduction of transfusion requirements from 2004 to 2009

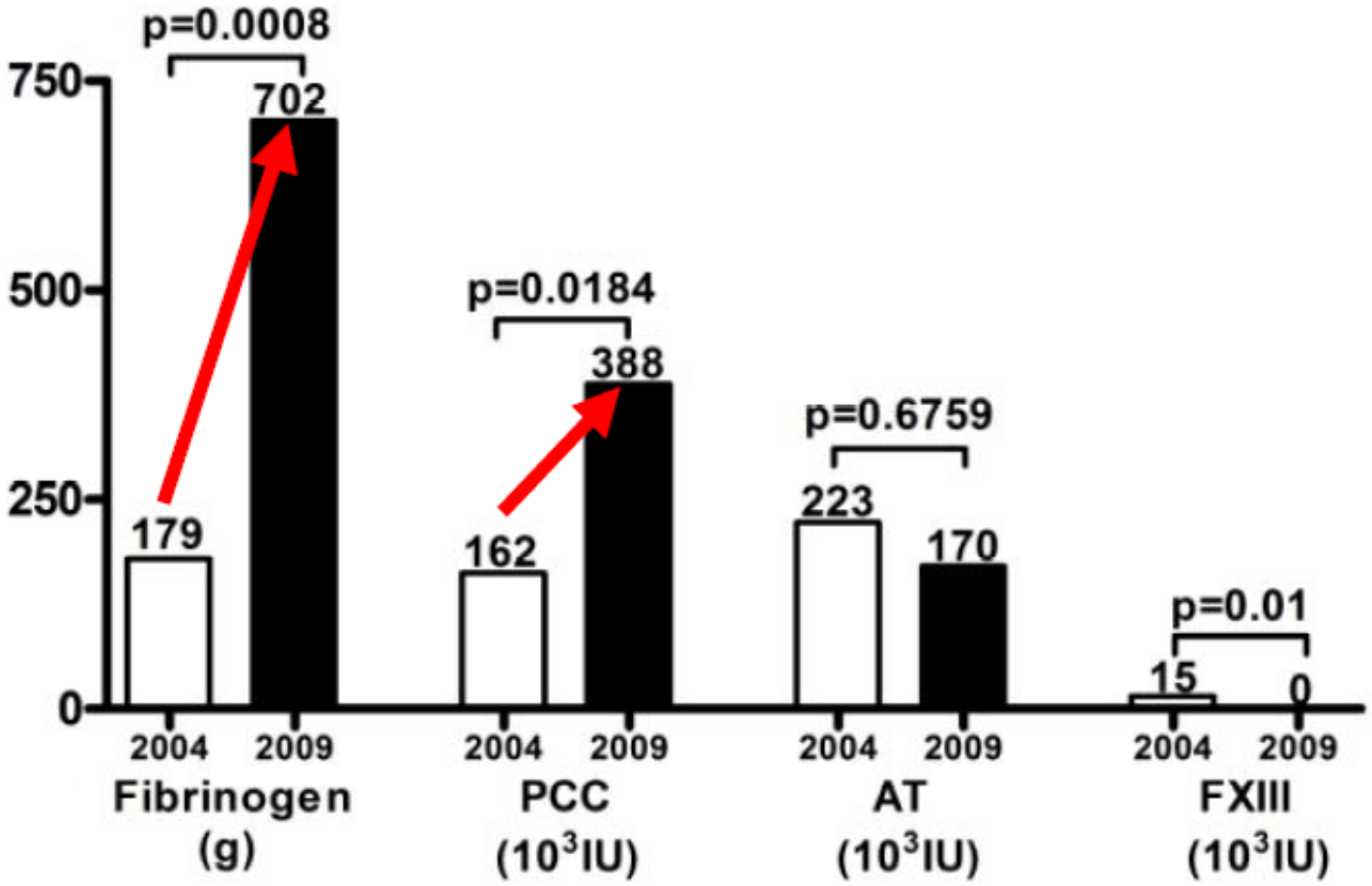


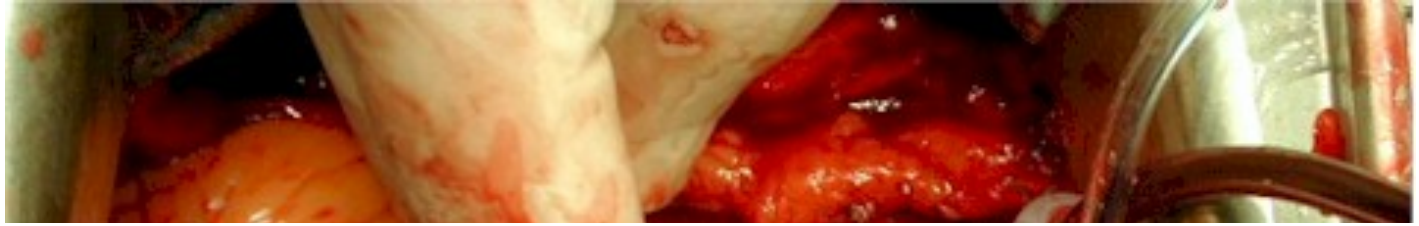
Incidence of intraoperative therapy with coagulation factor concentrates before (2004) and after (2009) implementation of POC coagulation management

POC: ´POJNT OF CARE
USO DE TROMBOELASTOGRAFO



Total intraoperative requirements per year for coagulation factor concentrates before (2004) and after (2009) implementation of POC coagulation management





Interactive CardioVascular and Thoracic Surgery Advance Access published May 23, 2012

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doi:10.1093/icvts/ivs224

ORIGINAL ARTICLE

Use of prothrombin complex concentrate for excessive bleeding after cardiac surgery

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8. Además de la vía anterógrada, se puede inyectar cardioplejia por haciendo un recorrido inverso al de la circulación fisiológica (desde las venas coronarias hacia los capilares) insertando otra cánula en el seno coronario. Este tipo de protección cardiaca se conoce como cardioplejia retrógrada y es especialmente útil en los casos con patología coronaria, que no permite que la cardioplejia anterógrada se distribuya adecuadamente por la circulación rdiaca.

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REVISIÓN

Indicaciones y usos del complejo protrombínico en cirugía cardiaca☆

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Tabla 1 Concentrados del complejo protrombínico

	Beriplex	Octaplex	Protromplex
FII (UI/ml)	20-48	11-38	30
FVII (UI/ml)	10-25	9-24	25
FIX (UI/ml)	20-31	25	30
FX (UI/ml)	22-60	18-30	30
PC (UI/ml)	15-45	7-31	> 20
AT (UI/ml)	0,2-1,5	ND	0,75-1,15
Heparina (UI/ml)	0,4-2,0	5-12,5	> 15
Inactivación por eliminación	Pasteurización, nanofiltración	Solvente/detergente, nanofiltración	Calor a presión, nanofiltración
Trasvasador	Mix 2 Vial	*Set* de transferencia estándar	*Set* de transferencia estándar
Velocidad de infusión	8,4 ml/min (210 UI/min)	3 ml/min (75 UI/min)	1 ml/min
Conservación	< 25 °C	< 25 °C	+2 a +8 °C
Validez	3 años	2 años	3 años

En el paciente cardiópata anticoagulado que precisa cirugía urgente (p. ej., el receptor de trasplante cardiaco), la reversión de la anticoagulación se debe realizar de manera rápida y segura y sin poner en peligro la oxigenación del paciente antes del trasplante cardiaco[25]. El receptor de corazón es un paciente con una fracción ventricular baja y una tolerancia mínima a la sobrecarga hídrica por el desarrollo rápido de insuficiencia respiratoria secundaria a edema agudo de pulmón. Hemos establecido, como protocolo de reversión de la anticoagulación del receptor de trasplante cardiaco, la administración de CCP, cuya dosis se calcula según la INR del paciente al ingreso hospitalario, y se va monitorizando dicha reversión según la INR en posteriores controles (cada 8 h postrasplante).

Indicaciones no establecidas en ficha técnica

El objetivo del tratamiento con CCP para la hemorragia grave es corregir la generación de trombina críticamente reducida que da lugar a hemorragia, consumo de factores de coagulación y administración de volumen. La utilización de CCP ha sido propuesta en la enfermedad hepática grave, y en el sangrado relacionado con traumatismo y perioperatorio[26]. La hemorragia masiva (pérdida de al menos un 20% de la volemia) contribuye al 30% de las muertes relacionadas con traumatismo, de ahí la necesidad de optimizar el tratamiento[23]. La principal indicación no establecida es la hemorragia masiva[25], ya que el CCP puede estar indicado cuando la sobrecarga de volumen o una disfunción cardiaca derecha grave desestimen el uso de plasma fresco congelado. Pero debemos recordar que el CCP no es un sustituto del plasma, ya que el primero no contiene algunos de los constituyentes del plasma que tienen un papel importante en la hemostasia, como son el fibrinógeno y el FXIII. También se ha utilizado en el sangrado microvascular en pacientes posquirúrgicos que no responden al tratamiento con PFC y plaquetas. Para casos de sangrado microvascular, se ha utilizado con éxito el rFVIIa[25].

En las situaciones en que se requiera una rápida corrección de la coagulopatía, tal como ocurre en las hemorragias intracraneales, los CCP ofrecen ventajas sobre el PFC, tal como su menor volumen, su almacenamiento a temperatura ambiente y la ausencia de necesidad de compatibilidad ABO, que se traducen en una reducción del tiempo de administración y/o disponibilidad[24].

Casos clínicos[27] y estudios como el de Bruce et al[25] refuerzan la utilidad de los CCP en pacientes sometidos a procesos quirúrgicos (como la cirugía cardiaca) con sangrado y sin coagulopatía hereditaria o relacionada con la toma de anticoagulantes; el uso de CCP se asoció a una disminución de transfusión y a la consecución de hemostasia con una mejoría de la tasa de supervivencia general[25].

Por otra parte, hay que destacar que hay pocos estudios publicados sobre la utilización de CCP en el sangrado perioperatorio o relacionado con traumatismo[23,28,29].

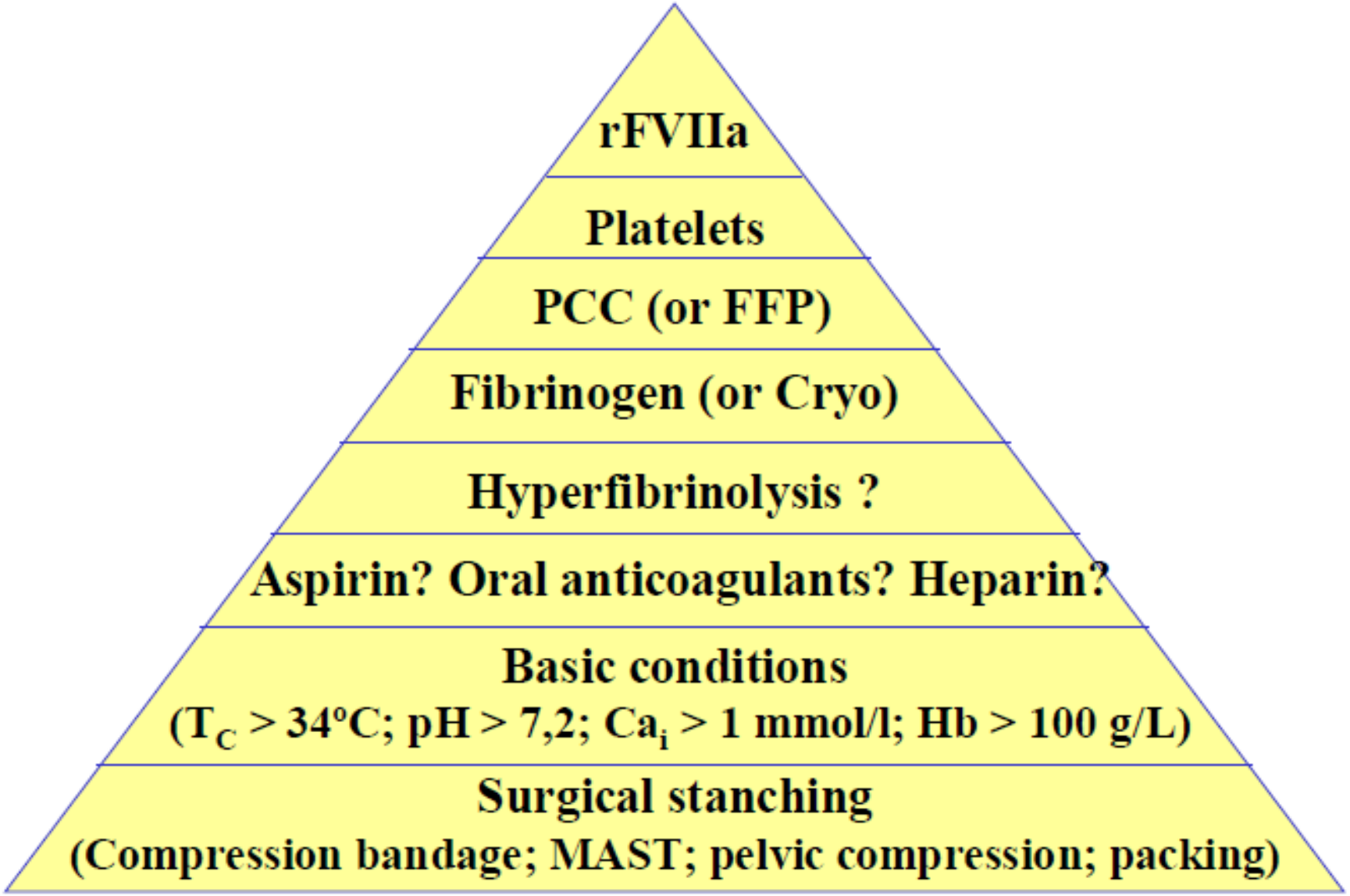
La cantidad a administrar y la frecuencia de administración siempre deben orientarse a la eficacia clínica en cada caso individual, si bien puede aceptarse que, para situaciones que precisen cirugía urgente o de sangrado activo en que INR > 5, la dosis adecuada sería 30 UI/kg, y en casos de INR < 5 la dosis sería 15 UI/kg, según recomienda el *British Committee for Standards in Haematology*[23]. Aunque la ficha técnica del producto indica mayor dosis (tabla 2), debemos ajustarnos a la dosificación recomendada por las guías clínicas actuales.

Contraindicaciones

Son contraindicaciones las reacciones alérgicas conocidas, trombocitopenia por heparina (HIT), enfermedad tromboembólica arterial reciente y alto riesgo de CID[39] (tabla 3).

La Sociedad Internacional de Trombosis y Hemostasia (2009) publicó la guía clínica de tratamiento de la CID, en la que se recomienda el uso de CCP en pacientes con CID, con parámetros analíticos TP y TTPa alargados, que presenten sangrado activo o precisen una intervención quirúrgica urgente y que no toleren la sobrecarga de fluidos que les produciría la transfusión de PFC, pero para algunos sólo tras el tratamiento apropiado con heparina, antitrombina III y antifibrinolíticos[40]. No está establecida la seguridad de su uso en embarazadas, en el periodo posparto precoz ni en menores de 17 años.

Pyramid of therapy in coagulopathy



Dosis, Precios y Pros/Contras

	Dosis	Supuesto	Uds	Coste	Pros/Contras
PFC	15 ml/Kg	70 Kg 1.050 ml	5 Bolsas	425,15 €	Conservación/preparación Admón. Lenta Volumen ↑↑ (2 litros !!) Riesgo infecciones TRALI Específico grupo sang.
CCP	INR>5 30 UI/Kg INR<5 15 UI/Kg	70 Kg INR<5	1.050 UI 2Viales	420 € PVL	Muy seguros (Contaminación $1/10^6$) Muy rápidos (URG!!!) No especif. grupo sang.
rVIIa					

Coagulation Monitoring

- **Laboratory tests**
  - APTT
  - INR
  - Fibrinogen
  - Thrombocytes
  - D-dimer
- **Bedside monitoring**
  - TEG, ROTEG
  - Sonoclot

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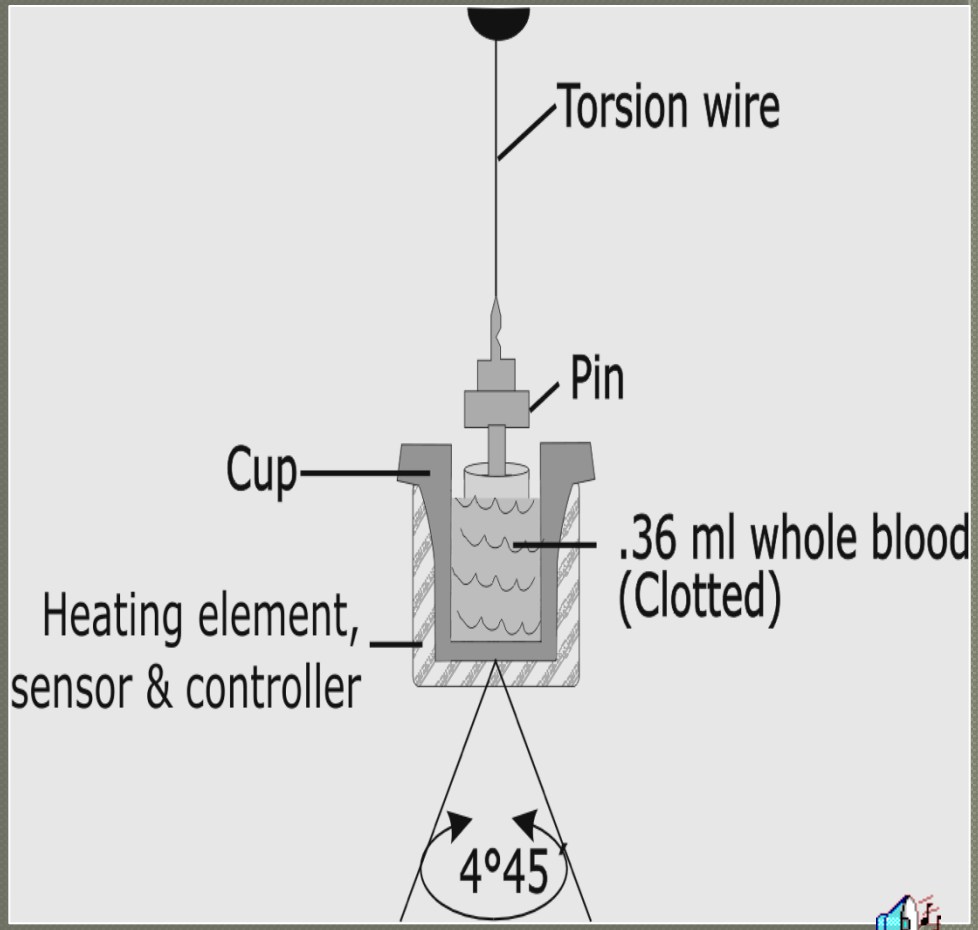

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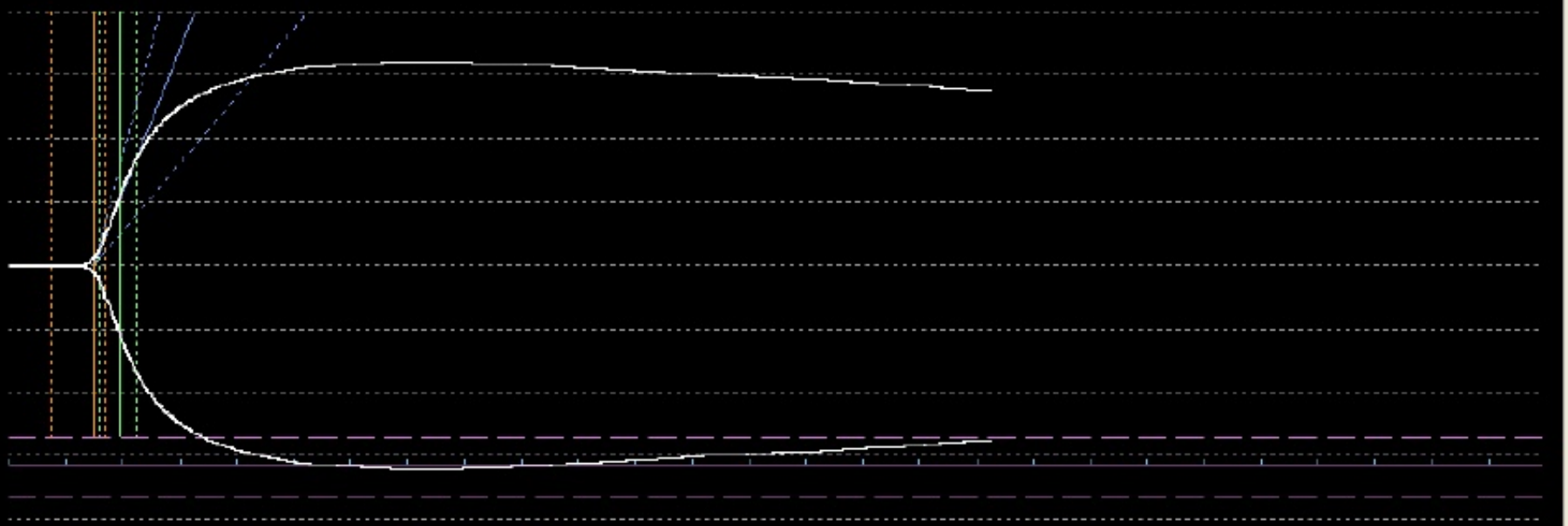
Paciente Sitio Activas Filtro Max Multi Datos PM Normal Ref Detalles SNotes TEG Principal

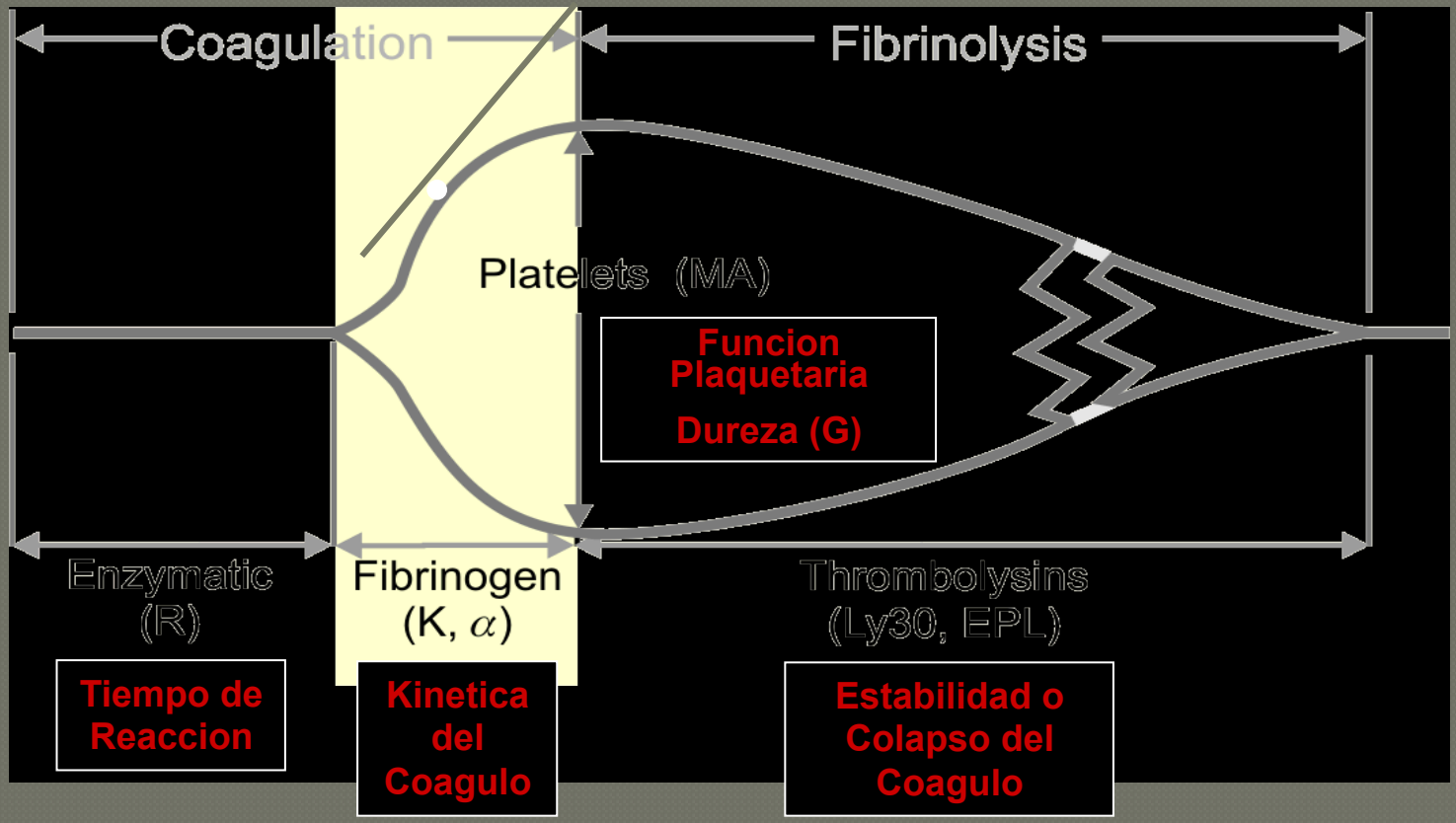
1 Tellez Velazquez, Carmen -- 9200 75 0600 Kaolin with heparinase

¶§CVM Muestra: 28/05/2008 10:03AM-11:29AM



R	K	Angle	MA	G	EPL	A	CI	LY30	A30
min	min	deg	mm	d/sc	%	mm		%	mm
7.3	2.2	66.0	62.8	8.5K	0.4	55.1	-0.7	0.4	61.2
4 — 8	0 — 4	47 — 74	54 — 72	6.0K — 13.2K	0 — 15		-3 — 3	0 — 8	

Kinetica del Coagulo
Hemostasia: El Balance lo es Todo



- Balance entre la formacion y la lisis del Coagulo
- Balance o desequilibrio en procoagulante y anticoagulante

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THROMBOSIS JOURNAL

REVIEW Open Access

A general review of major global coagulation assays: thrombelastography, thrombin generation test and clot waveform analysis

Marcus D Lancé

Abstract

Thrombosis and hemorrhage are major contributors to morbidity and mortality. The traditional laboratory tests do not supply enough information to diagnose and treat patients timely and according to their phenotype. Global hemostasis tests might improve this circumstance. The viscoelastic tests (ROTEM/TEG) demonstrated to ameliorate treatment of acute hemorrhage in terms of decreased amount of transfusion and lowered costs. Thrombin generation measurement is indicative for thrombosis and might also become an important tool in managing hemorrhage. While the clot waveform analysis is less well known it could be of worth in staging sepsis patients, early detection of DIC and also in diagnosis and treatment monitoring of hemophiliac patients. Although in different degree all three methods still need more background, standardization and acceptance before a wide clinical application.

Keywords: Global coagulation assays, Thrombosis, Hemorrhage, Hemophilia

Table 1 Thromboelastography parameters

Variable	TEG	ROTEM
From start until 2 mm baseline	R	Clotting time (CT)
From 2–20 mm above baseline	K	Clot formation time (CFT)
Alpha angle (°)	Slope	Angle of tangent at 2 mm
	Between R&K	
Maximum strength	Maximal amplitude	Maximal clot firmness
	(MA)	(MCF)
Clot lysis (CL) at minutes	CL 30, CL 60	LY30, LY 60

Conclusions

Our traditional coagulation tests do not cover all information the clinician needs to diagnose and treat thrombophilia, hemorrhage and inherited coagulation disorders. Global coagulation assays such as viscoelastic tests (TEM/TEG), thrombin generation test and clot waveform analysis care several advantages. While the viscoelastic tests proved to be worthwhile in management of acute hemorrhage, the thrombin generation test showed to be of use in thrombosis (venous and arterial) but also it might be a meaningful instrument in hemostatic therapy. The latter technique is at the beginning of a broad clinical use. Clot waveform analysis is even less well known. Although there is reasonable suspicion that this method might improve diagnosis and treatment of DIC, sepsis and hemophilia its application is not wide spread. Yet, there is need for more clinical data to support the current evidence.

Fig. 1 The lion, symbol of vigilance. This picture from an edition printed in Brussels in 1649 is from Saavedra's *Idea principis christiano politici*. The lion is a symbol of vigilance because he needs little sleep and if he sleeps it was believed he is doing so with his eyes open because he knows that he is 'non majestate securus': not safe in his majesty (http://www.emblematica.com/en/cd01-saavedra.htm).

GRACIAS