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Safety and effectiveness of a Patient Blood Management (PBM) program in surgical patients - the study design for a multi-centre prospective epidemiologic non-inferiority trial

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Abstract

Background: Preoperative and hospital-acquired anaemia is common among surgical patients. It is associated with an increased risk of morbidity and mortality and a strong risk factor for allogeneic blood transfusions with their own inherent risks. Patient Blood Management (PBM) concepts aim to increase and preserve autologous erythrocyte volume and to optimise haemotherapy. They thus have great potential to benefit patients.

Methods/Design: This prospective, multi-centre clinical trial tests the hypothesis that PBM programs are safe and effective in the care of adult surgical patients. Primary outcome is a composite endpoint of adverse events and in-hospital mortality.

Discussion: This trial will determine whether the implementation of a PBM program is safe and effective in terms of clinical outcome compared to a pre-implementation cohort. This trial is registered at www.clinicaltrials.gov (NCT01820949).

Keywords: Patient Blood Management, Red Blood Cell Transfusion Practice, Patient Safety, Anaemia, Clinical Outcome, Perioperative Care

Background

Anaemia has a high prevalence among surgical patients as it is often preexisting, acquired and/or exacerbated during hospital stay [1,2]. It is associated with higher risks of morbidity and mortality and is also a major risk factor for allogeneic blood transfusions. The transfusion of allogeneic red blood cell (RBC) units is by itself also associated with increased morbidity and mortality due to infectious, immunological, pulmonary and thromboembolic complications [3-5]. Surely, adequate RBC transfusion is a life-saving medical intervention for those in need of it, but transfusion practice varies significantly when comparing hospitals and physicians, which implies that insecurity regarding adequate utilisation exists [6,7]. Additionally, serious blood supply challenges are imminent due to changing population demographics. Therefore, modifiable risk factors for transfusion such as anaemia should be targeted and a rational use of RBC units and safe clinical transfusion practice is mandatory. The World Health Organisation encourages all member states to implement Patient Blood Management (PBM) programs employing multiple combined strategies to increase and preserve autologous erythrocyte volume in order to minimise unnecessary exposure to RBC transfusions [8]. Early detection and appropriate treatment of anaemia, multidisciplinary concepts designed to maintain haemoglobin concentration, to optimise haemostasis, and to minimise blood loss shall be thrived for in an effort to improve patient outcome and ensure adequate use of scarce resources [9,10].

Several public-based PBM initiatives are in progress, e.g. in Australia, to optimise utilisation of RBC concentrates [8,11].

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However, none of these initiatives is designed to provide scientific data in terms of safety issues. Thus, a large study with robust and relevant clinical endpoints is required. The object of this study is to demonstrate that the implementation of a PBM program is safe.

Methods

Trial design

This is a prospective multi-centre controlled epidemiologic non-inferiority trial with an approximated population of 100,000 patients undergoing surgical procedures. A patient-focused and evidence-based PBM program has been implemented in four German University Hospitals. Different time slots for control, implementation and study phases according to a non-randomised stepped wedge trial design were allocated for control, implementation and intervention periods.

Participants

Four German university hospitals are participating in the study: Frankfurt, Bonn, Kiel, Muenster. The PBM program includes all patients undergoing surgical procedures ranging anywhere from: orthopaedic and visceral surgery, general surgery, cardiothoracic surgery, trauma, otorhinolaryngology, gynecology and obstetrics, urology, oral and maxillofacial surgery, vascular surgery, and neurosurgery to increase applicability of the evidence obtained during this trial. Exclusion criteria are: <18 years, ophthalmologic or dermatologic or outpatient surgery. If a patient has multiple hospital admissions during the study period, the first hospital stay will be analysed.

The control group will be composed of the patients treated according to the standard protocol in charge before implementation of the PBM program. A period of three months was allowed for the implementation of the PBM components. Patients treated after implementation will be allocated to the PBM cohort until July 2015.

Management

For consistent implementation regular teaching sessions were held at the beginning of the program and are repeated every six months. The focus is on clinical practice, outcome and safety issues in order to increase knowledge on PBM and awareness of the clinical implications of anaemia and the need for alternatives to transfusion. The new program is additionally promoted through hand outs, posters, checklists and web-based information among health care providers and patients.

Our PBM program has three main pillars:

a) **Preoperative optimisation of haemoglobin levels:**

The preoperative detection, evaluation and therapy of anaemia diagnosis and treatment focuses specifically on those patients (aged 18 years and older) scheduled for elective surgery. Figure 1 shows the work-flow used at the University Hospital Frankfurt. Surgeries associated with a risk for transfusion >10% were identified by retrospective analysis of hospital data from 2011 with the hospital-information system Agfa ORBIS. Patients scheduled for elective surgery falling in that spectrum are screened and treated at the earliest possibility according

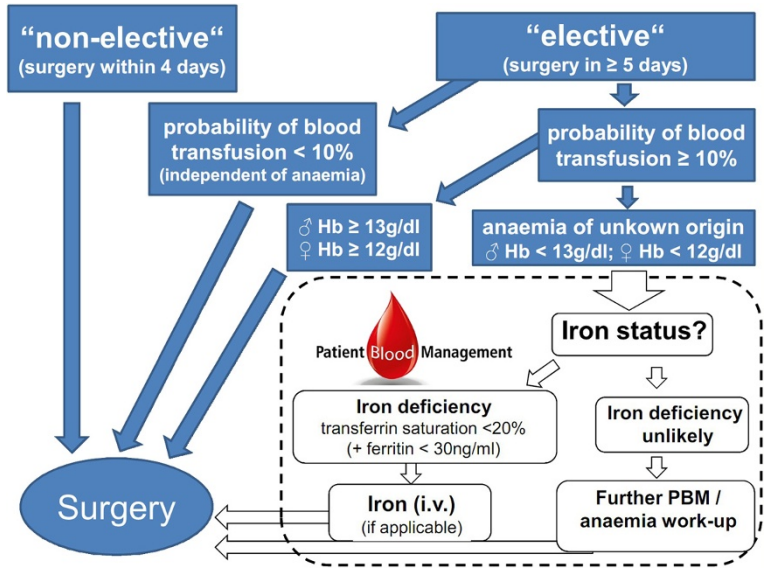

Figure 1 Algorithm for the detection, evaluation and management of anaemia at the University Hospital Frankfurt.

to NATA and SABM recommendations if surgery can be postponed for at least four days (Figure 1) [12]. Iron deficiency anaemia (IDA) is treated with intravenous iron. Anaemic patients are suggested to be scheduled for both haematological and/or gastroenterological consultations for further diagnostics and optimal treatment of anaemia in cases where iron deficiency anaemia is unlikely.

b) **Standardisation of transfusion practice according to evidence-based guidelines:**

Lectures on transfusion triggers according to the Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives of the German Medical Association [13]. The strict enforcement of guideline-based transfusion triggers for surgical patients is supported by checklists attached to each RBC and/or during electronic documentation of the indication for RBC in patient's record (Figure 2) and during the perioperative process (Figure 3).

c) **Alternatives to transfusion, and blood-sparing techniques:**

This part of the PBM program comprises a broad use of the cell saver system in defined subgroups of patients, temperature management, point-of-care diagnostics, optimised coagulation management, and restrictive blood sampling [14].

In support of the strategies above, a PBM Checklist was introduced to guide physicians through the perioperative process (Figure 3).

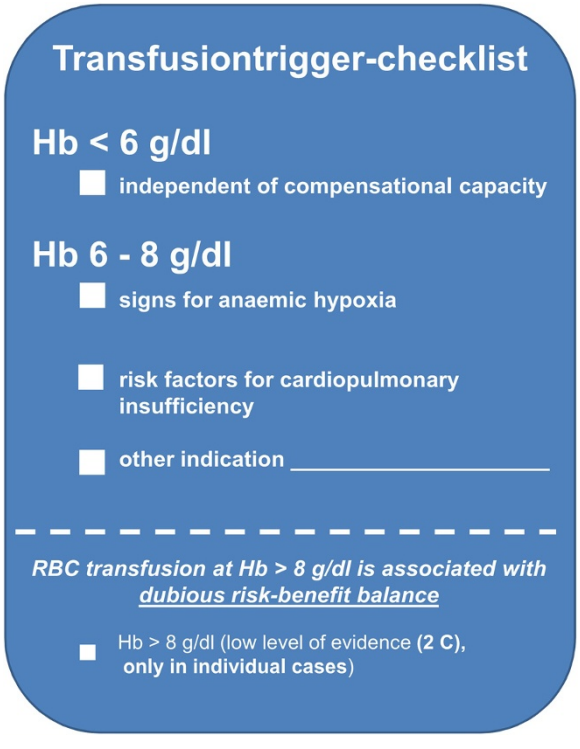

Figure 2 Transfusion trigger checklist.

Endpoints

Primary efficacy endpoint

Primary endpoints are the following composite endpoints: in-hospital myocardial infarction, stroke, acute renal failure, death of any cause, pneumonia and sepsis until discharge from hospital in patients before and after implementation of PBM program.

Secondary endpoints

- Length of stay on the intensive care unit
- Total hospital stay
- Quantitative utilisation of allogeneic RBC units, platelet concentrates, other blood products

Data recording

The efficacy endpoints will be monitored by means of the hospital-information system Agfa ORBIS, where the relevant diagnoses are encoded based on the ICD-10 system. All patient-related data will be analysed electronically and anonymised. The follow-up will last until discharge from the hospital.

Ethics

The PBM program is in accordance with state of the art transfusion guidelines and current recommendations for preoperative haemoglobin optimisation. This prospective multi-centre controlled epidemiologic trial (non-inferiority) has been approved by the ethics committees of the University Hospital Frankfurt (Ref.: 380/12) and of all participating centers. Data collection is performed anonymously. All collected data will be kept confidential. This study will be performed in accordance with the revision of the Declaration of Helsinki (2013) [15]. Since implementation will affect all hospitalised patients, information and informed consent of individual patients will not be obtained.

Statistics

Sample size and power calculation

According to preliminary data, the composite endpoint has an approximate incidence of 10%. A difference of 0,5% is set as the non-inferiority margin as this can be seen as the natural standard deviation. The level of significance of non-inferiority is determined be $\alpha = 2.5\%$. This is consistent with a two-sided 95% confidence range of $1 + \alpha = 95\%$ for the difference in the composite endpoint. A power of $1 + \beta = 80\%$ is sought. As the number of patients treated in each of the four university hospitals vary, an exact

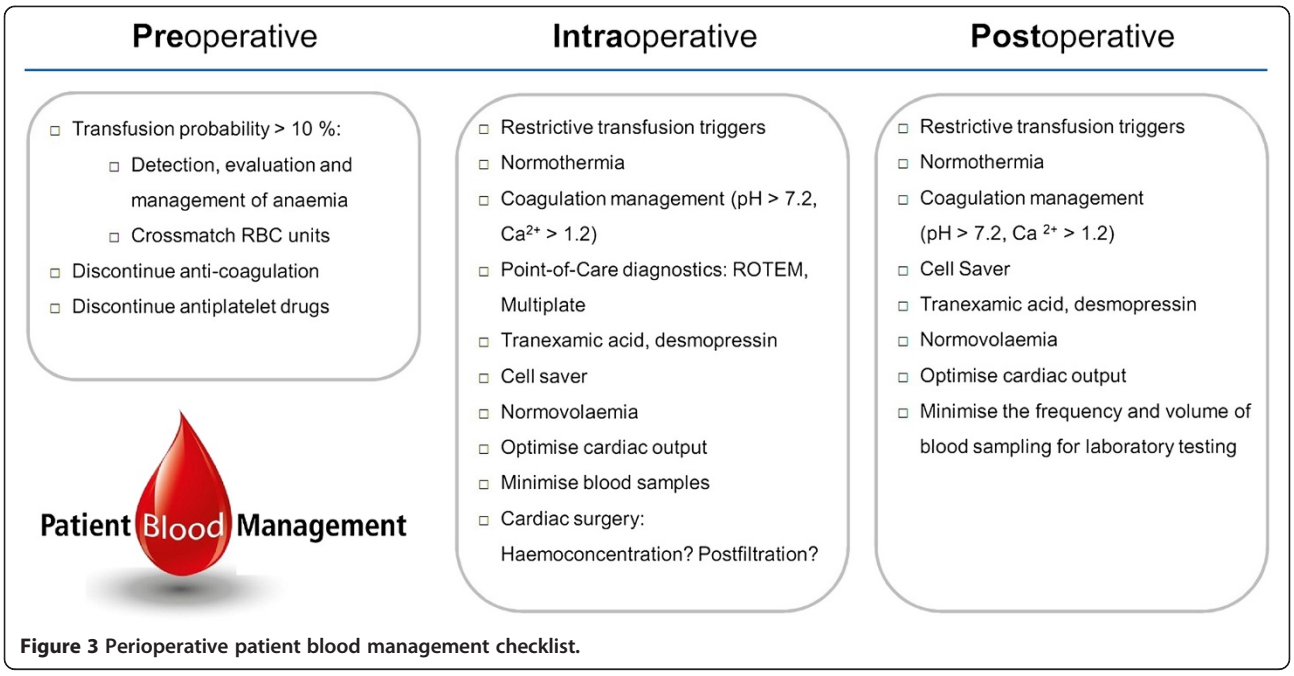

Figure 3 Perioperative patient blood management checklist.

sample size calculation is not possible to this date. However, we expect approximately 100,000 participating patients.

Statistical analysis

The primary aim is to prove non-inferiority of the intervention (PBM) cohort when compared with the control cohort stratified by center. The primary composite endpoint will be registered electronically by analysis of ICD-10 diagnoses and will be exported to a data base. It will be analysed with a one-sided Mantel-Haenszel test with significance level of α =2.5% for the odds ratio resulting in H0: $OR \geq OR^*$ vs. H1 $OR < OR^*$ with OR^* being derived from the incidence in the control cohort and an incidence rate of the PBM cohort which is increased by the non-inferiority margin of 0.5%. As secondary analysis, we will analyse two-sided 95% confidence interval for the difference in the frequency of the composite safety endpoint as well as for the odds ratios and the single components of the composite endpoint. Additionally, the influence of covariates, e.g. the calendar year, concomitant diseases, the asynchrony of the study periods at different sites will be assessed statistically. Should there be a significant influence on the incidence of the composite endpoint, the Mantel-Haenszel test will be supplemented with a respective multivariate approach accounting for covariates.

Secondary endpoints will be compared with a two-sided Wilcoxon-Mann–Whitney test using a significance level of α =5%. A subgroup analysis will assess if there is some bias from not excluding patients with multiple hospital stays for surgical intervention during the study period. A further subgroup analysis will assess if there is a difference of safety between a) elective patients who will receive preoperative haemoglobin optimisation compared to b) anemic patients who will not undergo preoperative haemoglobin optimisation due to failed postponement of surgery in case of surgical urgency or non-elective surgery, respectively.

Economic evaluation

A cost-utility analysis is being conducted. Resource use data such as blood products transfused, inpatient days by ward type, surgery, medications, complications and their treatment has been integrated into the statistical analysis. The average cost in each group will be calculated, and from this the incremental cost-effectiveness ratio will be derived.

Clinical study monitoring

An Independent Data Monitoring and Safety Committee will analyse the data on a regular basis. If the implementation of the PBM program will result in a 5% rise of the primary efficacy endpoint compared to the control cohort encompassing all recruited patients from all centers, the IDMC can recommend early termination of the study. Final decision for early termination will be done by the principle investigators.

Discussion

While transfusion of cellular blood components is a life-saving intervention, over-transfusion can be associated with short and long-term hazards. Therefore risks and benefits of transfusions should be weighed individually in every patient and modifiable risk factors for transfusion such as anaemia should be prevented and treated

accordingly [5,9,16,17]. An effective, patient-focused PBM program could help to save a scarce resource and to improve patient outcome and safety [18,19]. In the last ten years, different aspects of a PBM program have been implemented into clinical practice reducing the utilisation of allogeneic red blood cell transfusions and improved outcome [20-24].

Nonetheless, there remains uncertainty about the safety and effectiveness of PBM. Both fear of insufficient tissue oxygenation following a restrictive transfusion trigger and delay of surgery due to preoperative optimisation are the main concerns prevailing.

This study aims to investigate whether or not a PBM program is non-inferior in terms of patient outcome compared to a pre-implementation cohort. The acceptance of the PBM program among physicians will determine the success of this study.

In conclusion, this prospective, multi-centre trial intends to determine whether or not the implementation of a PBM program is safe and effective in about 100.000 hospitalised patients undergoing surgery.

Trial status and conclusion

This trial is registered at www.clinicaltrials.gov (Identifier: NCT01820949).

The Patient Blood Management program has been implemented in the four university hospitals of Frankfurt, Bonn, Kiel and Muenster.

Despite the complex nature of implementing new clinical standards, this trial has proceeded successfully. The experience and data from this study should help to design and implement fitting PBM programs in other hospitals.

Abbreviations

IDA: Iron-deficiency anaemia; PBM: Patient Blood Management; RBC: Red blood cells.

Competing interests

This study is supported by the commercial organizations as specified above. Additionally, Professor Zacharowski received grants from Fresenius Kabi, B. Braun Melsungen, Vifor Pharma und CSL Behring. Professor Zacharowski, Professor Meybohm and Dania Fischer received speakers' honoraria from CSL Behring, Vifor Pharma and CSL Behring. Christian Weber has the following conflicts of interests to declare: speaking honoraria from CSL Behring, Roche AG, Biotest, TEM International, Novartis, B Braun and Verum Diagnostica.

Authors' contributions

PM and DPF designed the research and wrote the paper. PM, DPF, CFW, EH, CG, MMM, BS, ES, KZ and The German PBM Study Core Group contributed vitally to the design and established means of implementation of the program at the diverse study sights. EH, JR, DB designed the research and analysed data. All authors read and approved the final manuscript.

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