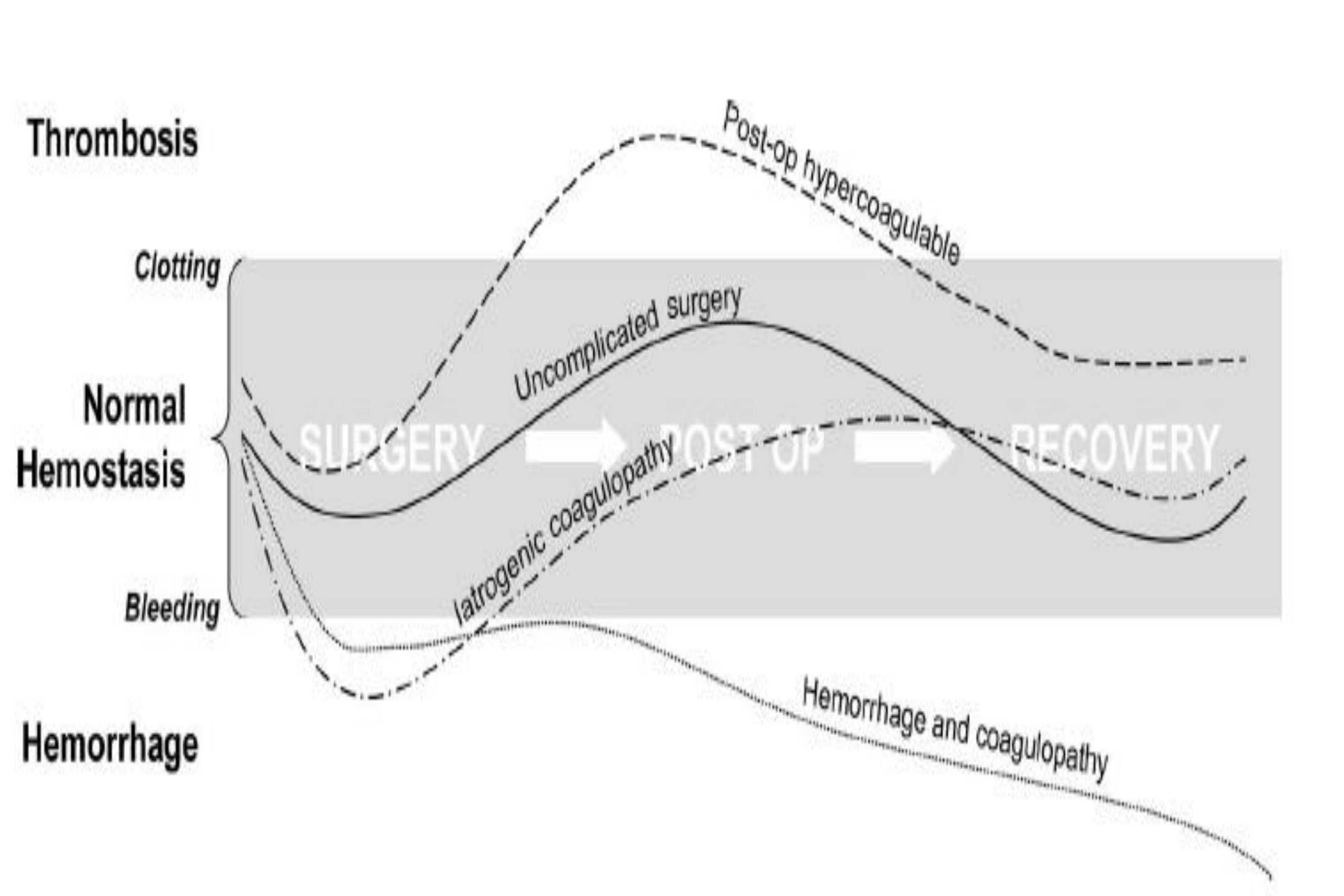

Hospital Universitario La Paz
SaludMadrid
Comunidad de Madrid
"Factors de coagulació exògens"
Dr. M. Quintana
Servicio de Medicina Intensiva
Hospital Universitario La Paz. Madrid

" el Conejo blanco preguntó
¿por dònde empiezo?
empieza por el principio, y cuando llegues al final, entonces para
- le contestó con gravedad el Rey "

Carrol, 1863

conflicto de intereses

…lo que sabemos


Thrombosis
Post-op hypercoagulable
Clotting
Uncomplicated surgery
Normal
Hemostasis
SURGERY
POST OP
RECOVERY
Iatrogenic coagulopathy
Bleeding
Hemorrhage and coagulopathy
Hemorrhage

directly inspected; and variable impact of pretreatment with anticoagulants or antiplatelet drugs. Specific hemostatic issues of the individual specialties will be considered below.

Cardiac/Vascular Surgery

Cardiac/vascular surgery patients represent a well defined but complex hemostatic challenge because of multiple factors including tissue injury, the use of heparin with protamine reversal, and preexisting antiplatelet and antithrombotic therapies. Cardiac surgery is further complicated by the use of CPB, which activates inflammatory, hemostatic, and fibrinolytic pathways.[8] Complex cardiac surgical procedures (e.g., repeat, combined, and aortic root procedures) are increasingly performed on patients at the extremes of age with underlying medical conditions. These patients have more extensive surgery, prolonged CPB times, and increased risk of bleeding. In addition, more patients receive anticoagulants and antiplatelet drugs preoperatively without clear therapeutic approaches for reversal or management (e.g., clopidogrel).[8]

With the withdrawal from marketing of aprotinin for use in high-risk cardiac surgery, there is an increasing need to further develop therapeutic approaches to manage refractor bleeding in cardiac surgery. Several studies suggest that transfusions are associated with worse outcomes in a dose-dependent manner, and there are adverse consequences to massive transfusion (beyond 4–5 U).[9–11] Koch et al.[9] reported an observational cohort study of 11,963 patients who underwent isolated coronary artery bypass from 1995 to 2002 of which 5814 (48.6%) were transfused. Transfusion of red blood cells (RBCs) was associated with a risk-adjusted increased risk for every postoperative morbid event: mortality (odds ratio [OR], 1.77), renal failure (OR, 2.06), prolonged ventilatory support (OR, 1.79), serious infection (OR, 1.76), cardiac complications (OR, 1.55), and neurologic events (OR, 1.37). Each unit of RBCs transfused was associated with incrementally increased risk for adverse outcome. Karkouti et al.[10] defined massive transfusion as receiving at least 5 U of RBCs within 1 day of surgery. Of 9215 patients analyzed associated with an 8.1-fold (95% confidence interval, 3.9–17.0) increase in the odds of death. Overall, multiple studies continue to suggest that transfusions are important risk predictors in adverse outcomes, especially in cardiac surgery.

Trauma Surgery and Resuscitation

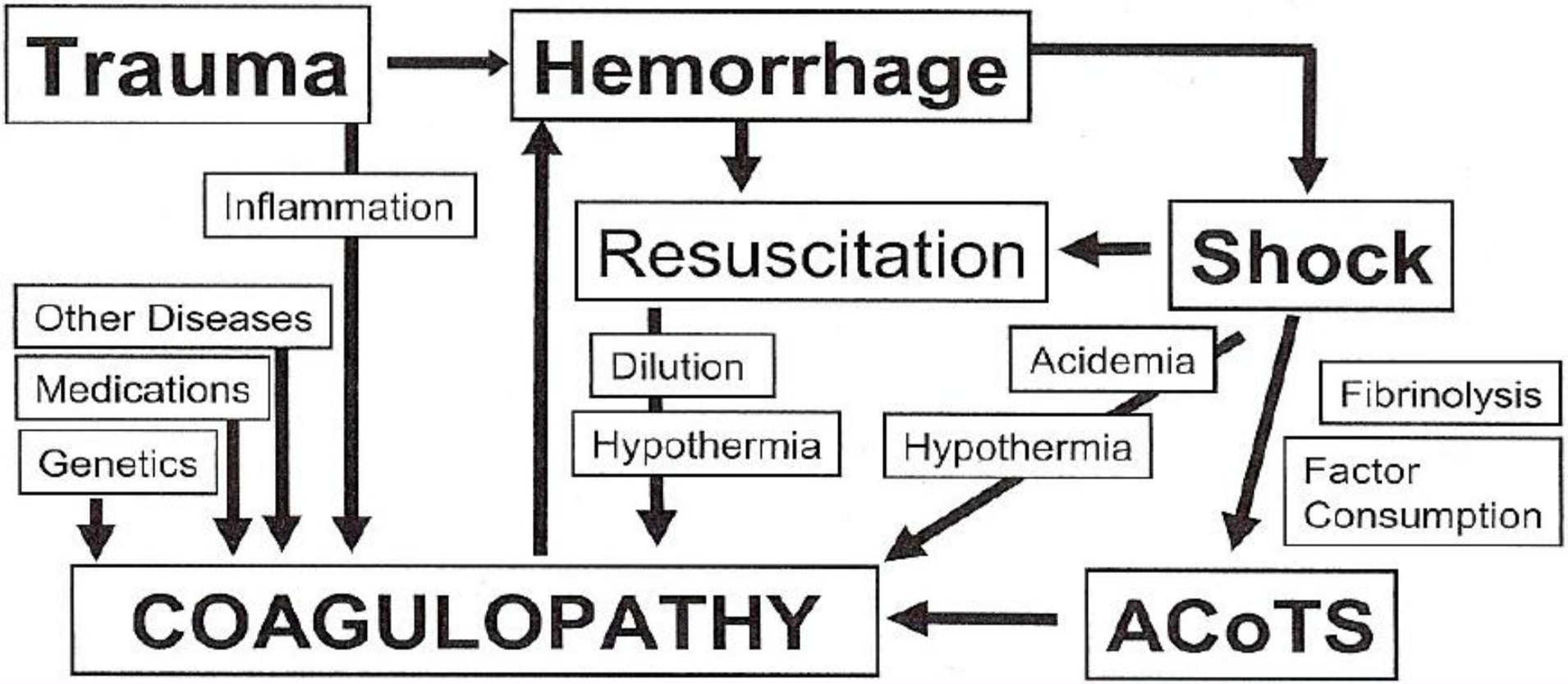
For the bleeding trauma patient, the approach is to control anatomic hemorrhage and initiate effective resuscitation. Acute, fatal hemorrhagic shock is characterized by progressive metabolic acidosis, hemodilution, and hypothermia, the so-called "lethal triad." Coagulopathy at this stage is difficult to reverse, even with massive transfusion that can also cause more coagulopathy, especially if "unbalanced" components such as only packed RBCs (PRBCs) are transfused without hemostatic factors. Many severely injured patients are coagulopathic at hospital admission (before fluid resuscitation even begins) as the result of tissue hypoperfusion triggering the release of inflammatory mediators. Hemodilution only compounds this problem. The role of blood loss, dilution, hypothermia, acidosis, fibrinolysis, inflammation, and other pathways as contributors to the coagulopathy of trauma remains to be fully elucidated.[12–15] On the basis of retrospective studies, some recommend that early resuscitation in hemodynamically unstable patients should be aimed at preserving hemostasis, and a transfusion protocol with a ratio of RBCs, plasma, and platelets in a 1:1:1 proportion should be used. This approach may improve outcomes,[2,16,17] but there is some controversy regarding this strategy of empiric fixed therapy because the current resuscitation approach is multifactorial. Clinical and laboratory variables are needed to identify the patients most likely to have abnormal hemostasis on admission and to complement early diagnosis of continuing hemorrhage, and thus identify those patients who would most benefit from directed therapy or possibly from a 1:1:1 resuscitation strategy.

Neurocritical Care

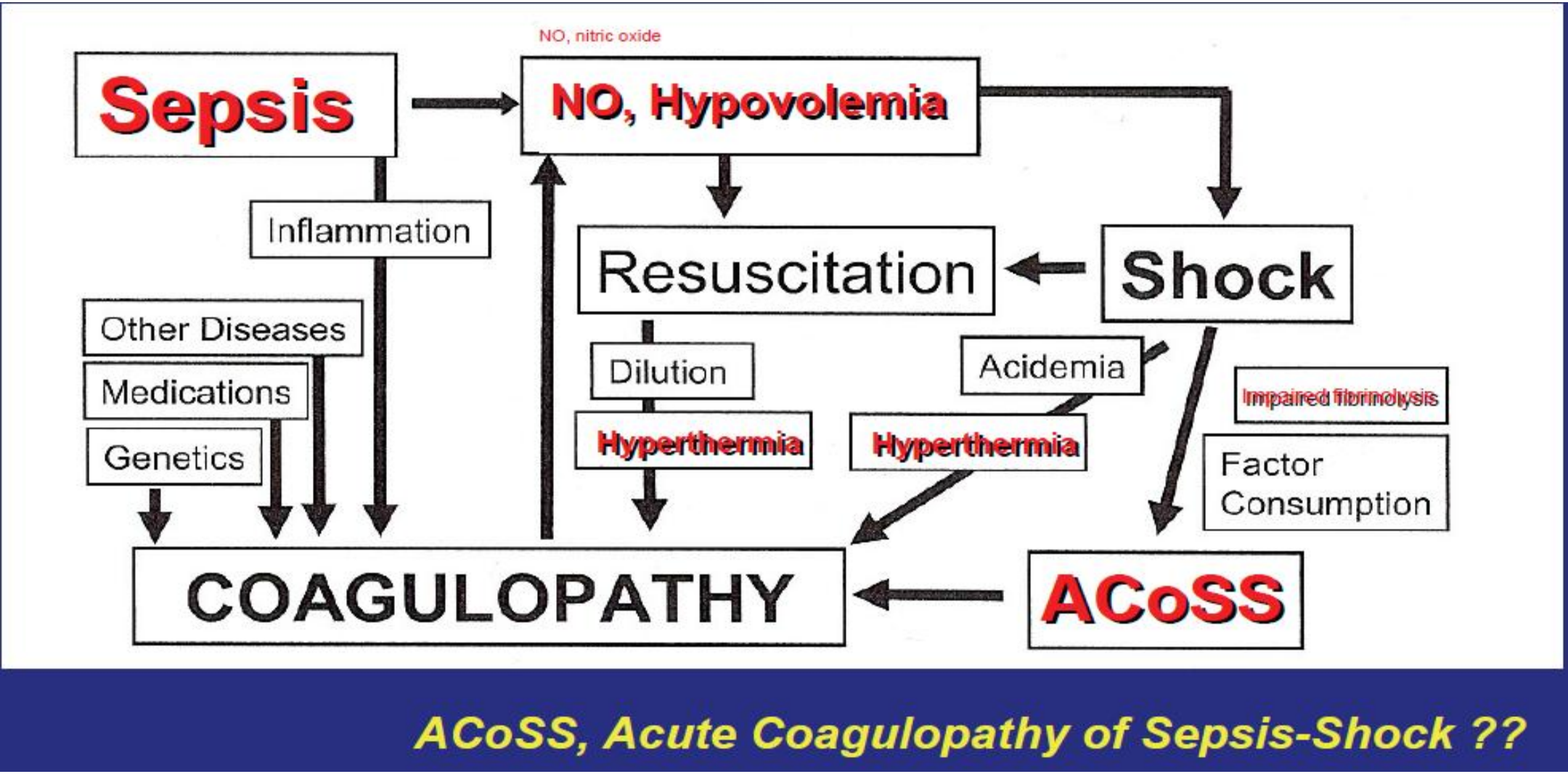
Intracranial bleeding caused by trauma, stroke, or to tolerate any amount of additional hemorrhage may be limited. Thus, efforts to diagnose and intervene regarding the hemostatic system in acute CNS hemorrhage must focus on the ability to target abnormalities immediately to avoid any additional hemorrhage, essentially from the time point of initial patient evaluation.

Obstetrics and Postpartum Hemorrhage

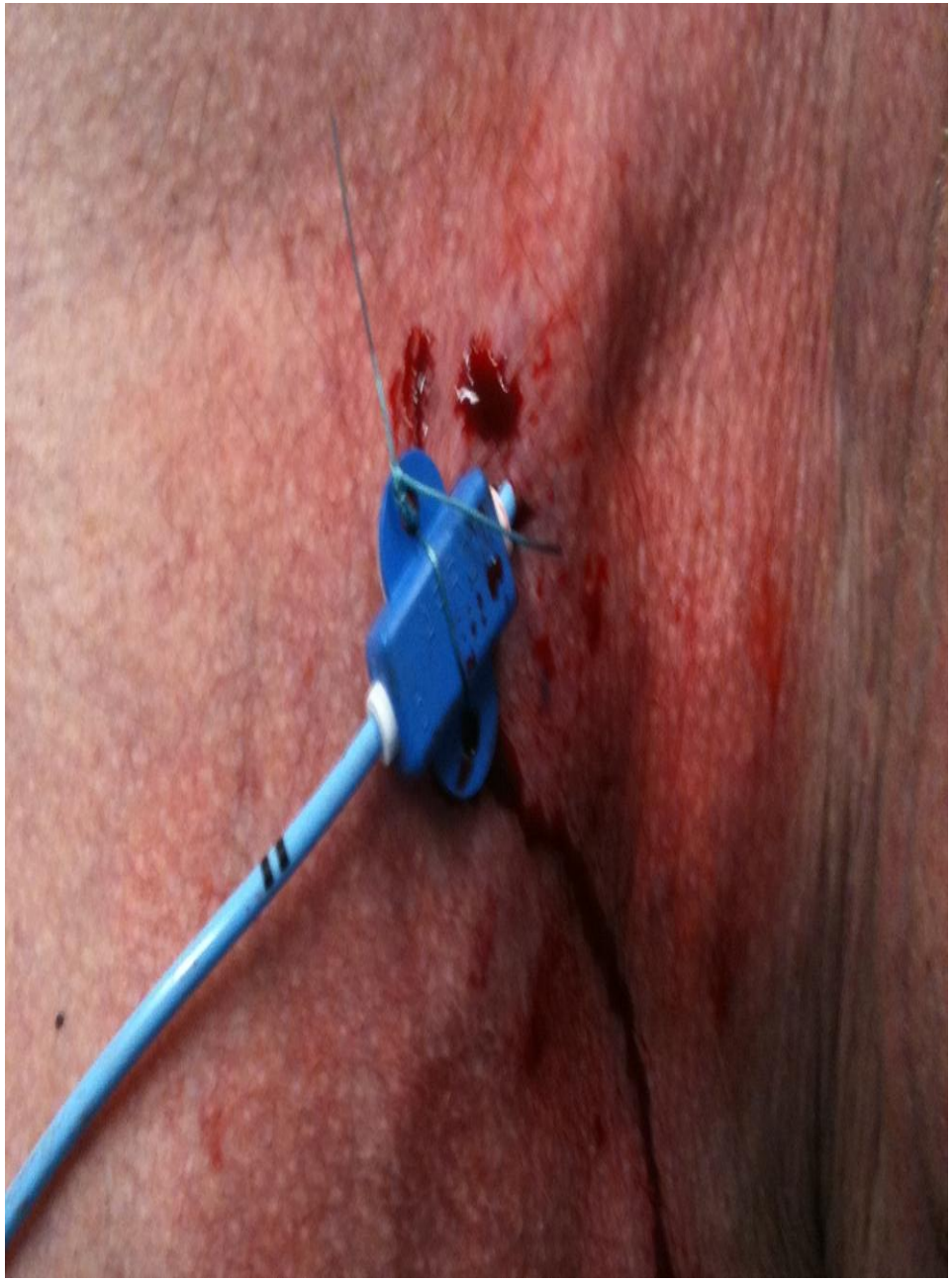
At the end of pregnancy, uterine blood flow is approximately 800 to 1000 mL/min, and after delivery of the placenta, the uterus must rapidly establish hemostasis. This process occurs via uterine involution, vasoconstriction, and localized thrombosis. If hemostatic events are not well orchestrated, excessive bleeding can result, often with disastrous consequences, as evidenced by the fact that postpartum hemorrhage is the leading cause of maternal mortality worldwide.[20] Given the increasing rate of cesarean delivery (approximately 30% of deliveries in the United States [US]) and the epidemic of maternal obesity, postpartum hemorrhage will continue to dominate maternal morbidity and mortality in the foreseeable future. Coagulopathy and transfusion rates range from 1% to 25% for first cesarean deliveries, and up to 15% to 67% for patients who have had multiple operative deliveries.[21] Factors associated with postpartum hemorrhage are multiple and include disorders associated with abnormal labor patterns, large or multiple fetuses, preeclampsia, lacerations, multiple gestation, history of antepartum or intrapartum hemorrhage, placental disorders such as placenta previa or placenta accreta, and general anesthesia.[22,23] Inherited and acquired bleeding disorders, as well as anticoagulation, contribute to postpartum hemorrhage.[24] Recurrence rates of bleeding are alarmingly high, occurring in approximately 15% for second and 22% for third and subsequent pregnancies.[25] Early and late postpartum hemorrhage (>500 mL and >1000 mL for vaginal and cesarean delivery) occur in 4% to 6% and 1% to 3% of pregnancies, respectively.[24] The early (primary) form occurs within 4 hours of delivery, and uterine atony is the cause in 75% to 90% of cases. Late (secondary) postpartum hemorrhage occurs between 24 hours and 6 weeks postpartum, and occurs in 1% to 3% of pregnancies.[26] Massive postpartum hemorrhage refers to blood

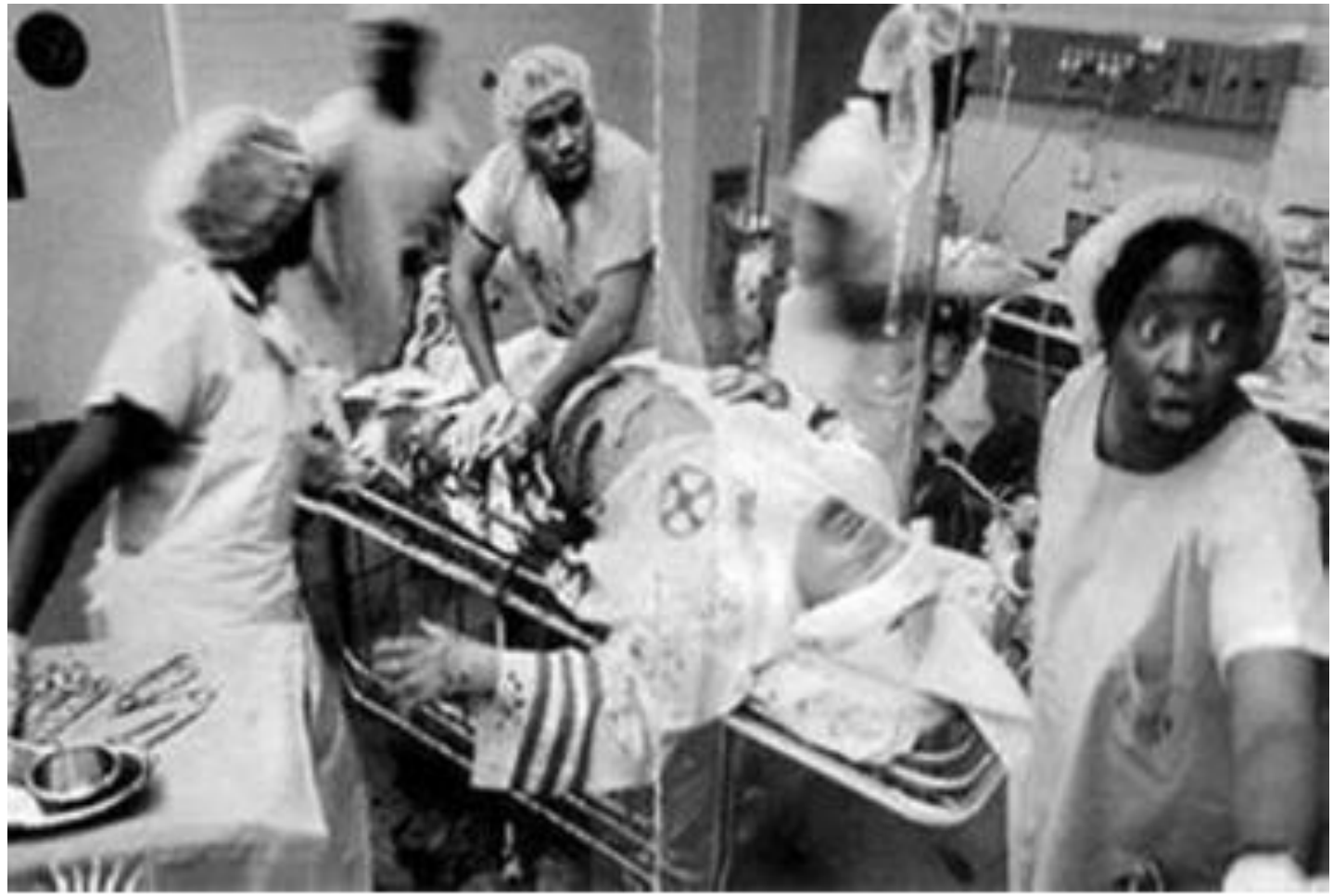


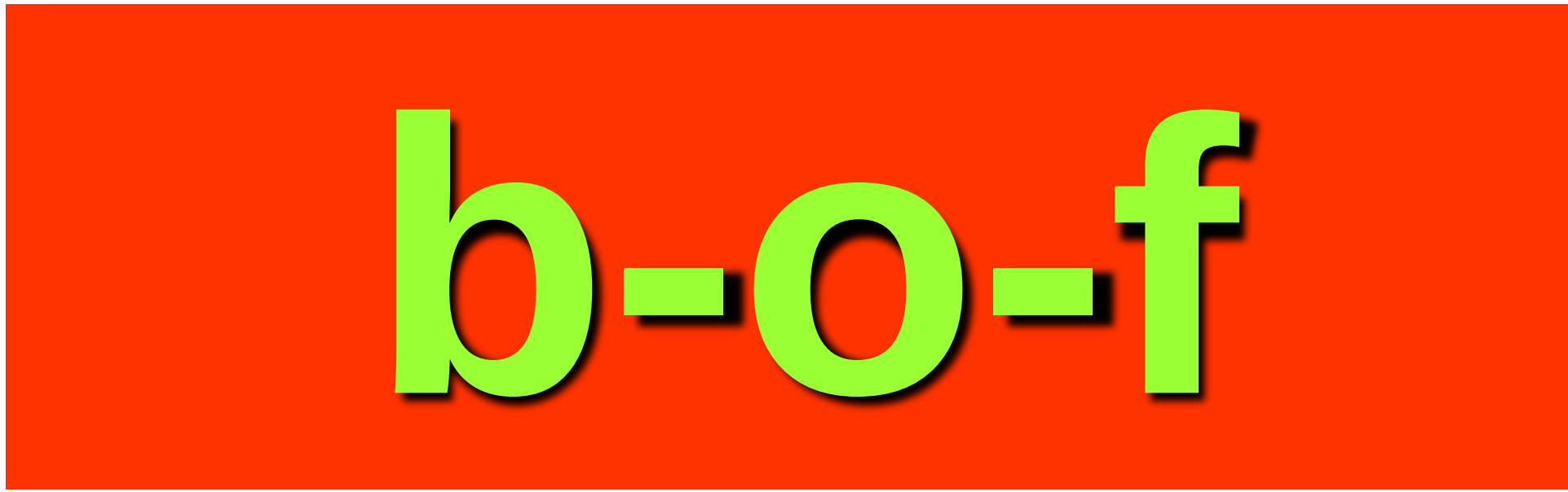
J Trauma 2008; 65:748-754.



ACoSS, Acute Coagulopathy of Sepsis-Shock ??






b-o-f


BLOOD
ON
FLOOR

- **¿Qué es una hemorragia grave y qué es una coagulopatía asociada?**
- **¿Qué origen tiene?**
- **¿Cómo la diagnosticamos?**
- **¿Cómo la tratamos y/o podriamos tratar?**

Fisiopatología de la Coagulopatía

- **Coagulopatía *"basal"***
- **Coagulopatía *"asociada"***
- **Coagulopatía *"derivada"***
- **Coagulopatía *"añadida"***

Fisiopatología de la Coagulopatía asociada al sangrado

- **Defecto en la firmeza del coágulo debido a la deficiencia de fibrinógeno y a la trombopenia**
- **Defecto en la estabilidad del coágulo debido a la hiperfibrinolisis y a la deficiencia de FXII**
- **Prolongación de la formación del coágulo debido a deficiencia de varios factores por consumo**

*Kozek-Langenecker S. Yearbook of Intensive care and Emergency Medicine 2007

es que tenemos
un problema!

Por qué es un problema?

- Poco tiempo para tomar decisiones
- Proceso dinámico
- Dificultad diagnóstica
- Dificultad en decidir la terapia más adecuada

Objetivos del tratamiento

Naturaleza multifactorial
de las alteraciones de la coagulación
en la hemorragia grave


The treatment of bleeding is
to stop the bleeding!

...donde estamos

Objetivos del tratamiento

- **Reemplazo del volumen sanguíneo intravascular**
- **Mantenimiento de la oxigenación tisular**
- **Control de la hemostasia**

“hematologic damage control”

“pyramid of therapy in coagulopathy”

Transfusion in trauma: why and how should we change our current practice?

Oliver M. Theusinger, Donat R. Spahn and Michael T. Ganter

Current Opinion in Anaesthesiology 2009, 22:305–312

Time for changing coagulation management in trauma-related massive bleeding

Dietmar Fries[a], Petra Innerhofer[b] and Wolfgang Schobersberger[c]

Current Opinion in Anaesthesiology 2009, 22:267–274

Holcomb *Critical Care* 2010, **14**:162
http://ccforum.com/content/14/3/162

CRITICAL CARE

COMMENTARY

Traditional transfusion practices are changing

John B Holcomb*

See related research by Schochl *et al.*, http://ccforum.com/content/14/2/R55

NEWSLET

April 2009 ▪ Volume 73 ▪ Number 4 Anesthesiologists: Physicia

Periopera
Med

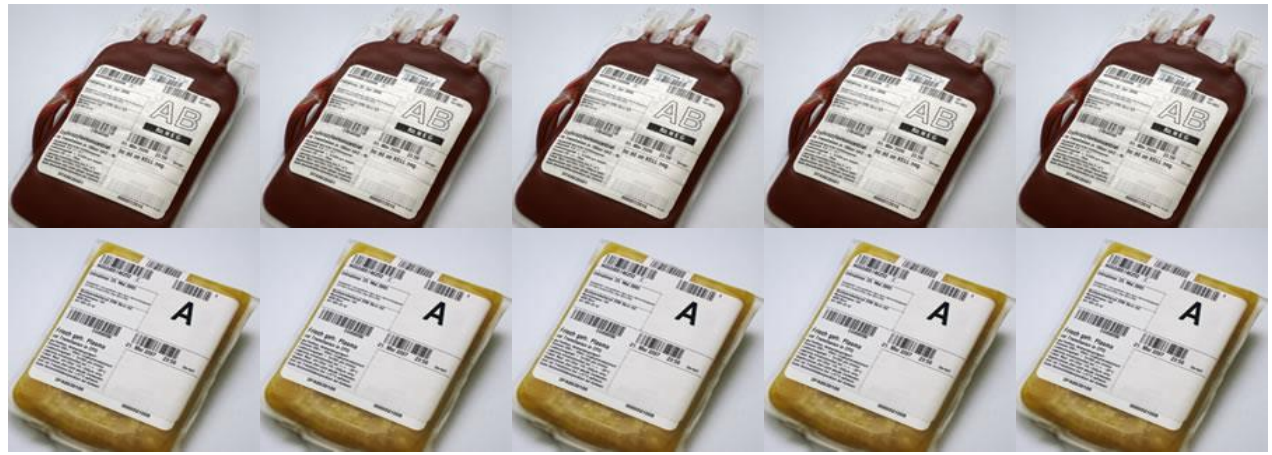
Re-Examining the Anesthe

American Society of Anesthesiologists

The Emerging Concept of Damage Control Resuscitation

Maureen McCunn, M.D., M.I.P.P., F.C.C.M.

Damage control resuscitation (also known as hemostatic resuscitation) supports 1:1:1 transfusion of packed red blood cells (prbcs) :FFP:platelets for patients with traumatic exsanguinating hemorrhage.



The Journal of TRAUMA® Injury, Infection, and Critical Care

J Trauma. 2008;65:272–278.

Review of Current Blood Transfusions Strategies in a Mature Level I Trauma Center: Were We Wrong for the Last 60 Years?

Juan C. Duchesne, MD, John P. Hunt, MD, MPH, Georgia Wahl, MD, NREMT-P, Alan B. Marr, MD, Yi-Zarn Wang, DDS, MD, Sharon E. Weintraub, MD, MPH, Mary J. O. Wright, MD, and Norman E. McSwain, Jr., MD

Holcomb *Critical Care* 2010, **14**:162
http://ccforum.com/content/14/3/162

CRITICAL CARE

COMMENTARY

Traditional transfusion practices are changing

John B Holcomb*

See related research by Schochl *et al.*, http://ccforum.com/content/14/2/R55

" Sería ideal transfundir sólo aquello que se necesita,...."

Fresh-Frozen Plasma and Platelet Transfusions Are Associated With Development of Acute Lung Injury in Critically Ill Medical Patients*

(CHEST 2007; 131:1308–1314)

Hasrat Khan, MD; Jon Belsher, MD; Murat Yilmaz, MD; Bekele Afessa, MD, FCCP; Jeffrey L. Winters, MD; S. Breanndan Moore, MD; Rolf D. Hubmayr, MD, FCCP; and Ognjen Gajic, MD, FCCP

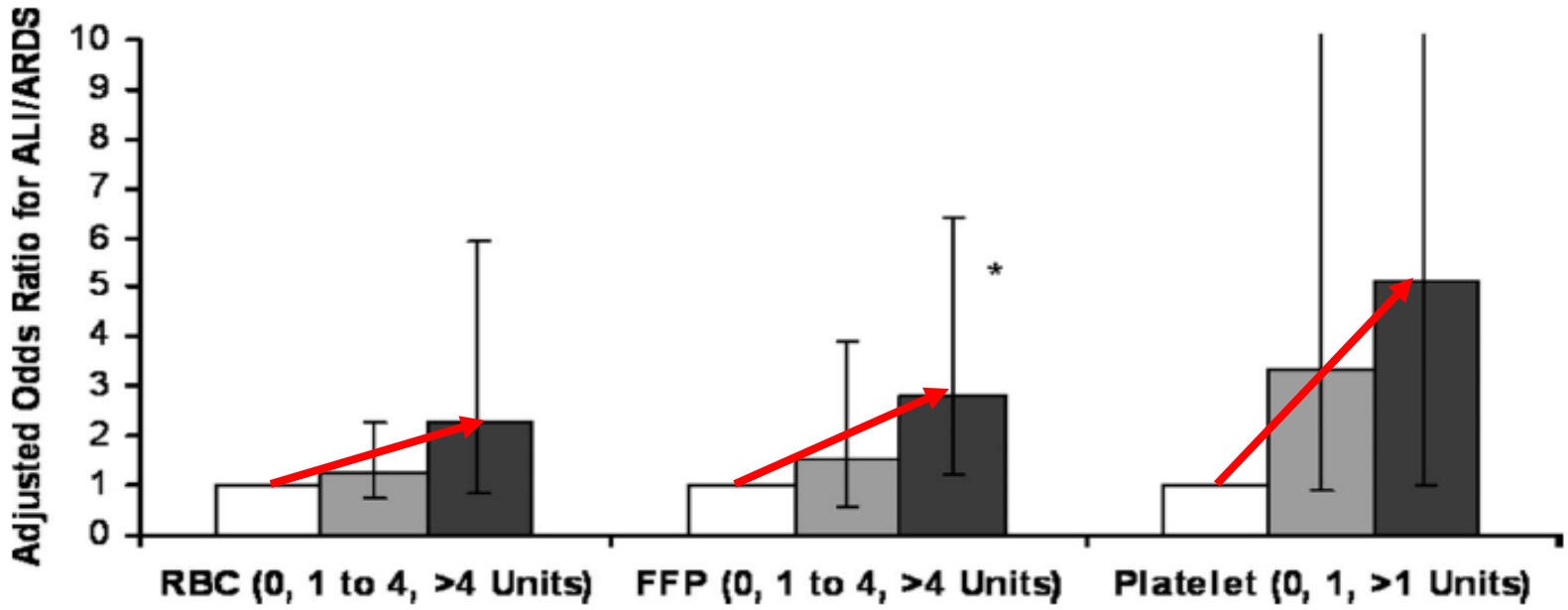


FIGURE 2. Adjusted ORs for the development of ALI/ARDS as a function of the number of individual blood product transfusions. * = $p < 0.05$.


puede matar!

Research

Open Access

Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: experience in a large tertiary hospital

David Bruce and Tim JC Nokes

Department of Haematology, Derriford Hospital, Brest Road, Plymouth, Devon PL6 8DH, UK

Corresponding author: Tim JC Nokes, tim.nokes@phnt.swest.nhs.uk

Received: 7 Apr 2008 Revisions requested: 9 May 2008 Revisions received: 1 Jul 2008 Accepted: 15 Aug 2008 Published: 15 Aug 2008

Critical Care 2008, **12**:R105 (doi:10.1186/cc6987)
This article is online at: http://ccforum.com/content/12/4/R105

In the future, it may be possible to use coagulation factor concentrates like fibrinogen, factor XIII and PCC as a substitute for fresh frozen plasma (FFP) to treat severe bleeding in a variety of peri-operative settings.

The future is now !

II Jornadas Nacionales sobre Alternativas a las Transfusiones Sanguíneas

HOSPITALES UNIVERSITARIOS
VIRGEN DEL ROCÍO. SEVILLA.

5 Y6 DE MARZO 2009.

GUÍAS DE USO DE HEMODERIVADOS Y ALTERNATIVAS TRANSFUSIONALES.

ÍNDICE

EVIDENCIA CIENTÍFICA

en

Complejos de protrombina

MANUAL DE ACTUACIÓN

OMC
ORGANIZACIÓN MÉDICA COLEGIAL DE ESPAÑA

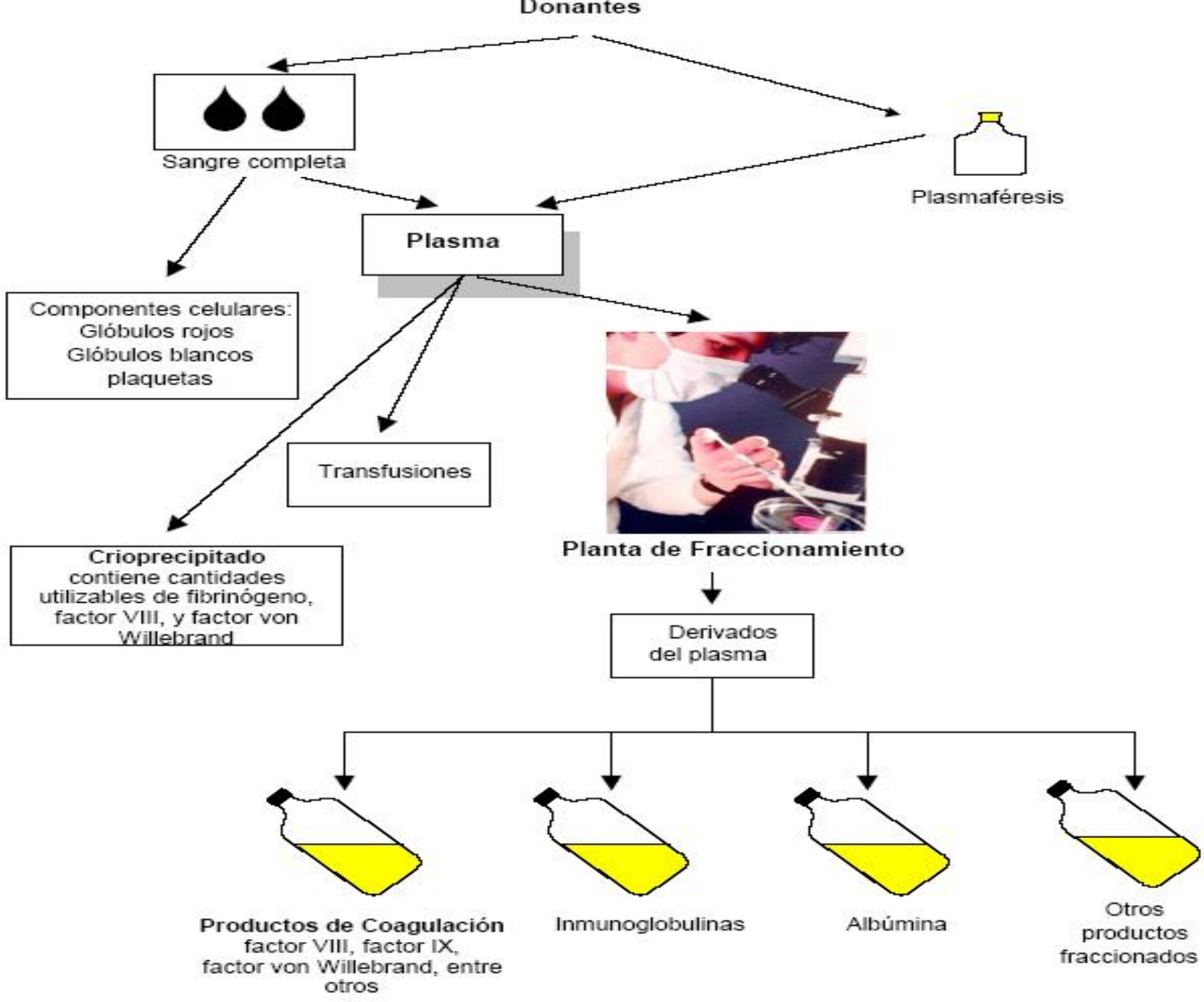
GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y POLITICA SOCIAL

No, gracias

vs

Sí, por favor

“Factors de coagulació exògens”


Donantes
Sangre completa
Plasmaféresis
Plasma
Componentes celulares:
Glóbulos rojos
Glóbulos blancos
plaquetas
Transfusiones
Crioprecipitado
contiene cantidades utilizables de fibrinógeno, factor VIII, y factor von Willebrand
Planta de Fraccionamiento
Derivados del plasma
Productos de Coagulación
factor VIII, factor IX, factor von Willebrand, entre otros
Inmunoglobulinas
Albúmina
Otros productos fraccionados

Derivados plasmáticos

Acción oncótica:

- Albúmina
- Fracción proteica plasmática

Acción hemostática:

- Concentrados de Fc VIII
- Concentrados de Fc von Willebrand
- Concentrados de Fibrinógeno
- Complejo protombínico
- Concentrados de Fc VII
- Concentrados de Fc XIII
- Antitrombina III
- Concentrados de Proteina C

Acción defensiva:

- Inmunoglobulinas intramusculares/envovenosas (Anti-D)

Otros:

- Fibronectina
- Concentrados inhibidor C1 esterasa
- Alfa 1- Anti Tripsina


rFVIIa

- **La administración profiláctica de FVIIa no se recomienda actualmente (A)**

- **El FVIIa no es una primera línea de tratamiento y sólo será efectivo una vez que se controle el origen del sangrado (E)**

- **Atención sobre los factores que alteran la coagulación (hipoTª, acidosis, hipoCa, Htco.) (E)**

- **Ante la persistencia del sangrado se puede utilizar FVIIa (E)**

Crit. Care 2006, 10:R120

- **50-100 U/Kg**
- **10-120 microgramos/Kg**

- **La actividad se reduce en un 20% con Tª de 33ºC**
- **La actividad se reduce 90% con pH de 7.0 pH > 7,2)**
- **Fibrinógeno > 0.5 gr**
- **Plaquetas > 50000**
- **Hto > 25%**

Uphill Battle

REVIEW

Efficacy and Safety of Recombinant Activated Factor VII to Control Bleeding in Nonhemophiliac Patients: A Review of 17 Randomized Controlled Trials

Jean-François Hardy, MD, FRCPC, Sylvain Bélisle, MD, FRCPC, and Philippe Van der Linden, MD, PhD

Department of Anesthesiology, University of Montreal, Université Libre de Bruxelles, Montreal, Quebec, Canada; Department of Anesthesiology, CHU Brugmann, Université Libre de Bruxelles, Belgium, Germany

We reassess all published randomized controlled trials that have evaluated the hemostatic efficacy or safety of recombinant activated factor VII (rFVIIa), or both, in nonhemophiliac patients. Seventeen trials published in 16 articles dealt either with the prophylactic (nine trials) or the therapeutic (eight trials) use of rFVIIa to prevent or to treat excessive bleeding. At present, the role of rFVIIa to prevent or to control bleeding and reduce transfusions in various patient populations remains unclear. In addition, the safety of rFVIIa remains a concern. Consequently, we conclude that the generalized use of rFVIIa to prevent or to control bleeding in nonhemophiliac patients can not be recommended.

(Ann Thorac Surg 2008;86:1038–48)

"…rFVIIa use should be restricted to clinical trials
Stanworth et al.
Cochrane Database Syst Rev 2007

the generalized use of rFVIIa to prevent or to control bleeding in nonhemophiliac patients can not be recommended

Hardy JF et al. Ann Thoracic 2009

There is little evidence to support routine use of rFVIIa for patients with massive bleeding based on the results of the randomized trials performed

Johanson P. Vox Sang. 2008

Factor VII activado

Se sugiere que el uso de rFVIIa sea considerado en pacientes con trauma cerrado en los que persiste el sangrado a pesar de los intentos estandard para controlar la hemorragia y el uso adecuado de hemoderivados.

La dosis inicial sugerida es de 200 µg/kg seguidos por dos dosis de 100 µg/kg administrados 1 y 3 horas despues de la primera dosis.

Grado 2C

USO del FACTOR VII

Anexo 5.- Utilización del Factor VII

El uso del factor VII en la mayoría de los enfermos sería contemplado como uso compasivo y nunca podría suplantar el correcto manejo de la hemorragia y la administración de otros componentes sanguíneos. A la vista de la actual evidencia científica se contemplan tres grupos de pacientes según el grado de evidencia científica:
Mayor beneficio:

- Hemorragia intracraneal no traumática en las primeras 4 horas.
- Hemorragias en politraumatizados con trauma cerrado.
- Hemorragias asociadas a Cirugía Cardíaca
- Hemorragia postparto refractaria

Con menor beneficio:

- Hemorragia refractaria en Neurocirugía y transplante renal
- Trombocitopenia refractaria
- Bernad-Soulier
- CID
- Hemorragias de otras etiologías refractarias

No estaría justificado su uso

- Cirróticos o sometidos a trasplante o cirugía hepática
- Profilaxis de sangrado quirúrgico
- Complicaciones del trasplante de células progenitoras hematopoyéticas.

Por el coste de dicho fármaco y la evidencia disponible el grupo elabora un indicador de uso de dicho fármaco.

Se acuerda contemplar su uso en el protocolo a partir de la administración del 3º paquete, a dosis de 100 micro/kg, hasta en tres dosis, con un periodo de evaluación de una hora.

Se deben tener en cuenta las condiciones a mejorar para aumentar efectividad:

- Hematocrito >24%
- Fibrinógeno de 100 mg/dl
- Plaquetas >50.000
- Ph >7,20

También se deben tener en cuenta la imposibilidad de corrección de estos parámetros como criterios de futilidad del tratamiento.

Anexo 6.- Utilización de antifibrinolíticos

Ante los últimos datos de la bibliografía y la suspensión cautelar de la comercialización de algunos de estos productos, desde el Grupo de Trabajo de Transfusión Masiva se decide no incorporarlo como recomendación, dejando su uso como discrecional por parte de los profesionales.

Factor VII

- El uso del factor VII en la mayoría de los enfermos sería contemplado como uso compasivo y nunca podría suplantar el correcto manejo de la hemorragia y la administración de otros componentes sanguíneos.
- A la vista de la actual evidencia científica se contemplan tres grupos de pacientes según el grado de evidencia científica:
- Mayor beneficio:
  - Hemorragia intracraneal no traumática en las primeras 4 horas.
  - Hemorragias en politraumatizados con trauma cerrado.
  - Hemorragias asociadas a Cirugía Cardíaca
  - Hemorragia postparto refractaria
- Con menor beneficio:
  - Hemorragia refractaria en Neurocirugía y transplante renal
  - Trombocitopenia refractaria
  - Bernad-Soulier
  - CID
  - Hemorragías de otras etiologías refractarias
- No estaría justificado su uso
  - Cirróticos o sometidos a trasplante o cirugía hepática
  - Profilaxis de sangrado quirúrgico
  - Complicaciones del trasplante de células progenitoras hematopoyéticas.

Hospital Universitario La Paz

SaludMadrid

Comunidad de Madrid

Factor VII

- **Por el coste de dicho fármaco y la evidencia disponible el grupo elabora un indicador de uso de dicho fármaco.**
- **Se acuerda contemplar su uso en el protocolo a partir de la administración del 3º paquete, a dosis de 100 micro/kg, hasta en tres dosis, con un periodo de evaluación de una hora.**
- **Se deben tener en cuenta las condiciones a mejorar para aumentar efectividad:**
  - **Hematocrito >24%**
  - **Fibrinógeno de 100 mg/dl**
  - **Plaquetas >50.000**
  - **Ph >7,20**
- **También se deben tener en cuenta la imposibilidad de corrección de estos parámetros como criterios de futilidad del tratamiento.**

World Prout Assembly

Economy of the People, For the People and By the People!
Put Economic Power in the Hands of the People!

Moralists of the world - unite!

Dangerous remedy: Military doctors in Iraq say that Factor VII saves wounded soldiers, but other doctors and medical research suggest that it can cause fatal clots

Medevac crew members carry Pfc. Caleb A. Lufkin to the Army's 10th Combat Support

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 4, 2010 VOL. 363 NO. 19

Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

CONCLUSIONS

In a large and comprehensive cohort of persons in placebo-controlled trials of rFVIIa, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events, especially among the elderly. (Funded by Novo Nordisk.)


CCP

paciente anticoagulado

paciente traumatizado

Estudio *"Prothrombin Complex Concentratet for oral anticoagulant reversal in neurological emergencies*

Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies

M. CARTMILL*, G. DOLAN†, J. L. BYRNE† & P. O. BYRNE

*Department of Neurosurgery, Queen's Medical Centre, University Hospital, Nottingham and †Department of Haematology, City Hospital, Nottingham, UK

Abstract

The incidence of spontaneous intracranial haemorrhage has increased markedly in line with the increased use of oral anticoagulant agents. Recent guidelines for reversal of this acquired coagulation defect in an emergency have been established, but they are not adhered to in all centres. Our unit is referred between 20 and 60 patients per year (1994–1999) who are anticoagulated and require urgent neurosurgical intervention. In order to investigate this, we performed a prospective study using prothrombin complex concentrate (PCC). PCC was given to the first six patients with intracranial haemorrhage admitted to the neurosurgical unit requiring urgent correction of anticoagulation (Group 1) and compared with patients receiving standard treatment with fresh frozen plasma and vitamin K (Group 2). Mean International Normalised Ratios of Group 1 were 4.86 pretreatment and 1.32 posttreatment, and of Group 2 were 5.32 and 2.30, respectively. Results for complete reversal and reversal time were significant for PCC with $p<0.001$. We recommend PCC for rapid and effective reversal of warfarin in life-threatening neurosurgical emergencies.

Key words: *Neurosurgical emergencies, oral anticoagulant reversal, prothrombin complex concentrate, warfarin.*

---

using prothrombin complex concentrate (PCC). PCC was given to the first six patients with intracranial haemorrhage admitted to the neurosurgical unit requiring urgent correction of anticoagulation (Group 1) and compared with patients receiving standard treatment with fresh frozen plasma and vitamin K (Group 2). Mean International Normalised Ratios of Group 1 were 4.86 pretreatment and 1.32 posttreatment, and of Group 2 were 5.32 and 2.30, respectively. Results for complete reversal and reversal time were significant for PCC with $p<0.001$. We recommend PCC for rapid and effective reversal of warfarin in life-threatening neurosurgical emergencies.

Cartmill M, Dolan JL et al. "Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergency". *Br. J. Neurosurg* 2000; 14:458-61

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

Intracerebral Hemorrhage Associated With Oral Anticoagulant Therapy: Current Practices and Unresolved Questions

Thorsten Steiner, Jonathan Rosand and Michael Diringer

Stroke 2006;37;256-262; originally published online Dec 8, 2005;

Background and Purpose—Life-threatening intracranial hemorrhage, predominantly intracerebral hemorrhage (ICH), is the most serious complication of oral anticoagulant therapy (OAT), with mortality in excess of 50%. Early intervention focuses on rapid correction of coagulopathy in order to prevent continued bleeding.

Summary of Review—This article reviews the epidemiology of OAT-associated ICH (OAT-ICH), and current treatment options, with the aim of providing a framework for future studies of unresolved questions. A number of acute treatments are available, but all have a significant risk of inducing thrombosis and other side effects, and vary in their rapidity of effect: vitamin K (very slow response time), fresh frozen plasma (slow response time, large volume of fluid required, transfusion-related acute lung injury), prothrombin complex concentrates, and recombinant activated factor VII. Current practice is to administer a combination of vitamin K and either fresh frozen plasma or prothrombin complex concentrates; the occasional use of recombinant activated factor VII has been reported. No prospective study has addressed the efficacy of, or outcomes from, the use of these practices.

Conclusions—Current management of OAT-ICH is varied and not based on evidence from randomized controlled trials. Well-designed clinical trials are essential if we are to identify the effective acute treatments for OAT-ICH that are urgently needed. (*Stroke*. 2006;37:256-262.)

Key Words: etiology ■ intracerebral hemorrhage ■ oral anticoagulant agents ■ therapy ■ warfarin

P233

Prothrombin complex concentrate versus fresh frozen plasma in patients on oral anticoagulant therapy undergoing cardiac surgery: a randomized study

R Demeyere[1], J Arnout[1], P Strengers[2]
[1]*UZ Gasthuisberg, Leuven, Belgium;* [2]*CAF-DCF, Brussels, Belgium*
Critical Care 2006, 10(Suppl 1):P233 (doi: 10.1186/cc4580)

Introduction To reverse oral anticoagulant (OAC) therapy, a number of treatment modalities is available. Fresh frozen plasma (FFP) is effective and is currently used for coagulation factor replacement, carrying a risk of volume overload, transmission of infective agents and being time consuming. Variable and frequently low potency of clotting factors results in minor haemostatic effects compared with prothrombin complex concentrates (PCC), which are considered very effective and safe. PCC PPSB-SD® has constant, highly concentrated levels of factors II, VII, IX and X compared with FFP. We studied the efficacy of the intraoperative administration of PCC and FFP in patients on OAC therapy undergoing heart surgery with cardiopulmonary bypass (CPB).

Method After Ethical Committee approval and informed consent, 40 patients (P group, $n = 20$; FFP group, $n = 20$) with a preoperative INR ≥2.1 were studied. PCC was supplied as 500 IU factor IX (20 ml) vials. The dose was calculated on the basis of body weight, the initial INR and the target INR aiming at an INR of 1.5 after protamine. One-half of this dose was administered before the start of CPB. After weaning from CPB and protamine, the second half-dose was given in order to reach a postoperative INR ≤1.5. In case the INR value was still too high a further dose of PPSB was given. In the FFP group, each patient received 4 units: one-half of this dose was given before CPB and the other half after CPB. Additional FFP was given until the INR had reached a satisfactory level. In cases of poor response and/or if there was a danger of volume overload, PCC was given. A portable coagulation monitor (CoaguChek) was used for INR measurements. Blood sampling was preoperative (T−1), preincision (T0), preadministration and postadministration before CPB (T1,T2), during CPB at 15 and 45 min (T3, T4), at the end of CPB (T5), after protamine administration (T6), and 15 and 60 min and 3 and 16 hours post-CB (T7–T10).

Analyses performed were: INR, PT, Hct, ACT, aPTT, ad factors II, VII, IX, X and FV. The amount of blood lost in the chest tube drainage and the blood products administered was also registered. Statistical evaluations were performed using the Student t test, repeated-measurements ANOVA and Fisher's exact test.

Results The P group was more successful in reaching the target INR. In the FFP group 16/20 (80%) patients received an additional dose of PPSB vs 6/20 (30%) in the PCC group. The INR with PCC treatment dropped sooner below 1.5 than that in the FFP group. More patients in this group reached the target INR in the first hour after ending CPB (T7, $P < 0.007$). We found a significant difference between groups in factor II ($P = 0.023$) and factor X ($P = 0.008$) levels over time.

Conclusion The results of our study support the use of PCC in patients on OAC therapy facing semi-urgent or urgent cardiac surgery. Treatment with PCC reverses anticoagulation safely, more rapidly and more effectively than FFP.

Comparación PFC vs CCP

	FFP	PCC
Volumen	Grande	Pequeño
Disponibilidad	Mínimo 30 min	Inmediata
Velocidad de administración	Lenta	Rápida
Inactivación Viral	(1 solo paso)	(2 pasos)
Grupo sanguíneo específico	si	No
Trombogenicidad	No	No

CCP y anti-coagulantes orales

- **INR > 5.0 - 30 UI / Kg**
- **INR < 5.0 - 15 UI / Kg**
  - (Vitamina K - terapeutica adjuvante)

- **El Brithish Committee for Standarts in Haematology, Transfusion task force y el American College of Chest fisicians, recomiendan la utilización de CCP como primera elección para la urgente reversión de ACO**

Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature

Cindy A. Leissinger,[1]* Philip M. Blatt,[2] W. Keith Hoots,[3] and Bruce Ewenstein[4]

Over-anticoagulation is a common problem with warfarin therapy and can lead to major or life-threatening bleeding. The goal of urgent warfarin reversal is to elevate or replace vitamin K-dependent clotting factors. In the United States, fresh frozen plasma (FFP) is considered the standard of care for warfarin reversal. Prothrombin complex concentrates (PCCs) offer an alternative to FFP for rapidly replacing deficient clotting factors and correcting the international normalized ratio (INR). However, few prospective clinical trials have been conducted to evaluate the effectiveness of these concentrates relative to other treatment modalities. A review of the published literature over the last 30 years found that PCCs offer a rapid and specific method for replacing vitamin K-dependent clotting factors and restoring normal hemostasis in the context of overcoagulation. In those studies in which PCCs were compared with FFP, PCCs were found more effective in shortening the time to INR correction and were associated with a low risk of thrombotic adverse events. Evidence-based treatment guidelines are needed to optimize the use of PCCs for warfarin reversal. Am. J. Hematol. 83:137–143, 2008.

CONCLUSION

Major haemorrhage in a patient on warfarin is most appropriately managed by rapid and complete reversal with a PCC and IV vitamin K, regardless of the reason for anticoagulation. This approach ensures that the acute effect of haemorrhage is minimised. Minor bleeding or asymptomatic high INR can be safely treated by dose omission or oral vitamin K (or IV vitamin K in selected cases), which results in partial reversal, with the aim of restoring the INR to the target value for the individual.

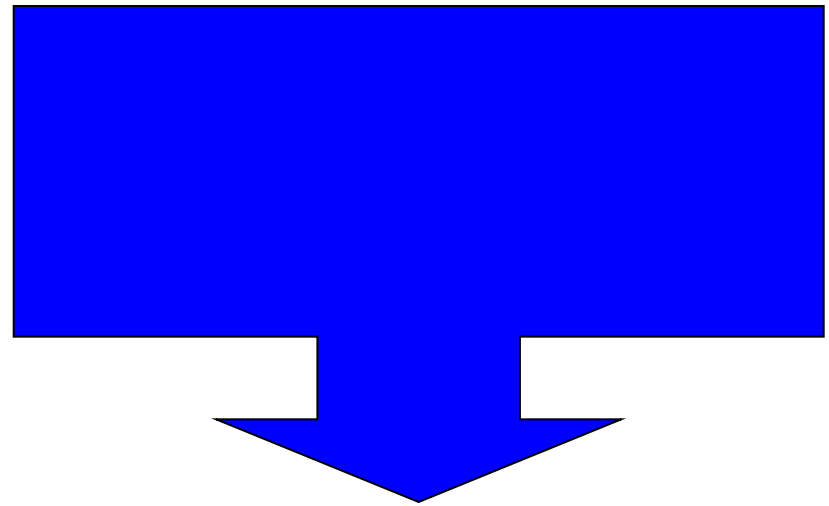
IN FOCUS

Urgent reversal of warfarin with prothrombin complex concentrate

M. W. LANKIEWICZ,* J. HAYS,† K. D. FRIEDMAN,* G. TINKOFF‡ and P. M. BLATT§

The Southeastern BloodCenter of Wisconsin, Wisconsin, WI; Departments of †Transfusion Service, ‡Trauma Service, and §Internal Medicine and Pathology, Christiana Care Health Systems, Newark, DE, USA

Los CCP elevan el pico de trombina más que el rFVII, y esta elevación tiene efecto sobre el TAFI, disminuyendo su activación



Disminución de fibrinolisis

Complejo Protrombínico

Se recomienda el uso de complejo protrombínico de acuerdo con las intrucciones del fabricante sólo en casos de emergencia para revertir los efectos de anticoagulantes orales (vitamina K dependientes)

Grado 1C

Complejo Protrombínico

Recommendation 29

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

BJA Advance Access published January 24, 2009

British Journal of Anaesthesia Page 1 of 10
doi:10.1093/bja/aen391

BJA

Prothrombin complex concentrate *vs* fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model

G. Dickneite[†]* and I. Pragst[†]

Department of Pharmacology and Toxicology, CSL Behring GmbH, Marburg, Germany
**Corresponding author. E-mail: gerhard.dickneite@cslbehring.com*

Conclusions. PCC was effective in correcting dilutional coagulopathy and controlling bleeding in an *in vivo* large-animal trauma model. In light of its suitability for more rapid administration than FFP, PCC merits further investigation as a therapy for dilutional coagulopathy in trauma and surgery.

Br J Anaesth 2009

Evidence for use of PCC in aquired factor deficiency

British Journal of Anaesthesia 97 (4): 460–7 (2006)
doi:10.1093/bja/ael191 Advance Access publication August 1, 2006

BJA

Efficacy of fibrinogen and prothrombin complex concentrate used to reverse dilutional coagulopathy—a porcine model

D. Fries[1]*, T. Haas[3], A. Klingler[3], W. Streif[4], G. Klima[5], J. Martini[1], H. Wagner-Berger[2] and P. Innerhofer[2]

20 pigs – dilutional coagulopathy – administration of fibrinogen and PCC

Results. During haemodilution, substitution of fibrinogen and PCC causes an enhancement of coagulation and final clot strength.

Evidence for use of PCC in aquired factor deficiency

British Journal of Anaesthesia **102** (3): 345–54 (2009)
doi:10.1093/bja/aen391 Advance Access publication January 24, 2009

BJA

Prothrombin complex concentrate *vs* fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model

G. Dickneite[†]* and I. Pragst[†]

47 pigs – dilutional coagulopathy – PCC vs. FFP

Results. Haemodilution markedly prolonged prothrombin time and reduced peak thrombin generation. PCC, but not FFP, fully reversed those effects.

Evidence for use of PCC in aquired factor deficiency

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Prothrombin complex concentrate (Beriplex P/N) for control of bleeding after kidney trauma in a rabbit dilutional coagulopathy model ☆

Ingo Pragst, Franz Kaspereit, Bärbel Dörr, Gerhard Dickneite *

19 rabbits – dilutional coagulopathy – PCC vs. rFVIIa

Results. In an animal model of dilutional coagulopathy and kidney trauma, PCC accelerated hemostasis and diminished blood loss compared with rFVIIa monotherapy

Evidence for use of PCC in aquired

Research

Open Access

Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: experience in a large tertiary hospital

David Bruce and Tim JC Nokes

Department of Haematology, Derriford Hospital, Brest Road, Plymouth, Devon PL6 8DH, UK

Corresponding author: Tim JC Nokes, tim.nokes@phnt.swest.nhs.uk

Received: 7 Apr 2008 Revisions requested: 9 May 2008 Revisions received: 1 Jul 2008 Accepted: 15 Aug 2008 Published: 15 Aug 2008

Critical Care 2008, **12**:R105 (doi:10.1186/cc6987)

Retrospective analysis of 30 patients receiving PCC
(w or w/o oral anticoagulants reversal)

Conclusion. The use of PCC in bleeding patients without hereditary or anticoagulation-related coagulopathy is novel, and further investigation is warrantedwarranted. In the future, it may be possible to use PCC as a substitute for fresh frozen plasma in this setting

fibrinógeno

- **La deficiencia de fibrinógeno es por**
  - **Incremento de la pérdida y por consumo**
  - **Hiperfibrinolisis**
    - **Trauma severo**
    - **Hemorragia postparto**
  - **El usos de expansores plasmáticos inducen una disfunción**

Fries et al. Br J Anaest 95(2):172-7 (2005)
Fenger-Eriksen et al. Br J Anaest 94(3)324-29 (2005)
Rahe Meyer et al Br J Anaesth. 2009 Jun;102(6):785-92
Haas T et al Anesth Analg 2008 Apr; 106(4):1078-86
Hiippala ST et al., Anesth Analg. 1995 Aug;81(2):360-5

- 3 retrospective clinical studies, total 142 patients
- Acquired hypofibrinogenaemia and bleeding
- Fibrinogen concentrate substitution:
  - Improvement of APTT, PT, fibrinogen levels
  - Reduced bleeding
  - Reduced transfusion requirements

Weinkove et al Transfus Med. 2008 Jun;18(3):151-7.
Fenger-Eriksen C at al, Br J Anaesth 2008;101(6):769-73
Danes AF, Cuenca LG, Bueno SR, et al. Vox Sang 2008;94(3):221-6

- Combat-related trauma
  - Increased fibrinogen:RBC ratio improved survival primarily by decreasing death from hemorrhage.

Stinger HK et al. J Trauma 2008;64(2 Suppl):S79-85;

Conclusiones

- **La deficiencia de fibrinógeno ocurre precozmente en el sangrado masivo**
- **El aporte de fibrinógeno**
  - **Aumenta la firmeza del coágulo**
  - **Reduce el sangrado**
  - **Reduce os requerimientos transfusionales**
- **Su administración debería estar guiada**

- Br J Anaesth. 2006 Oct;97(4):460-7. Epub 2006 Aug 1.Efficacy of fibrinogen and prothrombin complex concentrate used to reversedilutional coagulopathy--a porcine model.Fries D, Haas T, Klingler A, Streif W, Klima G, Martini J, Wagner-Berger H,Innerhofer P.
- Anesth Analg. 2006 Apr;102(4):1194-200.Fibrinogen concentrate reverses dilutional coagulopathy induced in vitro bysaline but not by hydroxyethyl starch 6%.De Lorenzo C, Calatzis A, Welsch U, Heindl B.
- Anesth Analg. 2006 Feb;102(2):347-51.The effect of fibrinogen substitution on reversal of dilutional coagulopathy: an in vitro model.Fries D, Innerhofer P, Reif C, Streif W, Klingler A, Schobersberger W,Velik-Salchner C, Friesenecker B.
- Br J Anaesth. 2005 Aug;95(2):172-7. Epub 2005 May 27.Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model.Fries D, Krismer A, Klingler A, Streif W, Klima G, Wenzel V, Haas T, InnerhoferP.

- **Br J Anaesth. 2008 Dec;101(6):769-73. Epub 2008 Sep 25.Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations.Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sørensen B.**
- **Transfus Med. 2008 Jun;18(3):151-7.Fibrinogen concentrate for acquired hypofibrinogenaemic states.Weinkove R, Rangarajan S.**
- **Vox Sang. 2008 Apr;94(3):221-6. Epub 2008 Jan 2.Efficacy and tolerability of human fibrinogen concentrate administration topatients with acquired fibrinogen deficiency and active or in high-risk severebleeding.Danés AF, Cuenca LG, Bueno SR, Mendarte Barrenechea L, Ronsano JB.**
- **Anesth Analg. 2007 Oct;105(4):905-17, table of contents.Hemostatic changes after crystalloid or colloid fluid administration during majororthopedic surgery: the role of fibrinogen administration.Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P.**
- **Haematologica. 2007 Jun;92(6):846-9.Cryoprecipitate versus commercial fibrinogen concentrate in patients whooccasionally require a therapeutic supply of fibrinogen: risk comparison in thecase of an emerging transfusion-transmitted infection.Pereira A.**
- **J Thromb Haemost. 2007 May;5(5):1019-25.The effect of fibrinogen concentrate on thrombocytopenia.Velik-Salchner C, Haas T, Innerhofer P, Streif W, Nussbaumer W, Klingler A, KlimaG, Martinowitz U, Fries D.**

British Journal of Anaesthesia 94 (3): 324–9 (2005)
doi:10.1093/bja/aei052 Advance Access publication December 17, 2004

BJA

Thrombelastographic whole blood clot formation after *ex vivo* addition of plasma substitutes: improvements of the induced coagulopathy with fibrinogen concentrate

C. Fenger-Eriksen[1,2], E. Anker-Møller[1], J. Heslop[1], J. Ingerslev[2]* and B. Sørensen[2]

Fibrinogen Concentrate Reverses Dilutional Coagulopathy Induced *In Vitro* by Saline but Not by Hydroxyethyl Starch 6%

Claudia De Lorenzo, MD, Andreas Calatzis, MD, Ulrich Welsch, PhD, and Bernhard Heindl, PhD

Department of Anesthesiology, Department of Hemostaseology and Transfusion Medicine, Department of Anatomy, Ludwig Maximilians University, Munich, Germany

Anesth Analg 2006;102:1194–1200

Cardiovascular Anesthesiology
Section Editor: Charles W. Hogue, Jr.

Cardiovascular and Thoracic Education
Section Editor: Martin J. London

Hemostasis and Transfusion Medicine
Section Editor: Jerrold H. Levy

Hemostatic Changes After Crystalloid or Colloid Fluid Administration During Major Orthopedic Surgery: The Role of Fibrinogen Administration

(Anesth Analg 2007;105:905–17)

Fibrinógeno

Se recomienda el tratamiento con concentrado de fibrinógeno o crioprecipitados en casos de hemorragia acompañada de niveles de fibrinógeno inferior a 1 g/l. Se sugiere una dosis inicial de fibrinógeno de 3-4 gr o 50 mg/kg de crioprecipitados, equivalente a 15-20 unidades en un adulto de 70 kg. La repetición de la dosis debe realizarse guiada por la valoración de los niveles posteriores de fibrinógeno.

Grado 1C

Fibrinógeno

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 1.5-2.0 g/l. (Grade 1C) We suggest an initial fibrinogen concentrate dose of 3-4 g or 50 mg/kg of cryoprecipitate, which is approximately equivalent to 15-20 units in a 70 kg adult. Repeat doses may be guided by thrombelastometric monitoring and laboratory assessment of fibrinogen levels. (Grade 2C).

British Journal of Anaesthesia 105 (2): 116–21 (2010)
doi:10.1093/bja/aeq161

BJA

Role of fibrinogen in trauma-induced coagulopathy

D. Fries[1]* and W. Z. Martini[2]

[1] Department of General and Surgical Critical Care Medicine, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria
[2] United States Army Institute of Surgical Research, Fort Sam Houston, TX, USA

* Corresponding author. E-mail: dietmar.fries@i-med.ac.at

Key points

- Fibrinogen levels decrease at an early stage in severe haemorrhage.
- Low fibrinogen levels are associated with increased perioperative bleeding.
- The threshold level for fibrinogen is not defined clearly.
- Early correction using fibrinogen concentrate can improve outcome.

Summary. Coagulation defects related to severe trauma, trauma-induced coagulopathy (TIC), have a number of causal factors including: major blood loss with consumption of clotting factors and platelets, and dilutional coagulopathy after administration of crystalloids and colloids to maintain blood pressure. In addition, activation of the fibrinolytic system or hyperfibrinolysis, hypothermia, acidosis, and metabolic changes can also affect the coagulation system. All of these directly affect fibrinogen polymerization and metabolism. Other bleeding-related deficiencies usually develop later in massive bleeding related to severe multiple trauma. In major blood loss, fibrinogen reaches a critical value earlier than other procoagulatory factors, or platelets. The question of the critical threshold value is presently the subject of heated debate. A threshold of 100 mg dl^{-1} has been recommended, but recent clinical data have shown that at a fibrinogen level of $<150–200$ mg dl^{-1}, there is already an increased tendency to peri- and postoperative bleeding. A high fibrinogen count exerts a protective effect with regard to the amount of blood loss. In multiple trauma patients, priority must be given to early and effective correction of impaired fibrin polymerization by administering fibrinogen concentrate.

Keywords: coagulation; transfusion; trauma

Concentrado de Fibrinógeno : conclusiones

- **Seguro y eficaz**
- Respuesta **predecible**
- ¿Monitorización **específica?**
- **¿ Modificar** criterios administración?
- …. Probablemente **infrautilizado**

CCP/fibrinógeno

TRANSFUSION 2006;46:1279-1285.

Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities

Omar I. Abdel-Wahab, Brian Healy, and Walter H. Dzik

CONCLUSION: It is concluded that transfusion of FFP for mild abnormalities of coagulation values results in partial normalization of PT in a minority of patients and fails to correct the PT in 99 percent of patients.

The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis

Mohammad Hassan Murad, James R. Stubbs, Manish J. Gandhi, Amy T. Wang, Anu Paul, Patricia J. Erwin, Victor M. Montori, and John D. Roback

TRANSFUSION Volume 50, June 2010

CONCLUSIONS

Very-low-quality evidence suggests that plasma transfusion is associated with a reduction in the risk of death and multiorgan failure in patients undergoing massive transfusion. This benefit was not demonstrated in most other populations. Plasma transfusion, however, significantly increased the risk of developing ALI.

Early Aggressive Use of Fresh Frozen Plasma Does Not Improve Outcome in Critically Injured Trauma Patients

Thomas M. Scalea, MD, Kelly M. Bochicchio, RN, BSN, MS, Kim Lumpkins, MD, John R. Hess, MD, MPH, Richard Dutton, MD, Anne Pyle, RN, BSN, MS, and Grant V. Bochicchio, MD, MPH

TABLE 4. Logistic Regression Model Examining the Impact of a 1:1 Packed Red Blood Cell to Fresh Frozen Plasma Ratio on Mortality

	Odds Ratio	95% CI	*P*
1:1 Ratio	0.57	0.19–1.66	0.34
Age	1.05	1.02–1.07	<0.01*
ISS	1.00	0.97–1.04	0.92
Gender	0.66	0.25–1.78	0.35
Admission APACHE	1.08	1.02–1.15	0.01*
Closed head injury	2.72	1.08–6.84	0.03*
Laparotomy	3.37	1.30–8.74	0.01*
ICU (d)	0.90	0.85–0.95	<0.01*

*$P < 0.05$.

Conclusion: Early and aggressive use of FFP does not improve outcome after civilian injury. This may reflect inherent differences compared with military injury; however, this practice should be reevaluated.

(*Ann Surg* 2008;248: 578–584)

Effect of early plasma transfusion on mortality in patients with ruptured abdominal aortic aneurysm

Matthew W. Mell, MD,[a] Amy S. O'Neil, BS,[c] Rachael A. Callcut, MD, MSPH,[b] Charles W. Acher, MD,[c] John R. Hoch, MD,[c] Girma Tefera, MD,[c] *and* William D. Turnipseed, MD,[c] *Stanford, CA, and Madison, WI*

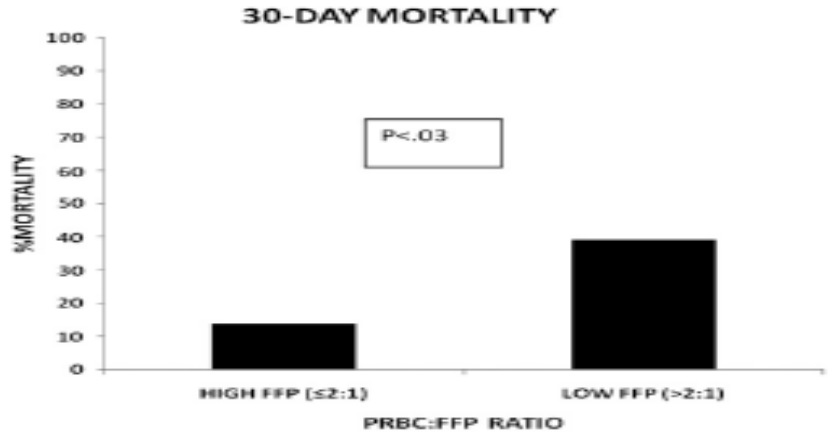


Fig 1. Patients with a PRBC:FFP ≤2:1 (HIGH FFP group) had significantly lower mortality (14.9% vs 39.0%; $P < .03$) than patients with a PRBC:FFP >2:1.

Conclusion. For RAAA patients requiring massive transfusion, more equivalent transfusion of PRBC to FFP (HIGH FFP) was independently associated with lower 30-day mortality. The lower incidence of colonic ischemia in the HIGH FFP group may suggest an additional benefit of early plasma transfusion that could translate into further mortality reduction. Analysis from this study suggests the potential feasibility for a more standardized protocol of initial resuscitation for these patients, and prospective studies are warranted to determine the optimum PRBC:FFP ratio in RAAA patients. (Surgery 2010;■:■-■.)

Advantages of Fibrinogen concentrate and PCC against FFP

- **Quick, effective** and **well predictable** rise in coagulation factor activity
- **Small volume (No risk of TACO!)**
- **No risk** of **TRALI** and **mistransfusion** (The most inportant risk factors for mortality in connection with blood transfusion!)
- **Effective viral inactivation / elemination**

Factor XIII

Best Practice & Research Clinical Anaesthesiology 24 (2010) 85–93

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

7

F. XIII in perioperative coagulation management

Wolfgang Korte, MD, PhD, Associate Professor of Medicine*

Institute for Clinical Chemistry and Haematology, Kantonsspital, 9007 St Gallen, Switzerland

The clinical significance of F. XIII in the maintenance of adequate haemostasis can be deduced from haemorrhagic symptoms observed in patients with F. XIII deficiency or inhibiting F. XIII antibodies.[4] Further, polymorphisms of the F. XIII gene lead to changes in clot properties.[6] Therefore, it can be concluded that F. XIII is apparently situated at the interface between the maintenance of clot integrity and clot breakdown.[7] Factor XIII also plays an important role in wound healing.[8] Given these observations and knowledge, it is not difficult to imagine that factor XIII might also play an important role in peri-interventional haemostasis.

Given the considerations and explanations mentioned above, a situation with reduced F. XIII activity should be accompanied by a reduction in clot firmness; and the risk of bleeding should thus increase with decreasing F. XIII availability. This raises the question whether there is any clinical evidence for this scenario. Although results from observational studies are somewhat controversial,[39,55,56] therapeutic studies indicate a benefit when normalising F. XIII levels is attempted, that is, when supplementing F. XIII perioperatively.[40,41]

Conclusions

F. XIII is an important component in guaranteeing adequate peri-interventional and perioperative haemostasis. Therefore, differential diagnosis and treatment of perioperative bleeding needs to take F. XIII deficiency into consideration. It has to be remembered that F. XIII has to be measured separately, as a deficiency cannot be identified using the aPTT or PT/INR. While very low levels of F. XIII activity are often sufficient to prevent bleeding in daily life in congenital deficiency, acquired deficiency in the surgical setting can manifest soon after levels have become abnormally low (i.e., when the levels are below the normal reference range). There is evidence to suggest that the use of F. XIII in cardiac surgery leads to a reduction in transfusion requirements. Visceral surgery patients with increased intraoperative bleeding display a significantly lower F. XIII availability, leading to decreased cross-linking, loss of clot firmness and, finally, increased blood loss. These patients show an increase in preoperative fibrin monomer concentration. Using increased fibrin monomer as a selection criterion in a prospective, randomised, double-blind and placebo-controlled trial, patients receiving F. XIII benefit over patients receiving placebo with a reduced loss of clot firmness, fibrinogen and reduced blood loss. Postoperative F. XIII deficiency due to previous consumption is a common finding and bleeding in this setting often responds to F. XIII replacement therapy.

Increased Risk for Postoperative Hemorrhage After Intracranial Surgery in Patients With Decreased Factor XIII Activity

Implications of a Prospective Study

Rüdiger Gerlach, MD; Fabian Tölle; Andreas Raabe, MD; Michael Zimmermann, MD; Annelie Siegemund, MD; Volker Seifert, MD, PhD

Background and Purpose—The functional integrity of the hemostatic system is a prerequisite for the safe performance of neurosurgical procedures. To monitor the individual coagulation capacity of each patient, standard tests are effective to detect deficiencies involving the generation of fibrin. However, fibrin clot strength depends primarily on coagulation factor XIII, which cross-links fibrin monomers and enhances clot resistance against fibrinolysis. Therefore, factor XIII is functionally involved in both the hemostatic and fibrinolytic systems. The objective of this prospective study was to determine the incidence and clinical relevance of perioperative decreased factor XIII with respect to standard coagulation parameters and the occurrence of postoperative hematoma.

Methods—In 876 patients, 910 neurosurgical procedures were performed. Prothrombin time (PT), partial thromboplastin time (PTT), platelet count, fibrinogen, and factor XIII were tested in each patient preoperatively and postoperatively.

Results—Postoperative intracranial hematoma (defined as requiring surgical evacuation) occurred after 39 (4.3%) of 910 surgical procedures. Patients with postoperative hematoma had significantly lower factor XIII and fibrinogen levels preoperatively and postoperatively than patients without hematoma. In patients with postoperative hematoma, PT and platelets differed significantly only postoperatively, whereas PTT was different neither preoperatively nor postoperatively. Of the 39 patients with a postoperative hematoma, 13 (33.3%) had a postoperative factor XIII <60% compared with 61 (7%) of 867 patients without hematoma ($P<0.01$, Fisher's exact test). The relative risk of developing a postoperative hematoma is therefore increased 6.4-fold in patients with postoperative factor XIII <60%. The risk is increased 12-fold in patients who additionally have postoperative decreased fibrinogen levels (<1.5 g/L) and 9-fold in patients with platelet count $<150\times10^9$/L and factor XIII <60%.

Conclusions—This is the first prospective study that demonstrates the association of decreased perioperative factor XIII with an increased risk of postoperative hematoma in neurosurgical patients. The risk is further increased in those patients with low factor XIII and additional abnormalities of fibrinogen, PT, platelets, and PTT. Factor XIII testing and specific replacement, as accepted for other clotting factors, may reduce the risk of postoperative hematoma. **(*Stroke*. 2002;33: 1618-1623.)**

Key Words: coagulation ■ craniotomy ■ factor XIII ■ factor XIII deficiency ■ fibrinolysis ■ hematoma ■ neurosurgical procedures

…donde estamos

Tienes claro lo que debemos hacer?

Si….ó NO…..

ante un sangrado crítico

en un manejo empírico!

- **Política transfusional restrictiva**
- **Esquemas transfusionales predeterminados**
- **Tromboelastografía**
- **Ineficacia del PFC**
- **Guías, protocolos, esquemas,…..**
- **Utilización de alternativas transfusionales farmacológicas**
- **Concentrados exógenos de factores**
- **……..**

" ... el problema no esta en lo que conocemos, sino en lo que creemos que conocemos y realmente no sabemos"

Robert Anthony

sequence of critical of clotting factor concentrations :

1. Fibrinogen
2. Prothrombin
3. Factor V
4. Factor VII
5. Platelets

Hiippala ST Anesth Analg 1995

Coagulation Management in traumatized and massiv bleeding patients

Task Force for perioperative Coagulation (AGPG) of the Austrian Society for Anaesthesia, Critical Care Medicine and Emergency Medicine (ÖGARI)

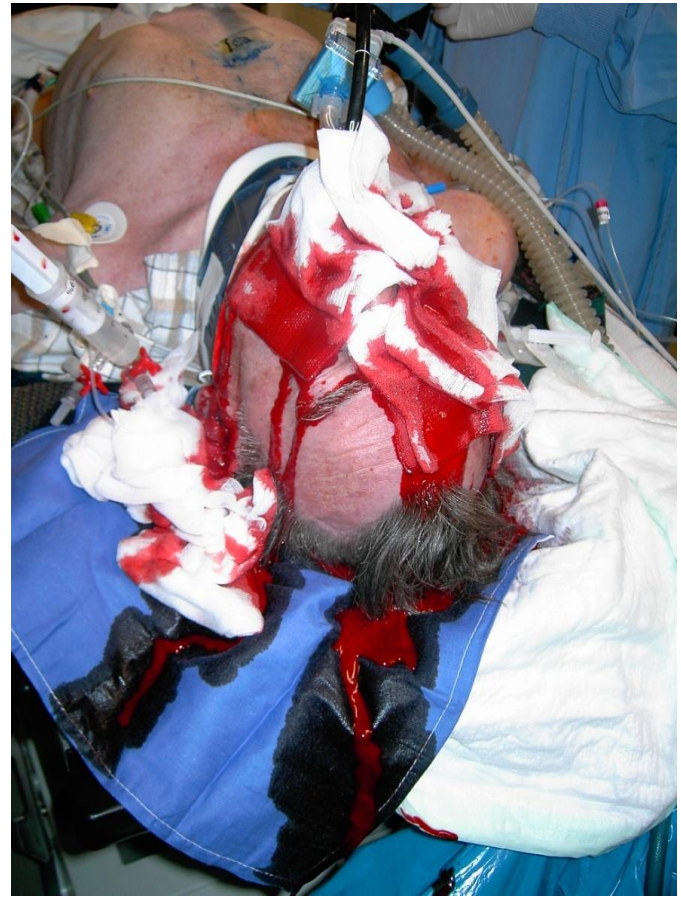
Prof Dr. Dietmar Fries.General and Surgical critical Care Medicine. Medical University Innsbruck. Austria

1. Fibrinogen concentrate: > 1,5 g/dL – 2,0 g/dL

2. Administration of PCC in case of prolongation of CT and/or blood loss of more than 150%

Tendencias 2011: "Severe Bleeding Cocktail"

- **PCC: 4,000 - 6,000 IU via central venous line (bolus)**
- **Fibrinogen: 2g**
- **Tranexamic acid: 1.5 g (up to 4.5 g/day)**
- **Desmopressin 24 μg / 3h**



No,

pero estamos mejorando !

ante un sangrado crítico

Sabes sumar? le preguntó la Reina Blanca

¿cuánto es uno más uno, y uno y uno y uno y uno y uno y uno y uno?

No lo se, respondió Alicia, he perdido la cuenta”

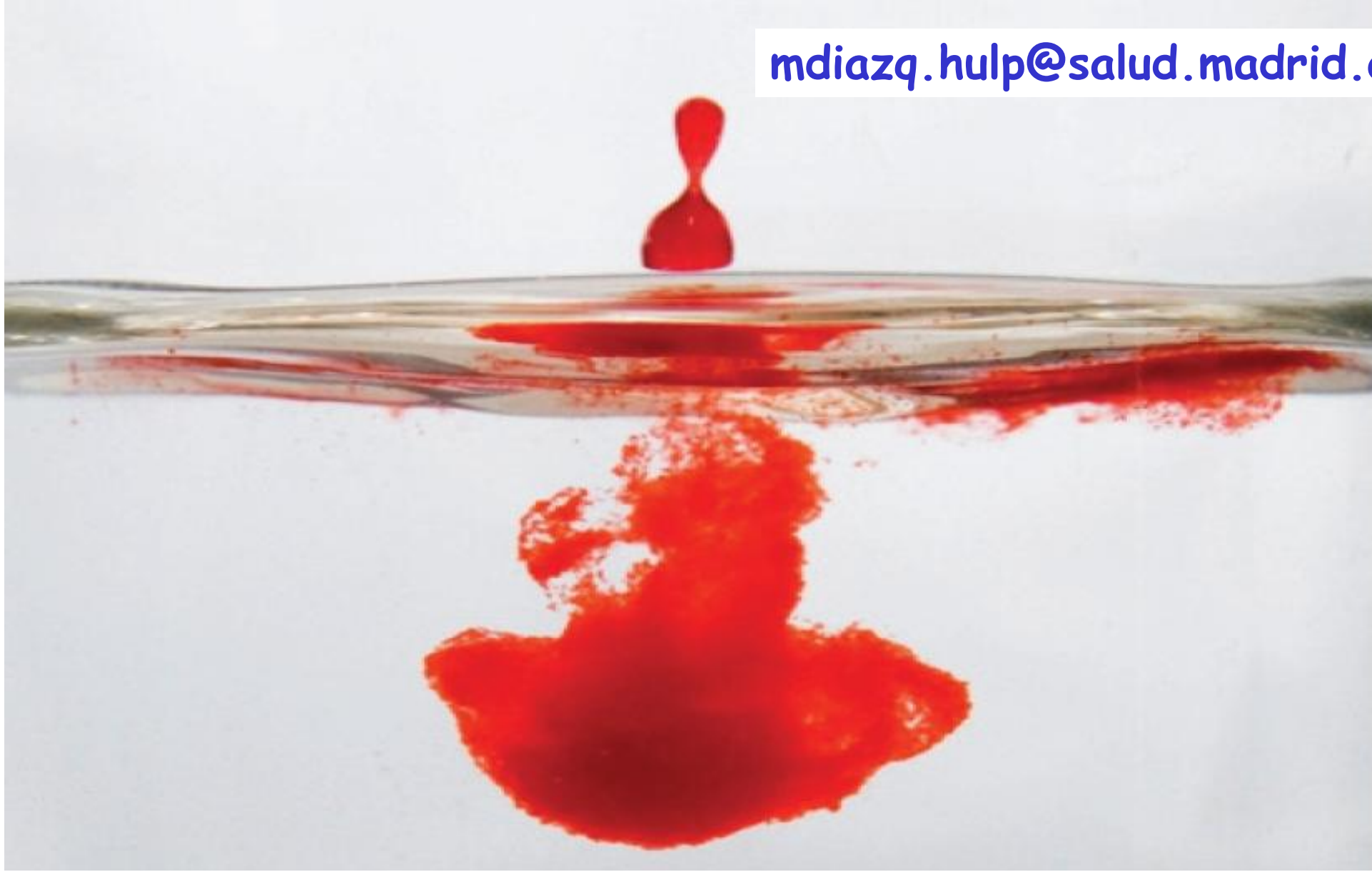
Carrol, 1872

El sistema de la coagulación es complicado

El sangrado no es bueno

Todos los tratamientos tienen riesgos

mdiazq.hulp@salud.madrid.org



Muchas gracias por vuestra atención

MQ