

It was with great interest that we read the article by Wild et al. hosted on the Ludwig Boltzmann Institute HTA website in February 2010 named “Haemocompletan® P alone or in combination with Fibrogammin® P in acquired hypofibrinogenemia – a systematic review” by Wild et al.. That article reviews major trials on the efficacy and safety of factor concentrate-based coagulation management as well as on point-of-care coagulation monitoring. The review has major flaws, and its interpretation of study results shows systematic errors.

General comments:

1. This systematic review on one therapeutic strategy remains inconclusive

A systematic review of only one therapeutic strategy will always be inconclusive:

If Wild et al. truly intended to objectively assess the issue of haemostatic resuscitation, it would have been mandatory - from the standpoint of basic scientific conventions - to also assess the treatment alternative: a plasma-based concept.

For this purpose, it would have been necessary to review the harmful effects of plasma such as acute lung injury TRALI, volume overload TACO, immunomodulation TRIMM, and infections. Scientific evidence for the harmful effects of the treatment alternative is readily available and must not be ignored.

Furthermore, there is strong evidence that administration of fresh frozen plasma is ineffective for the purpose of reversing coagulopathy in traumatized and massively bleeding patients. Objective clinical reviews on the use of plasma in severe bleeding as well as a synthesis of the scientific evidence and experience gathered by anaesthesiology experts are published in peer-reviewed journals (Critical Care Medicine, Journal of Trauma, Transfusion, etc.). We recommend these latter sources of information.

The ÖGARI recommendation on the management of trauma-induced coagulopathy has been accepted for publication in such a highly esteemed journal and provides a well-balanced critical synthesis of scientific evidence and expert anaesthesiological opinion (AINS).

2. The medical reviewer disclaims his approval to the present assessment

The sole medical reviewer of the Wild et al. review stated (personal communication to members of the ÖGARI task force) that he never saw the final version of the

assessment, nor does he agree with the personal interpretation made by Wild et al. We strongly recommend that Wild et al. reply on this very critical point.

3. Which guidelines Wild et al. focus on?

The so-called “local guidelines” were established and accepted several times by a multidisciplinary expert panel appointed by the Pharmaceutical Committee of the Tyrolean State Hospitals Ltd. (TILAK). To date, these guidelines have neither been published nor distributed to the hospital doctors for reasons unknown.

All committee members confirmed that they have observed confidentiality on the content of the expert panel meetings. It would be interesting to know how Wild et al. acquired knowledge of this coagulation management concept.

The current guideline for coagulation management gives a transfusion ratio of 1:1 for red blood cell concentrates to fresh frozen plasma. Beside several other inconsistent instructions, these guidelines recommend that the effect of oral anticoagulants should be reversed by administering vitamin K, even in an emergency setting. It would be a good first step for Wild et al. to review the current recommendation for coagulation management, initially installed by the Pharmaceutical Committee.

4. The authors cited several manuscripts which questioned the use of FFP

Needless to say, we are amazed that the authors cited several manuscripts that question the use of FFP. In their assessment of the recommendations made by the ÖGARI task force, Wild et al. did not evaluate those manuscripts.

Comments on specific topics:

1. Wild et al. focus within their review on old and out-dated guidelines

In their review Wild et al. focus on old and out-dated guidelines that not even their authors adhere to any more (personal communication to D. Spahn, 2010), these are presently being updated and adapted.

2. The cost calculation is definitively wrong

An exact calculation on the basis of the actual number of all TILAK hospital beds including those in outlying hospitals would give 67 vials per hundred beds and not the 137 we are asserted to have used in a calculation that took into consideration only

the beds at the so-called “one” hospital, which is obviously Innsbruck Medical University Hospital. The 67 vials are in the same the range as the other Austrian hospitals.

In addition, the price of fibrinogen is € 250 and not € 352.40 per gram as stated in the text. In summary, the cost analysis is worthless.

Beyond that, the authors did not calculate the costs for fresh frozen plasma: for example, to increase the fibrinogen reading in a patient of 85kg bodyweight and having 25% haematocrit % and 0.8g/l fibrinogen, 7.000 ml (!!!) of fresh frozen plasma would have to be administered to achieve a target fibrinogen of 1.7 g/l (again, a cut-off value of 1.5 to 2.0 g/l is not only recommended by the ÖGARI task force but also by the International Society for Intensive Care Medicine). The estimated cost for this therapy is approx. €1.700. By contrast, only 5g Haemocomplettan® would be needed to reach the target fibrinogen value of 1.7 g/l and the total cost would be approx. €1.250. Not to be forgotten is the fact that a total of 7.000 ml fresh frozen plasma can not be made available in an acceptable space of time and the patient would definitely suffer TACO.

3. Data interpretation related to costs of transfusions

Wild et al. further stated that overall treatment costs both for transfusions and prohaemostatic drugs were reduced by factor concentrate-based coagulation management, but they nevertheless misleadingly emphasized the higher cost of fibrinogen concentrates.

Giving consideration to only one cost factor and not to the costs both for allogeneic blood products and haemostatic resuscitation is a serious shortcoming. Nowadays it would be more appropriate for representatives of a health technology institute to also view cost savings from the perspective of health care economy (Shander, Spahn).

In this context the POC factor concentrate-based approach must be seen to have a clear advantage. In summary, it would be only appropriate for Wild et al. to issue an official erratum to correct their erroneous statements on increasing costs.

4. Wild et al. stated that the ÖGARI task force recommend the administration of FXIII with “should”

Wild et al. state that the ÖGARI task force recommends the administration of FXIII with the wording “should.” Wild et al. thereby misquote the ÖGARI recommendations. In the original manuscript, FXIII administration is mentioned only as “could.”

5. Cryoprecipitate

The statement about cryoprecipitate is unnecessary, because it is not available in Austria for reasons of well known safety concerns.

6. Wild et al. immoderately criticize the four clinical fibrinogen studies

Wild et al. disproportionately criticize the four clinical fibrinogen studies. An independent professional statistician from the Innsbruck Medical University made the following assessment: “most of the criticism voiced by Wild et al. is mere assumption. For example, Wild et al. point out randomisation errors and selection bias in all four clinical studies although the authors of the clinical studies stated that baseline characteristics did not differ.” In summary, the assessment of the clinical studies by Wild et al. is unilateral and subjective.

Wild et al. should also bear in mind that the manuscripts were all published in top journals in the field of anaesthesiology, intensive care medicine, emergency medicine and haemostasis. Nevertheless, the four small studies show fibrinogen to have a highly significant benefit. To the best of our knowledge, no study has to date been published that meets the authors' criteria for resuscitation in haemorrhagic shock.

We further insist that fibrinogen has according to the ACCP guidelines a grade 1b (!) recommendation for reducing blood loss and transfusion requirements.

7. Less transfusion rate due to the individual POC guided approach

True patient benefits are reported in the referenced studies, but Wild et al. did not mention the statistically significant and clinically relevant advantage for the intervention group treated with a POC-individualized approach:

At discharge haemoglobin levels were similar even after having received fewer allogeneic blood transfusions as compared to the control group. Likewise, a shorter ICU and/or hospital stay is also an advantage, but was ignored by Wild et al.

8. Cut off value of 1.5 - 2.0 g/l.

Wild et al. criticised the cut-off value of 1.5 - 2.0 g/l for fibrinogen in severely injured and massively bleeding patients; this cut-off value was also approved in March 2010 by the International Society for Intensive Care Medicine (ISICEM Symposium Brussels 2010).

The normal range for fibrinogen is between 2.0 and 3.5 g/l. Thus, the lower normal range is still above the cut-off level used in our guideline. However, we admit that this value does not stem from a prospective randomized double-blinded trial, but is the product of human evolution. Why do the authors believe that in an acute and massive bleeding situation, less fibrinogen than normal might be sufficient?

The cut-off value of 1.0 g/l has never been demonstrated to be sufficient in acute trauma bleeding. On the other hand, several publications show that even higher fibrinogen values (up to 4.0 g/l) protect against blood loss and transfusion in various acute bleeding situations. For detailed information, please consult the ÖGARI recommendations.

9. Comparison of Clauss Fibrinogen determination and the ROTEM® fib-tem assay.

The authors disqualify their review before even starting their comparison by saying they consider Clauss fibrinogen to be the “gold standard.”

In fact, Clauss fibrinogen is the most widely used fibrinogen determination method, mainly because of its ease of performance. Over the years numerous publications have looked at the advantages and drawbacks of the Clauss method. The calibrator used has been identified as a significant source of discrepancy (Chantarangkul V et al. Results of a collaborative study for fibrinogen measurement. Blood Coagul Fibrinolysis 1994) and Kalina et al. showed that the fib-tem assay on ROTEM® correlates well with Clauss fibrinogen in normal plasma samples (Kalina U et al. ROTEM for monitoring of fibrinogen concentrate therapy in fibrinogen deficiency. Blood Coagul Fibrinolysis 2008). A very recent study demonstrates that in the presence of colloids such as HAES, the various commercially available test kits using the Clauss method may significantly overestimate the fibrinogen content of a sample (Adam S et al. Photo-Optical Methods can Lead to Clinically Relevant Overestimation of Fibrinogen Concentration in Plasma Diluted With Hydroxyethyl Starch. V.Clin Appl Thromb Hemost. 2009). When linear dilutions were made and measured results were

compared with calculated results, it was found that, depending on the method, in the presence of HAES fibrinogen levels were overestimated by 20% to 100%.

In an operating theatre or intensive care environment, where patients are frequently treated with colloidal volume replacement fluids, Clauss fibrinogen results need to be interpreted with great care. Among other experts, laboratory specialists at the “one” hospital (Innsbruck Medical University Hospital) have publicly stated that fibrinogen measurements should be interpreted with “great caution” (Weigel G, et al. GTH 2010) because of precisely this issue.

Several authors have cautioned that fib-tem results may be a better indicator of the coagulopathy induced by HAES than is the Clauss assay. When discussing the fib-tem assay, the authors rightly state that the assay results are also dependent on haematocrit, suggesting that the assay is of less relevance because Clauss fibrinogen determination is - at first glance - not dependent on haematocrit. Fib-tem is a whole blood method, whereas Clauss fibrinogen determination uses plasma. Therefore, the haematocrit influence is eliminated by centrifugation during sample preparation.

Why is the surgeon or the anaesthetist interested in the fibrinogen value?

The information sought is not the fibrinogen concentration as a mathematical value. The question is, will the clot formed support haemostasis? For this purpose the plasma result needs to be translated back to the blood – where haematocrit (red cells) plays a role.

In Point 6.1.3 the authors discuss three studies that compared ROTEM® results including fib-tem with standard laboratory tests including fib-tem.

For the study by Coackley et al., the authors agree that there is “significant correlation between ROTEM® FIBTEM maximum amplitude (MA) and Clauss fibrinogen.” But then they state that there is “only moderate agreement ... as to when to substitute fibrinogen ($k= 0.42;p<0.01$).” What the authors do not mention is that the cut-off of 100 mg/dl for Clauss fibrinogen does not correspond to 8 mm of MCF, which is closer to 200 mg/dl.

Similarly, the other two studies conducted by French groups do not state the lack of influence of FXIII on Clauss fibrinogen as a possible cause of bias.

In the discussion the authors concede that thresholds for fibrinogen substitution have been empirically set at 1 g/l. No randomized, blinded studies support this threshold. One of the authors’ points of criticism concerning the (ROTEM®-guided) transfusion

of fibrinogen (and FXIII) deals with the lack of randomized studies. However, they themselves accept the same lack for their preferred concept.

Conclusion

The review by Wild et al. raises several questions: Why did the authors of this non-peer-reviewed publication introduce such a systematic error to their interpretation? It may well be that it is impossible to understand the management strategies of acute perioperative bleeding from the office desk perspective. Proposing a score is a nice try, but one that will never work in the acute situation: it would be time-consuming - and time is life in such a clinical setting. A score for the bleeding risk is not what helps manage acute and massively bleeding patients, but early goal-directed resuscitation does. It is also naive to suggest that therapy be administered in 2-3 infusions daily. We do not have several days at our disposal, as in internal medicine, when treating static coagulation disorders.

Another explanation for the fundamentally misleading interpretation of the available scientific evidence may be a bias stemming from the fact that this article might have been written under contract. Wild et al. criticize the authors of some of the referenced papers for reporting their potential conflicts of interest, which is undoubtedly good scientific practice. An official disclosure concerning the conflicts of interest on the part of Wild et al. is a must.

Attached note:

In the meanwhile, the updated European guideline for management of bleeding following major trauma (April 2010; Crit Care) support the ÖGARI recommendation concerning the role of thrombelastometry/-graphy and fibrinogen concentrate in trauma related bleeding.

Task Force for Coagulation of the Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine (ÖGARI)