PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised trial
AUTHORS	Vrbica, Kamil; Hudec, Jan; Hrdy, Ondrej; Galko, Michal; Horalkova, Hana; Demlova, Regina; Kubelova, Michaela; Repko, Martin; Gal, Roman

VERSION 1 – REVIEW

REVIEWER	Karkouti, K University of Toronto, Anesthesia
REVIEW RETURNED	04-Feb-2023

GENERAL COMMENTS	The proposal is for a pilot study exploring the prophylactic use of fibrinogen concentrate in patients undergoing scoliosis surgery. It is a well written proposal that addresses a clinically relevant question and the study has initiated. I did have several questions and comments: It is not clear whether the stated aims apply to the pilot trial or to the future full trial. Please clarify what the specific primary and secondary endpoints of this pilot trial. As it reads, it seems that the primary endpoint is safety, for which this pilot study is severely underpowered. The rationale for sample size of the pilot study is stated to be based on guidelines for pilot studies. I have not reviewed the cited references, but in my view using an arbitrary sample size is not appropriate, even if it is a pilot study. Rather, the sample size whenever possible should be based on the objectives of the pilot study, such as some of the feasibility measures that are outlined. Standard of care management is based on clinician's clinical judgment, which is a weakness. It would be more appropriate to establish a standard coagulation management strategy given the objectives of the study related to transfusions and blood loss. Please provide the rationale for the dose of fibrinogen concentrate that will be administered. Since it is a prophylactic dose in elective cases, it's not clear why there is a dose range based on participants' clinical condition? Please also comment on the appropriateness of administering fibrinogen concentration without first measuring fibrinogen levels. Blinding protocol as outlined might be difficult to manage. An assessment of blinding success should be part of the objectives of the pilot trial. Please provide more details on how the randomization schedule will be prepared and assigned to participants. It would be useful to provide an estimate of the sample size for the main study based on the proposed primary outcome by obtaining your current safety data. It is unlikely that a small pilot study will

	provide enough information to allow for a robust sample size calculation for the main study.

REVIEWER	Mahrous, Rabab SS Alexandria University, Department of anesthesia
REVIEW RETURNED	25-Feb-2023

GENERAL COMMENTS	Aim: - you should specify the primary outcome to the blood loss and the secondary outcomes to be: number of blood units transfused, adverse effects, ICU length of stay and hospital stay. - how will you measure the safety - specify the adverse effects - what additional safety you will investigate as a secondary outcome comparison: - control group should receive placebo infusion after induction in order to be a blinded study - on what base the fibrinogen can be administered to all patients if indicated as you said Data collection: - should add the preoperative Cobb's angle and the operative time to the collected data - the viscoelastic hemastatic assays should be included during and after surgery. - what are the diagnostic criteria for DVT and PE, will ultrasound and CT be done routinely to all cases Ethics: - too much details about the consent, no need for all this details

VERSION 1 – AUTHOR RESPONSE

Dear Reviewer 1,

we would like to thank You for Your comments and suggestions. We have tried to implement most of them in the final text of the article. We believe these suggestions can improve and extend the article. Attached find point-by-point response to the comments of the reviewers.

Comments to the Author:

The proposal is for a pilot study exploring the prophylactic use of fibrinogen concentrate in patients undergoing scoliosis surgery. It is a well written proposal that addresses a clinically relevant question and the study has initiated.

Answer: Thank you for your appreciation.

I did have several questions and comments:

It is not clear whether the stated aims apply to the pilot trial or to the future full trial. Please clarify what the specific primary and secondary endpoints of this pilot trial.

Answer: We emphasised that the stated aims are applied to the pilot study. This information was added in the section “Aims and objectives”.

As it reads, it seems that the primary endpoint is safety, for which this pilot study is severely underpowered. The rationale for sample size of the pilot study is stated to be based on guidelines for

pilot studies. I have not reviewed the cited references, but in my view using an arbitrary sample size is not appropriate, even if it is a pilot study. Rather, the sample size whenever possible should be based on the objectives of the pilot study, such as some of the feasibility measures that are outlined.

Answer: The primary aim of our pilot study is safety, it is cleared in the section “Aims and objectives”. State Institute of Drug Control of the Czech Republic insisted on setting safety as a primary outcome. These results will provide data to determine a fully powered study, which will be focused on safety and efficacy too. The sample size of 32 participants is the limitation and it is mentioned in the section “discussion”. This situation is explained in the section “Aims and objectives”.
The sample size was defined according to the recommendation of good practice and guidelines in cooperation with the State Institute of Drug Control of Czech Republic, statisticians and investigators. It should be more cleared in the section “Sample size” (See reference: Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004 May;10(2):307–12.)

Standard of care management is based on the clinician's clinical judgement, which is a weakness. It would be more appropriate to establish a standard coagulation management strategy given the objectives of the study related to transfusions and blood loss.

Answer: The standard of care management is based on current guidelines or recommendations at the time the study was created and local protocol which respects these guidelines (See reference: Kozek-Langenecker, Sibylle A.; Ahmed, Aamer B. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. European Journal of Anaesthesiology 34(6):p 332-395, June 2017.). We added more information about standard of care, including the indication of specific thresholds and management of bleeding. All information is cleared in the section “Intervention”.

Please provide the rationale for the dose of fibrinogen concentrate that will be administered. Since it is a prophylactic dose in elective cases, it’s not clear why there is a dose range based on participants’ clinical condition?

Answer: The prophylactic dose is based on a package leaflet of fibrinogen concentrate. This package leaflet contains the information about clinical conditions too, but it is not rational in our pilot study, so this information is erased now. We administer the dose of 20-30 mg/kg (based on the package leaflet) and investigators administer IMP in doses of hundred of mg in this range (rounded to closest hundred in dose range).

Please also comment on the appropriateness of administering fibrinogen concentration without first measuring fibrinogen levels.

Answer: The routine preoperative fibrinogen level test is mentioned in the section “Intervention”. Investigators know the fibrinogen level before surgery, however, if it is not significantly pathological, investigators respect pilot study protocol, in case of significant deviation, the haematologist will be invited, as mentioned in the section “Intervention”.

Blinding protocol as outlined might be difficult to manage. An assessment of blinding success should be part of the objectives of the pilot trial.

Answer: We emphasised the role of unblinded team during non/-administartion of IMP as the team, which maintains the anaesthesia. So a blinded surgical team can always leave the theatre during non/-administartion of IMP. Based on this measure, we are able to ensure absolute blinding of the surgical team.

Please provide more details on how the randomization schedule will be prepared and assigned to participants.

Answer: The randomization is performed electronically by an electronic case report form (REDCap) database by an unblinded person. The randomization list was generated by the study statistician and implemented in the eCRF by the study data manager. Patients will be randomised in a 1:1 ratio to receive fibrinogen or standard of care without further study medication. Afterward the unblinded person will indicate non/-administartion of IMP. The procedure is now emphasised in the section "Randomization and blinding".

It would be useful to provide an estimate of the sample size for the main study based on the proposed primary outcome by obtaining your current safety data. It is unlikely that a small pilot study will provide enough information to allow for a robust sample size calculation for the main study.

Answer: The safety and efficacy of prophylactic administration of fibrinogen is not known. The sample size was determined with cooperation of statisticians and the State Institute of Drug Control of the Czech Republic. However, to date we have included about ⅔ of participants and we are not able to provide an estimate of sample size for the full study.

Dear Reviewer 2,

we would like to thank You for Your comments and suggestions. We have tried to implement all of them in the final text of the article. We believe these suggestions can improve and extend the article. Attached find point-by-point response to the comments of the reviewers.

Comments to the Author:

Aim: - you should specify the primary outcome to the blood loss and the secondary outcomes to be: number of blood units transfused, adverse effects, ICU length of stay and hospital stay.

Answer: The primary and secondary outcome measures are cleared and specified in the section "Aims and objectives". The primary outcome is safety, the secondary outcomes are mentioned and more divided in the article.

- how will you measure the safety

Answer: The safety will be measured in accordance with European directive 2001/20/EC (new reference '26' - European Parliament and Council of the European Union (2001) Directive 2001/20/EC of the European Parliament and the Council of 4 Apr 2001. OJ L 121: 34–44. Available: http://eudract.emea.eu.int/docs/Dir2001–20_en.pdf.), specifically it is the incidence of any adverse events, adverse drug reactions, serious adverse events, serious adverse reactions, unexpected adverse reactions and suspected unexpected serious adverse reactions. The measure of the safety is explained and emphasised in section "Aims and objectives".

- specify the adverse effects

Answer: The adverse effects are more discussed and specified in section "Aims and objectives", according to the recommendation of the European directive (reference above).

- what additional safety you will investigate as a secondary outcome

Answer: Adverse Events of Special Interests, such as deep vein thrombosis, pulmonary embolism, and infection or healing disorder requiring re-surgery and/or the initiation of antibiotic therapy, are mentioned in section "Aims and objectives".

comparison: - control group should receive placebo infusion after induction in order to be a blinded study

Answer: The absence of the placebo in control is mainly caused by the requirements of the State Institute of Drug Control of the Czech Republic. It does not allow the administration of a placebo without

a therapeutic or preventive effect in the paediatric population. This fact is mentioned in the section "Comparison" now, we mentioned it as a limitation of the study in the section "Discussion".

- on what base the fibrinogen can be administered to all patients if indicated as you said

Answer: We mentioned the information about local protocol for bleeding management based on international guidelines in the section "Comparison". The local protocol and recommendations are mentioned in the section "Intervention".

Data collection: - should add the preoperative Cobb's angle and the operative time to the collected data

Answer: We added Cobb's angle and the operative time in the section "Data collection".

- the viscoelastic hemostatic assays should be included during and after surgery.

Answer: The viscoelastic hemostatic assays are part of the local protocol for bleeding as mentioned in section "Intervention" in revised manuscript. We are considering inclusion of viscoelastic hemostatic assays into fully powered study.

- what are the diagnostic criteria for DVT and PE, will ultrasound and CT be done routinely to all cases

Answer: We emphasised the individual approach to diagnosis of DVT or PE. CT scan or ultrasound will not be done routinely, as now mentioned in the section "Data collection".

Ethics: - too much details about the consent, no need for all this details

Answer: The pilot study is focused on the paediatric population, the vulnerable population. In addition, the data about effects of prophylactic fibrinogen administration on children are rare. We consider it necessary to discuss this ethical question in more detail.

VERSION 2 – REVIEW

REVIEWER	Mahrous, Rabab SS Alexandria University, Department of anesthesia
REVIEW RETURNED	21-Apr-2023

GENERAL COMMENTS	Accept