

BMJ Open Perioperative management with ferric carboxymaltose and tranexamic acid to reduce transfusion rate in gynaecological carcinoma surgery (TRANAFER-Study): study protocol for a single-blind, monocentre, randomised trial

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ABSTRACT

Introduction Radical abdominal surgery is part of the standard treatment for women with advanced gynaecological carcinoma. The surgery often leads to intraoperative blood loss frequently exceeding 1000 mL. Approximately 50% of women undergoing radical surgery require blood transfusions. Perioperative blood transfusions have been shown to increase the risk of postoperative complications, delayed wound healing, increased length of stay, increased postoperative morbidity and mortality. Previous studies have demonstrated an association between perioperative anaemia and surgical morbidity and mortality. By reducing transfusions and improving recovery from surgery, preoperative diagnostic and management of perioperative anaemia is a great opportunity to optimise postoperative patient outcome.

Methods and analysis This is a single-blind, monocentre, randomised trial with four parallel groups (three therapeutic groups and one control group without treatment according to current standards of care) conducted in women undergoing radical gynaecological surgery. The primary study objective is to determine the effect of perioperative treatment with either intravenous iron, tranexamic acid or with a combination of both medicines on the reduction of intraoperative and postoperative red blood cell transfusions in gynaecological carcinoma patients. A total of N=126 women with gynaecological carcinoma will be recruited at the University Hospital Basel, Department of Gynaecology. Blood parameters will be measured at the recruitment, prior to surgery, 2 days after surgery and on the 21st–28th day after surgery. Recruitment started in August 2021. **Ethics and dissemination** The study will be performed according to the guidelines of the Declaration of Helsinki and is approved by the Ethics Committee for Northwest and Central Switzerland in Basel (EKNZ Protocol ID 2020-01194). The results of this study will be published and presented in various scientific forums.

Trial registration number NCT03792464.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ For the first time to our knowledge, a randomised study will be performed in order to study the effect of perioperative treatment with intravenous iron, tranexamic acid and with both these medications on the reduction of intraoperative and postoperative red blood cell transfusions in gynaecological carcinoma patients.
- ⇒ Our findings aim to show the reduction of perioperative complications as well as postoperative morbidity and mortality, leading to improved recovery from surgery and could consequentially be implemented in clinical practice as a part of patient blood management.
- ⇒ Secondary outcomes include establishment of patient blood management in gynaecological cancer surgery can lower the costs associated with transfusion requirements, such as prolonged hospitalisation, postoperative complications, prolonged incapacity for work and so forth.
- ⇒ An important limitation of this study may be the size of the study population for the analysis of secondary outcomes since we only powered for our primary outcome. A further limitation might be a heterogeneous population due to inclusion of patients with varying gynaecological carcinoma.

INTRODUCTION

Radical abdominal surgery is part of the standard treatment for women with advanced gynaecological carcinoma.¹ The surgery often leads to intraoperative blood loss frequently exceeding 1000 mL. Approximately 50% of women undergoing radical surgery require blood transfusions.² Perioperative blood transfusions have been associated with the

increased risk of postoperative complications, delayed wound healing, increased length of stay, increased postoperative morbidity (eg, pulmonary complications, postoperative renal dysfunction, systemic sepsis and composite morbidity) and mortality.³⁻⁵

Previous studies have demonstrated an association between perioperative anaemia and surgical morbidity and mortality (eg, increased length of intensive care and hospital stay, postoperative complications and worse overall outcome).⁶⁻⁷ Patient blood management (PBM) aims to minimise blood transfusion administration, treat preoperative anaemia, reduce perioperative blood loss and thus improve patient outcome after surgery. Consequently, recognition and management of perioperative anaemia represents an opportunity to optimise haemoglobin (Hb) levels before surgery, thereby reducing blood transfusion and potentially improving recovery from surgery and associated postoperative outcomes.

Previous studies have shown a strong association between tranexamic acid and reduction of red blood cell (RBC) transfusions in surgery.⁸⁻¹¹ The important role of iron in perioperative PBM in major abdominal surgery could also be shown.¹²⁻¹⁷ However, the use of tranexamic acid and intravenous iron in gynaecological patients was only examined by Lundin *et al*¹⁸ and by Kim *et al*¹⁴ so far.

In our study, we will investigate the efficacy of perioperative treatment with intravenous iron and tranexamic acid on the reduction of intraoperative and postoperative RBC transfusions in gynaecological carcinoma patients undergoing radical abdominal surgery. We will compare the effect of these two medications administered in three different treatment groups. As part of the secondary analysis, the proportion of perioperative transfused women, blood loss, perioperative complications as well as perioperative morbidity and mortality will be examined.

METHODS AND ANALYSIS

Primary and secondary outcomes

The primary study outcome is to investigate the difference in the number of RBC transfusions administered during and after surgery between groups with current standard of care (group 4) and groups with intravenous iron (group 1), with tranexamic acid (group 2) and with both these drugs (group 3).

The secondary outcomes are:

- ▶ The difference in Hb prior to surgery compared with second day after surgery.
- ▶ The difference in Hb prior to surgery compared with day 21–28 after surgery.
- ▶ The rate of transfused women.
- ▶ Blood loss measured during surgery.
- ▶ The rate of different blood product transfusions (fresh frozen plasma, autologous whole blood).
- ▶ The rate of additional local or systemic haemostatic therapy (eg, Tabotamp, Tachosil, Dicynone).
- ▶ Duration of surgery (in minutes).
- ▶ Length of stay in hospital (in days).

- ▶ Incidence of early postoperative complications: abdominal pain, haemorrhage, need of reoperation due to intraabdominal bleeding.
 - ▶ Incidence of later postoperative complications: (delayed wound healing, pulmonary complications, postoperative renal dysfunction, systemic sepsis and composite morbidity).
 - ▶ Postoperative mortality.
- The study will examine the following safety outcomes:
- ▶ The rate and the severity of adverse events.
 - ▶ The rate of thromboembolism between visits 2 and 5.
 - ▶ The rate of hypophosphataemia after intravenous iron measuring serum phosphate prior to iron infusion and on days 21–28.
 - ▶ Clinical symptoms of hypophosphataemia.

Study design

This is a single-blind, monocentre, randomised trial with four parallel groups designed to study the efficacy of ferric carboxymaltose and/or tranexamic acid administered perioperatively in gynaecological carcinoma surgery.

Study settings

The study will be conducted at the University Hospital Basel, Department of Gynaecology. A total of N=126 women with gynaecological carcinoma (ovarian, Fallopian tube, endometrial or cervical carcinoma) will be recruited in our outpatient's department in order to obtain a total of 114 evaluable patients, considering a drop-out rate of 10%. The study commenced in August 2021. We expect to recruit all patients within 24 months (August 2021–August 2023) and we assume that the study will be completed in August 2024. The participants will randomly be enrolled after providing their informed consent and will be blinded. They will not be informed about the allocation and procedure.

Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- ▶ Informed consent as documented by signature.
- ▶ Women with gynaecological carcinoma surgery with a Hb level between 90 and 140 g/L and serum ferritin <250 µg/L (or ferritin index <3.19) at recruitment.
- ▶ Age >18 years.
- ▶ A negative pregnancy test in women younger than 50 years and in women older than 50 years with menstruation. A pregnancy test will be not conducted in women over 50 years of age with amenorrhoea lasting for more than 1 year.

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- ▶ Known hypersensitivity or allergy to ferric carboxymaltose or tranexamic acid.
- ▶ A history or present laboratory signs of bleeding disorders, coagulopathy or thromboembolic events.

- ▶ A history of myocardial infarction within the last year, present unstable angina or severe coronary disease.
- ▶ Increased plasma creatinine levels above 250 µmol/L.
- ▶ Inability to follow the procedure of the study (eg, barrier of language, severe psychiatric or mental disorders).
- ▶ Iron overload.
- ▶ Current administration of intravenous iron or previous intravenous iron therapy or blood transfusion within the last 3 months.
- ▶ Scheduled surgery is beyond 28 days after the date of recruitment.
- ▶ Other clinically significant concomitant diseases (such as severe hepatic dysfunction, severe cardiovascular dysfunction).
- ▶ Participation in another study with an investigational drug within 30 days.
- ▶ Enrolment of investigators, their family members, employees and others involved in this trial.

Randomisation and withdrawal

At the screening, the women will be informed about the study and will be asked to participate. If the woman wants to participate in the study, blood samples will be taken. If all inclusion criteria are met and a signed declaration is available, the patient will be randomised electronically at visit 2. A computer-generated randomisation schedule will be used. In participants randomised to group 1 or 3, an iron infusion will be administered at least 5 days prior to surgery. Participants will be informed that they are free

not to participate in the study and that they may withdraw consent to participate at any time. The reasons for withdrawal from the study are:

- ▶ Withdrawal of informed consent.
- ▶ Death.
- ▶ Non-compliance.
- ▶ Discontinuation of clinical trial.

Study procedures

Haematological parameters, iron status, serum phosphate, vitamin D, serum creatinine and ASAT/ALAT will be measured at the time of recruitment (table 1). The vital signs (blood pressure, pulse and temperature) will be examined on all visits. In addition, haematological parameters will be measured on visits 3, 4 and 5. Serum phosphate and vitamin D will be followed up on visit 5. Blood samples will be collected by venepuncture. Blood measurements will be conducted at the University Hospital of Basel, Department of Laboratory Medicine.

Haematological parameters (2.7 mL of blood)

This examination will be conducted on visits 1, 3, 4 and 5. Hb, RBC, HCT (haematocrit), MCV (the mean corpuscular volume), MCH (the mean corpuscular haemoglobin), HRC (hypochromic red blood cells), WBC (white blood cells) and PLT (platelet count) will be measured using a haematology analyser. Mean corpuscular Hb is automatically calculated from Hb and RBC.

Table 1 Study flow chart(s)/table of study procedures

Study periods	Screening	Treatment		Follow-up	
	1	2	3	4	5
Visit	1	2	3	4	5
Time (hour, day, week)	Between day -28 and -8	Between day -27 and -7	Day 0 Surgery	Day +2	Between day +21 and +28
Patient information	x				
Informed consent		x			
Demographics	x				
Medical history, height and weight	x				
Inclusion/exclusion criteria	x				
Vital Signs	x	x	x	x	x
Haematological parameters	x		x	x	x
Iron status (C-reactive protein, ferritin)	x				
Serum phosphate and vitamin D	x				x
Other parameter (liver, kidney parameters, etc)	x				
Pregnancy test if necessary	x				
Randomisation		x			
Administer study medication		x	x		
Primary variables				x	x
Secondary variables			x	x	x
Concomitant therapy	x				x
Adverse events		x	x	x	x

Serum ferritin, CRP, serum phosphate, vitamin D and biochemical parameters (7.5 mL of blood)

To exclude iron overload and infection, serum ferritin and C-reactive protein (CRP) will be investigated at the time of recruitment. Ferritin is assessed by chemiluminescence immunoassay and CRP by immunoturbidimetry. Serum phosphate is assessed by a phosphomolybdate UV-test. Vitamin D will be assessed by liquid chromatography-mass spectrometry.

All new medications will be documented on days 21–28 after surgery.

Study interventions

This trial consists of four groups including 32 patients in each.

In the first group, ferric carboxymaltose 20 mg/kg (with a maximum dose of 1000 mg ferric carboxymaltose in a single infusion) (Ferinject 1000 mg/20 mL) will be administered between day –27 and day –7. Ferric carboxymaltose (Ferinject 1000 mg/20 mL, Vifor (International) AG, St. Gallen, Switzerland) will be administered in 250 mL of 0.9% m/V sodium chloride solution over 15 min.

In the second group, tranexamic acid 10 mg/kg (Tranexam OrPha 1000 mg/10 mL, OrPha Swiss GmbH, Künsnacht, Switzerland) will be administered 15–30 min prior to surgery followed by infusion of tranexamic acid through a syringe pump (1 mg/kg/hour) till 4 hours postoperatively.

In the third group, ferric carboxymaltose (Ferinject 1000 mg/20 mL) between day –27 and day –7 and tranexamic acid (Tranexam OrPha 1000 mg/10 mL) will be administered 15–30 min prior to surgery followed by infusion of tranexamic acid through syringe pump (1 mg/kg/hour) till 4 hours postoperatively.

In the fourth group, no treatment, which corresponds to the ‘current standard of care’, will be given. There are no payments or compensation provided to study participants.

Assessment of primary outcome

The number of all perioperative (intraoperative and postoperative) administered RBC transfusions (the absolute rate of RBC transfusions) will be documented. The perioperative Hb cut-off level for administration of RBC transfusion will be 80 g/L.

Assessment of secondary outcomes

Secondary outcome parameters described previously will be recorded.

Two dimensions of blood loss will be assessed:

1. Blood loss measured during surgery:
 - Estimated perioperative blood loss: volume estimated by surgeon and anaesthetist concerning the amount of blood in sponges, drapes and the volume in suction bottles during surgery.
2. Total blood loss estimation based on the Hb balance method.¹⁹

Blood loss calculated according to the formula: blood

loss (ml)=1000 x Hb_{loss}/Hb_{preop}

$$Hb_{loss} = (Hb_{pre} - Hb_{post}) \times PBV + Hb_t$$

The predicted blood volume (PBV, L) is calculated according to the method described by Nadler *et al*²⁰ using body weight (W; kg) and height (H; m):

$$PBV = (0.3561 \times H^3) + (0.03308 \times W) + 0.1833.$$

Hb_t is the total amount of allogenic transfused Hb. One unit of erythrocytes contains 56 g of Hb.

3. Comparison of the measured blood loss and the calculated loss to the calculation of mean blood loss using these two values.

Blood loss calculated according to the formula: blood loss (mL) (mL)=1000 × Hb_{loss}/Hb_{preop}

$$Hb_{loss} = (Hb_{pre} - Hb_{post}) \times PBV + Hb_t$$

The PBV, L is calculated according to the method described by Nadler *et al*²⁰ using body weight (W; kg) and height (H; m):

Assessment of other outcomes of interest

In order to investigate the proportion of women with hypophosphataemia following iron infusion, serum phosphate will be examined prior to iron infusion and on the 21st–28th day after surgery. Serum phosphate should ideally be determined in the fasting state. A recent meal, high-glucose ingestion, insulin release or administration, muscular activity, hyperventilation and vitamin D can lower serum phosphate by causing a shift from the plasma into the cells. Clinical symptoms of hypophosphataemia will be documented.

Safety

Adverse events will be monitored and recorded in all subjects from the day of consent to completion of the study (visit 5). An adverse drug event will be defined as any untoward medical occurrence that does not necessarily have a causal relationship with the treatment under study, in a subject who had been administered a pharmaceutical product. An adverse event could, therefore, be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the application of a medicinal product. A related adverse event will be associated with the use of the drug if causality is possible, probable or certain. A serious adverse event will be defined as any untoward medical occurrence that at any dose resulted in death, is life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability/incapacity.

Determination of sample size

We used simulations to estimate the required sample size. Specifically, we generated 1000 synthetic datasets for a range of potential sample sizes and possible reductions in number of RBC transfusions due to treatment with intravenous iron, tranexamic acid or with both drugs.

We then applied the intended analysis (a Poisson regression that models the effects of treatment with

intravenous iron only, treatment with tranexamic acid only and treatment with both iron and tranexamic acid assuming that their effects are additive) to each of the simulated datasets. The simulations are based on the following assumptions:

- ▶ Group 1: Treatment with intravenous iron requires an estimated 25% fewer transfusions compared with the control group.¹⁶
- ▶ Group 2: Treatment with intravenous tranexamic acid requires an estimated 30% fewer transfusions compared with the control group.⁸
- ▶ Group 3: Treatment with intravenous iron and tranexamic acid has an additive effect for an estimated 55% fewer transfusions required.
- ▶ Group 4: The control group receiving the current standard of care requires between 2 and 2.5 transfusions.^{15 18}

The four treatment groups listed above are equal in size. Assuming that patients, receiving current standard of care, require two transfusions on average and that patients treated with intravenous iron require 25% fewer transfusions and those treated with tranexamic acid 30% fewer, 114 patients are needed in total in order to conduct the study. This sample size allows detection of a significant decrease in the average number of transfusions required with 90% probability (power). Assuming a drop-out rate of 10%, a total of 126 women should be recruited in order to have a total of 114 evaluable women. Since our study will only be carried out in one centre, the significance of these results might be limited. Only patients with complete data on number of transfusions will be included in the primary analysis. The sample size calculation has accounted for an estimated drop-out rate of 10%. The number of missing values in each endpoint and the number of drop-outs will be summarised.

Primary analysis

The primary study objective will be evaluated using a Poisson regression that models the number of transfusions necessary in regard to treatment with intravenous iron (yes/no), tranexamic acid (yes/no) or treatment with both intravenous iron and tranexamic acid assuming that the effects of the treatment are additive.

Secondary analyses

The secondary outcome parameters described before will be compared among the intervention groups. However, the power analysis was only conducted to examine the primary endpoint. For this reason, the significance of the secondary results might be limited.

Safety analysis

The study will aim to assess safety and tolerability in terms of incidence of:

- ▶ Adverse events.
- ▶ Clinical symptoms of thromboembolism on days 21–28 after surgery.
- ▶ Hypophosphataemia on days 21–28 after surgery.

- ▶ In case of hypophosphataemia, clinical signs will be documented.

If substantial deviations of the analysis as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate section of the final statistical report. Only patients with complete data concerning number of transfusions will be included in the primary analysis. The sample size calculation has accounted for an estimated drop-out rate of 10%. The number of missing values in each endpoint and the number of drop-outs will be summarised.

Data handling

Data management will be conducted by Clinical Trial Unit, University of Basel. The data review and data handling documents to be developed during the initiation phase of the study will include specifications for consistency and plausibility checks, as well as rules for obvious data errors.

The study data recorded in the case report form (CRF) will be transferred to a corresponding electronic CRF (e-CRF) by a designated person. All information recorded in the e-CRFs will be traceable to the source documents of the patient's file as well as date source files.

In compliance with the International Council on Harmonisation and GCP guidelines the investigator/institution will maintain all source documents that contain the data collected from each patient, and all documents as specified in Essential Documents for the Conduct of a study and as specified by the applicable regulatory requirements. The investigator/institution will take measures to prevent accidental or premature destruction of these documents. If the responsible investigator relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.

Record keeping/archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. The study data will be stored at University Hospital Basel, Department of Obstetrics and Gynaecology. The principal investigator and study coordinators have access to password protected trial data. The data will be electronically anonymised and stored securely. The study coordinators will enter the data in e-CRFs. The principal investigator will verify, validate the data and secure the database.

Monitoring

We plan four monitoring visits:

- ▶ Initiation visit.
- ▶ Two regular visits.
- ▶ Close-out visit.

The initiation visit will include: procedure for patient education, correct handling of the study medication and e-CRF training.

The second monitoring visit is planned when 40 participants have been included and the third monitoring visit when 80 participants have been included. These visits will include: verification that the study is conducted according to protocol, checking the e-CRFs (Key Data, Source Data Verification), review of the study status (eg, recruitment rate, drop-outs, exclusions) and correct handling of the test product (eg, accountability, storage).

The close-out visit will include: clarification of outstanding issues in e-CRFs/ SAEs / Source Data Verification, check for completeness of Investigator Site File/ Trial Master File and debriefing centre (archiving, final notification and so forth).

Data protection

Data generation, transmission, storage and analysis of health-related personal data and the storage of biological samples within this project will strictly follow the current Swiss legal requirement for data protection and will be performed according to the Ordinance HRO Art. 5.

Health-related personal data captured during this project and biological samples from participants are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality.

Project data will be handled with utmost discretion and only be accessible to authorised personnel. Direct access to source documents will be permitted for purposes of monitoring, audits or inspections. Only investigators and members of the research team will have access to the project plan, dataset, statistical codes and so forth during and after the research project.

All study findings and documents will be regarded as confidential. The investigators and members of the research team must not disclose information. The anonymity of participating patients must be maintained. Patients will be identified by screening number and birth date, not by name. Biological material and health-related personal data will be coded. The coding key will be located by the investigators and members of the research team. Access to this key will be limited to the investigators and members of the research team. The code may only be broken if it is necessary to avert an immediate risk to the health of the person concerned or to guarantee the right of the person (eg, in revoking the consent) or a legal basis exists for breaking the code.

Insurance will be provided by the sponsor investigator. In the event of project-related damage or injuries, the liability of the University Hospital Basel provides compensation, except for claims that arise from misconduct or gross negligence.

Storage of biological material and related health data

The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 10 years after the last approval. After measurement, biological material will be destroyed at the University hospital of Basel, Department of Laboratory Medicine.

Data sharing

The data generated by our research will be available as soon as possible, wherever legally and ethically possible. The data will be made available on reasonable request. The deidentified participant data from this study and related documents (study protocol, statistical analysis plan, patient consent form) will be made available on request. Researchers may request data to repeat the analyses or use the data for secondary analyses (eg, systematic review and meta-analysis). Changes to this plan will be noted in the data availability statement and updated in the registry record (to comply with ICMJE recommendations).

Patient and public involvement

There was no patient or public involvement in the design and conduct of this study.

Ethics

The study will be performed according to the guidelines of the Declaration of Helsinki and is approved by the Ethics Committee for Northwest and Central Switzerland in Basel (EKNZ Protocol ID 2020-01194). The study has been registered in the 'ClinicalTrials.gov' (<https://clinicaltrials.gov>) with trial registration number NCT04625530.

The principal investigator will ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study. This protocol will be followed exactly. To alter this protocol, amendments will be in writing. Approval from the appropriate personnel and Ethics Committee approval prior to implementation will be received. Administrative changes (not affecting the patient's benefit/risk ratio) may be made without the need for a formal amendment. Before each patient will be admitted to the study, signed informed consent will be obtained from the patient according to the regulatory and legal requirements. If a protocol amendment will be required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form will be revised, it must be approved and signed by all patients subsequently enrolled in the study.

Publication and dissemination

The findings of this study will be published in a peer-reviewed journal, and presented at national and international scientific conferences, to disseminate the results to academic and health professional audiences. In addition, data will be made available on our website to participants and to a wider public at the time of publication. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

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Competing interests None declared.

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