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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Comparison between five-year mortality of patients with and without red blood cell transfusion after percutaneous coronary intervention for ST-elevation acute myocardial infarction

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Abstract

Background: Red blood cell (RBC) transfusion can be lifesaving. However, in many clinical cases, including acute coronary syndromes, percutaneous coronary interventions (PCI), cardiac surgery, and acute critical care, detrimental effects (excess death and myocardial infarction [MI], and also lung infections) have been observed in patients after a RBC transfusion.

Aim: To evaluate the long-term impact on the prognosis of patients who received a RBC transfusion after PCI for the treatment of ST-segment elevation MI (STEMI).

Methods: Between 1999 and 2004, 2,415 consecutive patients, with an STEMI treated with PCI, were included in the analysis. The patients were divided into two groups: 82 patients with a RBC transfusion (3.5%) and 2,333 without a RBC transfusion (96.5%).

Results: The in-hospital mortality rate was 15.8% and 4.2% ($p < 0.0001$) and the five-year mortality rate was 42.7% and 19% ($p < 0.0001$) for patients who received and who did not receive a RBC transfusion, respectively. Moreover, multivariate analysis revealed that, after correction for baseline differences, RBC transfusion was an independent predictor of five-year mortality in patients treated with PCI (HR 1.45; 95% CI 1.0–2.1; $p = 0.04$).

Conclusions: Red blood cell transfusion is associated with higher five-year mortality in STEMI patients treated with PCI.

Key words: red blood cell transfusion, myocardial infarction, percutaneous coronary intervention

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INTRODUCTION

Red blood cell (RBC) transfusion can be lifesaving. However, in many clinical cases, including acute coronary syndromes (ACS), percutaneous coronary interventions (PCI), cardiac surgery, and acute critical care, detrimental effects (excess death and myocardial infarction [MI], and also lung infections) have been observed in patients after a RBC transfusion [1, 2]. The objective of this investigation, given that the available data is limited, was to evaluate the impact of RBC transfusion during hospitalisation on clinical outcomes while in the hospital and during a long-term follow-up period in patients with ST-elevation MI (STEMI) who underwent PCI. Based on the findings at a large interventional cardiology centre, we hoped to identify differences in patient characteristics and the clinical course. Furthermore, an analysis of the factors that affect the long-term prognosis was conducted, and an additional multifactorial analysis was undertaken to assess predictors of RBC transfusion.

METHODS

Study population

We conducted a single-centre analysis of 2,415 consecutive patients with STEMI who underwent immediate coronary intervention, at our centre, between January 1999 and

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December 2004. Within this group, a total of 82 (3.5%) patients received a RBC transfusion during their hospitalisation. Patients with cardiogenic shock on admission — defined as the presence of the following criteria: clinical (symptoms of shock, peripheral hypoperfusion) and haemodynamic (systemic systolic pressure < 90 mm Hg or systemic systolic pressure 90–110 mm Hg during intra-aortic balloon pumping [IABP] or while using inotropic drugs) [3] — were included in the analysis.

Anaemia was defined using the World Health Organisation criteria of a haematocrit value at initial presentation of < 39% for men and < 36% for women [4]. Glomerular filtration rate (GFR) was estimated using Cockcroft-Gault.

The clinical data from all patients with STEMI was prospectively recorded in a computerised database as a part of a single-centre ACS registry. Follow-up information was obtained by direct phone calls, outpatient visits and from the National Health Fund database.

Procedure

At our centre, as previously described [5] an interventional cardiologist is on duty 24 h a day. All patients with acute STEMI (stenocardial pain lasting ≥ 30 min, with electrocardiographic features of an evolving MI, i.e. ST segment elevation ≥ 0.1 mV in two or more limb leads or ≥ 0.2 mV in two or more precardial leads, or a newly formed left bundle branch block, with time since onset not exceeding 12 h or, in the case of cardiogenic shock, 18–24 h) were treated with 300–500 mg of aspirin, 300 mg clopidogrel (since 2001) and 75 mg per day thereafter or ticlopidine 250 mg twice daily for a period at least eight weeks, 5,000–10,000 units of unfractionated heparin and 2.5–5 mg of morphine intravenously. Depending on the patient's condition, other medications were also used, and the patients were referred for urgent coronary angiography. Standard guide wires, balloon catheters and coronary stents were used in the above procedures. IABP was performed in some patients with MI complicated by cardiogenic shock, depending on their clinical status. Vascular sheaths were removed upon normalisation of blood coagulation parameters (i.e. activated partial thromboplastin time). After the intervention, apart from thienopyridines, all patients received 150 mg of aspirin daily indefinitely, as well as beta-blockers, angiotensin-converting enzyme inhibitors, and statins, if these agents were otherwise not contraindicated.

Twelve-month and five-year mortality was assessed. Angiographic success of infarct related artery angioplasty was defined as thrombolysis in myocardial infarction (TIMI), grade 3 flow and less than 30% residual stenosis.

Statistical analysis

Continuous parameters with a normal distribution are presented as the mean and standard deviation. The significance of differences between mean values was tested with the Student's *t*-test. Qualitative parameters were analysed with the χ^2 test (when numbers were anticipated to be less than 5, Yates' correction for continuity was implemented). Mortality curves up to five years after STEMI were constructed using the Kaplan-Meier method and compared using the log-rank test. To assess the impact of particular parameters on mortality, a multivariate analysis was performed using step-down Cox proportional hazards regression modelling, expressed as a hazard ratio (HR), with a 95% confidence interval (CI), that adjusted: age, male sex, anterior MI, multivessel coronary artery disease, initial TIMI flow grade 0–1, final TIMI flow grade < 3, left ventricular ejection fraction (LVEF), current smoking, arterial hypertension, diabetes, hyperlipidaemia, cardiogenic shock on admission, prior MI, glycoprotein IIb/IIIa blockers treatment, baseline anaemia, baseline haematocrit, baseline platelet count, stent implantation, thrombolysis before PCI, GFR (< 60 ml/min), gastrointestinal bleeding. To identify independent predictors of RBC transfusion, an additionally multivariate analysis was performed using step-down Cox proportional hazards regression modelling, expressed as a HR, with a 95% CI. Candidate variables included: age, female sex, anterior MI, multivessel coronary artery disease, initial TIMI flow grade 0–1, final TIMI flow grade < 3, LVEF, current smoking, arterial hypertension, diabetes, hyperlipidaemia, cardiogenic shock on admission, prior MI, glycoprotein IIb/IIIa blockers treatment, baseline anaemia, baseline haematocrit, baseline platelet count, stent implantation, thrombolysis before PCI, GFR (< 60 mL/min), gastrointestinal bleeding. The level of statistical significance was $p < 0.05$ (two-tailed). STATISTICA 10 software (StatSoft, Inc., Tulsa, OK, USA) was used for all calculations.

RESULTS

The baseline clinical and angiographic characteristics of the study groups are presented in Table 1. Patients treated with a RBC transfusion were older, more often female, and had a higher prevalence of diabetes, baseline anaemia and cardiogenic shock on admission than patients without a RBC transfusion.

In-hospital parameters differed significantly in the two groups. Patients treated with a RBC transfusion had a lower LVEF and GFR, more frequently had gastrointestinal bleeding, and had a longer hospital stay (Table 2). A total of 4.2% of patients without a RBC transfusion and 15.8% of patients treated with a RBC transfusion ($p < 0.0001$) died during hospitalisation. The significant difference in mortality rate was also maintained during the five-year follow-up: 19% of patients without, and 42.7% of patients with, a RBC transfusion ($p < 0.0001$) died during that time (Fig. 1).

Unadjusted Cox proportional-hazard analysis and multivariable adjusted Cox proportional-hazard analysis for 30-days, one-year and five-year transfusion showed an association between transfusion and mortality (Table 3). In the

Table 1. Baseline clinical and angiographic characteristics of the study groups

Variable	Red blood cell transfusion		P
	Yes (n = 82; 3.5%)	No (n = 2,333; 96.5%)	
Age [years]	67 ± 10.3	59 ± 10.7	< 0.0001
Men	32 (39%)	1,722 (73.8%)	< 0.0001
Duration of pain [h]	5.4 ± 4.0	5.6 ± 5.0	0.8
Thrombolysis before PCI	25 (30.5%)	456 (19.5%)	0.015
Anterior wall MI	35 (42.7%)	947 (40.6%)	0.7
Arterial hypertension*	51 (63%)	1,242 (53.6%)	0.09
Diabetes mellitus	25 (30.5%)	462 (19.8%)	0.018
Hyperlipidaemia†	45 (54.9%)	1,353 (58.4%)	0.5
Current smoker	41 (51.2%)	1,399 (60.7%)	0.09
Prior MI	8 (9.9%)	446 (19.2%)	0.03
Cardiogenic shock on admission	20 (24.4%)	193 (8.3%)	< 0.0001
Glomerular filtration rate (MDRD)	66 ± 8	81 ± 9	< 0.0001
Baseline haemoglobin [g/dL]	13 ± 1.6	14.2 ± 1.0	< 0.0001
Baseline haematocrit [%]	38 ±4.5	42 ± 4.2	< 0.0001
Baseline platelet count [$\times 10^3$ cells/mm^3]	223 ± 75	210 ± 68	0.11
Infarct related artery			0.08
Left anterior descending	30 (36.6%)	940 (41.1%)	
Right coronary artery	43 (52.4%)	955 (41.8%)	
Left circumflex	9 (11%)	438 (17.1%)	
Baseline TIMI flow grade 0–1	59 (73.7%)	1,701(73.6%)	0.9
Stent implantation	58 (71.6%)	1,756 (75.3%)	0.4
Glycoprotein IIb/IIIa blocker	8 (9.8%)	113 (4.8%)	0.045
Final TIMI flow grade 0–2	17 (20%)	262 (11.3%)	0.017
Angiographic success	65 (80%)	2,049 (88.7%)	0.017

*Defined as history of hypertension diagnosed and treated with medication, diet, and/or exercise, blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic on ≥ 2 occasions, or currently taking antihypertensive pharmacologic therapy
†Hyperlipidaemia defined as history of hyperlipidaemia diagnosed and/or treated by physician, documentation of total cholesterol > 200 mg/dL, low-density lipoprotein ≥ 130 mg/dL, high-density lipoprotein < 30 mg/dL, admission cholesterol > 200 mg/dL, or triglycerides > 150 mg/dL
MI — myocardial infarction; MDRD — Modification of Diet in Renal Disease; PCI — percutaneous coronary intervention; TIMI — thrombolysis in myocardial infarction

Table 2. In-hospital outcomes in the study groups

Variable	Red blood cell transfusion		P
	Yes (n = 82; 3.5%)	No (n = 2,333; 96.5%)	
Creatinine kinase max [IU]	2,526 ± 2,077	2,192 ± 2,350	0.2
Left ventricular ejection fraction [%]	40±8	45±9	0.0001
Re-occlusion angiographically confirmed (urgent PCI required)	4 (5%)	165 (7%)	0.44
Gastrointestinal bleeding	13 (16%)	57 (2.4%)	< 0.0001
CABG during hospitalisation	3 (3.6%)	36 (1.5%)	0.13
CABG arranged after discharge	1 (1.2%)	107 (4.6%)	0.14
Elective PCI in a non-infarct related artery vessel during hospitalisation	6 (7.4%)	234 (10%)	0.4
Stroke	3 (3.7%)	51 (2.2%)	0.37
Hospital stay [days]	8 ± 5	6 ± 5	< 0.0001

CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention

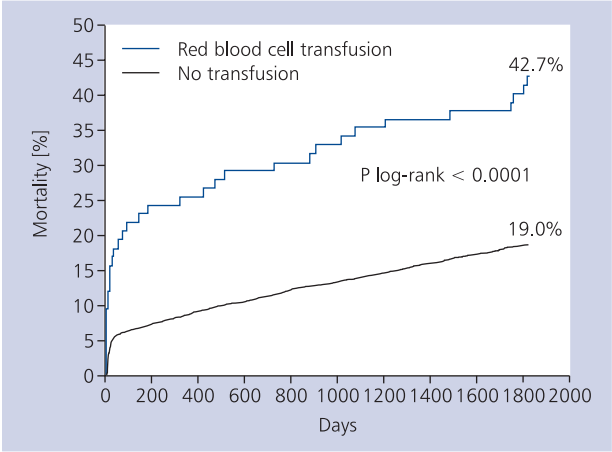

Figure 1. Five-year mortality for the study groups

multifactorial analysis of the entire study population, the RBC transfusion was an independent factor affecting the five-year mortality risk (HR = 1.45; 95% CI 1.0–2.1; p = 0.04) (Table 4).

Additional multifactorial analysis identified that independent factors affecting RBC transfusion were as follows: gastrointestinal bleeding, female gender, shock on admission, thrombolysis, baseline anaemia, smoking and older age (Table 5).

DISCUSSION

Current practice guidelines concerning the management of STEMI published by the European Society of Cardiology (ESC) and guidelines concerning myocardial revascularisation created both by the ESC and the European Association for Cardio-Thoracic Surgery (EACTS) do not take a position on the problem of the adverse impact of RBC transfusions in this subgroup of critically ill patients [6, 7]. However, the authors emphasise the poor effects of anaemia, without a conclusion concerning optimal morphology parameters for performing a RBC transfusion.

On the other hand, the current practice recommendations for the management of ACS without persistent ST-segment elevation (NSTE-ACS) published by the ESC bring up the problem of the blood transfusion with optimal morphology parameters threshold to perform transfusion in this group of patients [8]. However, these two populations: STEMI and NSTE-ACS patients differ widely [9].

In critically ill patients, RBC transfusion is commonly required. Because of the frequent use of this intervention in the intensive care unit, and the to-be-expected higher probability of the wider application of the RBC in STEMI patients as a result of the widely applied antithrombotic and antiplatelet therapy, it is important for cardiologists to be aware of recent developments in this continuously evolving field of medicine. There is limited data concerning the influence of RBC transfusion on the short-term and long-term results in patients with STEMI treated with PCI. Knowledge of their relationship might change the strategy used for transfusion and improve the outcomes.

The principal findings from our investigation were that RBC transfusion in STEMI patients treated with PCI increased the early and long-term mortality and was also a significant predictor of poor outcome, after adjustment, in the multivariate analysis. Secondly, we found that patients who had undergone a RBC transfusion had a higher baseline risk profile and lower angiographic success. Finally, the independent factors affecting RBC transfusion were as follows: gastrointestinal bleeding, female gender, shock on admission, thrombolysis, baseline anaemia, smoking and older age.

The presence of baseline anaemia has been reported in up to 20% of patients with ACS. Baseline anaemia has been associated with poorer clinical outcomes [10–14]. In acute MI, anaemia may worsen myocardial ischaemia, generate arrhythmias, and potentially increase the infarct size [15]. The primary aim of blood transfusion is to increase oxygen delivery (DO2), which is determined by cardiac output and

Table 3. Univariate and multivariable Cox proportional hazards survival models for blood transfusion according to 30-day, one--year, and five-year mortality for the entire study population

Variable	No. of deaths (%)	Hazard ratio (95% confidence interval)	P
Entire study population			
30-day	110 (4.5)		
Unadjusted	–	3.37 (1.93–5.86)	< 0.001
Multivariable adjusted	–	3.1 (1.41-6.8)	0.005
One-year	227 (9.4)		
Unadjusted	–	3.16 (2.02–4.96)	< 0.001
Multivariable adjusted	–	2.33 (1.30–4.17)	0.004
Five-year	477 (19.7)		
Unadjusted	–	2.68 (1.90–3.78)	< 0.001
Multivariable adjusted	–	1.45 (1.0–2.1)	0.04

Table 4. Predictors of five-year mortality in the entire study population (Cox proportional hazards model results)

	HR	95% CI	P
Shock on admission	3.05	2.4–3.8	< 0.0001
Gastrointestinal bleeding	2.05	1.27–3.33	0.003
Initial TIMI flow grade 1–2	1.6	1.2–2.0	0.0001
Red blood cell transfusion	1.45	1.0–2.1	0.04
Smoker	1.3	1.1–1.6	0.01
Baseline anaemia	1.3	1.0–2.1	0.04
Diabetes	1.25	1.0–1.6	0.05
Anterior MI	1.24	1.0–1.5	0.03
Age (per one year more)	1.05	1.04–1.06	< 0.0001
GFR (< 60 mL/min)	0.98	0.91–0.99	0.003
Final TIMI flow grade 3	0.7	0.5–0.9	0.002
Stent implantation	0.71	0.6–0.9	0.002
Male sex	0.71	0.6–0.9	0.003
LVEF (per 1% more)	0.96	0.95–0.97	< 0.0001

CI — confidence interval; GFR — glomerular filtration rate; HR — hazard ratio; LVEF — left ventricular ejection fraction; MI — myocardial infarction; TIMI — thrombolysis in myocardial infarction

Table 5. Predictors of red blood cell transfusion (Cox proportional hazards model results)

	HR	95% CI	P
Gastrointestinal bleeding	5.75	2.8–11.8	< 0.0001
Female sex	3.5	2.1–5.8	< 0.0001
Shock on admission	2.7	1.5–4.7	0. 0008
Thrombolysis before PCI	2.4	1.4–4.05	0.001
Baseline anaemia	2.1	1.1–3.8	0.02
Smoker	1.8	1.1–3.05	0.03
Age (per one year more)	1.07	1.04–1.09	< 0.0001

CI — confidence interval; HR — hazard ratio; PCI — percutaneous coronary intervention; TIMI — thrombolysis in myocardial infarction

arterial content of oxygen, the latter being dependent on the haemoglobin level. Interestingly, anaemia and the need to restore adequate DO2 are the most common indications for transfusion, rather than acute bleeding [16–19]. However, some authors suggest that bleeding, not transfusion, could be the major factor affecting higher mortality in ACS [20]. In STEMI, which is associated with increased viscosity and thrombogenicity, RBC transfusion perhaps heightens these parameters, leading to a further decrease in microcirculatory flow and poor DO2 [21–24].

A number of observational studies investigating RBC transfusion consequences in acute MI patients and non-emergency PCI were hampered by selection bias and have reported differing results [1, 2, 25–29]. In two series of patients with STEMI, increased early and long-term mortality associated with RBC transfusion were reported [20, 28]. However only in our investigation a long-term follow-up period is presented.

The rate of RBC transfusion has been reported as approximately 4% of patients with STEMI — consistent with outcomes obtained in our investigation [20]. The direct, unambiguous reasons for the harmful effect of the RBC transfusion are unknown and have been widely discussed. The underlying mechanism of the increased mortality in STEMI patients treated with RBC transfusion can be partly explained by their greater risk profile. These patients tend to have diabetes mellitus, baseline anaemia and renal insufficiency, a lower LVEF, lower angiographic success, and cardiogenic shock on admission more often than patients without a RBC transfusion. However, after adjustment for these differences in the baseline characteristics in a multivariate Cox regression analysis, RBC transfusion remained an independent predictor of greater five-year mortality.

Other factors that might contribute to the adverse outcomes in patients treated with RBC transfusion compared to nontransfused patients may be found in several detrimental effects of transfused blood, globally referred to under the acronym 'Non-Infectious Serious Hazards Of Transfusion' or NISHOT [30]. These include, among others, deleterious effects on the immune system (transfusion-related immunomodulation or 'TRIM') or on the cardiopulmonary system, e.g. transfusion-related acute lung injury ('TRALI') [31] or transfusion-associated circulatory overload ('TACO'); the latter is currently the leading reported cause of transfusion-associated mortality [32].

The harmful effect of blood transfusion in the case of STEMI may also be due to RBCs being stored for prolonged periods [33, 34]. During storage, RBCs undergo a series of biological and biochemical changes which are known as 'the storage lesion'. However, the clinical consequences of storage lesions are still not clear [35]. Several large, randomised, controlled trials in adult intensive care and cardiac surgery patients are currently ongoing to address the clinical relevance of RBC storage [36, 37]. Perhaps their results can be used to determine the optimal storage time.

Limitations of the study

The main limitation of our study was that it was not a prospective, randomised trial, but a single centre registry, which could affect the results. Additionally, our database did not include certain important factors such as the main reason why RBC transfusion was ordered and how many units of RBC were used. Consequently, the reported significantly higher mortality in STEMI patients treated with RBC transfusion should be interpreted with caution. The retrospective nature of our analysis is a potential weakness. Even after data adjustment, the results could be biased by potentially important parameters that are not available in the registry; thus, despite using

multivariable analysis, the conclusions require confirmation by a randomised trial.

CONCLUSIONS

RBC transfusion is associated with higher five-year mortality in STEMI patients treated with PCI. Our study results highlight the need for prospective, randomised trials to assess in which group of STEMI patients, with regard to the most appropriate haematocrit or haemoglobin threshold, RBC transfusion improves the outcomes.

Conflict of interest: *none declared*

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Wpływ przetoczenia koncentratu krwinek czerwonych na śmiertelność pięcioletnią u chorych z zawałem serca z uniesieniem odcinka ST leczonych przezskórną interwencją wieńcową

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Streszczenie

Wstęp: Przetoczenie krwi może być zabiegiem ratującym życie. Jednakże obserwowano, że w niektórych sytuacjach klinicznych (ostre zespoły wieńcowe, przezskórne interwencje wieńcowe, operacje kardiochirurgiczne, stan krytyczny) transfuzja krwi może prowadzić do niekorzystnych następstw, takich jak zgon, zawał serca czy infekcje układu oddechowego.

Cel: Celem badania było oszacowanie wpływu przetoczenia koncentratu krwinek czerwonych (RBC) na rokowanie odległe u chorych z zawałem serca z uniesieniem odcinka ST (STEMI) leczonych przezskórną interwencją wieńcową (PCI).

Metody: W latach 1999–2004 łącznie 2415 chorych ze STEMI leczonych PCI włączono do analizy. Pacjentów podzielono na dwie grupy: 82 chorych poddanych transfuzji RBC (3,5%) i 2333 chorych bez transfuzji RBC (96,5%).

Wyniki: Śmiertelność wewnątrzszpitalna wyniosła 15,8% i 4,2% ($p < 0,0001$), natomiast śmiertelność 5-letnia — 42,7% i 19% ($p < 0,0001$), odpowiednio dla chorych, u których wykonano i nie wykonano transfuzji RBC. W analizie wieloczynnikowej wykazano, że transfuzja RBC jest niezależnym predykatorem śmiertelności 5-letniej (HR 1,45; 95% CI 1,0–2,1; $p = 0,04$).

Wnioski: Transfuzja RBC wiąże się z wyższą śmiertelnością 5-letnią u chorych ze STEMI leczonych PCI.

Słowa kluczowe: transfuzja koncentratu krwinek czerwonych, zawał serca, przezskórne interwencje wieńcowe

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