

Gerinnungstherapie am NAW und im Schockraum: FFP oder Faktoren?

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international collaboration:

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US Army, Fort Sam Houston, Texas, USA
Coalition Warfare Program - US Army
Dept. of Bioengineering, Univ. of San Diego, USA

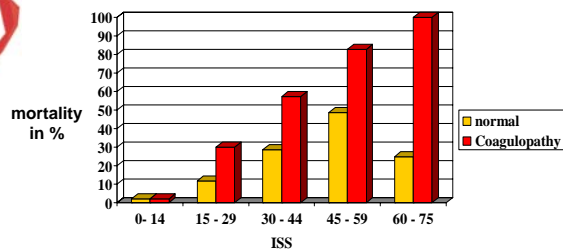
conflict of Interest:

Astra Zeneca, Baxter, Braun,
Biotest, CSL Behring, Delta Select,
Dade Behring, Fresenius, Glaxo,
Haemoscope, Hemogem, Lilly, LFB,
Mitsubishi Pharma, NovoNordisk,
Pentapharm, US Army.




Coagulopathy in Trauma Patients

Brohi K: J. Trauma (2003) 55:1127



Trauma Induced Coagulopathy = TIC
complex and not predictable

1. Massive bleeding – consumption coagulopathy
2. Dilutional coagulopathy: - interaction: colloids – coagulation „fibrinpolymerisation disturbance“
3. Hypothermia
4. Acidosis
5. Hyperfibrinolysis
6. Anaemia
7. Electrolyte disturbances



Gerinnungsmanagement
=
Blutungsmanagement

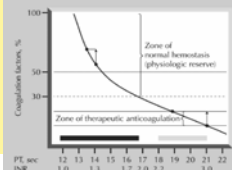
1. Monitoring
(Standardgerinnungstests versus POC)
2. Therapieoptionen
(Plasma versus Konzentrate und mögliche Alternativen)

Gerinnungsmonitoring

Predicting Haemorrhage Using Preoperative Coagulation Screening Assays
Walter H. Dzik Current Haematology reports 2004

Why are the PT (INR) and aPTT such poor predictors for bleeding?

1. relationship between coagulation factors and PT/pTT is non-linear
2. mildly abnormal test occur in patients with normal coagulation
3. overestimation of deficiencies in the upper limb and underestimation of deficiency in the lower limb
4. overestimation of coagulation factor depletion, if more than one factor is reduced
5. **PT and pTT were never designed to predict bleeding**



Gerinnungsmonitoring

Thrombelastography and tromboelastometry in assessing coagulopathy in trauma

Pär I Johansson*, Trine Stissing, Louise Bochsén and Sisse R Ostrowski

Author	No.	ISS	Study type	Major conclusions	Ref.
Kaufman (1997)	69	13/29	RS	Moderately injured patients (ISS 13) were hypercoagulable whereas severely injured (ISS 29) patients were hypo-coagulable according to VHA	[51]
Schreiber (2005)	65	23	RS	62% of the patients were hypercoagulable 14-day of trauma according to VHA which is more sensitive to identify this state than RCoT.	[52]
Rugeri (2007)	90	22	PO	VHA rapidly detects systemic changes of in vivo coagulation in trauma patients, and it might be a helpful device in guiding transfusions.	[76]
Plodin (2008)	44	21	RS	VHA is a more accurate indicator of transfusion requirements than PT, APTT and INR	[77]
Levrat (2008)	87	2075	PO	VHA provides rapid and accurate detection of hyperfibrinolysis in severely injured trauma patients	[78]
Schödl (2009)	33	47	PO	VHA based diagnosis of hyperfibrinolysis predicted outcome in severely injured trauma patients	[79]
Carroll (2009)	161	20	PO	Abnormal VHA parameters correlated with fatality. Coagulopathy as evaluated by VHA was present already on the scene of accident.	[80]
Jäger (2009)	20	1	RS	RapidTEG provides earlier detection of coagulopathy than standard VHA and RCoT	[81]
Porik (2009)	78	20	PO	VHA detected hypercoagulability and this was not seen with RCoT in trauma patients	[82]
Kashuk (2009)	44	29	RS	RapidTEG may effectively guide transfusion therapy in trauma patients	[83]

RCoT = routine coagulation tests, RS = Retrospective study, PO = Prospective observational study

Gerinnungsmonitoring

Influence of different HES solutions on fibrinogen measurement in HES diluted plasma

Adam S et al. Thromb Haemost 2009

Overestimation of fibrinogen (Clauss derived method) after administration of HES of up to 100%

A 30% dilution

B 50% dilution

Gerinnungsmonitoring

Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders

Christian Fenger-Eriksen, Gary W. Moore, Savita Rangarajan, Jørgen Ingerslev, and Benny Sørensen

30% und 50% Dilution mit HES (130/0.4):

Fibrinogen nach Clauss steigt

FibTEM sinkt !?!

Fig. 2. Fibrinogen levels measured by different automated coagulation analyzers employing methods of antigen, Clauss, and ROTEM (Fb-TEM) measurement in plasma diluted 50% with the investigated plasma expander. A = RCT; B = Sysmex; C = MDI; D = Destiny mechanical; E = Destiny optical. N = 8. Data are presented as mean ± SD. *Significantly different from plasma diluted with isotonic saline using the same analyzer. ■ Isotonic saline; □ human albumin; ▨ HES 130/0.4.

Management of bleeding following major trauma: an updated European guideline

Critical Care 2010, 14:R52 doi:10.1186/cc8943

recommendation 12:

„We recommend that routine practice to detect post-traumatic coagulopathy include the measurement of international normalised ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and platelets. **INR and APTT alone should not be used to guide haemostatic therapy (Grade 1C).**

We suggest that thrombelastometry also be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy. (Grade 2C).“

Gerinnungsmonitoring

Gerinnungsmanagement = Blutungsmanagement

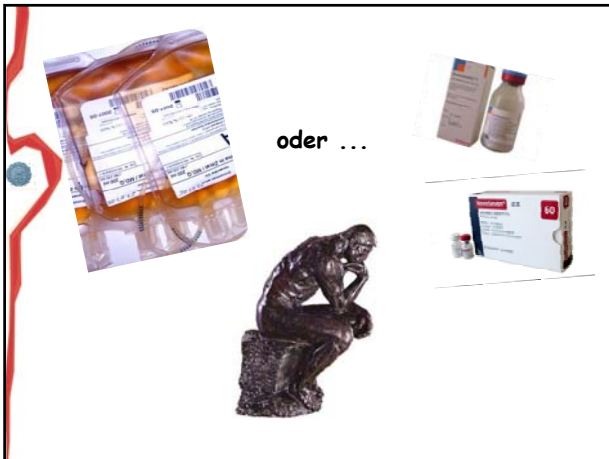
1. Monitoring

(Standardgerinnungstests versus POC)

2. Therapieoptionen

(Plasma versus Konzentrate und mögliche Alternativen)





10 – 15 ml/kg FFP

Management of bleeding following trauma:
a European guideline Rossaint R et al. Crit Care 2010

Management of bleeding following trauma:
a European guideline Spahn D et al. Crit Care 2007

British Committee for Standards in Haematology
Stainsby D et al. Brit J Haematol 2006

Key issues in advanced bleeding care in trauma
Rossaint R, et al. Shock 2006



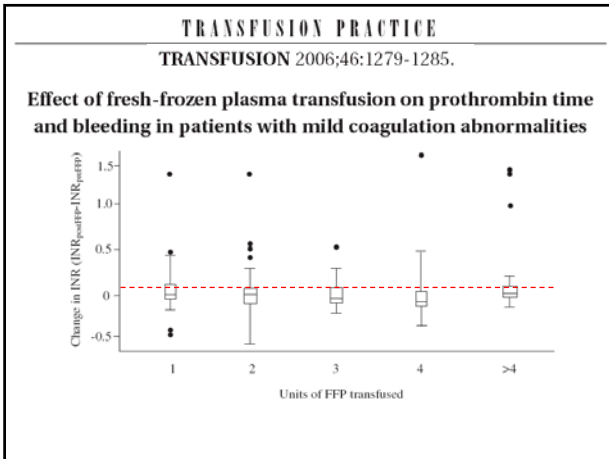
Volume expansion and plasma protein clearance during intravenous infusion of 5% albumin and autologous plasma.

Hedin A and Hahn E. Clinical Science 2005;10:217-224

10mL/kg 5% Albumin vs FFP

Albumin	FFP
PV + 17%	PV + 21%
Fib -12%	Fib + 6%
AT -16%	AT + 3%
Plt - 7%	Plt -10%
PT ↑	PT ↓
aPTT ↑	aPTT ↓

- FFP causes **volume expansion** and dilution
- **no relevant increase** in clotting factor concentrations



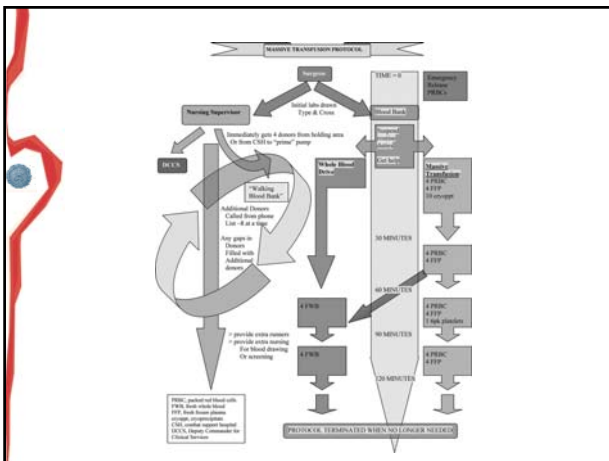
FFP- effective ?

“Is FFP clinically effective?” A systematic review of randomized trials.

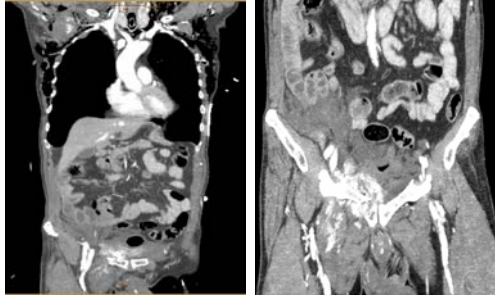
57 studies: only 5 studies with possible benefit
Stanworth SJ BJH 2004

- “The role of prophylactic FFP in decreasing blood loss and correcting coagulopathy in cardiac surgery”
- A systematic review

6 studies: no effect on blood loss
Casbard AC Anaesthesia 2004



Coagulation management with FFP and clotting factor concentrates in severe traumatized patient:
CT scan at admission to trauma centre



Coagulation management with FFP and clotting factor concentrates in severe traumatized patient

	12 RBC 1 TK		
	15 FFP	10 g Fibrinogen	
FibTEM MCF:	6 mm	3 mm	27 mm
exTEM MCF:	48 mm	27 mm	61 mm
Fibrinogen:	232 mg/dL	60 mg/dL	285 mg/dL

**The Relationship of Blood Product Ratio to Mortality:
 Survival Benefit or Survival Bias?**

retrospective analysis in 134 patients
 the first unit PRBC:
 – median 18 minutes (1– 348 min)
 the first unit of FFP:
 – median 93 minutes (24 – 350 min)

"Therefore, it could be concluded that the Non-survivors in our study population did not die because they got a lower FFP:PRBC ratio;
They got a lower ratio because they died"

Snyder C: J Trauma 2009;66 358



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

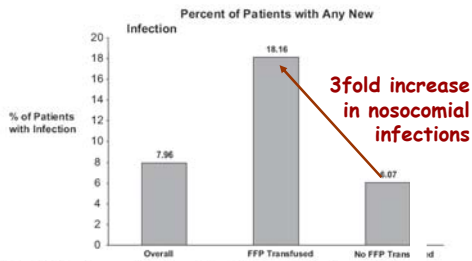


Figure 1. Patients who received fresh frozen plasma (FFP) were significantly more likely to develop an infection than those who did not receive FFP in a univariate model ($p < .01$).

Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy

Saqib I. Dara, MD; Rimki Rana, MD; Bekele Afessa, MD; S. Breannan Moore, MD; Ognjen Gajic, MD

Table 2. Outcome of patients who did and did not receive fresh frozen plasma (FFP) transfusion

Outcome	FFP (n = 44)	No FFP (n = 71)	p Value
New bleeding episodes, n (%)	3 (6.8)	2 (2.8)	.269
New onset acute lung injury, n (%)	8 (18.2)	3 (4.2)	.021
Hospital mortality, n (%)	11 (25.0)	20 (28.3)	.764
Median (IQR) ICU length of stay, days ^a	2.4 (1.7-6.8)	2 (0.9-3)	.184

Conclusion:

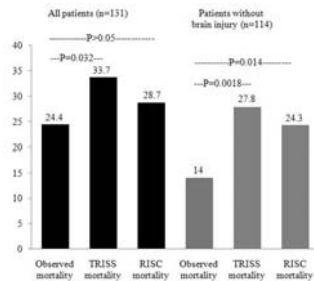
- no difference in new bleeding episodes
- new onset acute lung injury was more frequent in the transfused group (18% vs. 4%, $p = .021$).
- risk-benefit ratio of FFP transfusion in critically ill medical patients with coagulopathy may not be favorable.

Crit Care Med. 2005; 33(11):2667-2671

Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM®)-guided administration of fibrinogen concentrate and prothrombin complex concentrate
Herbert Schöchl, Wolfgang Voelckel, et al. Crit Care 2010

n= 131 mit 5 EK in 24 Std.

- > 128 Fibrinogen
- > 98 PCC
- > 12 FFP
- > 29 Thrombozyten



sequence of critical of clotting factor concentrations :

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




Hiippala ST Anesth Analg 1995

critical level of fibrinogen in clinical practice?

- > Charbit B et al. : fibrinogen as an early predictor for **severe PPH**. *J Thromb Haemost* (2007)
- > Gerlach R et al. : postoperative haemorrhage after **intracranial surgery** and fibrinogen. *Stroke* (2002)
- > Blome M et al. : fibrinogen and postoperative bleeding in **CABG**. *Thromb Haemost* (2005)
- > Ucar HI et al. : Preoperative fibrinogen and postoperative bleeding after **open heart surgery**. *Heart Surg Forum* (2007)
- > Karlsson H et al. : plasma fibrinogen level and **CABG**. *Transfusion* (2008)
- > Stinger H et al. : high ratio of F1:transfused RBC improved mortality in **combat causality and massive transfusion**. *J Trauma* (2008)

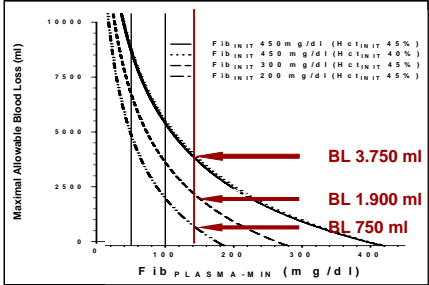
increased bleeding tendency, if fibrinogen level is below 1.5 – 2.0 g/dL

Critical Care 

Management of bleeding following major trauma: an updated European guideline
 Critical Care 2010, 14:R52 doi:10.1186/cc9543

recommendation 28:
 „we recommend treatment with FI if significant bleeding is accompanied by **TEG signs of functional fibrinogen deficit** or a **plasma FI level of less than 1.5 – 2.0 g/l (Grade 1C)**. We suggest an initial fibrinogen concentrate dose of **3-4g or 50mg/kg**. **Repeated doses may be guided by TEG monitoring and laboratory assessment (Grade 2C).**“

Critical blood loss - fibrinogen baseline concentration
 Singbartl K et al. Anesth&Analg 2003



Legend:
 - - - - FIB_{INIT} 450 mg/dl (Hct_{INIT} 45%)
 - - - - FIB_{INIT} 450 mg/dl (Hct_{INIT} 40%)
 - - - - FIB_{INIT} 300 mg/dl (Hct_{INIT} 45%)
 - - - - FIB_{INIT} 200 mg/dl (Hct_{INIT} 45%)

Annotations:
 - BL 3.750 ml (at FIB PLASMA-MIN ≈ 1.5 mg/dl)
 - BL 1.900 ml (at FIB PLASMA-MIN ≈ 1.0 mg/dl)
 - BL 750 ml (at FIB PLASMA-MIN ≈ 0.5 mg/dl)

FI ≥ 150 mg/dL: 750 ml or 3.750 ml
Critical FI levels may be reached before the need of RBC's!!!

FIBRINOGEN DOSE CALCULATOR

Patient Information

Value	Unit
Body Weight	85 kg
Hematocrit	25%
Plasma Volume	3805 ml
Blood Volume	4647 ml

Baseline Fibrinogen

Baseline Fibrinogen Concentration	0.8 g/l
Target Fibrinogen Concentration	1.7 g/l

Concentration of Fibrinogen in product

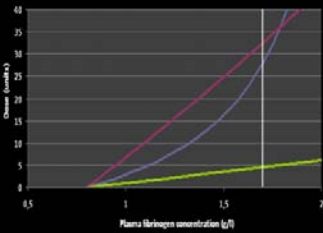
FFP Concentration	25 g/l
Cryo Concentration	32 g/l
FibCon Concentration	20 g/l

Volume of product per unit

FFP Volume per unit	250 ml
Cryo Volume per unit	32.5 ml
FibCon Volume per unit	50 ml

Dose Calculation

FFP	28	31	1	units
Volume	7000	422.5	250	ml
Resultant Fibrinogen Concentration	1.70	1.71	1.70	g/l



Legend: FFP (blue), Cryo (red), FibCon (green), Target (black)

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Early Versus Late Recombinant Factor VIIa in Combat Trauma Patients Requiring Massive Transfusion

Jeremy G. Perkins, MD, Martin A. Schreiber, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Retrospektive Analyse von 365 Massivtransfusionen, wobei 32% rFVIIa erhalten haben.

„Frühe Gabe“: rFVIIa Gabe **VOR** Transfusion von 8 EKs
 „Späte Gabe“: rFVIIa Gabe **NACH** Transfusion von 8 EKs

	Early rFVIIa (88 units blood)	Late rFVIIa (110 units blood)	p Value
Dose rFVIIa (mg)	9.6 (4.6-19.2)	9.6 (4.6-19.2)	0.8
Transfused erythrocytes	109 (70-240)	110 (80-270)	0.9
→ 24-hr total blood units (RBC + FFW)	18 (12-44) [20.6]	22 (10-56) [25.7]	0.048
Stored red blood cells (RBC)	14 (7-20) [16.7]	20.5 (9-49) [21.7]	0.048
Fresh whole blood (FWB)	0 (0-2) [3.9]	2.5 (0-20) [4.0]	0.5
Fresh frozen plasma	8 (2-26) [10.7]	10.5 (5-40) [13.1]	0.3
Cryoprecipitate	10 (0-38) [12.0]	10 (0-40) [15.2]	0.4
Platelet transfusion	0 (0-6) [1.0]	0 (0-7) [1.2]	0.8
24-hour crystalloid (L)	10.6 (4.4-17.5) [11.2]	10.0 (3.6-20.5) [11.0]	0.8

Data are expressed as median (range) [mean].

rFVIIa

Guidelines for the use of rFVIIa. Israeli Multidisciplinary rFVIIa Task Force

Martinowitz et al. J Thromb Haemost 2005

1. massive blood loss (100% blood loss in 24 hours, 50% in 3 hours, 150 ml/min, 1,5 ml/min/kg in 20 min)
2. failure of all conventional methods (surgery, radiology, packing, ...)
3. „appropriate replacement therapy“ including FFP, Cryo, platelets
4. buffer therapy at a pH < 7.2
5. warming in case of hypothermia is recommended but not required

New local haemostyptic dressings

1. QuickClot®
2. HemCon®
3. Combat Gauze®
4. Celox®
5. Hemostat®
6. WoundStat®
7. TraumaDEX®
8. FSD = fibrin sealant dressing



lokale Hämostyptika

QuickClot® = Zeolite

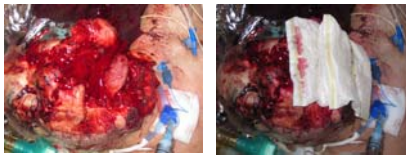
- QuickClot® ACS+™ (Zeolite) ist ein „molekularer Schwamm“. Es ist biologisch inert und bindet Wassermoleküle in einer Hydrogenverbindung
- QuickClot® soll eine lokalisierte Gerinnelbildung mit einem stabilen Clot ermöglichen. Es wird nicht absorbiert.



lokale Hämostyptika

Use of QuickClot®

Shot-gun injury – bridging for surgical treatment
Huge wound area



lokale Hämostyptika

HemCon® = poly- β -N-acetyl-D-glucosamin=Shrimps

- > FDA Zulassung: 2003 (... Operation „Iraqi Freedom“)
- > Bis 2006 wurden weit mehr als 100.000 Verbände verkauft
- > Bestandteil des sog. Prehospital Trauma Life Support Military Section; Anwendung wird bei allen Special Operations Forces trainiert

- > Deacetylierte Form von Chitin
- > Chitosan hat topische hämostatische Wirkung ...



lokale Hämostyptika

Use of HemCon®

Use of HemCon after tracheotomy.
After application of the wound dressing, bleeding stopped.

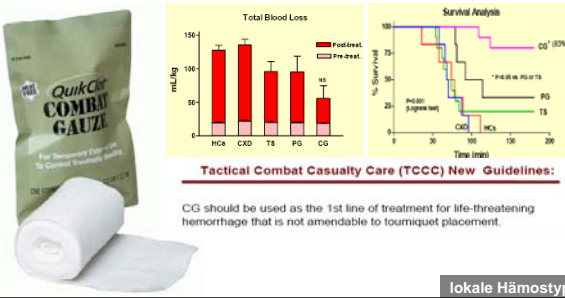


lokale Hämostyptika

Combat Gauze and WoundStat: New Choices of Hemostatic Treatment for Combat Wounds

Bijan S. Kheirabadi, Jason W. Edens, Irasema B. Terrazas, Michael R Scherer, Michael R. Perez, Ashley B. Cox, J. Scot Estep, Michael A. Dubick, and John B. Holcomb

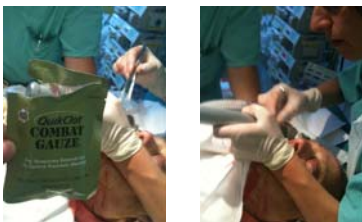
United States Army Institute of Surgical Research, Fort Sam Houston, TX 78234-6315



lokale Hämostyptika

Use of Combat Gauze®

Use of Combat Gauze® because of oral bleeding after severe maxillary and facial trauma



lokale Hämostyptika

7th Innsbruck Winter Symposium for Coagulation
„Trauma and massive bleeding“
dietmar.fries@i-med.ac.at
www.clotwork.at