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Relationship between the dual platelet-inhibited ROTEM® Sigma FIBTEM assay and Clauss fibrinogen during postpartum haemorrhage

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This scientific letter highlights the observation made by a Welsh group on the change introduced in the ROTEM Sigma FIBTEM test and its repercussion on fibrinogen transfusion thresholds in puerperal haemorrhage.

The FIBTEM test informs about the fibrinogen contribution and the firmness of the clot, and A5 amplitude (FIBTEM amplitude within 5 minutes of the start of the clot formation) has been used in clinical practice as a fibrinogen equivalent measured using the Clauss method, taking therapeutic decisions following algorithms established for each bleeding situation.

Originally, FIBTEM used cytochalasin as an inhibitor of platelet aggregation, so that the clot firmness is solely attributed to fibrinogen plasma level, although such inhibition may be influenced or reduced by a high platelet count.

Since 2022, FIBTEM uses double platelet inhibition, with cytochalasin and tirofiban to reduce the influence of the platelet count and ensure the contribution of fibrinogen only to the firmness of the clot.

Clinical guidelines recommend maintaining plasma levels of fibrinogen above 2 grams/litre in obstetric haemorrhage.

In Wales, since 2017, these bleedings are managed under OBS Cymru (Obstetric Bleeding Strategy for Wales), an algorithm using ROTEM for decision-making.

According to this decision tree, a FIBTEM A5 > 11 mm corresponds to 2 g/l fibrinogen using Clauss.

Since 2023, ROTEM sigma cartridges with double platelet inhibition in FIBTEM entered the market in Wales, and some clinicians observed abnormal relationships between A5 and fibrinogen as measured in plasma using Clauss.

212 FIBTEM and Clauss paired retrospective data were gathered in patients with postpartum haemorrhage.

The correlation between FIBTEM A5 and Clauss from the double platelet inhibition in FIBTEM proved to be stronger when compared to FIBTEM results with single platelet inhibition.

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In double inhibition, a FIBTEM A5 <= 11 identifies all patients with fibrinogen in plasma below 2g/l, although it was also observed that a great deal of patients with fibrinogen above 2 presented A5 below 11 mm, which means they received fibrinogen concentrates inappropriately.

The analysis of these results led to a change in the A5 threshold to 8 mm, which is equivalent to an A5 threshold of 11 mm in the single inhibition reagent.

The hypothesis of the Welsh group is that a more intense platelet inhibition makes FIBTEM more dependent on the fibrinogen level, and therefore it becomes more robust as a marker.

The conclusion that can be drawn is the need for a good communication of all the updates implemented in coagulation points of care to their end users, in order to appropriately evaluate their impact on different scenarios.

The role of factor XIII in patient blood management

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Factor XIII (FXIII) is indisputably "in style," as proven by this great review reflecting what we know and what still needs to be elucidated.

FXIII is a plasma transglutaminase acting at the end of the coagulation cascade, which converts fibrinogen to fibrin and stabilizes the clot by intertwining α and γ fibrin fibres. It also has a significant antifibrinolitic function, on the one hand, diminishing the plasminogen bond and the tissue activator of plasminogen to the fibrin network, and on the other hand, improving the resistance of fibrin by increasing its diameter and density in the clot. It is also involved in the repair of tissues, in cicatrisation and in the immune response to infection.

Congenital FXIII deficiency (recessive autosomal inheritance) has a low prevalence (1 case for every 2-3 million births). However, one of the main challenges is the difficulty of diagnosis because, as happens with acquired deficiency, laboratory coagulation studies (prothrombin time or activated partial thromboplastin time) are normal. Acquired deficiency may be due to an autoimmune condition, an oncological disease, a monoclonal gammopathy, or treatment with isoniazid, but hyperconsumption is particularly relevant. Thus, FXIII deficiency has shown a fundamental role in persistent bleeding or anaemisation in polytraumatized patients, major burn patients, carriers of extracorporeal support therapies (ECMO), postoperative and neurosurgery, or obstetric patients.

Clinical use of FXIII is still under study, not just in terms of diagnosing acquired deficiency after bleeding and supplementation, but also as a "prophylactic" in patients undergoing major surgery and already presenting a deficiency (levels below 50%) in the preoperative stage. Moreover, given its role in cicatrisation, FXIII deficiency has been associated with a worse evolution in patients with complicated ulcers or major burns. We do not know as much about the role of FXIII in controlling infections, where the presence of FXIII favours that certain bacteria *(Streptococcus pyogenes, Eschericha coli, Staphylococcus aureus)* remain trapped in the clot, their potential being diminished.

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Quantitative measurement of FXIII by immunological methods, although expensive, allows to determine the concentration of different antigens (FXIII-A, FXIII-B, FXIII-A2B2) and thus to classify FXIII deficiency. Qualitative methods—both specific and non-specific (viscoelastic tests)—are less developed and reliable.

The administration of FXIII is indicated for a congenital or acquired deficiency, and long-term prophylaxis is indicated in cases with congenital or chronic deficiency. Furthermore, as discussed, the indication may also be considered in patients with levels below 60% undergoing surgery. About the safety of FXIII (beyond the lack of data in newborns, babies, or other particular circumstances), over 20 years of pharmacovigilance, side effects have been rare, including 12 cases of anaphylaxis (1/98,400 doses), 5 cases of production of FXIII inhibitors (1/236,200), and 20 cases of pathogen transmission (1/59,100 doses). The authors make no reference to a potential thrombotic risk.

FXIII doses when used as prophylaxis in cases of congenital deficiency are well established, with a monthly pattern to maintain levels between 5 and 20%. FXIII levels above 3-5% are considered sufficient to prevent spontaneous bleeding. In case of bleeding or minor surgery, a 15-20 mg/kg dose of tranexamic acid may be enough, adding 10-40 UI/kg of FXIII for massive bleeding or major surgery, depending on the time of the last prophylactic dose. In pregnant patients, more frequent checks are recommended, every 14-21 days, maintaining and FXIII activity above 0.2 UI/ml; an additional FxIII dose of 10-40 UI/kg is recommended at the beginning of labour or before a C-section.

The management of acquired deficiency is more controverted. In that case, the authors suggest an initial FXIII dose of 20 Ui/kg upon diagnosis or clinical suspicion (persistent bleeding despite an appropriate haemostatic therapy). Ideally, the FXIII dose should be customized to the clinical situation and the FXIII levels, taking into account that, since the half-life of FXIII is 7-12 days, a new dose would not be necessary in the following 7 days—it could be partial between the 7th and 21st day and full from the 21st-28th day on. Nevertheless, the target level in these patients is still not defined, and different guidelines suggest different thresholds. Thus, in the perioperative setting, a minimum level of 30% has been suggested, and 60% in patients with multiple traumas, for the administration of a 15-20 UI/kg dose of FXIII.

In summary, this excellent review states the need to monitor FXIII for its appropriate replacement in bleeding patients. Further studies are required for its interpretation based on viscoelastic tests.

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A randomized controlled trial comparing effectiveness of different fibrinogen preparations in restoring clot firmness

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The **administration of fibrinogen** in patients undergoing **cardiac surgery** due to critical haemorrhage can be frequent (10-50% of patients).

Currently, there are **three different medical preparations** of fibrinogen: RiaSTAP® (CSL Behring), Fibryga® (Octapharma), and FibCLOT® (LFB).

The published in vitro studies comparing the efficacy (increase in the firmness of the clot) of RiaSTAP® vs Fibryga® do not find any differences. However, FibCLOT® is found to be superior to RiaSTAP®. Therefore, the goal of this article is to confirm whether such superiority is also found *in vivo*, in a cardiac surgery setting.

Methodology. Randomized double-blind single-site pragmatic trial.

Exclusion criteria: hemopathies, emergency surgery, hypersensitivity to any of the components of fibrinogen, liver disease, or DIC

Inclusion criteria: ≥ 18 years of age, preoperative fibrinogen < 300 mg/dL, complex cardiac surgery—more than one procedure, or aortic dissection surgery.

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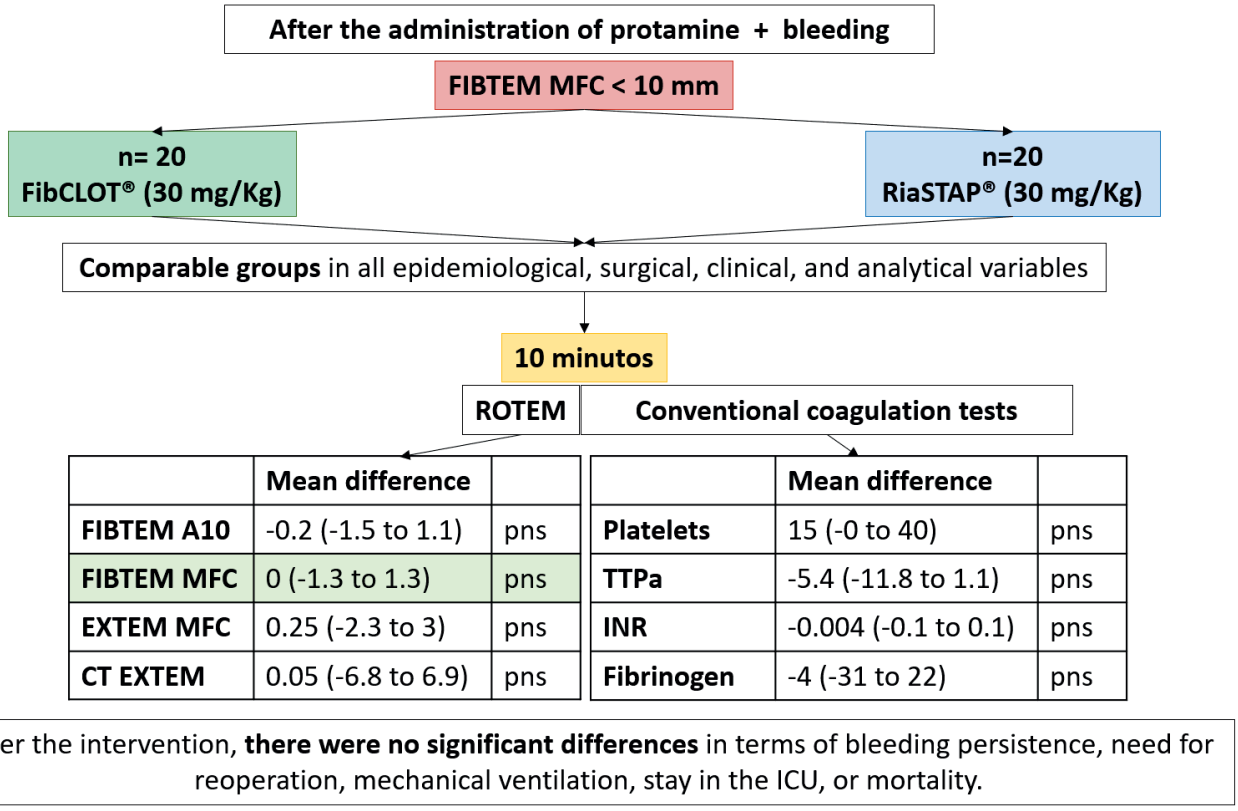

	Mean difference	
FIBTEM A10	-0.2 (-1.5 to 1.1)	pns
FIBTEM MFC	0 (-1.3 to 1.3)	pns
EXTEM MFC	0.25 (-2.3 to 3)	pns
CT EXTEM	0.05 (-6.8 to 6.9)	pns

	Mean difference	
Platelets	15 (-0 to 40)	pns
TTPa	-5.4 (-11.8 to 1.1)	pns
INR	-0.004 (-0.1 to 0.1)	pns
Fibrinogen	-4 (-31 to 22)	pns

After the intervention, **there were no significant differences** in terms of bleeding persistence, need for reoperation, mechanical ventilation, stay in the ICU, or mortality.

The **average increase of FIBTEM MFC** was **4 mm** in both groups.
Other haemostatic agents were not administered concomitantly. In cases of persisting bleeding, the appropriate haemostatic corrections were introduced under the hospital protocol.

Limitations.

- Small sample size, low power.
- Only low doses of fibrinogen are tested, and so potential differences after the administration of high doses cannot be ruled out.

Conflicts of interest. Study funded by CLS Behring, among others.

Conclusions. The study **cannot confirm that the efficacy of FibCLOT® is superior to RiaSTAP®, in vivo, in a cardiac surgery setting**. It has low power, and so further studies will be needed with the right sample size.