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Chapter 8

Further improvement in Patient Blood Management

We showed that despite a restrictive transfusion trigger still a quarter of the patients receive transfusions for elective total hip- and knee surgery. Autologous re-infusion by use of a cell saver or a post-operative drain re-infusion device was not effective to further decrease RBC use. Pre-operative use of Epo, however, is an effective transfusion alternative, but against unacceptably high costs. Therefore, these transfusion alternatives should not be used for the average elective orthopaedic patient. Further improvement in Patient Blood Management may be gained by looking at patient-specific factors. In this chapter, risk indicators for receiving a red blood cell (RBC) transfusion and for adverse clinical outcome (morbidity and mortality) in elective hip-and knee surgery are discussed. Since preoperative anaemia has been identified as an independent risk indicator for blood transfusion and has been associated with adverse outcome, one of the strategies for optimal blood management is to treat preoperative anaemia in order to aim for normal Hb values before surgery. This is discussed in the light of future studies (i.e. more attention to the preoperative anaemic patient, including the evaluation of the use of intravenous iron). Finally, the issues for further improvement in Patient Blood Management by prognostic modelling are discussed.

RISK FACTORS FOR TRANSFUSION IN ELECTIVE HIP-AND KNEE REPLACEMENT SURGERY

The need for a red blood cell (RBC) transfusion in patients scheduled for hip or knee surgery may depend on several factors: surgical factors (e.g surgical time, type of surgery and surgical technique), patient factors (e.g. co-morbidity) and blood management protocols. A restrictive RBC transfusion trigger is a powerful tool to reduce RBC transfusions. This has been investigated in two randomised trials, reported in chapters 2,3 and 7.These studies showed that the majority of these patients are relatively healthy and do not need RBC transfusions, and subsequently should not be treated with blood sparing modalities. Therefore, it is necessary to look for patient characteristics that can be identified as risk indicators for RBC transfusions. Of all reported risk indicators, a low preoperative Hb value was found to be a strong independent predictor for RBC transfusions [1-7].

In Table 1, other risk indicators are reported as well, but these were not identified consistently. Our own data showed, that patients with Hb levels of 8.1 mmol/L (=13 g/dL) or lower, are three times more often transfused than patients with Hb levels above 8.1 mmol/L (24% versus 8%) (the TOMaat study data). In patients with a preoperative Hb of 8.1 mmol/L or lower, Epo reduced the transfusion rate to 12% (OR 0.50; 95% CI 0.3 to 0.7), but at unacceptably high costs per avoided transfusion. Studies investigating other, less costly alternatives for Epo, are therefore necessary. Furthermore, by identifying more predictors for the use of a RBC transfusion, selective application of blood saving measures to a certain well-defined group of patients would be possible for optimal cost-efficiency.

Table 1. Preoperative risk indicators for red blood cell (RBC) transfusions in hip-and knee replacement surgery

Author (year)	Type of surgery (numbers)	Study design	Risk factor (if available OR and CI is included)
Keating (1998) [2]	Unilateral TKR (n=279) Bilateral TKR (n=280)	Retrospective Logistic multivariable regression analysis	Preop Hb 10-13 g./dL vs >13 g/dL
Faris (1999) [6]	THR/TKR (n=276)	Retrospective Logistic regression curve	Preoperative Hb 10-13 g/dL
Rosencher (2003) OSTHEO study [32]	THR n=2640 TKR n=1305	Prospective Logistic regression plot	Inverse relation Hb and RBC transfusion: transfusion risk if Hb=8 g/dL 75% for women and 69% for men; if Hb=13 g/dL: 32% for women and 22% for men
Bong (2004) [3]	TKR (n=1402)	Retrospective Multivariable regression analysis all p<0.05	Preop Hb: 10-13 g/dL OR 1.83 <10 g/dL OR 4.17 Age: 65-74 OR 1.54 75-84 OR 2.88 >85 OR 4.50 use of LMWH: OR 2.08
Guerin (2007) [4]	THR and TKR (n=162)	Prospective Multivariable regression analysis	Preop Hb level < 13 g/dL
Walsh (2012) [7]	Revision THR (n=210)	Prospective Multivariable regression analysis	Preoperative Hb (change per g/dL increase in Hb): OR. 0.44 [0.33-0.58] Weight (change per kg, increase): OR 0.98 [0.96-1.00] blood loss (change per mL increase in blood loss): OR1.002 [1.002-1.003] re-infusion of perioperative salvaged blood (yes/no): OR 0.31 [0.11-0.82]

Abbreviations: n=numbers; TKR=Total Knee Replacement; OR=Odds Ratio; CI=Confidence Interval; THR=Total Hip Replacement; LMWH= Low Molecular Weight Heparin

PREOPERATIVE ANAEMIA AS A RISK INDICATOR FOR ADVERSE CLINICAL OUTCOME IN ELECTIVE HIP-AND KNEE SURGERY

Besides having an increased transfusion risk, preoperative anaemia has also been identified as an independent risk indicator for mortality and morbidity after surgery. Beattie and co-workers reported a strong association between anaemia and peri-operative mortality in a large non-cardiac surgery cohort of more than 7000 patients. However, the subgroup of orthopaedic surgery patients was not specified (Table 2) [8]. Musallam and co-workers investigated a large cohort of 227.425 patients including 69.227 anaemic patients (10.758 were orthopaedic surgery patients), and found an increased risk for morbidity and mortality 30 days after surgery in the anaemic patients compared to the non-anaemic patients [9]. This study found an increased risk for composite morbidity (e.g. myocardial infarction (MI), stroke, pneumonia, renal insufficiency, wound infection, sepsis, thrombo-embolism) of 53% (OR1.53 [95% CI 1.23 to 1.90]). Complications were increased in 42% of the sample of 10.000 anaemic orthopaedic patients .This association, however, could not be confirmed by Mantilla and co-workers who performed a case-control study of hip-and knee replacement surgery patients (50% elective, 50% emergency), and matched for type of surgery, age and sex [10]. The investigators found that preoperative Hb value was not a risk for mortality or MI, but identified other existing co-morbidities such as cardiovascular, cerebro-vascular or pulmonary disease as the most important risk indicators. This risk model applied to both emergency as well as to elective surgery subgroups. The authors discussed that their population included patients with a relatively high mean age (78 years) with a high prevalence of co-morbidities (65% cardiovascular diseases) compared to other studies. In an earlier and descriptive study on a large study population of 10.244 primary total hip and knee arthroplasty patients over a 10 year period, the same authors (Mantilla (2002) reported on the frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis and postoperative death and found a frequency of 2.2% of these complications within 30 days after surgery, mainly in the older age group (>70 years). However they did not evaluate the association between these complications and anaemia [11].

Since high age and co-morbidities are also identified as risk indicators for adverse outcome in hip fracture surgery patients, it seems that some overlap exists in risk indicators for patients scheduled for elective orthopaedic surgery and patients who had more acute orthopaedic surgery after a hip fracture (Table 3) [10,11]. These latter patients are also referred to as "the frail elderly" in contrast to the vital healthy elderly. The frail elderly group has been associated with impaired physical function, gait speed and impaired cognition and have a higher risk of death and disability. An alternative to identify frailty is to estimate the biological age of the patient, which has been performed in 1000 randomly recruited ambulatory 75-year old women in Sweden. In that study, the biological age was predictive for both future fractures (OR 7.52: oldest tertile compared to youngest tertile), and overall mortality (OR 3.65) [12].

Anaemia may also be associated with "frailty", and the presence of anaemia, whatever its cause, may well be a proxy for "the frail elderly". So by identifying and treating the anaemic preoperative patient, the surgical outcome may be influenced in a positive way.

Table 2. Risk indicators for adverse outcome in (elective) hip-and knee replacement surgery

Author (year)	**Type of surgery (numbers)**	**Study design / type of analysis**	**Risk factors/ predictors**
Mantilla (2002) [11]	Elective THR/TKR (n=10244)	Retrospective, descriptive data	Age (>70 y) (higher frequencies) Outcome: MI, pulmonary embolism, death
Beattie (2009) [8]	Non-cardiac surgery (n=7759) (orthopaedic surgery not specified)	Retrospective, multivariable analysis	Preoperative anaemia OR 2.36 [1.57-3.41] Outcome: mortality
Musallam (2011) [9]	Non-cardiac surgery (n=227425) (orthopaedic surgery not specified)	Retrospective, multivariable analysis	Preoperative anaemia OR 1.42 [1.31-1.54] Outcome: 30-day morbidity and mortality
Sabate (2011) [33]	Non-cardiac surgery (n=3387) (34% was orthopaedic surgery)	Prospective, multivariable analysis	Existing co-morbidities, blood transfusion: Coronary artery disease: OR 2.2 [1.3-3.5]; Congestive heart failure: OR 2.3 [1.4-3.9]; Chronic kidney disease: OR 1.9 [1.2-3.2] Cerebrovascular disease: OR 2.9 [1.7-4.7] RBC transfusion: OR 2.7 [1.9-4.1] Outcome: major cardiac and cerebrovascular events
Mantilla (2011) [10]	Elective and emergency THR/TKR (n=391+391)	Case-control, multivariable analysis	Cardiovascular disease: OR 3.27 [2.27-4.72]; cerebrovascular disease: OR 1.99 [1.24-3.19]; pulmonary disease: OR 1.62 [1.00-2.61] Outcome: MI, death

Abbreviations: n=numbers; Y=Years; TKR=Total Knee Replacement; THR=Total Hip Replacement; OR [CI]=Odds Ratio [Confidence Interval]; MI=Myocardial Infarction

Table 3. Risk indicators or predictors for adverse outcome after hip fracture surgery

Author (year)	**Type of surgery (numbers)**	**Study design/ data analysis**	**Risk factor**
Lu-Yao (1994) [34]	Hip fractures -femoral neck n=13167 -per-trochanteric n=13767 Total n= 26424 Age ≥65 years	Cross-sectional multivariable analysis Outcome: 90-d (here shown) and 3y-mortality	Age (1-y increase): OR 1.07 [1.06-1.07] Male: OR 2.21 [2.04-2.40] Nursing home OR 1.39 [1.28-1.52] Pertrochanteric fracture site OR 1.18 [1.06-1.30] Charlson* co-morbidity score >0 OR 1.89 [1.75-2.04]
Nettleman (1996) [35]	Hip fracture (not specified) n=390 all ages	Retrospective Multiple logistic regression analysis Outcome: 30-d mortality	Predictors: - CHF OR 32.2 [5.4-92] - angina 25.7 [3.6-184] - COPD 11.1 [2.0-62]
Gruson (2002) [36]	Hip fracture (femoral neck and intertrochanteric) n=395 age ≥65 years	Prospective, multivariable logistic regression analysis Outcome: 3-,6-,12-m mortality	Predictive factor: preoperative anaemia: OR 1.4 [0.5-4.0] n.s. (3-month mortality) OR 2.9 [1.2-7.3] (6-m mortality) OR 2.6 [1.2-5.5] (12-m mortality)
Richmond (2003) [37]	Hip fractures (not specified) n=836 age ≥65 years	Prospective Standardised Mortality Ratio (SMR) Outcome: 2 year-mortality	ASA 3-4 in age 65-84: SMR 3.2 Not increased in: ASA 1-2 and/or age >84
Roberts (2003) [38]	Femur neck fractures n=32590 age ≥65 years	Retrospective Case Fatality Rates (CFR) Outcome: 30-d, 90-d and 365-d mortality (CFR)	CFR by age, and by sex: from OR 7.2 in men 65-69y to OR 33.7 in men >90y (30-d) compared to women (from OR 2.7 to OR 22.7 (30-d); Social class IV and V (adjusted for age and sex): OR. 2.47 [1.79-3.42] (30-d) ORs are further increased after 90-d and 365-d mortality
Halm (2004) [39]	Hip fracture (femoral neck, inter- and sub-trochanteric) n=550 all ages	Prospective Multivariable regression analysis Outcome: death 60-d after discharge	Preoperative Hb level: OR 0.69 [0.49-0.95]

Table 3. *Continued*

Author (year)	Type of surgery (numbers)	Study design/ data analysis	Risk factor
Roche (2005) [40]	Hip fractures (not specified) n=2448 age ≥ 60 years	Prospective, multivariable analysis Outcome: 30-d mortality	Three or more co-morbidities: OR 2.5 [1,6-3.9]; respiratory disease: OR 1.8 [1.3-2.5] Malignancy: OR 1.5 [1.01-2.3]
Maxwell (2008) [41]	Femur neck fractures (n=5162) all ages	Prospective, multivariable analysis Outcome: 30-d mortality	Age >65 y: OR 4.34 [1.34-14.0] Male gender: OR 1.63 [1.15-2.39] Two or more co-morbidities: OR 1.63 [1.15-2.32] MMS score 6 or less: OR 1.55 [1.01-2.39] Malignancy: OR 1.76 [1.13-2.74]
Burgos (2008) [42]	Hip fracture (not specified) n=232 age ≥65 years	Prospective ROC curve: AUC ≥0.7 As acceptable predictive value Outcome: A. Serious complications B. 90-d mortality	Predictive preoperative risk scores (AUC): Risk- VAS: 0.707 (for A) Charlson: 0.833 (for A) POSSUM 0.726 (for A) None were predictive for B
Vochteloo (2011) [43]	Hip fracture (femoral neck, inter- and sub-trochanteric) n=1262 age ≥65 years	Retrospective and prospective, multivariable analysis Outcome: mortality (in-hospital, 3 m and 12 m)	Preoperative anaemia: not predictive for mortality: OR 1.30 [0.96-1.76] RBC transfusion: predictive for in-hospital mortality, 3-m and 12-m

*Charlson index: scores pre-operative co-morbidity as a predictor for adverse postoperative outcome
Abbreviations: n=numbers; OR=Odds Ratio [95% confidence interval]; n.s.=not significant; m=months; d=day; y=year; CHF=Congestive Heart Failure; COPD= Chronic Obstructive Pulmonary Disease; MMS= Minimal Mental State; ROC=Receiver Operation Curve; AUC=Area Under Curve; RISK-VAS=Visual Analogue Scale for Risk; POSSUM=Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

PREOPERATIVE ANAEMIA IN THE OLDER PATIENT

Several surveys report a relationship of prevalence of anaemia and increasing age [13-15] with an overall prevalence of 11% in males and of 10% in females older than 65 years according to the WHO criteria [16]. One-third can be explained by nutritional causes (of which half was due to iron deficiency), one third by Anaemia of Chronic Disorder (ACD) and Unexplained Anaemia (UA) in the remaining one third of patients. These latter two categories of patients are characterized by low erythropoietin levels and low levels of pro-inflammatory cytokines [17,18].

If anaemia is due to nutritional causes, correction might be easily performed by supplementing the deficient components. However, if anaemia is due to ACD or UA, it may be necessary to find the underlying disease that causes the anaemia (e.g. kidney failure, malignancy). If a patient is then still eligible for elective surgery, preoperative measures to increase the Hb level can be considered.

OPTIMISING PATIENT BLOOD MANAGEMENT AND POSTOPERATIVE OUTCOME BY OPTIMISING THE PREOPERATIVE HB LEVEL

Since the preoperative Hb level was consistently reported as an independent significant risk factor for a RBC transfusion, it was included in the workup for optimising Patient Blood Management [19,20]. A Patient Blood Management Protocol was developed by a NATA working party aiming for preoperative non-anaemic levels in the elective orthopaedic surgery population. Due to the elective character, the optimal preoperative treatment can be explored, which however can be a problem if the waiting period for surgery is less than 4 weeks. Use of Epo (with oral iron) to increase Hb to normal levels, is very costly. An alternative may be the use of IntraVenous (IV) iron, since IV iron therapy may increase Hb values not only in iron deficient patients, but also in patients with ACD, bypassing the blocking effect of hepcidin that makes iron unavailable for incorporation in red blood cells [21]. Whether patients with UA benefit from either IV iron or Epo therapy or are refractory to both treatments, is unknown and must be further evaluated.

The efficacy and safety of IV iron compared to oral iron, or to placebo had been studied in several randomised trials, and was reported in a systematic review [22]. The authors concluded, that ferric carboxymaltose (Ferinject) significantly increased Hb levels compared to placebo, oral iron and intravenous iron sucrose (Venofer). Furthermore, the use was comparably safe.

In orthopaedic surgery, no randomized trials are published that primarily evaluated the use of IV iron as an transfusion alternative and compared its effect to other blood management modalities. Of four published randomized studies using IV iron, none investigated RBC use as a primary outcome: three of them combined preoperative use with or without Epo and scored the frequency to preoperatively donated autologous blood as primary outcome [23-25], a fourth study evaluated postoperative use of IV iron and its effect on Hb recovery [26]. Another problem of these studies was the low numbers of patients.

Since these randomized studies only investigated IV iron at a limited level and hardly as a blood sparing modality, more insight in the response to preoperative intravenous iron in the elderly population for elective hip-and knee surgery is important. For this purpose, a new study protocol was designed: the Preoperative Orthopaedic Patients- Iron (POP-I) study.

The POP-I study

In this study, patients with a preoperative Hb value between 6.2 (10 g/dL) and 8.1 mmol/L (13 g/dL) will be equally randomised for IV iron therapy (ferric carboxymaltose), for Epo (+oral iron) and for a control group. Control patients will be supplemented with oral iron in case of an iron deficiency anaemia. Primary outcome is the proportion of transfused patients and cost-effectiveness will be evaluated. IV iron and Epo will be prescribed at least 4 weeks before surgery and Hb levels will be monitored. With this study, we may provide evidence for using IV iron as a cost-effective alternative for Epo.

Interestingly, a same type of study is ongoing in hip fracture patients, comparing IV iron to IV iron+ Epo and to placebo (a multi-centre, randomised study: the PAHFRAC-01project; NCT01154491).

OPTIMISING PATIENT BLOOD MANAGEMENT BY DEVELOPING A PROGNOSTIC MODEL

Optimal tailor-made treatment (in Dutch: Op Maat) can be attained by developing a model in which several outcome results (i.e. to be transfused, or morbidity or mortality) can be predicted with a certain likelihood. Development of such a multivariable prognostic model can be performed best by using data from a prospective cohort study, although data from randomised intervention studies can also be used [27]. If such a model is developed and validated it can also be used to evaluate whether the predictors identified in elective orthopaedic surgery patients are valid for other patients groups, such as the “frail elderly” undergoing hip fracture surgery.

Prediction models for RBC transfusions have been proposed, but none of the models has been widely accepted and used. A systematic review on patient characteristics and its association with perioperative RBC transfusions was published by Khanna and coworkers, who analysed 46 studies of which 13 were among elective knee-and hip replacement surgery patients [28]. They found that a low preoperative Hb level was most frequently associated with RBC transfusions, being identified as a strong predictor in all studies. The other factors commonly associated with risk for transfusion in literature, were advancing age (3 studies), female gender (6 studies), and small body size (4 studies). Only 2 non-orthopaedic studies validated their predictive model for RBC transfusion on other prospective data and confirmed robustness of their model. However, the retrospective nature (lack of data), the small sample sizes and heterogeneity of the studies made it impossible to use the data in a combined dataset to define a clinically useful prediction model for allogeneic RBC transfusion.

Having access to reliable predictors for adverse outcome, the clinician may outweigh the benefit of an elective lower extremity joint replacement against the risk of an adverse outcome for an individual patient. The PROPER study (PROject PEroperative Risk) compared preoperative risk factors to postoperative adverse outcome during hospital stay in 1471 elective general surgery and orthopaedic surgery patients, and found four predictive factors for adverse outcome in the overall group (orthopaedic patients were not separately specified): a risk-Visual Analogue Score (VAS), ASA score, age and surgical stress (a four point scale scoring minor to extensive procedures, to estimate the magnitude of surgical stress imposed upon the patient). However, a prediction model was not developed, because all predictors had moderate sensitivity and specificity and a too low predictive value for individual patient counselling [29].

By using data from the 2500 randomised patients from our collected TOMaat-study dataset, that included more than 250 transfused patients, we aim to develop a prognostic model for prediction of RBC transfusions, which can further be validated in collected datasets from other orthopaedic surgery patients. For the prediction of adverse postoperative outcome, other databases will be needed to have sufficient numbers of adverse events for input in a model. The most important and significant predictors can then be identified, assigning relative weights to each predictor, and estimating the model's predictive performance with adjusting the model for overfitting. Finally, validating the model will be done in new datasets.

PATIENT BLOOD MANAGEMENT: FUTURE DIRECTIONS

Despite the fact that blood components are safe in the Western world, there is an ongoing aim for "bloodless surgery" [30,31], which refers to optimalisation of peri-operative Patient Blood Management. We demonstrated that in elective knee-and hip surgery, due to the use of a restrictive transfusion trigger and continuously improving surgical techniques, some transfusion alternatives are no longer effective in reducing RBC use (autologous re-infusion devices such as cell saver or postoperative drain re-infusion devices), or are not cost-effectively reducing RBCs, such as Epo, and are thus not considered as appropriate transfusion alternatives. By identifying predictors for transfusion, the use of (other) blood sparing modalities may be further evaluated and applied to the high risk patients only.

Nowadays, the scope for optimal Patient Blood Management has changed to the preoperative setting, in which the anaemic patient, which is a proxy for patients with some kind of co-morbidity, needs more thorough evaluation to prevent adverse postoperative outcome. This is underscored by the identification of preoperative anaemia as a strong predictor for transfusion. Patients with a preoperative anaemia must be treated to increase Hb levels to normal, thus reducing peri-operative RBC use and possibly also reducing the postoperative complication rate. Use of Intravenous iron can be explored in patients with iron deficiency anaemia and ACD as a cost-effective alternative for Epo.

In conclusion, a clinically relevant prediction model with respect to allogeneic RBC transfusions, will support a Tailor Made (in Dutch: Transfusie Op Maat) Patient Blood Management strategy for a specific group of patients, in which the use of transfusion alternatives may be applied. By identifying predictors for worse outcome (i.e. mortality and high morbidity), a decision model for the clinician may assist in the decision whether the benefits of a joint prosthesis outweighs the risks for adverse postoperative outcome. Future studies must include prognostic modeling leading to optimal Patient Blood Management.

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