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Health economics of Patient Blood Management: a cost-benefit analysis based on a meta-analysis

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Background and Objectives Patient Blood Management (PBM) is the timely application of evidence-based medical and surgical concepts designed to improve haemoglobin concentration, optimize haemostasis and minimize blood loss in an effort to improve patient outcomes. The focus of this cost-benefit analysis is to analyse the economic benefit of widespread implementation of a multimodal PBM programme.

Materials and Methods Based on a recent meta-analysis including 17 studies (>235 000 patients) comparing PBM with control care and data from the University Hospital Frankfurt, a cost-benefit analysis was performed. Outcome data were red blood cell (RBC) transfusion rate, number of transfused RBC units, and length of hospital stay (LOS). Costs were considered for the following three PBM interventions as examples: anaemia management including therapy of iron deficiency, use of cell salvage and tranexamic acid. For sensitivity analysis, a Monte Carlo simulation was performed.

Results Iron supplementation was applied in 3·1%, cell salvage in 65% and tranexamic acid in 89% of the PBM patients. In total, applying these three PBM interventions costs €129·04 per patient. However, PBM was associated with a reduction in transfusion rate, transfused RBC units per patient, and LOS which yielded to mean savings of €150·64 per patient. Thus, the overall benefit of PBM implementation was €21·60 per patient. In the Monte Carlo simulation, the cost savings on the outcome side exceeded the PBM costs in approximately 2/3 of all repetitions and the total benefit was €1 878 000 in 100·000 simulated patients.

Conclusion Resources to implement a multimodal PBM concept optimizing patient care and safety can be cost-effectively.

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Introduction

The World Health Organization (WHO) defined Patient Blood Management (PBM) as '*...a patient-focused, evidence-based and systematic approach to optimize the management of patients and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products....*' [1]. Since the release of this statement in 2011, several PBM programmes evolved incrementally [2–5]. PBM is a multimodal concept and focuses on three pillars: (1) comprehensive anaemia management; (2) minimization of hospital-acquired anaemia such as unnecessary blood loss; and (3) harnessing and optimizing the patient-

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specific physiological tolerance of anaemia [6–8]. The decision to transfuse red blood cells (RBC) is often based on haemoglobin level only. However, as stated in many guidelines, this decision should also consider physiological status, haemodynamic and respiratory parameters, volume status and dynamics of bleeding [9,10]. Recently, Althoff and colleagues conducted a meta-analysis on 17 studies in the field of PBM including more than 235 000 patients and assessed the impact of the implementation of at least one PBM measure in each of the three pillars on surgical outcome. They found that PBM measures were associated with a significant reduction in transfusion rate of RBC by 39%, hospital length of stay (LOS) by 0·45 days, complication rate by 20%, and mortality rate by 11% [11,12].

However, in times of increasing healthcare costs, it is essential to assess the cost-benefit, too. So far, the cost-benefit of PBM has been mostly determined based on the cost of blood acquisition or arbitrary costs, thereby underestimating costs associated with further PBM interventions or further outcomes such as LOS. For example, implementation of PBM in Western Australia resulted in a reduction of blood products by 41% and yielded cost savings of AU$ 18·5 M (US$ 18·1 M) taking into account blood product costs only [3]. Kleinerüschkamp and colleagues assessed the clinical and economic impact of PBM compared to Pre-PBM therapy considering the risks of postoperative complications in a simulated hypothetical cohort of 10 000 randomized patients. In total, 1768 fewer complications (17·68%) and 411 fewer deaths (4·11%) occurred in the non-cardiac surgical PBM cohort and 1245 fewer complications (12·45%) and 304 fewer deaths (3·04%) were found in the cardiac surgical PBM cohort. The incremental cost was €2885 in non-cardiac and €1761 in cardiac surgical patients of the hypothetical control cohort [13].

In this study, a cost-benefit analysis of PBM was performed based on a recent meta-analysis [11].

Material and methods

Data sources

To assess the economic impact of PBM, a cost-benefit analysis was performed based on the meta-analysis by Althoff *et al*. [11] including 17 studies comprising a total of 235 779 patients (100 886 pre-PBM (control group) and 134 893 PBM patients). Briefly, studies were included in the analysis that addressed each of the three PBM pillars with at least one measure per pillar, for example preoperative anaemia detection and treatment plus cell salvage plus rational transfusion strategy. Endpoints were transfusion rate (number of patients transfused), transfused RBC units per patient, LOS, total number of complications, and mortality. As detailed information about the number of patients screened for anaemia and iron deficiency (ID) was not provided by the studies included in the meta-analysis, data from a prospective observational study by Meybohm *et al*. [14] including 1830 patients undergoing major surgery with expected blood loss of ≥500 ml and transfusion probability of ≥10% were used, too. Cost of material and staff has been described previously [15]. Intravenous iron therapy costs €176·68, use of cell salvage €155·90 and administration of tranexamic acid (TXA) €9·06 (Table 1). Laboratory diagnostics (including ferritin, transferrin saturation, serum folate, holotranscobalamin, serum vitamin B12) costs about €48·69–123·88 depending on type of anaemia [15]; here, we considered €48·69 (Table 1).

Cost analysis of three perioperative PBM interventions

The following three PBM interventions were considered as examples: anaemia management including intravenous iron supplementation of iron-deficient (ID) anaemic patients, use of cell salvage and TXA. We assessed the percentage of patients receiving TXA and cell salvage according to the proportion of studies with indicated TXA or cell salvage application in patients after implementation of PBM. With this approach, a systematic bias towards studies with large cohorts of patients could be avoided. Mean costs per patient were calculated.

Cost-benefit analysis of PBM-associated benefits

The following PBM-associated outcomes were included in this cost-benefit analysis: RBC transfusion rate, the average number of transfused RBC units, and mean LOS [11] (Table 2). Cost and savings were calculated based on Kleinerüschkamp *et al*. [13,15]. Briefly, patient-related costs of materials and services were evaluated at the University Hospital Frankfurt in 2013. Personnel costs of all major processes were quantified based on the time required to perform each step [15]. A health economic model was developed to calculate cost-effectiveness of PBM (PBM arm vs control arm) for simulated cohorts of 10 000 cardiac and non-cardiac surgical patients based on the results of the meta-analysis [11] and costs [13].

Statistical analysis

The mean baseline outcome probabilities of the control group were calculated for each outcome with respective study weights according to the random-effect model (REM) in order to account for the heterogeneity of the

Table 1 Costs associated with PBM interventions as examples, adapted from Kleinerüschkamp *et al.* [13,15], Meybohm *et al.* [14] and Althoff *et al.* [11]

	Costs	Application rate (%)	Costs according to application rate
Anaemia management			
Iron status	48·69 €	33·3[a]	16·21 €
Iron therapy	127·99 €	3·1[a]	3·90 €
Subtotal-I	176·68 €		20·11 €
Blood-saving measures			
Cell salvage	155·90 €	65	100·88 €
Tranexamic acid	9·06 €	89	8·05 €
Subtotal-II	164·96 €		108·93 €
Total	369·08 €		129·04 €

[a]Data from University Hospital Frankfurt.

Table 2 Outcomes adapted from Althoff *et al.* [11]

Endpoint	Effect size (95% CI)
Transfusion rate (RR)	0·61 (0·55; 0·68)
RBC units per patient (MD)	−0·43 (−0·54; −0·31)
LOS in days (MD)	−0·45 (−0·65; −0·25)

CI, 95% confidence interval; MD, mean difference; RR, risk ratio.

included studies. The associated outcome values for the PBM group were then determined using the respective pooled effect estimate (risk ratio (RR) or risk difference (RD)) from the meta-analysis. For sensitivity analysis, a Monte Carlo simulation was performed to test the impact of variations in the outcome probabilities on the overall result of the cost-benefit analysis. According to the 95% confidence interval of the pooled effect estimates for the outcome endpoints, the distribution of the associated cost savings was calculated for 100 000 random samples. Costs were calculated in euros (€). No discounting of the cost calculation was necessary due to the time-independent cost assessment of the measures and outcomes. All analyses were performed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) and Excel (2016) with VBA-Makro for Monte Carlo simulation.

Results

PBM intervention associated costs

Considering our recent work including 1830 surgical patients screened for the presence of preoperative anaemia, about 33·3% (n = 608) suffered from anaemia and were investigated for ID before surgery [14]. Iron was supplemented in 3·1% of the patients. Taking into account the number of patients with no treatment (96·6%) costs amounted to €20·11 (Table 1). In total, 11 out of 17 studies (65%) included in the meta-analysis used cell salvage within surgery and 15 out of 17 (89%) studies administrated TXA. Overall, costs added up to €100·88 for the intraoperative use of cell salvage and €8·05 for TXA, respectively (Table 1). To compare the economic impact of PBM interventions, the mean costs for the whole group of PBM patients were calculated by multiplying the cost of an intervention accordingly with the application rate in PBM patients. In total, use of the three exemplary PBM interventions was associated with mean costs of €129·04 per patient.

PBM outcome benefit associated savings

Implementation of PBM measures in 235·779 surgical patients was associated with decreased RBC utilization and LOS [11]. The mean number of transfused RBC units per patient declined from 1·67 (Pre-PBM) to 1·25 (PBM). In addition, the number of patients with transfusion needs was reduced from 29·9% (Pre-PBM) to 18·24% (PBM) [11]. Overall, the mean cost for transfusion per patient was reduced from €68·62 (Pre-PBM) to €32·41 (PBM) resulting in savings of €36·21 (more than 50%; Table 3). Implementation of PBM was associated with reduced mean LOS by 0·45 [11] days which resulted in cost savings of €114·43 (Table 3). Overall, the implementation of PBM yielded to savings of €150·64 per patient.

Thus, the overall benefit of PBM implementation was €21·60 per every surgical patient.

Monte Carlo simulation

Monte Carlo simulation is a method based on repeated random sampling of inputs to a deterministic model or calculation procedure. According to the uncertainty of the real effect size of outcome in the meta-analysis by Althoff *et al.* [11], a sensitivity analysis of the associated cost savings was performed. The Monte Carlo simulation with 100 000 repetitions showed a distribution of cost savings from € −253·01 to −31·46 (Fig. 1) and a mean value of € −150·63 (95% CI (−200·75; −100·45)). In the Monte Carlo simulation, the cost savings on the outcome side exceeded the PBM intervention associated costs in approximately 2/3 of all repetitions and the total benefit of 100 000 simulated patients was €1 878 000.

Discussion

Anaemia is an emerging health problem and has been recognized as an independent predictor of poor outcome. Up to 30% of the surgical patients suffer from

Table 3 Costs and savings of PBM associated with reduction of RBC transfusion rate and LOS, adapted from Kleinerüschkamp *et al.* [13,15]

	Pre-PBM	PBM
1. Costs for RBC		
First RBC unit	147·73 €	
Any additional RBC unit	121·78 €	
Mean number of transfused RBC units per patient[a]	1·67	1·25
Transfusion per patient	229·55 €	177·73 €
Transfusion rate[a]	29·90%	18·24%
Mean cost for transfusion per patient	68·62 €	32·41 €
Savings		−36·21 €
2. Costs for hospitalization (normal ward)		
Per day	254·22 €	
Mean LOS per patient (day)[a]	9·98	9·53
Mean difference[a]		−0·45
Savings		−114·43 €
Total cost savings per patient		−150·64 €

LOS, length of hospital stay; RBC, red blood cells.
[a]Weighted mean from Althoff *et al.* [11]

preoperative anaemia [16], which is mainly caused by ID [17] and is the most prevalent, preventable, and treatable cause of anaemia worldwide. As a result, the awareness of the effective role of iron supplementation to treat ID anaemic patients in the preoperative setting is increasing [18–20]. For example, an increment in haemoglobin concentration of more than 2 g/dl can be accomplished with intravenous iron in severe anaemic ID patients [21–23]. Transfusion with allogeneic blood products has been the first choice to treat anaemia for many decades. However, the costs and risks associated with blood transfusion have led to the use of anaemia management and further therapeutic strategies such as re-transfusion of autologous blood using cell salvage or the use of haemostatic drugs. A recent meta-analysis by Meybohm and colleagues demonstrated that cell salvage is efficacious in reducing transfusion rate by 39% [24]. Furthermore, TXA is a cost-effective method to reduce bleeding in patients undergoing elective surgery and thereby decreasing transfusion rates and avoiding complications associated with low blood volume [25]. These measures are an integral part of PBM.

Translating evidence-based medicine into clinical practice generally relies on adopting a conglomeration of interventions, rather than a single treatment. Hence, it is important to assess cost benefits of recommended PBM measures to ensure further dissemination and implementation of PBM programmes. We conducted a cost-benefit analysis based on the first meta-analysis including 17 studies [11] and compared costs associated with the implementation and outcome of PBM. We focused on three interventions as examples—therapy of ID with intravenous iron, use of cell salvage and TXA—and outweighed costs associated with these interventions with savings following reduced transfusion rate and LOS. Diagnosis and treatment of ID occurred in 33·3% and 3·1%, respectively [14]. Cell salvage was used in 65% and TXA in 89% of the studies [11]. Based on 17 included studies with more than 235 000 patients, implementation of PBM was associated with a significant decrease in transfusion rate by 39%, in RBC utilisation with 0.43 RBC units per patient, and in LOS by 0·45 days [11]. Overall, the costs of anaemia management, use of cell salvage and TXA amounted to €129·04 per patient. In contrast, PBM was associated with a decreased transfusion rate and LOS and led to savings of €150·64 per patient. Thus, the overall return on investment of PBM was €21·60 per every surgical patient. The probabilistic sensitivity analysis of 100 000 time repeated simulation confirmed the robustness of the cost-benefit results. In the Monte Carlo

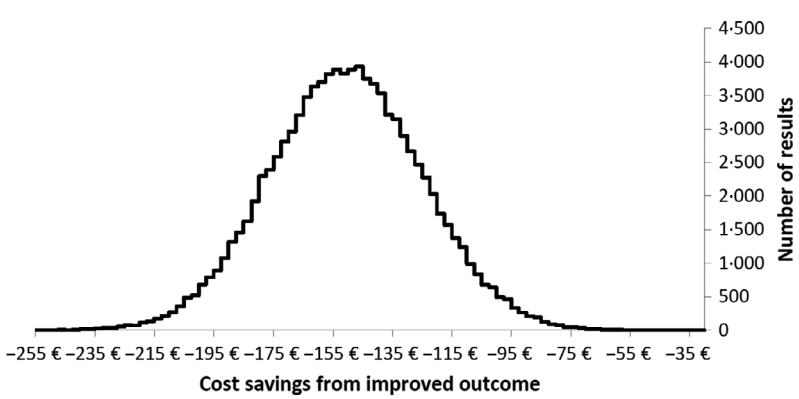

Fig. 1 Histogram of cost savings of Monte Carlo simulation in 100 000 repetitions: With Monte Carlo simulation, cumulative uncertainties of nature values can be integrated in a socio-economic cost-benefit analysis. The graph shows distribution of 100 000 repetitions for costs savings for improved outcome. The simulation shows a distribution of cost savings from €253·01 to 31·46 with a mean value of €150·63.

simulation, cost savings by reduced transfusion rate and LOS exceeded the PBM interventions costs in approximately 2/3 of all repetitions. Thus, the total benefit was €1 878 000 in 100 000 simulated patients.

Appropriate use of blood products is a key component of PBM. However, only few studies compared transfusion rate of platelets and fresh frozen plasma before and after implementation of PBM [3,26–29]. Overall, adherence to transfusion guidelines was associated with significant reduction of transfused platelets and plasma [3,26,29]. Interestingly, other studies did not find any differences in transfusion rate [30,31]. An analysis of 244 013 hospitalized patients revealed that platelets and plasma were mostly transfused to patients of the haematology and oncology (25·2%) service followed by cardiac surgery (19·5%), cardiology (12·7%) and stem cell transplantation (11·6%) [32]. We hypothesize that adherence to transfusion guidelines may prevent inappropriate platelets and plasma transfusion and leads to additional cost savings [3,26,33].

The idea of a holistic PBM programme focusing on the individual need of the patient and rejecting the one-size-fits-all approach has been communicated more than 20 years ago [34]. Since then, several concepts have been formulated defining the programme in three pillars with perioperative applications [35] and more than 100 single measures [10]. The complexity of the programme and associated costs concerns may have impeded the implementation in many hospitals and may also explain why only few regulatory authorities support the implementation of PBM worldwide. For example, the National Blood Authority supported the implementation of PBM in Western Australia in 2008 [9] and the National Institute for Health and Care Excellence guidelines in the UK postulated treatment with iron in iron-deficient anaemic patients 2 weeks before surgery [36]. At this time, Italy is the only country in which implementing PBM is mandatory by law [37]. With our cost-benefit analysis, we show that implementation of certain PBM measures is effective to improve patients' health and thereby reduce costs.

As we particularly used data from a PBM programme that covered all three pillars of PBM, our analysis cannot reveal, which PBM measure was most cost-effective. Till now, only few studies conducted cost-benefit analysis of single measures including material and personnel costs. Calvet and colleagues, for example, compared cost implication of different iron strategies including costs of iron infusion, transfusion and hospitalization and found cost savings of €274 per patient for ferric carboxymaltose compared to oral iron [38]. Cell salvage is indicated in patients with an expected blood loss of 500 ml or more. Lemke and colleagues also showed that cell salvage is most effective in patients with an increased risk of blood transfusion [39]. Importantly, PBM is a comprehensive concept encompassing multiple measures with synergistic effects. From our point of view, it would be unethical to focus on the most cost-effective measures and to withhold other beneficial interventions (e.g. blood sparing techniques, smaller blood tubes, coagulation management). Thus, we argue that clinicians and policy makers should concentrate their efforts on the initial adoption of the three-pillar framework including detection and treatment of anaemia (first pillar), any strategy to reduce blood loss and bleeding by autologous cell salvage, use of antifibrinolytic agents (second pillar), and compliance with restrictive transfusion thresholds (third pillar).

Although this cost-benefit analysis provides important and novel data, there are few limitations of our study. PBM was associated with a reduction of perioperative complications (including acute renal failure, infection, thromboembolic events, cardiac events, bleeding as well as any additionally reported adverse events) by 20% [11]. Costs associated with complications were not addressed in our cost-benefit analysis; however, we assume that a reduced complication rate would lead to additional cost savings. Therapy costs were determined at a single German hospital which may be limited transferable to other institutions.

Taken together, our cost-benefit analysis revealed that PBM measures—for example, anaemia management, cell salvage and TXA—may be overall cost-effective.

Conflict of interests

PM and KZ received grants from B. Braun Melsungen, CSL Behring, Fresenius Kabi and Vifor Pharma for the implementation of Frankfurt's Patient Blood Management programme and honoraria for scientific lectures from B. Braun Melsungen, Vifor Pharma, Ferring, CSL Behring and Pharmacosmos. All other authors have no conflicts of interest.

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