CSL Behring

More or less?

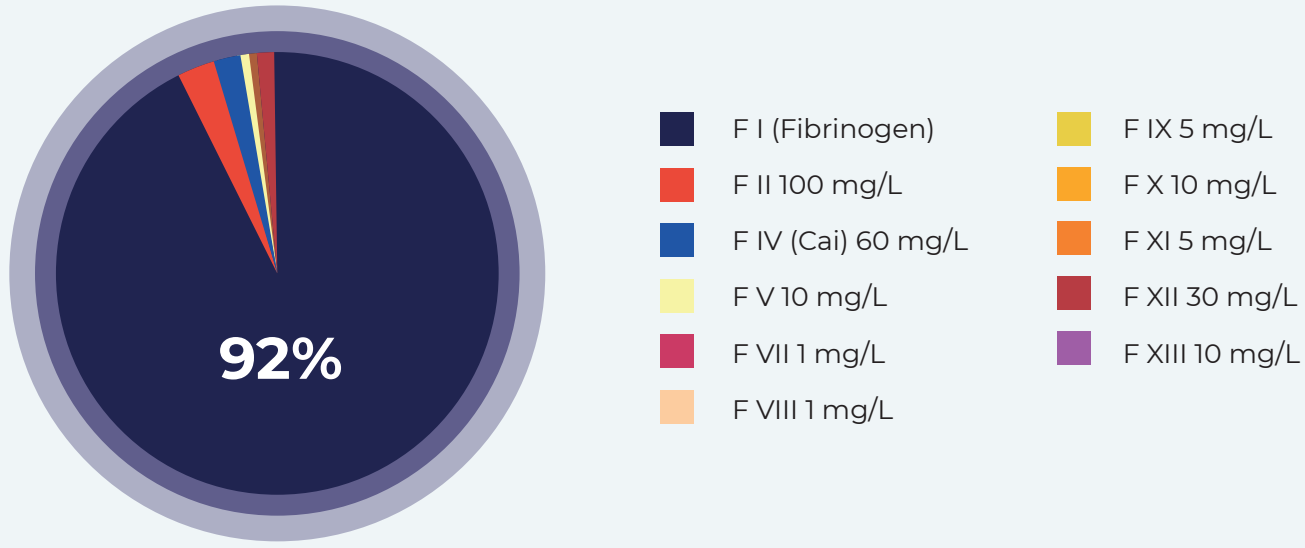
Chair: Tina Tomic Mahecic y Lidia Mora

Thursday 18th of April, 2024

1. FIBRINOGEN: THE HIGHER THE BETTER?

Kai Zacharowski

Fibrinogen accounts for 92% of coagulation factors in plasma. Its critical concentration is 1 g/L, and in massive bleeding or hemodilution situations, fibrinogen is the first factor to be significantly reduced in the patient's plasma.



Can the treatment with fibrinogen concentrate increase plasma levels in such a way thrombotic risk increases after trauma?

A retrospective study concluded that treatment with fibrinogen within 24 hours after admission to hospital of patients with traumatic bleeding had no impact on the evolution of fibrinogen levels between day 3 and day 7 post-trauma when compared to the control group.

Schlimp et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2016) 24:29
10.1186/s13049-016-0221-8

Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

ORIGINAL RESEARCH Open Access

Fibrinogen levels in trauma patients during the first seven days after fibrinogen concentrate therapy: a retrospective study

Christoph J. Schlimp[1], Martin Ponschab[1], Wolfgang Voelckel[2], Benjamin Treichl[3], Marc Maegele[4] and Herbert Schöchl[1,2*]

Abstract

Background: Fibrinogen concentrate (FC) is increasingly used as first line therapy in bleeding trauma patients. It remains unproven whether FC application increases post-traumatic plasma fibrinogen concentration (FIB) in injured patients, possibly constituting a prothrombotic risk. Thus, we investigated the evolution of FIB following trauma in patients with or without FC therapy.

Methods: At the AUVA Trauma Centre, Salzburg, we performed a retrospective study of patients admitted to the emergency room and whose FIB levels were documented thereafter up to day 7 post-trauma. Patients were categorized into those with (treatment group) or without (control group) FC therapy during the first 24 h after hospital admission. A subgroup analysis was carried out to investigate the influence of the amount of FC given.

Results: The study enrolled 435 patients: treatment group, $n = 242$ (56 %); control group, $n = 193$ (44 %), with median Injury Severity Score of 34 vs. 22 ($P < 0.001$) and massive transfusion rate of 18.4 % vs. 0.2 % ($P < 0.001$). In the treatment group (median FC dose 6 g), FIB was lower on admission and up to day 2 compared with the control group. In patients receiving high (≥10 g) doses of FC, FIB was lower up to day 5 as compared to controls. At other timepoints, FIB did not differ significantly between the groups. In the treatment vs. the control group, other coagulation parameters such as prothrombin time index and platelet count were consistently lower, while activated partial thromboplastin time was consistently prolonged at most timepoints. Inflammatory parameters such as C-reactive protein, interleukin-6 and procalcitonin were generally lower in controls.

Discussion: The rise of FIB levels from day 2 onwards in our study can be attributed to an upregulated fibrinogen synthesis in the liver, occurring in both study groups as part of the acute phase response after tissue injury.

Conclusions: The treatment of severe trauma patients with FC during bleeding management in the first 24 h after hospital admission does not lead to higher FIB levels post-trauma beyond that occurring naturally due to the acute phase response.

Keywords: Blood coagulation tests, Fibrinogen, Plasma, Trauma

	Fibrinogen concentrate	Control
	242 patients	193 patients
Average ISS	34	22*
Massive transfusion rate	18.4%	0.2%*

ISS, Injury Severity Score
* P < 0,001
Patients with a higher severity score were the most frequently polytransfused ones, and so they received higher doses of fibrinogen.

The increase in plasma fibrinogen observed in both groups was the result of an acute response to tissue damage, and the activation of hepatic synthesis of fibrinogen occurred in both groups[1]. Therefore, the administration of high doses of fibrinogen is a necessary tool for the correction of hemostasis in trauma patients. However, from a physiological standpoint, starting on the second day of evolution, hepatic synthesis will increase plasma levels of this factor, with no differences observed between the control and treatment group.

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2. THE FUTURE OF IRON THERAPY

Gavin Murphy

Pre-operative anaemia in an independent factor that increases mortality and morbidity after cardiac surgery[2]. However, treatment with intravenous iron 10-42 days before major surgery has not proven to decrease the need for a transfusion[3].

Observational studies have concluded that red blood cell transfusions are associated to increases in post-operative mortality, but also in morbidity and costs[4]. Paradoxically, the application of restrictive transfusion thresholds has not resulted in a statistically significant decrease of such mortality, morbidity, and costs, as observed in a randomized controlled trial[5].

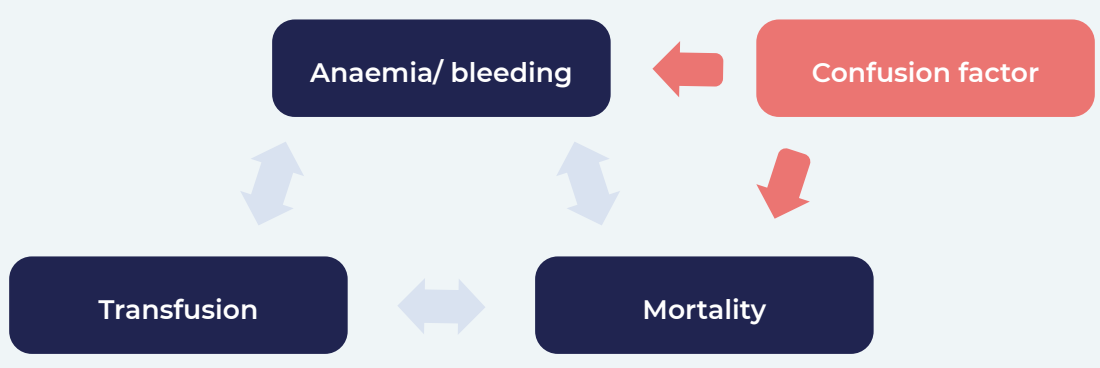
Regarding the coagulopathy and bleeding, it has been described that tranexamic acid brings about reductions in a composite variable of potentially lethal hemorrhage, severe hemorrhage, or hemorrhage in a critical organ within 30 days, but it is not inferior to placebo in a composite variable of safety, including myocardial damage, non-hemorrhage cerebrovascular accident, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism[6].

In general, PBM strategies addressed at reducing transfusions, anaemia, and post-operative hemorrhage, have an observed efficacy in the reduction of transfusions and bleeding, and to shorten the length of hospital stays. However, they are not effective and do not involve clinical benefits[7].

With benefits	Without benefits
Transfusion risk	Mortality
Fresh frozen plasma transfusion	Acute kidney damage/dialysis
Platelet transfusion	Acute brain injury
Reoperation required due to bleeding	Infarction
Hospital stay	Infection/Sepsis
ICU stay	Low cardiac output

Apparently, long-term multiple conditions before cardiac surgery are the cause for 96% of mortality variation between sites in the UK[8].

In view of these results, there would not exist a direct cause and effect relationship between transfusion and mortality, or between anaemia, bleeding, and mortality. Therefore, an unknown confusion factor would exist, which may be inflammatory aging:



- Iron deficiency anaemia, in the context of cardiac surgery, is caused by inflammatory aging and progressive chronic disease.
- Inflammatory aging and progressive chronic disease can also cause organ damage and death in patients undergoing cardiac surgery.
- Treating iron deficiency anaemia with intravenous iron is not effective for these patients.

According to this hypothesis, treating inflammatory aging together with the administration of intravenous iron might be helpful to achieve clinical effectiveness.

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3. PLATELET TRANSFUSION, WHERE ARE WE?

Alexander Vlaar

Platelet transfusion for prophylactic and therapeutic purposes in the field of Hematology, as well as the transfusion thresholds applied, have been the focus of research since 1997[9].

However, a study published in 2016 revealed that an intervention with platelets in patients with intracranial hemorrhage arising from an antiplatelet treatment increased the risk of death or dependency[10]. A higher transfusion threshold was also associated to a higher risk of death and massive hemorrhage in full-time newborns with severe thrombocytopenia[11]. The hypothesis that may explain these results is that platelet transfusion can make active inflammatory processes worse, and therefore, the currently adopted transfusion threshold is < 10,000 platelets/mm^3, or no interventions are performed until a low platelet count has been corrected.

For the placement of a central venous catheter, a type of intervention with limited complications and a high success rate, there are different prophylactic thresholds according to each clinical guideline[12-14]:

Federatie Medisch Specialisten	British Society for Haematology (Listening • Learning • Leading)	ESICM (European Society of Intensive Care Medicine)
< 50 x 10^9 / L	< 20 x 10^9 / L	10 x 10^9 / L

The PACER trial was the first one to prospectively study the hypothesis that skipping the platelet transfusion prior to the placement of a venous catheter may trigger the same occurrence of bleeding complications in critical and hematological patients with thrombocytopenia[15]. This study concluded that patients not receiving a prophylactic platelet transfusion before central venous catheter placement have a higher risk of hemorrhage related to such central venous catheter placement (RR [90% CI] = 2.45 [1.27 -4.70]). The trial was conducted with patients with a count between 10 and < 50 x 10^9 / L, and in the subgroup analysis the following risk factors were found:

- Non-tunneled catheter
- Lower baseline platelet counts
- Care in Hematology services
- Low platelet counts after the intervention

Therefore, skipping the prophylactic platelet transfusion comes with a cost reduction, but also with an increase in hemorrhage events related to the placement of the catheter.

- The risk of catheter-induced hemorrhage is higher than reported.
- Is proportional to the count.
- It is higher in hematological patients — lower monitoring than those in ICU — and with non-tunneled catheter.
- The risk of post-operative transfusion is also higher in patients with low counts.

Recommendations

- **Considering skipping platelet transfusion in the ICU, combined with a low threshold for therapeutic platelet transfusion.**
- **Considering prophylactic platelet transfusion in hematological patients with counts < 30 x 10^9 / L.**
- **Considering higher thresholds for patients with tunneled catheters.**

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