A model-based cost-effectiveness analysis of Patient Blood Management

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Background. Patient blood management (PBM) is a multidisciplinary concept focused on the management of anaemia, minimisation of iatrogenic blood loss and rational use of allogeneic blood products. The aims of this study were: (i) to analyse post-operative outcome in patients with liberal *vs* restrictive exposure to allogeneic blood products and (ii) to evaluate the cost-effectiveness of PBM in patients undergoing surgery.

Materials and methods. A systematic literature review and meta-analysis were performed to compare post-operative complications in predominantly non-transfused patients (restrictive transfusion group) and patients who received one to three units of red blood cells (liberal transfusion group). Outcome measures included sepsis with/without pneumonia, acute renal failure, acute myocardial infarction and acute stroke. In a second step, 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 and costs.

Results. Out of 478 search results, 22 studies were analysed in the meta-analysis. The pooled relative risk of any complication in the restrictive transfusion group was 0.43 for non-cardiac and 0.34 for cardiac surgical patients. In the simulation model, PBM was related to reduced complications (1,768 *vs* 1,245) and complication-related deaths (411 *vs* 304) compared to standard care. PBM-related costs of therapy exceeded costs of the control arm by € 150 per patient. However, total costs, including hospitalisation, were higher in the control-arm for both non-cardiac (€ 2,885.11) and cardiac surgery patients (€ 1,760.69). The incremental cost-effectiveness ratio including hospitalisation showed savings of € 30,458 (non-cardiac and cardiac surgery patients) for preventing one complication and € 128,023 (non-cardiac and cardiac surgery patients) for prevention of one complication-related death in the PBM-arm.

Discussion. Our results indicate that PBM may be associated with fewer adverse clinical outcomes compared to control management and may, thereby, be cost-effective.

Keywords: patient blood management, transfusion, outcome, cost-effectiveness-analysis, health economics.

Introduction

Recent evidence indicates that anaemia, bleeding and exposure to allogeneic blood products are independent risk factors for increased peri-operative morbidity and mortality[1-5]. Despite the undeniable importance of allogeneic blood products to compensate for life-threatening blood loss, transfusion of red blood cells (RBC) is associated with an increased risk of complications and prolonged length of stay (LOS) in hospital[6,7]. In this respect, patient blood management (PBM) is an evidence-based concept focused on management of (pre-operative) anaemia, minimisation of iatrogenic blood loss and a rational transfusion strategy.

The costs of PBM measures and transfusion have been analysed in various institutions; however, the cost-effectiveness of PBM has been mostly determined based on the cost of blood acquisition. In a cohort of 281 patients, anaemia treatment costs amounted to £ 16,695 of which £ 12,625 were offset by reduced RBC transfusions and savings in acquisition costs[8]. Ejaz and colleagues examined a restrictive transfusion strategy in 3,027 patients undergoing abdominal surgery and showed that RBC utilisation costs could be reduced by up to $ 94,516 per year[9]. Similar effects were observed within the ONTraC-blood conservation programme, in which reduced RBC transfusion and shorter LOS lead to a total estimated savings of 14,950,000 Canadian dollars[10]. Although the introduction of PBM is initially cost-intensive, successful implantation leads to cost redistribution for allogeneic blood components in favour of blood-sparing techniques[11].

To the best of our knowledge, the cost-effectiveness of

PBM compared to control treatment with regard to post-operative complications and prolonged hospitalisation has not yet been evaluated. The objective of this study was to assess the clinical and economic impact of PBM considering the risk of post-operative complications.

Materials and methods

Meta-analysis and effect estimates

A systematic literature search was conducted using PubMed to compare outcomes in cardiac and non-cardiac surgery patients exposed to 0 or 1 unit of RBC (restrictive transfusion group) and patients exposed to 1 to 3 units of RBC (liberal transfusion group). Our search included articles published between January 1st, 2004 and December 31st, 2014 with the following filters activated: species (humans), languages (English), and age (≥19 years). Articles were eligible if they: (i) investigated the association between allogeneic transfusion and outcome in surgical patients; (ii) had an observational period of 30-65 days or used terms such as "acute" or "in-hospital" referring to adverse events; and (iii) reported the number of units of RBC transfused. Outcomes of interest were defined as follows: septic complications (sepsis, septic shock), pulmonary complications (pneumonia, respiratory infection, chest infection), renal complications (renal failure, kidney injury, renal insufficiency, requirement for dialysis), cardiac complications (myocardial infarction or cardiac arrest, low cardiac index), and neurological complications (neurological deficit, stroke, transient ischaemic attack, coma, paralysis) (Online Supplementary Content, Table SI). In addition, a non-systematic literature search was conducted by hand for mortality (in-hospital or 30 days) and LOS associated with each complication. Since data did not allow any further differentiation, mortality and LOS were assumed to be independent of: (i) prior assignment to the therapy groups or exposure to RBC and (ii) type of surgery (cardiac or non-cardiac).

The meta-analysis was performed with OpenMetaAnalyst, free software from the Center for Evidence Synthesis in Health (CESH), Brown University, Providence, RI, USA.

Health economic model

A decision tree model (Online Supplementary Content, Figure S1)[12,13] representing probabilities of complications and consequential mortality rates was developed to calculate the cost-effectiveness of PBM (PBM-arm) and control treatment (control-arm) with a simulated cohort of 10,000 randomised patients. The following clinical endpoints were analysed for cardiac and non-cardiac surgery patients: sepsis with or without pneumonia, acute renal failure, acute myocardial infarction, acute stroke and no complications. Endpoints of the model excluded each other, i.e. patients could not experience more than one event. The time horizon of our model was a hospitalisation period of up to 30 days. The model was constructed using the health economic decision modelling software TreeAge Pro 2015 (TreeAge Software Inc., Williamstown, MA, USA).

Published data on sepsis in cardiac surgery were scant. However pneumonia is often associated with sepsis and was therefore categorised as a subcategory of sepsis allowing an estimation of the probability of sepsis in cardiac patients[14-16]. To calculate the probability of sepsis with pneumonia in cardiac patients, data on sepsis in non-cardiac patients were combined with data on pneumonia in cardiac patients. The probability of sepsis without pneumonia was calculated as the difference between estimated effects for sepsis and pneumonia in cardiac with respect to non-cardiac patients. Mortality from sepsis without pneumonia was derived from pooled data on mortality due to sepsis (total). Mortality from sepsis with pneumonia was calculated considering the probabilities of both circumstances (sepsis with or without pneumonia). Mortality rates differed greatly in both scenarios which were specifically addressed in sensitivity analyses. With regard to renal complications only mortality from acute kidney injury stage 2 (AKIN-2) or risk-injury-failure-loss-and-end-stage renal disease stage 1 (RIFLE-I)[17] was considered to avoid an overestimation. The mortality rate in the absence of complications was considered to be 0.78%[5]. Data on LOS due to post-operative complications were pooled according to the weighting of mortality rates in the meta-analysis. In the case of pneumonia (sepsis with pneumonia) the pooled LOS in the intensive care unit (ICU) exceeded the LOS in hospital. Therefore, the proportional LOS in the ICU was calculated for septic complications, regardless of the occurrence of pneumonia. For renal complications only data on LOS related to AKIN-2 or RIFLE-I were considered. The average LOS in the absence of complications was determined as 7.2 days of which 1 day was assumed to be spent in the ICU based on the data for surgical patients supplied by the Information System of the Federal Health Monitoring for Germany[18].

Cost estimates

Therapy costs per patient for both groups were derived from a systematic cost-analysis at Frankfurt University Hospital[11]. Briefly, the total cost for a RBC transfusion was € 147.43, which included the cost of a RBC unit (€ 90.50), materials (2 monovettes, adapter for the luer taper, material for transfusion and bedside testing; € 0.86), tests for ABO and Rhesus D (€ 8.16), a Coombs' test (€ 5.83), cross-matching (€ 11.66) and working time for physicians (18 min) and nurses

(23 min) (€ 30.42). Therapy costs in the PBM-arm, including material costs (€ 0.18), diagnosis of iron-deficiency anaemia (€ 109.00), treatment with iron (Ferinject® [Vifor France, Neully-sur-Seine, France]; € 117.59) and working time for physicians (17 min) and nurses (15 min) (€ 25.10), came to a total of € 251.87. Furthermore, the cost of volume therapy ranged between € 1.22 (for 1,000 mL of Sterofundin®ISO [B. Braun Melsungen AG, Melsungen, Germany]) and € 3.92 (for 500 mL of Tetraspan® [B. Braun Melsungen AG]), intensified haemoglobin monitoring and optimisation of haemostatic parameters including warming cost roughly € 21.79, cell salvage roughly € 155.99 and administration of tranexamic acid (500 mg) € 3.66[11].

Hospitalisation costs of each endpoint were calculated on the basis of literature data on LOS and costs per day on normal wards and in the ICU[19,20]. Proportional costs of ICU days correspond on a percentage basis to the data on LOS in the ICU. Mean costs per day were calculated for the four most common diagnosis-related groups in cardiac surgery at Frankfurt University Hospital (F06F: coronary artery bypass surgery; F03F: cardiac valve surgery with cardio-pulmonary bypass; F03E: cardiac valve surgery with cardio-pulmonary bypass including complicating procedures; F07A: other surgery with cardio-pulmonary bypass;, age <1 year or complicating procedures) and relevant data were obtained from the hospital's reimbursement system database[21]. The relevant mean costs per day were € 254 and € 1,489 for normal ward and ICU care, respectively.

Statistical analysis

Since populations of patients reported in the literature were not homogeneous, comparisons of absolute event rates were inappropriate. Therefore, risk ratios (RR) were used to calculate event rates in the PBM-arm compared to the control-arm. The RR of each complication was pooled using the binary fixed effect model (Mantel-Haenszel) and examined in forest plots. The presence of heterogeneity was detected by I^2 statistic. These event rates were used to calculate the number of events for our hypothetical cohort. Specific event probabilities were combined with relevant cost data to determine the expected cost per patient. Based on outcome and costs in the control-arm, additional costs and number of avoided complications and deaths in the PBM-arm were calculated.

The incremental cost-effectiveness ratio (ICER) of PBM reflects additional costs when choosing the PBM-arm to avoid one adverse event. It was calculated with and without hospitalisation costs as these may have a much higher variance and uncertainty in the assessed data. Data are provided as mean ± standard deviation when indicated and p values <0.05 were considered statistically significant.

Results

Treatment costs[11] as well as the results of the meta-analysis were used for the simulated model calculation. The simulation enabled a calculation of the cost-effectiveness ratio taking into account both therapy costs and post-operative outcome in terms of complications.

Meta-analysis and effect estimates

A total of 478 citations were retrieved from the systematic literature search on complications: of these, 453 did not meet our inclusion criteria, leaving 22 relevant studies for the meta-analysis (Online Supplementary Content, Figure S2)[1,6,7,22-40]. Six out of the 22 studies were performed before 2007, when the first article referring to PBM was published[41] (Table I; Online Supplementary Content, Table SII). Patients in the restrictive transfusion group were predominantly not transfused with the exception of three studies reporting transfusion of 1 and 2 units of allogeneic[23,29] or autologous[38] RBC.

The pooled RR of complications in the restrictive group was 0.43 in non-cardiac and 0.34 in cardiac surgery patients (Table II, Online Supplementary Content, Figure S3). For non-cardiac and cardiac surgery patients the greatest differences between the restrictive and liberal groups were observed in the event rate of sepsis without pneumonia (11.08 *vs* 1.56%; p<0.01) and acute myocardial infarction (3.03 *vs* 0.07%; p<0.01).

Thirty-one studies retrieved by the non-systematic literature search provided data on mortality and LOS related to each complication[42-72]. The mortality rate was highest in patients with septic complications, especially in the case of sepsis with pneumonia, which was associated with a mortality rate of 51.95% (p<0.01) (Table III, Online Supplementary Content, Figure S4). The average LOS resulting from complications ranged from 13.9 days for acute myocardial infarction to 23.8 days for acute stroke (Table IV).

Health economic model

In the simulated cohort of 10,000 patients, 1,768 complications and 411 deaths were avoided in the non-cardiac surgery PBM-arm, while 1,245 complications and 304 deaths were avoided in the cardiac surgery PBM-arm (Table V). Among the non-cardiac surgery patients, the number-needed-to-treat (NNT) with PBM to prevent one complication compared to standard therapy was only six, while that for complication-related death was 25. The corresponding figures for cardiac surgery patients were 9 and 33, respectively.

Table I - Eligible articles included in the meta-analysis.

Reference	Type of surgery	Time of transfusion	Liberal group (Units)	Restrictive group (Units)	Liberal group (%)	Restrictive group (%)	Liberal group (n)	Restrictive group (n)	Outcome	Time
Sepsis complications										
Bernard *et al.* 2009	General	Intra-operative	1	0	19.6	3.2	1,343	120,389	Sepsis/septic shock	30 days
Bernard *et al.* 2009	General	Intra-operative	2	0	24.5	3.2	1,903	120,389	Sepsis/septic shock	30 days
Ferraris *et al.* 2011	Thoracic	Intra-operative	1-2	0	17.8	6.5	579	7,875	Sepsis with septic shock	30 days
Glance *et al.* 2011	Non-cardiac	Intra-operative	1-2	0	16.4	9.81	2,160	7,940	Sepsis/septic shock	30 days
O'Keeffe *et al.* 2010	Vascular	Intra-operative	1-3	0	12.9	5.0	1,971	6,827	Sepsis/septic shock	30 days
Pulmonary complications										
Bernard *et al.* 2009	General	Intra-operative	1	0	9.7	1.4	1,343	120,389	Pneumonia	30 days
Bernard *et al.* 2009	General	Intra-operative	2	0	10.7	1.4	1,903	120,389	Pneumonia	30 days
Croce *et al.* 2005	ICU/Trauma	After first 48 hours from admission	1-2	0	14	2.2	778	4,482	Ventilator-associated pneumonia	In-hospital
Carson *et al.* 1998	Orthopaedic	Post-operative	2	0	4.8	0	42	42	Pneumonia	In-hospital
Foss *et al.* 2009	Orthopaedic	Peri-operative	2	1	3	2	60	60	Pneumonia	n.a.
Chelemer *et al.* 2002	Cardiac	Peri-operative	1-2	0	3.75	1.7	178	262	Respiratory infections	30 days
Horvath *et al.* 2013	Cardiac	Intra-/post-operative	3	0	3.59	1.23	2,481	2,677	Pneumonia	65 days
Ali *et al.* 2004	Cardiac	Peri-operative	3	0	19.8	14.7	116	116	Chest infection	In-hospital
Oz *et al.* 2013[a]	Cardiac	Intra-/post-operative	3.2	2	3.8	0.6	160	163	Pneumonia	n.a.
Renal complications										
Ferraris *et al.* 2011	Thoracic	Intra-operative	1-2	0	6.9	3.1	579	7,875	Kidney injury or dialysis	30 days
Glance *et al.* 2011	Non-cardiac	Intra-operative	1-2	0	2.69	1.85	2,160	7,940	Progressive renal insufficiency or renal failure	30 days
O'Keeffe *et al.* 2010	Vascular	Intra-operative	1-3	0	3.0	1.0	1,971	6,827	Renal failure or insufficiency (no dialysis)	30 days
Khan *et al.* 2014	Cardiac	Intra-operative	1-2	0	4.0	3.0	206	894	Doubling of serum creatinine	Acute
Paone *et al.* 2014	Cardiac	n.a.	1-2	0	2.5	1.0	5,951	10,884	Renal failure	30 days
Karkouti *et al.* 2011	Cardiac	Day of surgery	1	0	2.2	1.9	464	462	Kidney injury (>50% decrease in GFR)	Acute
Karkouti *et al.* 2011	Cardiac	Day of surgery	1	0	2.8	1.4	455	984	Kidney injury	Acute
Karkouti *et al.* 2011	Cardiac	Day of surgery	2	0	4.6	1.9	691	462	Kidney injury	Acute
Karkouti *et al.* 2011	Cardiac	Day of surgery	2	0	2.2	1.4	459	984	Kidney injury	Acute

[a]Transfusion of autologous RBC in the restrictive group; n.a.: not available; RBC: red blood cell; GFR: glomerular filtration rate; ICU: intensive care unit; TIA: transient ischaemic attack.

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Blood Transfus 2019; 17: 16-26 DOI 10.2450/2018.0213-17

Table I - Eligible articles included in the meta-analysis. (*Continued from previous next page)*

Reference	Type of surgery	Time of transfusion	Liberal group (Units)	Restrictive group (Units)	Liberal group (%)	Restrictive group (%)	Liberal group (n)	Restrictive group (n)	Outcome	Time
Koch *et al.* 2006	Cardiac	Intra-/post-operative	2	0	1.81	0	5,812	6,151	Renal failure requiring dialysis	New
Hajjar *et al.* 2010	Cardiac	Peri-operative	2	0	5	4	253	249	Renal failure requiring dialysis or hemofiltration	Acute
Bracey *et al.* 1999	Cardiac	Post-operative	1.4	0.9	2	4	216	212	Renal failure or creatinine level >2.5 mg per dL	n.a.
Cardiac complications										
Carson *et al.* 1998	Orthopaedic	Post-operative	2	0	0	0	42	42	Myocardial infarction	In-hospital
Carson *et al.* 2011	Orthopaedic	Post-operative	2	0	2.3	3.8	1,007	1,009	Myocardial infarction	30 days
Bursi *et al.* 2009	Vascular	Intra-/post-operative	3	0	21.1	6.8	95	264	Myocardial infarction	30 days
Foss *et al.* 2009	Orthopaedic	Peri-operative	2	1	0	2	60	60	Myocardial infarction	Acute
Ferraris *et al.* 2011	Thoracic	Intra-operative	1-2	0	2.1	1.3	579	7,875	Myocardial infarction or cardiac arrest	30 days
Glance *et al.* 2011	Non-cardiac	Intra-operative	1-2	0	2.08	1.4	2,160	7,940	Myocardial infarction or cardiac arrest	30 days
Bracey *et al.* 1999	Cardiac	Post-operative	1.4	0.9	0	0.5	216	212	Myocardial infarction	n.a.
Koch *et al.* 2006	Cardiac	Intra-/post-operative	2	0	3.03	0.05	5,812	6,151	Low cardiac index or myocardial infarction	In-hospital
Neurological complications										
Ferraris *et al.* 2011	Thoracic	Intra-operative	1-2	0	0.9	0.6	579	7,875	Stroke or coma	30 days
Glance *et al.* 2011	Non-cardiac	Intra-operative	1-2	0	0.69	0.58	2,160	7,940	Cerebrovascular accident or coma lasting > 24 hours	30 days
Rubinstein *et al.* 2013	Vascular	Intra-operative	1-2	0	6.3	1.3	80	160	Stroke with neurologic deficit	30 days
Carson *et al.* 1998	Orthopaedic	Post-operative	2	0	2.4	0	42	42	Stroke	In-hospital
Carson *et al.* 2011	Orthopaedic	Post-operative	2	0	0.5	0.1	1,007	1,009	Stroke or TIA	In-hospital
Foss *et al.* 2009	Orthopaedic	Peri-operative	2	1	2	2	60	60	Cerebrovascular event	n.a.
Mariscalco *et al.* 2015	Cardiac	Peri-operative	1	0	0.7	0.5	1,194	8,504	Stroke (persistent neurological deficit)	New
Mariscalco *et al.* 2015	Cardiac	Peri-operative	2	0	1.1	0.5	2,814	8,504	Stroke	New
Mikkola *et al.* 2012	Cardiac	Peri-operative	1-2	0	2.1	1.5	401	983	Stroke (neurological deficit lasting >24 hours)	Immediate
Paone *et al.* 2014	Cardiac	n.a.	1-2	0	1.5	0.6	5,951	10,884	Permanent stroke	30 days
Koch *et al.* 2006	Cardiac	Intra-/post-operative	2	0	2.41	0.37	5,812	6,151	Focal/global deficits or death without awakening	In-hospital
Bracey *et al.* 1999	Cardiac	Post-operative	1.4	0.9	4					n.a.

[a]Transfusion of autologous RBC in the restrictive group; n.a.: not available; RBC: red blood cell; GFR: glomerular filtration rate; ICU: intensive care unit; TIA: transient ischaemic attack.

Table II - Meta-analysis-based effect estimates as input for the cost-effectiveness model.
Event probabilities are shown for patients in the liberal and restrictive groups. The probabilities of complications in the restrictive group were calculated with a pooled relative risk (RR) compared to the liberal group. The lower and upper bounds of the 95% confidence interval (CI) are given.

Probabilities	Pooled effect liberal group	Pooled relative risk	Effect estimate restrictive group in % (95% CI)	p-value
Non-cardiac surgery				
Sepsis (total)	19.32%	0.30	5.72% (5.41-6.05)	<0.01
a) Sepsis with pneumonia	11.08%	0.14	1.56% (1.41-1.74)	<0.01
b) Sepsis without pneumonia	8.24%	0.50	4.16% (4.00-4.31)	<0.01
Acute renal failure	4.02%	0.49	1.98% (1.65-2.38)	0.01
Acute myocardial infarction	5.96%	0.76	4.50% (3.58-5.66)	0.02
Acute stroke	1.58%	0.63	1.00% (0.64-1.55)	<0.01
Total (any complication)	30.88%	0.43	13.20% (11.28-15.64)	
Cardiac surgery				
Sepsis (total)	11.31%	0.41	4.61% (3.39-6.29)	0.04
a) Sepsis with pneumonia	6.48%	0.41	2.65% (1.94-3.60)	<0.01
b) Sepsis without pneumonia	4.82%	0.41	1.97% (1.45-2.68)	<0.01
Acute renal failure	2.50%	0.38	0.94% (0.78-1.13)	<0.01
Acute myocardial infarction	3.03%	0.02	0.07% (0.02-0.18)	<0.01
Acute Stroke	1.90%	0.35	0.66% (0.54-0.81)	<0.01
Total (any complication)	18.73%	0.34	6.28% (4.73-8.4)	

Table III - Literature data on complication-related mortality as the input for the cost-effectiveness model.
Rates of mortality considered to be caused by complications, regardless of assignment to the liberal or restrictive transfusion group. The lower and upper bounds of the 95% confidence interval (CI) are given.

Mortality (in-hospital/30 days) from complications (non-cardiac and cardiac surgery)	Pooled effect estimate equal for both groups in % (95% CI)	p-value
Sepsis (total)	28.70% (28.50-28.90)	<0.01
a) Sepsis with pneumonia	11.40% (11.20-11.60)	<0.01
b) Sepsis without pneumonia	51.95% (51.75-52.15)	<0.01
Acute renal failure	28.40% (28.00-28.90)	<0.01
Acute myocardial infarction	13.20% (12.90-13.40)	<0.01
Acute stroke	23.20% (20.10-26.40)	<0.01
No complication	0.78% (0.62-0.94)	

Cost estimates

Costs of the PBM-arm could be subdivided into three modules: costs for anaemia management (PBM I = € 176.68), costs for rational use of RBC (PBM II = € 28.62) and material expenses and process costs for measures to reduce allogeneic blood transfusion (PBM III = € 214.19) with total expenses of € 419.49. Costs of the control-arm comprised administration of two units of allogeneic RBC and were € 269.21 (Online Supplementary Content, Table SIII). Thus, total therapy costs of the PBM-arm exceeded costs of the control-arm by € 150.28.

On the outcome side, the effects were quantified in terms of postoperative complications and related LOS. The average hospitalisation cost without complications was € 3,066 per patient. In the case of complications, the cost of hospitalisation was € 24,001 for sepsis (€ 27,804 without pneumonia; € 21,170 with pneumonia), € 7,464 for acute renal failure, € 12,303 for acute myocardial infarction and € 16,490 for acute stroke (Table IV). Considering therapy and hospitalisation costs, the control-arm (Table V) showed significantly higher expected costs per patient for both non-cardiac and cardiac surgery patients due to a higher risk of complications compared to the PBM-arm. The incremental cost in the control-arm was € 2,885 in non-cardiac surgery patients and € 1,761 in cardiac surgery patients (Online Supplementary Content, Table SIV).

Cost-effectiveness

Considering therapy costs to avoid one complication, the ICER of PBM was € 850.02 in non-cardiac and € 1,206.81 in cardiac surgery patients. The ICER of PBM per avoided death was € 3,653.50 in non-cardiac and € 4,940.45 in cardiac surgery patients. However, when costs of hospitalisation were also taken into account, the ICER of PBM turned negative, showing that PBM could yield savings of

Table IV - Length of stay in hospital and hospitalisation costs.
The table shows hospitalisation costs per patient in the case of complications and in the absence of complications. Calculations are based on literature data regarding average costs and LOS in hospital and in the ICU. LOS on normal wards was calculated as the difference between LOS in hospital and LOS in the ICU.

Complications	LOS not in ICU (days)	LOS in ICU (days)	LOS in hospital (total days)	Hospitalisation costs[a,b] (€)
Without complication	6.2	1.0	7.2	3,065.51
Sepsis (total)	4.0	15.4	19.4	24,000.50
a) Sepsis with pneumonia	3.5	13.6	17.1	21,170.47
b) Sepsis without pneumonia	4.6	17.9	22.5	27,804.40
Acute renal failure	11.2	3.1	14.3	7,464.21
Acute myocardial infarction	6.8	7.1	13.9	12,302.93
Acute stroke	15.3	8.5	23.8	16,489.93

[a]Cost per day for non-ICU patient: € 254.22; [b]Cost per day for ICU patient: € 1,489.33. LOS: length of stay; ICU: Intensive Care Unit.

Table V - Number of events in simulated cohorts of 10,000 surgical patients
The table shows the calculated number of events (complications and related deaths) in hypothetical cohorts of 10,000 patients for non-cardiac and cardiac surgery.

Non-cardiac surgery	Complications (number of events)			Deaths related to complications (number of events)		
	Control-arm	PBM-arm	Difference	Control-arm	PBM-arm	Difference
Sepsis (total)	1,932	572	1,360	554	234	320
a) with pneumonia	1,108	156	952	126	18	108
b) without pneumonia	824	416	408	428	216	212
Acute renal failure	402	198	204	114	56	58
Acute myocardial infarction	596	450	146	79	59	19
Acute stroke	158	100	58	37	23	13
Total	3,088	1,320	1,768	784	373	411
Cardiac surgery	**Complications (number of events)**			**Deaths related to complications (number of events)**		
	Control-arm	PBM-arm	Difference	Control-arm	PBM-arm	Difference
Sepsis (total)	1,313	461	669	324	132	192
a) with pneumonia	648	265	384	74	30	44
b) without pneumonia	482	197	286	251	102	148
Acute renal failure	250	94	156	71	27	44
Acute myocardial infarction	303	7	296	40	1	39
Acute stroke	190	66	124	44	15	29
Total	1,873	628	1,245	479	175	304

PBM: Patient Blood Management.

€ 16,319 (non-cardiac surgery) and € 14,139 (cardiac surgery) while preventing one complication. The ICER regarding the prevention of one complication-related death was € −70,140 (non-cardiac surgery patient) and € −57,883 (cardiac surgery patient) (Table VI).

Table VI - Incremental cost-effectiveness of PBM compared to standard therapy.

Incremental cost effectiveness of PBM	Per avoided complication (€)	Per avoided death (€)
Without hospitalisation costs		
Non-cardiac patients	850.02	3,653.50
Cardiac patients	1,206.81	4,940.45
Including hospitalisation costs		
Non-cardiac patients	−16,318.79	−70,140.58
Cardiac patients	−14,139.04	−57,882.56

PBM: Patient Blood Management.

Sensitivity analysis

To verify the validity of the results, probabilistic sensitivity analyses were conducted for the model input variables. The probabilities of complications and mortality rates were adjusted according to the upper and lower bounds of the pooled effect

estimates (Tables II and III). Additionally, variations in hospitalisation costs with a range of ±25%, were tested. In probabilistic Monte Carlo simulations with 10,000 trials, the analyses showed a robust effect of the model results regarding PBM, being the dominant therapy strategy in more than 95% with a positive ICER.

Discussion

In times of increasing health-care costs, it is of great interest to assess cost-effectiveness of new interventions carefully. Given the worldwide interest in PBM[4,73], critical evaluation of its appropriateness and assessment of its cost-effectiveness are crucial for continued implementation of this tested but still new concept. Our meta-analysis suggests that a restrictive transfusion strategy is associated with fewer complications compared to a liberal transfusion strategy. Taking into account that a reduced complication rate is not consequently associated with a reduction in costs, we conducted an economic evaluation to elucidate costs and consequences of PBM[74].

In this simulation model, treatment according to the principles of PBM, including a restrictive transfusion strategy, was related to a reduced total complication rate in both non-cardiac and cardiac surgery patients. Moreover, our health economic model revealed that 17.68% of complications and 4.11% of deaths in non-cardiac surgery patients would have been avoided by PBM, while 12.45% of complications and 3.04% of deaths would have been avoided in the patients undergoing cardiac surgery. The observed prevalence of post-operative complications in our study is similar to the findings in other studies, for example that by Lasocki and Colleagues, who assigned 1,543 patients to either non-PBM or PBM treatment. Patients who were anaemic pre-operatively experienced a significantly higher rate of post-operative complications (36.9 *vs* 22.2%) and longer hospitalisation (11.7±9.6 *vs* 8.8±5.9 days) compared to non-anaemic patients. Furthermore, prolonged LOS was independently observed with RBC transfusion and non-PBM treatment[75]. Implementation of PBM measures[73] was reported to be associated with 1.5 times higher expenses due to additional material costs for anaemia management, including iron therapy, blood-sparing techniques, cell salvage, administration of antifibrinolytics and management of coagulopathy. PBM does, however, have the potential to reduce complications and shorten LOS, which lowers hospitalisation costs. In our simulation, the savings per avoided complication were € 16,318.79 for non-cardiac and € 14,139.04 for cardiac surgery patients. Muñoz and Colleagues analysed economic aspects of intravenous iron therapy in 182 orthopaedic surgery patients. Administration of iron was associated with a reduced rate of allogeneic transfusions (11.5 *vs* 26.4%) without causing incremental costs[76]. Vigna-Taglianti and Colleagues conducted a cost analysis of administration of an antifibrinolytic drug in patients who underwent orthopaedic surgery among whom the transfusion rate of autologous or allogeneic blood could be reduced by 45%: this was associated with savings of € 138 per patient[77]. Recently, the impact of a jurisdiction-wide PBM programme was assessed in a large retrospective study including more than 600,000 patients in West-Australia. Implementation of PBM was associated with significant reductions of in-hospital mortality (28%), LOS in hospital (15%), hospital-acquired infection (21%), stroke (31%) and utilisation of RBC units (41%). Additionally, PBM and reduced blood product utilisation were associated with product-acquisition cost savings of $ 18.1 million[78]. Goodnough and Colleagues improved blood use by implementing a real-time clinical decision support and best practice alert into physicians' order entry for blood transfusion. The transfusion rate for patients whose haemoglobin level exceeded 8 g/dL decreased from 57-66% (2008) to 35% (2010) and remained below 30% (2012): estimated net savings in purchase costs for RBC units were $ 1,616,750[79].

Taken together, our simulation model-based analysis demonstrates that additional costs arising from PBM compared to control treatment were economically worthwhile because of the potential of decreased post-operative complications, which are responsible for the major part of hospitalisation costs.

A few limitations of our study need to be taken into account. Our model calculated therapy costs in the control-arm for patients receiving two RBC units and therefore costs are likely to be underestimated for patients transfused with three or more RBC units. Additionally, our results may not be transferable to cases of excessive blood loss that require substitution with more than three units of RBC, irrespectively of the treatment approach. Clinical outcome was determined by differences in the number of units transfused and the analysis was based on relevant literature data. An effort was made to deal with the problem of heterogeneous cohorts of patients by calculating effect estimates based on a systematic meta-analysis with pooled RR and performing sensitivity analyses with adjusted values. Several studies did not indicate exact time points of transfusion and therefore transfusion of additional units of RBC in the control- and PBM-arms could not be ruled out. Furthermore, we cannot exclude that outcome investigated or post-operative complications were exclusively due to transfusion and not on other conditions such as underlying diseases. Complications with very low incidence, transfusion-related infections

and adverse events (e.g. transfusion-related lung injury) were not included in our analysis. We assessed the outcome 30 days after surgery and therefore long-term complications were not included in our calculation. Therapy costs were determined from an institutional perspective at one German hospital which depends on local conditions and may not be transferable to other institutions. For example, the average LOS in the United States of America is 4.5 days[80] compared to 7.2 days in Germany and therefore total therapy costs might differ between countries. Finally, mortality rates were assessed using a non-systematic review approach and therefore might not reflect actual numbers. However, it is worth noting that our initial approach included mortality as outcome but resulted in no eligible studies for our analysis since mortality was always considered as outcome related to blood transfusion and not associated with complications.

Conclusions

There is an expanding body of evidence demonstrating the effectiveness of PBM in improving patients' outcome. Our results from a meta-analysis and simulation model-based analysis highlight potential cost-effectiveness associated with a decreased rate of complications in surgical patients. Thus, PBM is an economically desirable therapeutic concept that can improve patients' outcome.

Authorship contributions

AK, PM, NS designed and conducted the analysis with input from SC and KZ. AK, PM, NS, KZ and SC wrote the manuscript.

Conflicts of interest disclosure

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. None of the other Authors have any potential conflicts of interest.

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Arrived: 19 September 2017 - Revision accepted: 9 January 2018
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