SPECIAL ARTICLE

Low vs. high haemoglobin trigger for transfusion in vascular surgery: protocol for a randomised trial

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Trial registration
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Background: In patients with cardiovascular disease, guidelines for administration of red blood cells (RBC) are mainly based on studies outside the vascular surgical setting with the recommendation to use a haemoglobin (hb) trigger-level lower than by guidelines from The European Society for Vascular Surgery. Restricting RBC transfusion may affect blood O_2 transport with a risk for development of tissue ischaemia and postoperative complications.
Methods: In a single-centre, open-label, assessor blinded trial, 58 vascular surgical patients (> 40 years of age) awaiting open surgery of the infrarenal aorta or infrainguinal arterial bypass surgery undergo a web-based randomisation to one of two groups: perioperative RBC transfusion triggered by hb < 8 g/dl or hb < 9.7 g/dl. Administration of fluid follows an individualised strategy by optimising cardiac stroke volume and near-infrared spectroscopy determines tissue oxygenation. Serious adverse event rates are: myocardial injury (troponin-I ≥ 45 ng/l or ischaemic electrocardiographic findings at day 30), acute kidney injury, death, stroke and severe transfusion reactions. A follow-up visit takes place 30 days after surgery and a follow-up of serious adverse events in the Danish National Patient Register within 90 days is pending.
Discussion: This trial is expected to determine whether a RBC transfusion triggered by hb < 9.7 g/dl compared with hb < 8 g/dl results in adequate separation of postoperative hb levels, transfusion of more RBC units and maintains a higher tissue oxygenation. The results will inform the design of a multicentre trial for evaluation of important postoperative outcomes.

Vascular surgical patients have high rates of comorbidity including coronary artery disease (CAD)[1–3] and during major surgery such as abdominal aortic aneurysm (AAA) repair, the subsequent blood loss may precipitate myocardial ischaemia, which increases mortality.[1,4,5] Thus, the central blood volume needs to be maintained through administration of intravenous fluids to aim for a normovolaemic condition.[6] When blood loss exceeds a certain level and especially with ongoing bleeding, tissue oxygenation may be compromised and red blood cell (RBC) transfusion is in need, however, the optimal haemoglobin (Hb) level is unknown. While RBC transfusion is necessary to maintain oxygen delivery,[7,8] use of blood products may be associated with increased mortality and morbidity during non-cardiac surgery,[9,10] including vascular surgery[11,12] and in patients with myocardial infarction.[13] It seems that perioperative use of RBC has shifted into a more conservative approach although prospective randomised clinical trials (RCTs) are unavailable to support such strategy as superior for patients with cardiovascular disease (CVD) including symptomatic CAD[14] and cardiac surgery.[15] Similar findings are reported for patients in upper gastrointestinal bleeding[16] and in hip fracture surgery patients.[17] In patients with CVD it is suggested that a conservative strategy for RBC administration is abandoned until further RCTs have been undertaken.[18]

The conflicting findings are reflected by that the European Society for Vascular Surgery recommends Hb to be maintained above 10 g/dl for patients undergoing open AAA repair[19] while The Danish Health Authority and The AABB recommend 8.0 g/dl in perioperative patients with CVD.[20,21] Therefore, a large multicentre trial to assess the optimal Hb trigger level for RBC administration during vascular surgery is warranted. Before a multicentre trial is planned, it needs to be addressed whether perioperative Hb levels as triggers for RBC transfusion separate postoperative Hb levels and use of blood product. This protocol presents the rationale, methods and detailed statistical analyses plan for such a trial.

Methods

Trial design

Single-centre, randomised, open-label trial.

Patients, outcome assessor and the statistician will be blinded to the allocated transfusion trigger. The anaesthetists will be blinded to the Near-infrared spectroscopy (NIRS) monitor. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist and assessment figure of the trial can be found in Data S1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Participant interventions and outcomes

Trial setting

University Hospital. One trial site: Regional Hospital Slagelse, Denmark.

Eligibility criteria

Inclusion.

1. Patients for planned open surgery of infrarenal AAA or infrainguinal arterial bypass AND
2. Age $\geq$ 40 years AND
3. Hb < 9.7 g/dl

Exclusion criteria.

1. Documented wish against transfusion OR
2. Previous serious adverse reaction with blood products OR
3. Unable to understand the benefits and risks of testing or sign written informed consent OR
4. Previous participation in the TV-trial

Interventions

After preoperative consent to join the trial, patients are randomised when the Hb is < 9.7 g/dl and allocated to an intervention or control group with the following RBC transfusion triggers:

1. intervention: Hb < 8 g/dl
2. control: Hb < 9.7 g/dl

Randomisation takes place no earlier than the day before operation and up until 30 days postoperatively. The intervention is given from randomisation and until 30 days after surgery, also in case of readmission. The triggers 8.0 and

9.7 g/dl correspond to the following haemoglobin units used in Denmark: 5 and 6 mmol/l, resp.

The attending anaesthetists will be in charge of the RBC transfusions during surgery and postoperative care. After discharge to the vascular surgery ward, the vascular surgeon will be responsible for protocol adherence.

Protocol suspension

The protocol may temporarily be suspended if the clinician in charge finds indication for additional RBC transfusions in case of clinical emergency:

1. severe hypotension (mean arterial pressure < 65 mmHg) unresponsive to fluid replacement OR
2. uncontrollable bleeding, defined as loss of surgical haemostasis resulting in overt or imminent haemodynamic instability with insufficient tissue oxygenation and increasing lactate production OR
3. stroke or ischaemia in extremities or intestines OR
4. RBC transfusion is omitted in case of suspected decompensated heart failure.

The protocol suspension will be discontinued when clinical stability is restored. Data collection will continue throughout periods of protocol suspension.

Criteria for discontinuing participation in trial—drop out

The patient can drop out of the trial by withdrawal of informed consent. In this case, the patient will be asked permission to continue the data registration and will be followed up in the intention-to-treat analysis.

Anaesthesia and surgery

Surgery is in accordance with local clinical guidelines. Fasting is 6 h for food and 2 h for clear fluids. All patients receive sevoflurane, fentanyl and rocuronium for general anaesthesia. For patients undergoing open AAA repair, epidural analgesia is used intra-operatively (1–3 ml bupivacaine 5 mg/ml repeated as needed) and for postoperative pain treatment (bupivacaine 2.5 mg/ml with fentanyl 2 μg/ml).

All patients are monitored with: invasive blood pressure (inserted in the arm with the highest non-invasively determined systolic blood pressure), 5-lead electrocardiogram, temperature, pulse oximetry and urinary output. In addition, AAA patients have central venous pressure monitoring. Heart rate is aimed for 40–90 min^{-1}, mean arterial pressure is maintained above 65 mmHg with noradrenaline if stroke volume is not affected by additional fluid, see below. Patients are mechanically ventilated (control mode) with a tidal volume ≥ 8 ml/kg to maintain end-tidal PCO_2 between 4.5 and 6.0 kPa, inspiratory oxygen fraction is set to 0.5 and positive end-expiratory pressure at 5 cm H_2O. Normothermia is ensured by forced-air warming and fluids and blood products are infused through blood warmers. The Hb level is measured every ½ h during ongoing bleeding.

Goal directed fluid therapy and tissue oxygenation

The primary i.v. fluid is Ringer's acetate solution. A cardiac output monitor, Edwards Flotrac 4.0®, guides fluid therapy by optimisation of cardiac stroke volume to aim for a normovolaemic condition. That is, stroke volume unaffected by fluid administration or an increase in stroke volume is below 10%.[22] Patients are also monitored by NIRS (Invos 5100c Cerebral Oximeter, Troy, MI, USA), with optodes is placed on the forehead and biceps, to assess changes in tissue oxygenation, which reflect the balance between O_2 supply and demand.[23]

Fluid strategy

Blood loss will be replaced by Ringer's Acetate in a 1 ml: 2–3 ml ratio in accordance with guidelines recommended by the Danish Society of Anaesthesia and Intensive Care.[24] When blood loss replacement exceeds 3 l of Ringer acetate, the bleeding will be replaced by 5% human albumin until the allocated transfusion threshold is reached. After 4–6 transfused RBC units, further transfusion will be supplemented with fresh frozen plasma (FFP) in a 1 : 1 RBC: FFP ratio. Bleeding exceeding 1.5 l prompts ROTEM analysis. In case of massive bleeding with deteriorated haemodynamics the protocol will be suspended and a balanced transfusion

strategy (RBC:FFP:trombocyte concentrate—balance of 4 : 4 : 1) commence.

Antithrombotic therapy

Practice for discontinuation of antithrombotic medicine adheres to the guideline of Danish Society of Thrombosis and Haemostasis.[25] All patients will intra-operatively receive a push dose of unfractionated heparin (50 IE/kg) intravenously 1 min before cross-clamp of the aorta or the common femoral artery.

Adherence to protocol

The principal investigator will follow-up on all RBC unit transfused during the trial period, register the reason for any non-adherence to the protocol and give feedback to the health care provider (doctor, nurse) to increase adherence.

Comcomitant care

All routine treatments including acute medical intervention are allowed during the trial. Use of synthetic colloids is prohibited.

Outcome measures

Primary outcome

Mean postoperative Hb day 0–15 (longitudinal outcome).

Secondary outcome

1. Units of RBCs transfused during hospital stay
2. Recruitment rate (number of randomised patients divided by number of eligible patients)
3. Proportion of patients having their protocol suspended
4. Adherence to Hb concentrations used for transfusion triggers
5. Intra-operative tissue oxygenation of the forehead (ScO_2) and biceps muscle (SmO_2) as determined by NIRS. Baseline is at the point where the patient is normovaemic according to the goal directed therapy principle after inducing anaesthesia before start of surgery. The outcome measure is defined as lowest value before a RBC transfusion. Area-under-baseline calculations are also applied; see statistical analysis plan in Data S4.
6. Coagulation competence determined by ROTEM at the end of surgery. Baseline sample drawn when placing arterial line.
7. Serious adverse events < 30 postoperative days
   a. myocardial injury as reflected by
      i. cardiac troponin-I ≥ 45 ng/l within two postoperative days OR
      ii. new onset of adverse electrocardiographic recordings on day 30 (bundle-branch block, Q-wave, inverted or flattened T-wave, ST-elevation or depression of 1 mm or more in two or more contiguous leads)
   b. acute kidney injury defined by the Kidney Disease: Improving Global Outcome criteria, see Data S2 for stage definition
      i. S-creatinine increment ≥ 26.5 μmol/l (≥ 0.3 mg/dl) within 48 h OR
      ii. S-creatinine increment × 1.5 times the preoperative level which has occurred within the prior 7 days OR
      iii. Urine production < 0.5 ml/kg/h within 6 h
   c. mortality
   d. ischaemic apoplexia
   e. severe adverse transfusion reactions, see definitions in Data S2

Explorative outcome measures at day 90 postoperative

1. Mortality
2. Major cardiovascular events (acute myocardial infarction, stroke, renal replacement therapy, vascular reoperation and amputation)
3. Days alive outside hospital within 90 days

Mortality data will be obtained from the CPR-registry (Danish Registry of National Identification Numbers) and major cardiovascular event data from The NPR (National Patient Registry).

For sub-analyses and bonferroni correction, see the detailed statistical analyses plan in Data S4.

For background literature related to the outcome measures see Data S2.

Participant timeline

Eligible patients will be approached consecutively and on the weekday before surgery, see Flow Chart in Data S5. For assessment of outcome, see Data S3—SPIRIT schedule of enrolment, assessments and interventions in the TV-trial.

Sample size

A review of 20 patient files at Slagelse Hospital in 2014 showed the following values for AAA repair patients, expressed as mean (standard deviation):

RBC transfusion: 750 ml (718 ml)
Postoperative Hb: 11.1 g/dl (1.45 g/dl)
ScO_2-standard deviation of 7%[26]

With a total of 50 randomised patients, a maximal type 1 error risk of 5%, and standard deviations as mentioned the trial has a power of:

1. 95% to show a difference in postoperative Hb of 1.6 g/dl with 44 patients.
2. 80% to show a difference of 600 ml of RBC volume transfused with 46 patients.
3. 80% to detect a difference in NIRS-determined ScO_2 of 6% during surgery with 44 patients.
4. And produces a 97.5% confidence interval (CI) equal to the sample adherence prevalence plus or minus 8% when the true prevalence of adherence is hypothesised to be 90% (as reported in Ref. 27).

Of note, we are not able to estimate the required sample size for area-under-baseline calculations due to lack of data for NIRS-monitored AAA repair patients.[28]

Recruitment

Based on a patient file review of 2014, where 120 bypass and 45 AAA operations were performed and anaemia (Hb < 9.7 g/dl) occurred at rates of 50% and 70%, resp, a 10 months trial period yields 76.25 recruitable patients: $(120 \times 0.50 + 45 \times 0.70) \times 10/12$. Assuming 1/3 of patients will not consent or be eligible, 50 recruited patients are expected.

Assignment of interventions

Adequate allocation sequence generation and concealment: computer-generated random numbers via a central web page provided by Copenhagen Trial Unit.

Implementation: Patients will be randomised and assigned by the investigator.

Stratification

Randomisation will be stratified for type of surgery: open AAA operation or infrainguinal arterial bypass.

Data collection, management and analysis

Data are continuously recorded in the paper-based case report form (CRF) and transferred with double entry into the trial database using OpenClinica®.

The trial has been accepted by The Danish Data Protection Agency (Region Zealand journal number 15-00024). Region Zealand and Copenhagen Trial Unit have signed an agreement on trial data processing (journal no. 2008-58-0020) including data management and statistical analyses.

It is possible to gain access to the trial protocol in accordance with The Law concerning Access to Public Records. Information obtained during the trial is confidential.

Baseline variables and paraclinical tests during hospital stay

See Data S3—SPIRIT schedule of enrolment, assessments and interventions in the TV trial.

Statistical analyses

It is assumed that the strategy with transfusion triggered by Hb < 9.7 g/dl compared to a transfusion triggered by Hb < 8 g/dl results in different postoperative Hb levels, units of RBC's transfused and tissue oxygenation. These hypotheses will thus be tested as in a superiority trial. Recruitment rate is presented with 95% confidence interval (CI). Furthermore, the secondary outcomes of proportion of patients having their protocol suspended and transfusions given adherent to Hb triggers will be calculated and tested. Our primary, secondary and explorative analyses will be based on the intention-

to-treat population and adjusted for age and the stratification variable. For all continuous outcomes, we will additionally adjust analyses for the baseline value. Missingness will be examined and in case of more than 5% of missing data and Littles test being statistical significant, we will perform best- and worst-case scenarios. If conclusions are different in the best- and worst-case scenarios, multiple imputation (MI) will be performed. Only two-sided tests will be used and $P < 0.05$ will be considered statistically significant.

1. Longitudinal data will be analysed using generalised estimating equations (GEE) or area under the curve (AUC) as appropriate according to the distribution of data and the assumptions for doing the analysis.
2. Count data will be analysed using van Elteren test.
3. Dichotomous outcomes will be analysed using generalised linear model (log link) or Fishers' exact test if there are few events.
4. Continuous outcomes will be analysed using linear regression.
5. Survival data will be analysed using both:
   a. Logistic regression presented with landmark serious adverse event forrest plot and odds ratios, 95% CI.
   b. Serious adverse event free days will be analysed with cox proportional hazards analysis of time to first event presented with Kaplan–Meier curve.

For further details regarding the statistical analyses plan, see Data S4.

Ethics and dissemination

Research ethical approval

The Scientific Ethical Committee of Region Zealand approved this protocol on May 12th 2015 (SJ-426).

Protocol amendments

1. The Scientific Ethical Committee of Region Zealand has approved extending the trial period to the end of 2016 due to an unanticipated 30% reduction in scheduled vascular surgery operations.
2. The Scientific Ethical Committee of Region Zealand approved extending the sample size to 58 patients and the trial period to 31 June 2017 to compensate for an unexpected high rate of patients randomised postoperatively and thus to secure a sufficient sample size ($n = 44$) of patients randomised intra-operatively.

Informed consent

The patient will be approached and presented for the trial when scheduled for surgery. On the day before the operation, the investigator will obtain informed consent.

Ethics

Patients receive the best treatment consistent with local and national recommendations. Participation in the trial will not delay diagnosis, surgery or discharge to the vascular surgery wards from the postoperative care. The Helsinki II declaration and national regulations will be respected.

No firm evidence exists from RCTs on the potential benefit or risk of RBC transfusion in vascular surgery. RBC transfusion is a part of current treatment of the majority of AAA operations and the triggers reflect practice and recommendations.

Due to the small sample size, no data monitoring committee, formal auditing or interim analysis has been implemented. Thus, the participants will not be exposed to known risks in the trial.

Injury and compensation

All trial participants are treated in the Danish public healthcare system and are thus lawfully entitled to get compensation through The Patient Compensation Association in case of injuries occurring in connection with the trial or any other injury during hospital stay not associated with the trial.

Dissemination policy

The results of the study are planned to be published as three different manuscripts. All manuscripts will be submitted for peer-reviewed publication and abstracts will be submitted for

presentation at national and international society meetings for anaesthesiology, vascular surgery and clinical immunology. The planned manuscripts are the main manuscript, a publication on ROTEM data, and a manuscript including observational data on bleeding, Hb levels and serious adverse events on enrolled, but excluded patients, due to sustained Hb ≥ 9.7 g/dl throughout the trial. A trial report is also provided to the funds of the trial and to those participants, who stated a wish for information in their consent form.

Discussion

This trial will assess postoperative Hb separation, use of blood product and adherence to protocol for perioperative RBC transfusion triggered by a Hb < 9.7 g/dl compared to a Hb < 8.0 g/dl. The trial is also expected to deliver information on recruitment rate and whether 9.7 g/dl results in a higher tissue oxygenation than 8.0 g/dl, though this cannot test or be extrapolated to differences in treatment effects on important patient centred outcomes. A large multicentre trial for evaluation of postoperative mortality in a high-risk surgical population is warranted.

Further work to prepare for the definitive trial includes a national registry study of 15 years of blood transfusion in vascular surgery to inform inclusion criteria and sample size estimation. We also plan a systematic review with meta-analyses and trial sequential analysis of randomised clinical trials testing conservative RBC use vs. a liberal transfusion strategy to inform the best design of a future large pragmatic trial.

Trial status

Enrolment started 13 July 2015 and the 58th patient was randomised on 8 December 2016, see "Fig. 1. Status of patients randomised in the TV trial". National patient registry follow-up on serious adverse events within 90 days is pending.

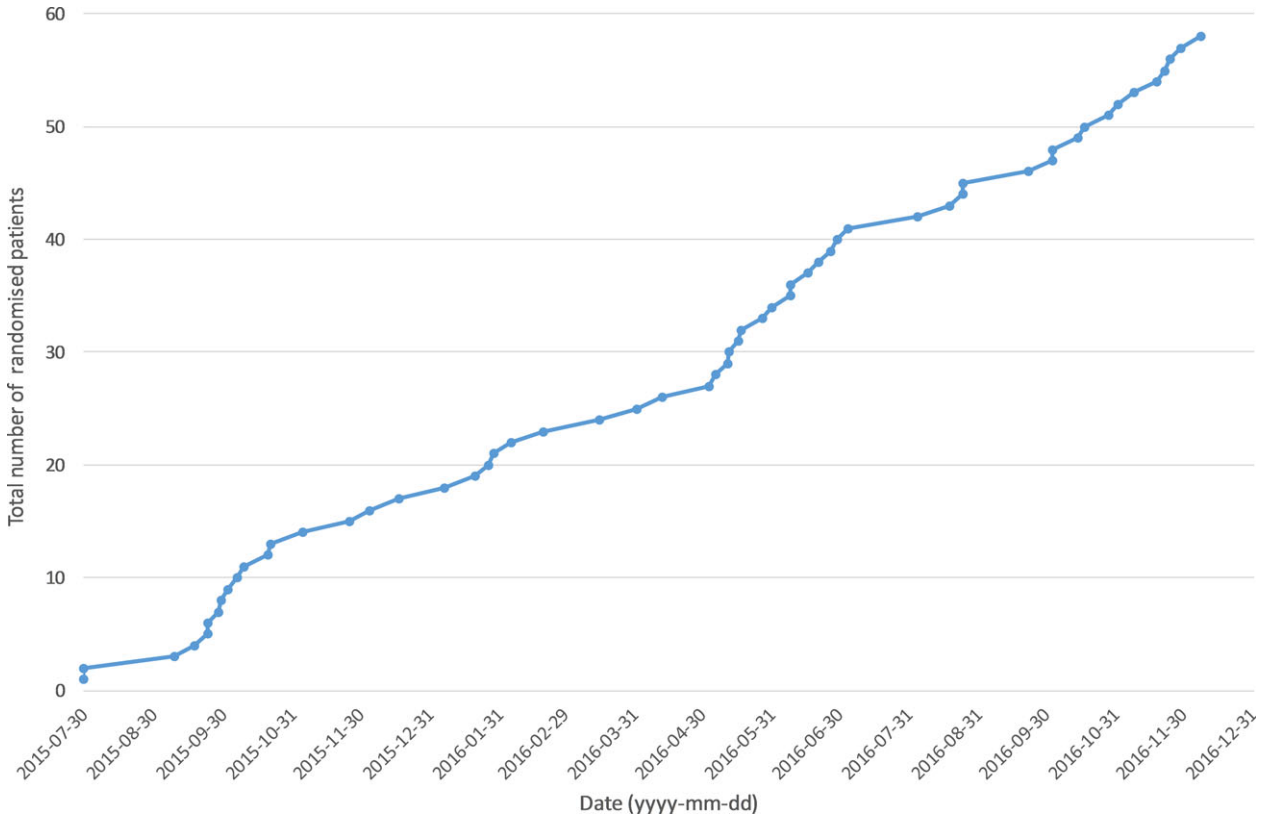

Fig. 1. Status of the TV trial. [Colour figure can be viewed at wileyonlinelibrary.com]

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1. Checklist: Recommended items to address in a clinical trial protocol and related documents*.
Data S2. Definitions and literature on the serious adverse event outcome measures used in the TV trial.
Data S3. SPIRIT schedule of enrolment, assessments and interventions in the TV trial.
Data S4. Detailed statistic analysis plan.
Data S5. The TV trial flow chart.