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Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised trial

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ABSTRACT

Introduction Fibrinogen is one of the essential coagulation factors. Preoperative lower plasma fibrinogen level has been associated with higher blood loss. Scoliosis surgery presents a challenge for the anaesthetic team, one of the reasons being blood loss and transfusion management. Recently, the prophylactic fibrinogen administration has been a debated topic in various indications. It has been described for example, in urological or cardiovascular surgery, as well as in paediatrics. This pilot study is focused on verifying the feasibility of potential large randomised trial and verifying the safety of prophylactic fibrinogen administration in paediatric scoliosis surgery.

Methods and analysis A total of 32 paediatric patients indicated for scoliosis surgery will be recruited. Participants will be randomised into study groups in a 1:1 allocation ratio. Patients in the intervention group will receive prophylactic single dose of fibrinogen, in addition to standard of care. Patients in the control group will receive standard of care without study medication prior to skin incision. The primary aim is to assess the safety of prophylactic fibrinogen administration during scoliosis surgery in children, the incidence of any adverse events (AEs) and reactions will be monitored during participation in the study. The secondary objective is to investigate the additional safety information, feasibility and efficacy of a prophylactic fibrinogen administration. The incidence of AEs and reactions according to selected adverse events of special interest will be monitored. All collected data will be subjected to statistical analysis according to a separate statistical analysis plan.

Ethics and dissemination This trial follows the applicable legislation and requirements for good clinical practice according to the International Conference on Harmonisation E6(R2). All essential trial documents were approved by the relevant ethics committee and national regulatory authority (State Institute for Drug Control) and their potential amendments will be submitted for approval.

Trial registration number NCT05391412.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Results of this study might improve knowledge about prophylactic fibrinogen administration in the paediatric population during scoliosis surgery.
⇒ The results of this feasibility study will provide data to plan a fully powered randomised trial.
⇒ Results of this study might support the claim about the safety of the fibrinogen administration before surgery.
⇒ The participants are younger than 18 years at the time of recruitment, according to national legislation, the informed consent must be signed by both parents or legal guardians.
⇒ The feasibility assessment may indicate a lack of data to determine the influence on blood loss and bleeding management.

BACKGROUND

Scoliosis is defined as an abnormal lateral deviation of the spine of >10° in the frontal plane, with deviation in the sagittal plane and vertebral rotation. It is one of the most common spinal deformities in children.[1–3] The approach to the treatment is multidisciplinary and depends on the scoliotic curve severity and progression.[4] The surgery is commonly indicated in patients with progressive curves and Cobb angle >40° to stop further progression of the curve and prevent the development of multiple organ disease.[4] Except for musculoskeletal disorders, cardiovascular, respiratory, gastrointestinal or psychosocial problems are described in patients with scoliosis.[5] Anaesthesia for scoliosis surgery is a highly challenging task for the whole team. The specifics of such anaesthesia include long operation time, body temperature decrease, high blood losses, positioning or intraoperative neurophysiological monitoring.[6 7]

During scoliosis surgery, high blood loss and the necessity of blood transfusions are described, while allogeneic derivatives are necessary in the perioperative period in about

30%–60% of cases.[8] Bleeding complications and adverse events (AEs) associated with blood transfusions prolong and increase the cost of hospitalisation and increase the mortality.[9] Well-known and commonly applied approaches to reduce blood loss include antifibrinolytics, such as tranexamic acid, which can be administered before surgery,[10 11] permissive hypotension, which can be used to reduce blood loss. Prevention of hypothermia is another way to reduce bleeding, and cell selvage, especially in high-risk patients, where it is preferred to minimise allogeneic blood transfusions.[12]

Fibrinogen is essential for clot formation and stopping bleeding.[13 14] Hypofibrinogenaemia or dysfibrinogenaemia leads to more severe bleeding during high-extensive surgery.[15–17] Moreover, some studies describe less blood loss in patients with higher preoperative fibrinogen levels.[18] Prophylactic administration of fibrinogen is a widely discussed theme, but to date, the data are limited.[19] Some studies described a significant reduction in blood loss and a secondary reduction in allogeneic derivatives administration. Prophylactic fibrinogen administration has been described in cardiovascular or urological surgery.[20–22] Additionally, early administration has been reported to be safe in the paediatric population.[23]

However, the effect of prophylactic fibrinogen administration in paediatric scoliosis surgery remains unclear. We designed this study to verify the feasibility of prophylactic fibrinogen administration in paediatric scoliosis surgery. The results will be used to plan a sufficiently large randomised trial with the aim to clarify the impact of prophylactic fibrinogen application on the magnitude of blood loss and the need for transfusion. This study is focused on the safety, efficacy and feasibility of prophylactic administration of fibrinogen in scoliosis surgery. The clinical outcome of each participant is studied, particularly the incidence of potential AEs such as thromboembolism, allergic reactions or fevers. The results of this study may improve knowledge about prophylactic fibrinogen application. All participants in this study will contribute to this socially beneficial knowledge.

METHODS AND ANALYSIS

Study design

The setting of the study is two-arm, prospective, monocentric, randomised, double-blind pilot trial with a 1:1 allocation ratio testing safety, efficacy and feasibility of prophylactic fibrinogen administration during scoliosis surgery in the paediatric population. The pilot study started on 1 June 2022 and the estimated end of the study is planned on 30 September 2023. The study protocol is compiled according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.[24]

Aims and objectives

This pilot study is conducted before designing a fully powered study and it aims to assess the safety, feasibility and efficacy of prophylactic fibrinogen administration during scoliosis surgery in the paediatric population. Results will be used to optimise the fully powered study design and determine the final sample size.

The primary aim of a pilot study is to assess the safety of perioperative infusion of fibrinogen during scoliosis surgery in children. The incidence of any AEs, adverse drug reactions, serious AEs, serious adverse reactions, unexpected adverse reactions and suspected unexpected serious adverse reactions will be monitored during participation in the study. These primary outcomes monitoring respects European directive 2001/20/EC.[25]

The secondary aim is to investigate the additional safety information, feasibility and efficacy of a prophylactic administration of fibrinogen. The incidence of AEs and reactions according to the following adverse events of special interest (AESI) will be monitored. Monitored AESI include deep vein thrombosis verified on ultrasound imaging, pulmonary embolism confirmed on CT scan and infection or healing disorder requiring resurgery and/or the initiation of antibiotic therapy. Additional safety information include intensive care unit (ICU) and hospital length of stay (days) and 28-day mortality.

Other end points and monitored parameters, such as additional safety information, demographic characteristics, laboratory values, comparison of blood loss or feasibility assessment, are mentioned in the section ‘Data collection’.

Participants

Eligibility criteria

All patients admitted to the hospital for scoliosis surgery will be screened for inclusion criteria. When inclusion criteria will be met, the exclusion criteria will be checked. Only patients with fulfilled all inclusion criteria and without all exclusion criteria will be considered for participation in the study.

Inclusion criteria

- Elective scoliosis surgery.
- Age <18 years at the time of enrolment.
- Signed the relevant informed consent form (ICF).
- Sexually active participants (aged ≥15 years) must agree to the use of following methods of contraception for the duration of this clinical trial:
  - Women—proper use of a highly reliable method of contraception, that is, combined hormonal contraception (oral, vaginal or transdermal form), gestagen hormonal contraceptives associated with ovulation inhibition (oral or injectable form) or sexual abstinence.
  - Men—sexual abstinence or the use of an adequate contraceptive method (ie, condom) in case of sexual intercourse.

Exclusion criteria

- Diagnosed congenital or acquired coagulopathy.
- Use of anticoagulants with the exception of perioperative prophylactic administration of low molecular weight heparin to prevent venous thromboembolism.
- Known hypersensitivity to the active substance or to any of the excipients of investigational medicinal product (IMP).
- History of deep vein thrombosis or pulmonary embolism.
- Pregnancy and lactation.

Recruitment and withdrawal

The study is conducted at University Hospital Brno, Czech Republic, in cooperation with the Department of Anaesthesiology and Intensive Care Medicine and the Department of Orthopaedic Surgery. The study is controlled by research infrastructure CZECRIN. All patients eligible for the study and the patient's parents/legal guardians will be asked to participate in the Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS) study. The informed consent has to be signed by both parents or legal guardians. For patients who reach the age of 12 years at the time of enrolment, adapted written information and an informed consent is prepared considering the level of knowledge and the age of patients. All participants or their parents/legal guardians can withdraw at any time without giving any reason, but they must notify the investigator.

Sample size

Since this is a pilot study, a power calculation to determine sample size is not required. The sample size was defined in consensus by the State Institute of Drug Control of the Czech Republic, statisticians and investigators. Thirty participants (15 in both arms) were defined as a sample size according to standard guidelines for pilot studies and recommendation of good practice.[26–28] Considering a 5% dropout rate, 32 participants will be recruited.

Randomisation and blinding

Patients will be randomised in a 1:1 ratio to receive fibrinogen or standard of care without further study medication. Randomisation will be performed electronically in the electronic case report form (eCRF) Research Electronic Data Capture (REDCap) database. This eCRF was created by study statisticians and study data managers and contains a randomisation list. Unblinded person will perform the randomisation after controlling all inclusions and exclusions criteria before induction to the anaesthesia. Based on the randomisation process, an unblinded person indicates IMP application/non-application before skin incision.

The study medication will be prepared by the unblinded study nurse outside the operating theatre. It will be administered after induction of anaesthesia before the beginning of surgery under the supervision of an unblinded investigator. The study nurse and investigator will be unblinded for the duration of this study and will not be part of the operating team. The blinded surgical team (orthopaedist, anaesthesiologist and anaesthesiology nurse) will be outside the theatre during the IMP application/non-application. The unblinded study team maintains the anaesthesia respecting local protocol for paediatric scoliosis anaesthesia during the IMP application/non-application. After IMP application/non-application, unblinded study nurse and unblinded investigator will leave the operating room, and the blinded operating team will enter back to the theatre. Based on these blinding measures, we are able to ensure absolute blinding of the surgical team.

The data management group and statisticians will work with a pseudo-anonymised data set. Emergency unblinding before the end of the study should occur only in exceptional circumstances when knowledge of the actual treatment is necessary for further management of the patient's treatment. This activity can be performed directly in the REDCap electronic database. The investigator must report all unblindings (with reason) as they occur on the corresponding eCRF page.

Intervention

Choice of comparators

Bleeding and coagulopathy are present during scoliosis surgery, and lack of fibrinogen plays a crucial role in it. We decided to reduce blood loss and coagulopathy development, the fibrinogen will be administered preventively in the intervention arm. The standard of care presents respecting local protocol based on international guidelines (see section 'Standard of care'). This standard approach will be compared with the intervention.

Standard of care

All study participants will receive standard of care in blood and coagulation management for scoliosis surgery. Blood tests including haemoglobin (Hb), haematocrit (Htc), platelet count (Plt), fibrinogen level (Fbg), activated partial thrombin time (aPTT), prothrombin time (PT) and thrombin time (TT) will be performed before the surgery. Values will be checked before surgery, and in case of significant pathology, the surgery will be delayed and the haematologist will be invited. Tranexamic acid will be administered to all patients before the skin incision in a dose of 10–15 mg/kg. The standard of care includes the restrictive administration of blood transfusion, plasma derivative and fluids during the perioperative period. The anaesthesiologist or attending physician in the ICU will administer fluids, blood transfusions and derivatives depending on clinical judgement, blood loss, blood count, coagulation tests and vital signs. This administration is directed by the local protocol of the investigator's hospital which respects international guidelines. 'Goal-directed therapy' approach is preferred in case of bleeding in perioperative period. When the blood loss exceeds about 25% of estimated total blood volume of the patient, blood samples (blood count,

coagulation status and/or viscoelastic haemostatic assay) are performed and blood transfusions and derivatives are managed according to the results. The goals during bleeding are Hb 70–90 g/L, fibrinogen >2 g/L, platelets >50×10^9/L and normalisation of coagulation status. In case of life-threatening bleeding, the transfusion strategy of fibrinogen concentrate with red blood cells or fresh frozen plasma with red blood cells in ratio of at least 1:2 is performed. The local protocol respects international guidelines.[29]

Intervention description

Participants in the intervention group will receive the standard of care, and in addition, a single dose of fibrinogen prior to the skin incision. IMP is administered intravenously and is immediately available at a plasma concentration corresponding to the dose. It is in a powder form in a vial, and it is necessary to solve this powder carefully. The reconstitution procedure should follow the instructions in the package leaflet. Patients in the intervention group will receive a single dose of IMP intravenously, 20–30 mg/kg. This dose range is based on the package leaflet and investigators will administer IMP in doses of hundreds of mg in this range (rounded to closest hundred in dose range). The medicinal product will be diluted in a 100 mL infusion bag and will be administered after induction to anaesthesia before surgery. The infusion rate should not exceed approximately 5 mL/min. The IMP will be administered according to the above study blinding rules.

Comparison

Participants in the intervention group will receive standard of care and IMP before skin incision. Participants in the control group will receive standard of care without study medication before skin incision. In the control group, the placebo will not be administered. It is caused by the requirements of the national regulatory authority (State Institute of Drug Control of the Czech Republic), which does not allow the administration of a placebo in the paediatric population unless it has therapeutic or preventive effect.

The blinded operating team will manage both groups according to the standard of care after the initial intervention/non-intervention. Therefore, fibrinogen can be administered to all patients if indicated in perioperative period according to the local protocol for bleeding management (see section Standard of care).

Primary and secondary outcomes will be compared between intervention and control groups to assess the potential feasibility of a large-scale study.

Trial feasibility

The trial feasibility assessment is one of the secondary aims of this study. We will monitor the recruitment rate of eligible patients who will be approached for consent to participate. The feasibility criterion is >75% of enrolled participants. We will also evaluate the percentage of missing outcomes and clinical data. The goal is to have <10% missing outcome data, including ICU and hospital length of stay (LOS) and survival, and <10% missing clinical data obtained from clinical medical notes and electronic patient records.

Clinical outcomes

The clinical outcome focuses on reducing blood loss and transfusions in paediatric patients after prophylactic fibrinogen administration during scoliosis surgery. Blood loss and plasma derivatives management will be reported for each participant. Blood count and coagulation parameters will be monitored before surgery, in the end and 24 hours after the surgery. All parameters will be recorded in the eCRF database.

Data collection

During the course of the trial, subjects will be monitored during hospitalisation and after discharge. According to medical records, all data will be collected in an eCRF. Data of blood count (Hb, Hct, Plt) and coagulation status (PT, aPTT, TT, Fbg) will be filled in eCRF before surgery, after surgery and 24 hours after surgery. Information about inclusion and exclusion criteria, informed consent and demographic data will be obtained on the day of enrolment. Collected participant demographic data will be age (years), sex (male, female), weight (kg) and Cobb's angle (°). Blood samples will be taken before surgery according to standard of care, postoperative blood samples will be taken immediately after surgery and 24 hours after surgery. We will record operative time, blood loss, the volume of blood loss for the surgical segment of the spine and urinary output during surgery and 24 hours after surgery. We will track the number, type and volume of administered transfusion products, plasma derivatives, crystalloid solutions and colloid solutions during surgery and in 24 hours postoperative period. The critical part of monitored data will be the incidence of AEs and reactions according to the following AESI. These reactions will include deep vein thrombosis verified on ultrasound imaging, pulmonary embolism confirmed on CT, infection or healing disorder requiring resurgery and/or the initiation of antibiotic therapy. Ultrasound imaging or CT scan will be indicated individually, only in patients with suspicion of AESI according to the clinical condition.

Other monitored additional safety information will be:

- Hospital LOS.
- ICU LOS (day of admission and day of discharge will be counted as 1 day).
- Twenty-eight-day mortality (number of patients who are not alive 28 days after randomisation).

According to the SPIRIT checklist, the schedule of enrolment, interventions and assessments is summarised in table 1.[24]

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books and

Table 1 Clinical trial schedule

	Study period						
	Screening	Allocation	Postallocation		Hospital discharge	Follow-up	Premature termination
Timepoint	D_0	D_{0-1}	D_1	D_2	D_{3-28}	D_{28}	*Anytime*
Enrolment							
Inclusion/Exclusion criteria	X						
Informed consent	X						
Pregnancy testing*	X						
Randomisation		X					
Intervention							
Study medication application†			X				
Assessments							
Demographic data‡	X						
Adverse events			X	X	X	X	X
Laboratory testing§			X	X			
Blood loss¶			X	X			
Urinary output**			X	X			
Transfusion products consumption††			X	X			
Fluid therapy††			X	X			
ICU LOS (days)					X		
LOS (days)					X		
28-day mortality						X	
Reason for premature termination							X

*Urine pregnancy testing.
†Fibrinogen infusion or standard of care.
‡Age, sex, weight, Cobb's angle.
§Haemoglobin, haematocrit, platelet count, fibrinogen, aPTT, PT, TT.
¶Volume (mL) during surgery and in the 24-hour postoperative period and volume (mL) related to the surgical segment of the spine.
**Volume (mL) in the 24-hour postoperative period.
††Type and volume (mL) during surgery and in the 24-hour postoperative period.
aPTT, activated partial thrombin time; ICU, intensive care unit; LOS, length of stay; PT, prothrombin time; TT, thrombin time.

other listings that link participant ID numbers to additional identifying information will be stored in a locked file in an area with limited access. No later than 3 years after the collection of the 1-year postrandomisation, we will deliver a completely blinded data set to an appropriate data repository for sharing purposes. Statistical codes will be archived in accordance with standard operating procedures.

Statistical analysis

A separate statistical analysis plan (SAP) will be prepared to provide details on the approach to analyses. The SAP will be finalised before the database lock. All eventual deviations from the SAP will be described and justified in the relevant part of the Clinical Trial Report. As a general approach for the descriptive analysis, the following statistics will be provided for continuous variables: the number of subjects with available data (n), mean, SD, median, minimum and maximum. The number and percentage of patients will be provided for categorical variables. For a comparison of continuous variables between treatment groups, two-sample t-test or its non-parametric alternative Mann-Whitney U test will be used, where appropriate. Pearson's χ^2 test or Fisher's exact test will be used to compare categorical variables, where appropriate. All statistical tests will be two-sided. P values <0.05 will constitute statistically significant differences. During the pilot study, the interim analysis is not planned.

Protocol non-adherence will be assessed by the principal investigator case by case. Patients with major deviations from the study protocol will be excluded from the analysis. Missing data are not planned to be imputed. However, in the event of substantial missing data for any parameter, a sensitivity analysis using any method of imputation could also be used.

Patient and public involvement

Patients or the public will not be involved in the study development. This EFISS study was proposed and designed by an expert team of University Hospital Brno and the Faculty of Medicine, Masaryk University Brno in the Czech Republic.

Monitoring and auditing

The trial centre will be monitored according to the monitoring plan provided by research infrastructure CZECRIN. The objectives of the monitoring are to ensure that the trial participant's safety and rights are respected, that accurate, valid and complete data are collected and that the trial is conducted in accordance with the trial protocol, the principles of good clinical practice (GCP) and national legislation. Sponsor, regulatory authority and ethics committees have the right to inspect/audit the trial site.

ETHICS AND DISSEMINATION

This trial follows the applicable legislation and requirements for GCP according to the ICH E6(R2). Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected and that the clinical trial data are credible.

All essential trial documents were approved by the relevant ethics committee and national regulatory authority (State Institute for Drug Control) and their potential amendments will be submitted for approval. The study was approved by University Hospital Brno's Ethics Committee (No.: 24/22MONO) and by State Institute for Drug Control (No.: sukls11048/2022). This clinical study includes patients belonging to the category of vulnerable subjects, namely children and adolescents under 18 years of age.

Informed consent procedure

The parents/legal guardians will receive written information and an ICF. The investigator will inform in a comprehensible manner about the nature, purpose and significance of the clinical trial simultaneously. This procedure will take place before enrolling the child in the study. Parents/Legal guardians will also be informed of the measures to protect personal data. That liability insurance has been arranged for investigators and sponsors in the event of health damage due to a clinical trial, including possible compensation for trial subjects. Paediatric patients will receive from the investigator information on the clinical trial adapted to their level of knowledge and intellectual abilities, including details on the benefits and risks of participating in this clinical trial. The explicit wish of instructed paediatric patients to refuse to participate or to withdraw from a clinical trial at any time is always respected. Written information and an informed assent form are prepared for patients who reach the age of 12 years at the time of enrolment. Paediatric patients and their parents/legal guardians will get sufficient time to study the written information and the ICF carefully and will ask additional questions to which the investigator must respond satisfactorily. All legal representatives (both parents) must sign the ICF at the end of the process.

Supervision of the informed consent procedure

The process of obtaining informed consent from the patient's parents/legal guardians, or patients, must always be adequately documented by the investigator using valid forms and the patient's medical records. The clinical trial monitor will check the process during monitoring visits. Significant deviations in the process will lead to the termination of the patient's participation in the trial.

DISCUSSION

Prophylactic fibrinogen administration before high-risk surgeries is a widely discussed topic across medical fields. Preoperative lower levels of fibrinogen are associated with higher blood loss in adolescent idiopathic scoliosis surgery. However, if the effect of prophylactic fibrinogen administration will lead to blood loss reduction in these patients is unclear.[16 17 30]

The safety of fibrinogen administration in the paediatric population has been demonstrated in several studies.[23 31] However, in these studies, fibrinogen was substituted during the surgery according to the viscoelastic haemostatic assays, the substitution was not prophylactic. In addition, the number of participants was low. In summary, data on prophylactic administration in children and adolescents are insufficient, more studies are needed.

We can see some similarity with tranexamic acid administration. In recent years, tranexamic acid has been commonly used in scoliosis surgery to reduce blood loss.[32–34] The efficacy of tranexamic acid is unambiguous, it reduces blood loss, the need for blood transfusions and the length of hospitalisation.[32] The use of tranexamic acid is incorporated in orthopaedic recommendations for blood management.[35] However, some studies have provided evidence of the thromboembolic potential of tranexamic acid.[36 37] In contrast, fibrinogen is not associated with higher thromboembolic risk repeatedly.[38] It is appropriate to study fibrinogen concentrate to see if it has the same positive properties as tranexamic acid without possible side effects.

This pilot study also has some limitations. The sample size is designed according to standard guidelines for pilot studies, so it is limited to 32 patients. Participants are under the age of 18 years, so informed consent has to be signed by both parents or legal guardians, which may lead to limited enrolment. Data are collected 28 days after randomisation, which may not be an adequate interval to evaluate safety and feasibility. And final limitation is the absence of placebo administration in the standard of care group. This absence is mainly caused by the requirements of the national regulatory authority, which does not allow

the administration of a placebo without a therapeutic or preventive effect in the paediatric population.

CONCLUSION

This pilot study should demonstrate the safety and feasibility of the intended intervention and form the basis for a later large study which could have extensive impact in scoliosis surgery and bleeding management. But the results will not prove most likely the efficacy of prophylactic administration of fibrinogen in scoliosis surgery.

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Disclaimer The sponsor has no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or the decision to submit results.

Competing interests In the past 5 years, KV and RG have received honoraria for lecturing from CSL Behring.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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