Title: Intraoperative transfusion of packed red blood cells (PRBCs) in elderly patients on chronic antithrombotic therapy undergoing elective surgery.

Background

Antithrombotic therapy (AT) is a well-known risk factor for bleeding, especially during emergency surgery where optimization of coagulation is not always possible. In elective surgery, however, there should be sufficient time to plan for avoidance of additional bleeding risk by interrupting and bridging antithrombotic therapy, although bridging anticoagulation has been shown to increase the risk of major bleeding in elective surgery (1). Nevertheless, a previous study concluded that patients undergoing commonly performed elective general surgeries can be safely maintained on clopidogrel without an increased risk of perioperative bleeding (2) as well as another study found that only long acting anticoagulants are predictors of intraoperative transfusion in older patients undergoing cancer surgery (3). However, most data on this area is limited to either specific high-risk patients e.g. patients with atrial fibrillation, specific types of surgeries and predominantly includes middle-aged patients rather than the elderly population ≥80 years of age.

Since blood loss during surgery, including elective surgery has been shown to cause a greater mortality, the assessment of antithrombotic therapy and bleeding risk in elective surgery is important (4). This is especially relevant in the elderly population, since many elderly patients are treated with antithrombotics and compared to younger patients are particularly vulnerable to both surgery and blood loss due to limited physiological reserve. Furthermore, the elderly population is continuously increasing. Hence, there may be more elderly patients at risk of surgical bleeding in the future.

The premise for this study is that clinically important information on the risk and benefits of chronic antithrombotic therapy (anticoagulants and/or antiplatelets) in relation to intraoperative transfusion of packed red blood cells and mortality in the elderly population can be obtained by accessing the database of the POSE study (Peri-interventional Outcome Study in the Elderly), a European multicenter, prospective observational cohort study. The POSE study previously aimed to provide estimates for all-cause mortality in the elderly surgical population. In this secondary analysis of the POSE study we aim to assess the risk of intraoperative transfusion of packed red blood cells (PRBCs) during elective surgery in the elderly patients on chronic antithrombotic therapy (anticoagulants and/or antiplatelets).

Purpose

The purpose of the study is to assess if chronic antithrombotic therapy (anticoagulants and/or antiplatelets) is a predictor for intraoperative transfusion of packed red blood cells (PRBCs) in elderly patients undergoing elective surgery.

Hypothesis

We hypothesize that the risk of intraoperative transfusion of packed red blood cells (≥1 PRBC units given intraoperatively) in elderly patients undergoing elective surgery is higher in the elderly on chronic antithrombotic therapy (anticoagulants and/or antiplatelets) than those that do not receive chronic antithrombotic therapy.

Materials and methods

This study is a prospective observational study and a secondary analysis of the POSE study, which included 9500 elderly (≥80 years of age) surgical and non-surgical patients in 177 European centers who were followed for 30 days from the day they were anesthetized. For our secondary analysis we will include POSE patients who underwent elective surgery and with available data on chronic antithrombotic therapy (yes/no). Receiving chronic antithrombotic therapy is defined as intake of anticoagulants and/or antiplatelets until at least 7 days before intervention. Furthermore, we will include preoperative data, including demographic data (age, sex, weight, height), laboratory values (hematocrit and concentrations of hemoglobin, creatinine and albumin), American Society of Anesthesiology (ASA) class (I-V), and medical history of currently smoking (<1 year prior to intervention, excluding pipes, cigars, chewing tobacco, yes/no), diabetes (with oral or insulin treatment, yes/no), severe COPD (functional disability or chronic bronchodilator therapy or past hospitalization of FEV1 of <75%, yes/no), hypertension requiring medication (<30d prior to surgery,

yes/no), congestive heart failure (<30d prior to intervention, acute or chronic + symptoms, yes/no) and disseminated cancer (includes ALL, AML, Lymphoma °IV; excludes CLL, CML, Lymphoma °I-III, yes/no) as well as intraoperative data including type of surgery (minor, intermediate, major), surgical category (orthopedic, gynecologic, vascular, abdominal, cardio-thoracic, neurosurgical, other (ENT, plastic, ophthalmologic etc.)), intraoperative transfusion (packed red blood cells, plasma and platelets: ≥1 units, yes/no) and postoperative data including in and out of hospital complications (venous thromboembolism/blood clot, stroke, return to operating room), hospital length of stay, and all cause 30-day mortality (in and out of hospital deaths).

Primary outcome: *Intraoperative transfusion of packed red blood cells in elderly on chronic antithrombotic therapy* (anticoagulants and/or antiplatelets) defined as transfusion of 1 or more units of PRBCs given intraoperatively.

Secondary outcomes:

1. Intraoperative transfusion of platelets and/or fresh frozen plasma (≥1 units, yes/no)
2. Frequency of complications (venous thromboembolism/blood clot, stroke, return to operating room (combined outcome))
3. Hospital length of stay
4. All cause 30-day mortality

Statistical analysis

We will use R for all statistical analyses.

Primary outcome analysis

The primary outcome will be analyzed using logistic regression model adjusted for age and sex as well as predetermined variables by the authors that may act as potentially predictors of intraoperative transfusion of packed red blood cells, including American Society of Anesthesiology (ASA) class (I-V), Body Mass Index (underweight: <18.5 kg/m^2, normal weight: 18.5–24.9 kg/m^2, obesity: ≥25.0 kg/m^2), baseline hemoglobin level and disseminated cancer (yes/no), surgery type (major, intermediate, minor) and surgical categories (orthopedic, gynecologic, vascular, abdominal, cardio-thoracic, neurosurgical, other (ENT, plastic, ophthalmologic etc.)(3). In addition, we will use backward elimination in a secondary analysis. Outcome is dichotomous intraoperative transfusion of packed red blood cells (≥1 units given intraoperatively, yes/no) with Odds Ratio (OR) and 95% confidence interval for antithrombotic therapy (anticoagulants and/or antiplatelets). Similar methods will be used for the secondary outcomes except hospital length of stay which will be analyzed using Mann-Whitney-U-test . P value <0.05.

Multiple Imputation will be used to handle missing data.

The estimated number of included patients is approximately 7100 patients undergoing elective surgery. In the original POSE study 6.1% received PRBCs. 37% patients received antiplatelets, hence we will be able to detect a difference of PRBC incidence of 7 versus 5% in patients with or without antiplatelets before surgery with a power of 90% at the 0.05 significance level.

Project participants

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Timeline

It is expected that data analysis and writing of first draft of manuscript will be 6 months from data receipt.

Funding

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Ethics

This is a non-interventional secondary analysis based on prospectively collected data from the POSE study, which we will gain access to via data transfer agreement with the University Hospital RWTH Aachen, why there are no ethical concerns regarding the included patients. The proposal for the study is approved by the Steering Committee (SC) of the POSE study and we will furthermore follow the secondary analysis guideline outlined by the POSE study. This guideline covers approval of the final manuscript of the secondary analysis by the SC before submission to a journal as well as inclusion of the original paper as a reference for our article and incorporation of all relevant individuals from the POSE study group as coauthors. This secondary analysis will not be published nor will presentations related to the project be held until the main POSE study manuscript is published.

Publication

The goal for this study is to have the article published in an international journal in compliance with the ICMJE criteria for authorship written by the Vancouver Convention.

Perspective

This study will provide information on the risks of chronic antithrombotic therapy, including intraoperative transfusion of PRBC, complications, and mortality in the elderly population (≥80 years of age) undergoing elective surgery. The results may address the need for optimization of coagulation strategies in the elderly. If this study shows that the elderly on chronic antithrombotic therapy (anticoagulants and/or antiplatelets) is at greater risk of intraoperative PRBC transfusion during elective surgery than those not on chronic antithrombotic therapy, it may indicate that interruption and bridging regimes may not be sufficient in this elderly population, why further evaluation is needed. The elderly patients on chronic antithrombotic therapy may need a wider interruption period or a lower dose of bridging therapy than the present guidelines indicate to reduce the risk of intraoperative PRBC transfusion. Further research on this topic will help ensure the best management of antithrombotic therapy in the elderly to reduce the risk of intraoperative PRBC transfusion during elective surgery, which may lead to a reduction in mortality.

References

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