Influence of red blood cell transfusion on mortality and long-term functional outcome in 292 patients with spontaneous subarachnoid hemorrhage*

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Objective: **To analyze the influence of red blood cell (RBC) transfusions on mortality and outcome of patients with spontaneous subarachnoid hemorrhage (SAH) and to determine predictors of unfavorable neurologic long-term outcome in this patient population.**

Design: **Cohort study with post–intensive care unit (ICU) prospective evaluation of functional long-term outcome.**

Setting: **Ten-bed neuro-ICU in a tertiary care university hospital.**

Patients: **A consecutive cohort of 292 patients with spontaneous SAH admitted to a neuro-ICU during a 70-month period.**

Interventions: **None.**

Measurements and Main Results: **A total of 292 consecutive patients with SAH were enrolled in the study. At admission, mean hemoglobin was 13.3 g/dL (±SD 1.8 g/dL), comparable in all Hunt and Hess groups ($p = 0.61$ by analysis of variance). Seventy-nine patients received at least one unit of RBC transfusion in the study period. In-ICU mortality was 20.5% (n = 60). Binary logistic regression analysis comparing survivors with nonsurvivors found only higher Hunt and Hess grades (i.e., Hunt and Hess 3–5) to be significantly ($p < 0.01$) associated with mortality in the neuro-ICU, whereas transfusion, sex, and even age had no significant influence. Functional long-term outcome was assessed after a mean of 3.3 years (SD ±1.7 years) by evaluating modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS). More than 41% of all patients have almost fully recovered (i.e., mRS 0–1; GOS 4–5). Factors associated with unfavorable long-term outcome (i.e., GOS 1–3 and mRS 2–6) were age (odds ratio 1.06; 95% confidence interval 1.03–1.09; $p < 0.01$), Hunt and Hess Grade (odds ratio 11.43; 95% confidence interval 4.1–31.9; $p < 0.01$) but not transfusion ($p = 0.46$).**

Conclusion: **Transfusion of RBCs was not associated with in-neuro-ICU mortality or unfavorable long-term outcome. Of all patients with SAH, >41% have almost fully recovered with favorable neurologic long-term outcome. (Crit Care Med 2009; 37: 1886–1892)**

KEY WORDS: subarachnoid hemorrhage; long-term outcome; red blood cell transfusion; mortality

Nontraumatic subarachnoid hemorrhage (SAH) is a neurologic emergency affecting up to 40,000 patients yearly in the United States, thus, incidence being 10 per 100,000 per year (1, 2). Today, with various treatment options, still the major goal is an early aneurysm repair to prevent rebleeding (3, 4). Treatment of patients with SAH often requires prolonged and aggressive intensive care management with subsequent medical complications that may have an impact on outcome (5). In several prospective studies, up to 80% of intensive care unit (ICU) patients developed anemia (6–8). Reduced red blood cell (RBC) development from bone marrow dysfunction, frequent blood sampling (iatrogenic), reduced iron availability, and increased consumption of RBCs because of secondary medical complications, such as inflammation or sepsis, have been identified, among others, as potential triggers of anemia (1, 9). Transfusion of RBCs is still the treatment of choice when correcting anemia, although the potential deleterious effect of transfusion on outcome of ICU patients has been shown; in patients with SAH, recent publications have discussed this issue controversially (1, 10–13). It still remains unclear whether reducing viscosity or increasing oxygen-carrying capacity of blood is more important in patients with SAH (1). The optimal target hemoglobin value in SAH and the impact of RBC transfusions on outcome and mortality need to be clarified and are, therefore, still a matter of discussion. Various mechanisms of action, such as deranged nitric oxide metabolization or defect microcirculation of transfused erythrocytes, have been discussed to be potential reasons for the unfavorable outcome in ICU patients receiving RBC transfusions (10, 11, 13–15).

Measurement of (long-term) outcome is an adequate tool not only to reflect the intensivists daily work but also to legitimize its important implications for allocating hospitals resources. The average case fatality rate of patients with SAH is approximately 50%, with almost 30% of survivors needing lifelong care (16, 17). Given the SAH associated morbidity and economic effect, a more detailed understanding of this particular patient population may facilitate care and management decisions (18, 19).

***See also p. 2104.**

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The aim of our study was to investigate the influence of RBC transfusion on neuro-ICU mortality and long-term functional outcome of patients with SAH and evaluate possible predictors of unfavorable neurologic outcome.

MATERIALS AND METHODS

Setting. This study was performed at the University Hospital Innsbruck, Austria, a 1500-bed tertiary care hospital with approximately 74,000 admissions per year. The hospital provides six specialty ICUs (medical, neurologic, neurosurgical, pediatric including neonatal, surgical, and trauma). The neuro-ICU is a ten-bed neurocritical care unit admitting, on a nonelective basis, approximately 450 adults per year.

Patients. All consecutive patients with spontaneous SAH admitted to the Clinical Department of Neurology, Neurologic Intensive Care Unit, Innsbruck Medical University, during a 70-month period, were enrolled (January 1, 2000 to October 31, 2005). The diagnosis of SAH was established by computed tomography at admission or by xantochromia of the cerebrospinal fluid if the computed tomography scan was not diagnostic. Patients with aneurysmal or nonaneurysmal spontaneous SAH were included. Nonaneurysmal SAH was defined as angiogram (digital subtraction angiography) negative SAH. Neurosurgical intervention (i.e., clipping of ruptured aneurysm or cerebrospinal fluid drain) on patients initially admitted to the neuro-ICU usually led to readmission. Only patients who were readmitted for postoperative care were included in the study. Patients with SAH from trauma, arteriovenous malformations, or other secondary causes as well as patients younger than 18 years were excluded.

Institutional Review Board. The protocol was in accordance with the ethical standards of our hospitals committee for the protection of human subjects (protocol number UN 2579). Written informed consent was obtained from each patient before telephone interview. From those patients who were incompetent at the time point of telephone interview, the informed consent was obtained by next of kin.

Data Collection. In-hospital variables (i.e., age, sex, length of stay (LOS), admission date, and discharge date) were collected retrospectively for all patients via patients hospital chart review or review of an electronic database.

Hunt and Hess Grade. For all patients, the Hunt and Hess grade was evaluated at the time of admission to the neuro-ICU. The gradation was conducted by the attending full-time neurologist and entered into a database system (4D Client, version 8.08a, 4D, San Jose, CA). If the patient was intubated at the time of admission, preintubation status, signs and symptoms were used to grade the patient.

Measuring of Outcome Variables. Functional outcome was evaluated in all neuro-ICU survivors by means of Glasgow Outcome Scale (GOS) and modified Rankin Scale (mRS) in a telephone interview. GOS and mRS were chosen as validated and widely accepted outcome parameters in ICU patient trials (20–22). All data were collected by a single physician (H.C.) who has been specifically trained in administration of disability and quality-of-life questionnaires. The interviewer was blinded regarding clinical data, such as Hunt and Hess grading, LOS, and transfusion. After informed consent, the previously defined outcome parameters of each patient were assessed and documented in an electronic questionnaire. To minimize misunderstandings, the questionnaire was kept short and simple: 1) Is the patient still alive?; 2) Evaluation of GOS; 3) Evaluation of mRS; and 4) Date of telephone interview. If the patient was not able to communicate, information on health status was collected through close relatives or healthcare professionals, such as general practitioners. Lost to follow-up was defined as no telephone contact for four times on different days at different daytimes.

GOS and mRS were dichotomized to receive binary outcome measures for logistic regression analyses. GOS was categorized into values for unfavorable outcome (GOS 1–3, i.e., unable to live independently or worse) and favorable outcome (GOS 4–5, i.e., able to live independently); mRS was dichotomized into values for unfavorable outcome (mRS 2–6, indicating slight disability or worse) and favorable outcome (mRS 0–1, indicating no disability).

Medical Staff. During the entire study period, there was no change in specialized neuro-ICU medical staff in our department. All three senior physicians are full-time neurologists and intensivists.

SAH Treatment. The recommendations for ICU management of patients with spontaneous SAH has been described in detail previously (5, 23, 24). In all patients in whom an aneurysm was detected in digital subtraction angiography an intervention either coiling or clipping was aimed for. Anatomical considerations led to preference of endovascular or neurosurgical intervention. Patients experiencing symptomatic vasospasm received triple H therapy (hypertension, hypervolemia, and hemodilution), involving a target central venous pressure of >8 mm Hg. Hypertension was induced using norepinephrine or epinephrine to maintain systolic blood pressure at about 180 mm Hg. All patients received nimodipine at a daily dose of 300 mg, unless hemodynamic instability or hypotension occurred. In the light of a retrospective analysis, our study lacks a predefined angiographic protocol to compare grades of vasospasm between the treatment groups. Therefore, vasospasm was not included in the outcome analysis.

Persistent hyperglycemia exceeding 180 mg/dL was treated with subcutaneous sliding-scale insulin every 3–6 hours. Insulin infusion was not routinely used unless subcutaneous treatment was unsuccessful or ketosis developed.

RBC Transfusion. We conducted this study in cooperation with the Central Institute for Blood Transfusion, University Hospital Innsbruck. During the entire study period, storage or preparation techniques of the infused RBC transfusions remained unchanged. Maximum storage of RBC transfusions is limited at 42 days in our department. In contrast to other countries, only leukocyte-depleted RBC units are in routine clinical use in Austria. For each patient, we retrospectively evaluated the number of RBC transfusions as well as all measured hemoglobin values during neuro-ICU stay. Reduction of hemoglobin data was achieved by calculating the mean of all measured HGB values per patient. These data were then used for further statistical analyses.

Statistical Analysis. To receive binary outcome measures, GOS or mRS, respectively, were dichotomized (GOS: 1–3 and 4–5; mRS: 0–1 and 2–6). Risk factors for unfavorable long-term outcome were analyzed by binary logistic regression. For detailed analysis, we used two models. In model 1, all patients with respective outcome data were included. In model 2, we excluded all patients who died within 3 days in the neuro-ICU to minimize bias introduced by patients with low likelihood of RBC transfusion and, thus, assess whether possible selection bias would have influenced our results (Tables 4 and 5). Covariates for these analyses (i.e., age at SAH, LOS, Hunt and Hess grade, intervention on aneurysm (i.e., coiling or clipping), detected aneurysm, and sex) were selected as generally accepted clinically meaningful parameters of patients with spontaneous SAH. To check for a putative selection bias, baseline characteristics (age, sex, LOS, Hunt and Hess grade) for patients with long-term follow-up and those lost to follow-up were compared using analysis of variance (age), Mann-Whitney *U* test (LOS) or chi-square test (sex, Hunt and Hess grade), respectively. A p value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS 14.0.1 for Windows.

RESULTS

Patients' Characteristics. During the study period of 70 months, we enrolled 292 individuals of whom 176 (60%) were female. An aneurysm was identified in 234 patients, in 17% (n = 39) of whom the aneurysms were not treated mostly due to moribund status (the in-neuro-ICU mortality rate being 82% among these patients) or for anatomical considerations, the localization and the configuration rendering the aneurysm both unsuitable for coiling or clipping, respectively. In 195 patients, the aneurysm was

Table 1. Characteristics of the patients at admission (n = 292)

Variable	n (%) or Mean ± SD
Female	176 (60.3)
Age (yrs)	54.5 ± 12.9
Hunt and Hess grade	
1 = Asymptomatic, headache, or meningismus	87 (29.8)
2 = Moderate to severe headache, nonfocal examination	76 (26)
3 = Drowsiness, confusion, or mild deficit	56 (19.2)
4 = Stupor, hemiparesis	27 (9.2)
5 = Deep coma and decerebrate rigidity	46 (15.8)
First measured hemoglobin (g/dL)	13.2 ± 1.8
Aneurysm	234 (80.1)
Clipping (% of patients with aneurysm)	37 (15.8)
Coiling (% of patients with aneurysm)	158 (67.5)
No intervention (% of patients with aneurysm)	39 (16.7)

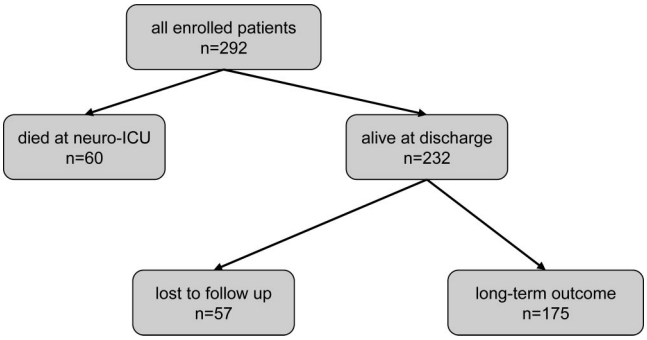

Figure 1. Distribution of study population. *ICU*, intensive care unit.

successfully occluded either with endovascular coiling (n = 158) or clipping (n = 37). Baseline characteristics of the study population are listed in Table 1. We compared patients with follow-up and those lost to follow-up with respect to age, sex, LOS, and Hunt and Hess grade. No significant differences could be found for the respective variables between these groups. Figure 1 shows study distribution of patients.

Transfusion Parameters. Seventy-nine patients (27.1%) received at least one RBC transfusion in the study period. Median number of packed RBC was 4 (range 1–36 packs) per transfused patient. At the time of admission to the neuro-ICU mean hemoglobin (HGB) was 13.3 g/dL (SD ±1.8 g/dL), not showing any significant difference between Hunt and Hess groups ($p = 0.61$ by analysis of variance). Patients in grade 4 had the lowest HGB values similar to what has been published before (1). Patients who received a RBC transfusion (n = 79) had a significant lower mean HGB (10.3 g/dL ± SD 0.9) than patients with no transfusion (12.4 g/dL ± SD 1.6) ($p < 0.01$). The minimum HGB values were 8.5 g/dL (patients without RBC transfusion) and 8.0 g/dL (patients with RBC transfusion). Review of hemoglobin (g/dL) at the time of RBC transfusion revealed indication for transfusion was set in 11% at a HGB >9 g/dL, in 60.1% at HGB >8 g/dL ≤9g/dL, in 26.6% at HGB >7 g/dL ≤8 g/dL and in 2.3% at a HGB <7 g/dL. A binary logistic regression model indicated higher Hunt and Hess grade (i.e., Hunt and Hess 4–5, $p < 0.01$), LOS ($p < 0.01$) and neurosurgical clipping ($p < 0.01$) as independent risk factors for receiving a blood transfusion (Table 2). We could not find a statistical difference with regard to age ($p = 0.22$ Student's t test) at SAH and sex ($p = 0.78$, chi-square test) between patients with or without transfusion (Table 3).

None of the patients enrolled received erythropoietin during study period.

Neuro-ICU Mortality Analysis. In-neuro-ICU mortality rate was 20.5% (n = 60). Binary logistic regression analysis comparing survivors with nonsurvivors revealed that only high Hunt and Hess grades (i.e., Hunt and Hess 3–5) were significantly ($p < 0.01$) associated with mortality in the neuro-ICU, whereas transfusion, sex, and even age had no significant influence. The only parameter associated with a significant ($p < 0.01$) reduction of risk for death in-neuro-ICU was LOS (Table 4). In the group of patients without transfusion, mortality analysis revealed that almost half (49%, n = 24) of those patients who died in the neuro-ICU, died within 3 days after admission. In contrast, in the group of transfused patients, only 18% (n = 2) died within the same period.

Outcome Analysis. Functional long-term outcome data (i.e., GOS and mRS) were not available for 57 (19.5%) of the 292 patients. Outcome measurement was assessed by telephone interview at a mean time of >3 years (mean 3.3 years SD ± 1.7 years) after discharge. GOS and mRS of all neuro-ICU survivors (n = 232) were dichotomized to receive binary outcome data comparing groups of patients with favorable vs. unfavorable long-term outcome. GOS was categorized into values for unfavorable outcome (GOS 1–3, i.e., unable to live independently or worse, n = 100) and favorable outcome (GOS 4–5, i.e., able to live independently, n = 135). mRS was dichotomized into values for unfavorable outcome (mRS 2–6, indicating slight disability or worse, n = 114) and favorable outcome (mRS 0–1, indicating no disability, n = 121). Subsequent logistic regression analyses yielded age and higher Hunt and Hess grade (i.e., Hunt and Hess 3–5 vs. Hunt and Hess 1–2) as independent predictors of unfavorable long-term functional outcome (all $p < 0.01$, Tables 4 and 5). Interestingly, LOS and transfusion of RBC did not have any significant association with functional outcome. In a second step, we repeated this analysis, but excluded patients who died within the first 3 days in the neuro-ICU to minimize bias introduced by patients with low likelihood of RBC transfusion. Nevertheless, levels of significance remained unchanged in this approach (Tables 4 and 5).

DISCUSSION

The aim of this study is to contribute to the discussion whether RBC transfusion may be an independent predictor of long-term functional outcome in patients with spontaneous SAH. In our cohort, what some authors consider to be a non-liberal transfusion regimen (14) did not have significant influence on in-neuro-ICU mortality or long-term functional outcome. These associations persisted even after correction for other known clinical predictors of outcome. Excluding patients, in the regression model, who died early in the ICU and, therefore, had a

lower likelihood for a RBC transfusion did not alter levels of significance. Although data on this topic are very limited, our findings are in contrast to results of previous studies discussing a possible deleterious effect of RBC transfusions on outcome in patients with SAH (1, 5, 11, 25). Smith et al (11) could find a significant worsening in outcome of patients with SAH if RBC transfusions were administered intraoperatively, whereas postoperative transfusion led to increased rate of vasospasm but not worsening of outcome. In two other trials, risk of poor outcome was increased if patients received transfusion or developed anemia (1, 5). In a recent publication, both, anemia and even more transfusion, led to a significant increase in poor outcome in patients with SAH (25). But again, the authors concluded that transfusion could still only be a risk marker rather than being causative (25).

Strengths of our data include a comparison of baseline characteristics of patients with long-term follow-up and those lost to follow-up, which did not yield statistically significant differences between those groups and prospective collection of outcome data (mortality, GOS and mRS). Hence, we are confident that a selection bias should not adversely influence the interpretation of our data. In our cohort, 27% received at least one RBC transfusion, which lies within the range reported, that varies widely from 20% to 53% in ICU patients (26). Today, the optimal hemoglobin value is still discussed controversially but levels between 7 and 9 g/dL are assumed to be safe in ICU patients and maybe beneficial regarding the outcome (14, 26). If this also holds true for patients with SAH is under debate because not only anemia but also transfusion may alter outcome negatively (25). Mean HGB levels per patient were significantly different in both treatment arms with 10.3 and 12.4 g/dL, respectively, but clearly above the 10 g/dL threshold that is thought to be the optimal balance between lower viscosity and oxygen-carrying capacity in patients with SAH (25, 11, 27). It has been shown that RBC transfusions are associated with nosocomial infections, severe neurologic disability, and delayed cerebral infarction (25). In contrast, in our cohort, we could not find increased mortality or long-term neurologic sequelae in patients receiving transfusions. A possible explanation could be that transfusions were mostly administered at hemoglobin values between 7 and 9 g/dL with mean hemoglobin in all patients above 10 mg/dL. Although these data do not clearly allow us to conclude that this is the target or

Table 2. Risk analysis for receiving a red blood cell transfusion (n = 292)

Parameter	Odds Ratio	95% Confidence Interval		*p*
In-neuro-ICU mortality	1.15	0.33	4.00	0.82
Age at SAH (yrs)	0.99	0.97	1.03	0.96
Sex	0.68	0.31	1.50	0.34
LOS neuro-ICU	1.16	1.11	1.21	<0.01
Hunt and Hess grade				
1 = Asymptomatic, headache, or meningismus	Reference Category			
2 = Moderate to severe headache, nonfocal examination	1.68	0.57	4.92	0.35
3 = Drowsiness, confusion, or mild deficit	2.00	0.63	6.29	0.24
4 = Stupor, hemiparesis	7.79	1.69	35.84	0.01
5 = Deep coma and decerebrate rigidity	5.70	1.52	21.40	0.01
Aneurysm	0.81	0.14	4.70	0.82
No intervention on aneurysm	Reference Category			
Clipping	19.76	3.41	114.50	<.01
Coiling	2.90	0.70	11.98	0.14

SAH, subarachnoid hemorrhage; LOS, length of stay; neuro-ICU, neurologic intensive care unit. Model was calculated using binary logistic regression analysis.

Table 3. Characteristics of patients with or without red blood cell transfusion

Parameter	Patients Receiving no Transfusion, n (%) or Mean ± SD n = 213	Patients Receiving Transfusions, n (%) or Mean ± SD n = 79	*p*
Age (yrs)	53.9 ± 13.3	56 ± 11.7	0.2
Female	127 (59.6)	49 (62.0)	0.78
Male	86 (40.4)	30 (38.0)	
LOS (d)	8.7 ± 8.4	30.5 ± 21.0	<0.01
Hunt and Hess grade			<0.01
1 = Asymptomatic, headache, or meningismus	77 (36.2)	10 (12.6)	
2 = Moderate to severe headache, nonfocal examination	55 (25.8)	21 (26.6)	
3 = Drowsiness, confusion, or mild deficit	38 (17.8)	18 (22.8)	
4 = Stupor, hemiparesis	13 (6.1)	14 (17.7)	
5 = Deep coma and decerebrate rigidity	30 (14.1)	16 (20.3)	
Neuro-ICU mortality	49 (23.0)	11 (13.9)	0.10
Intervention			0.04
Coiling	108 (50.7)	50 (63.3)	
Clipping	25 (11.7)	12 (15.2)	
None	80 (37.6)	17 (21.5)	
Minimum hemoglobin level (g/dL)	8.5	8.0	
Mean hemoglobin level (g/dL)	12.4 ± 1.6	10.3 ± .9	<0.01
Time to long-term follow-up (d)	1220.8 ± 564.3	1171.6 ± 616.7	0.52

LOS, length of stay; neuro-ICU, neurologic intensive care unit.

p Values were calculated with chi-square test and represent the overall level of significance for the association between treatment and severity or intervention groups.

Table 4. Risk analysis of all patients for neuro-ICU mortality (n = 292)[a] and risk analysis of all patients for neuro-ICU mortality, excluding patients who died in the neurologic intensive care unit (neuro-ICU) within 3 d (n = 274)[b]

Parameter	Model 1				Model 2			
	OR	95% CI		p	OR	95% CI		p
Age at SAH (yrs)	1.02	0.99	1.06	0.17	1.03	0.99	1.07	0.17
Sex	0.46	0.20	1.07	0.07	0.50	0.20	1.22	0.13
LOS neuro-ICU	0.92	0.87	0.96	<0.01	0.94	0.89	0.98	0.01
Hunt and Hess grade								
1 = Asymptomatic, headache or meningismus	Reference Category				Reference Category			
2 = Moderate to severe headache, nonfocal examination	4.47	0.82	24.46	0.09	3.45	0.60	19.95	0.17
3 = Drowsiness, confusion or mild deficit	17.31	3.50	85.52	<0.01	15.90	3.23	78.27	<0.01
4 = Stupor, hemiparesis	197.08	30.89	1257.31	<0.01	131.31	20.32	848.46	<0.01
5 = Deep coma and decerebrate rigidity	80.04	16.01	400.11	<0.01	42.10	7.86	225.37	<0.01
Transfusion	0.67	0.21	2.17	0.51	0.58	0.17	1.95	0.38

SAH, subarachnoid hemorrhage; LOS, length of stay; neuro-ICU, neurologic intensive care unit; OR, odds ratio; CI, confidence interval.
[a]Model 1; [b]model 2. Models were calculated using binary logistic regression analysis.

Table 5. Glasgow Outcome Scale (GOS): Outcome of all patients with complete outcome data, regarding unfavorable outcome in terms of GOS 1–3 (n = 235)[a] and outcome of all patients with complete outcome data excluding patients who died in the neurologic intensive care unit (neuro-ICU) within 3 d, regarding unfavorable outcome in terms of GOS 1–3 (n = 217)[b]

Parameter	Glasgow Outcome Scale								Modified Rankin Scale							
	Model 1				Model 2				Model 1				Model 2			
	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p
Age at SAH (yrs)	1.06	1.03	1.09	<.01	1.06	1.03	1.10	<.01	1.05	1.03	1.08	<.01	1.06	1.03	1.09	<0.01
Sex	0.77	0.39	1.52	0.46	0.83	0.42	1.65	0.59	0.53	0.28	1.01	0.05	0.54	0.28	1.05	0.07
LOS neuro-ICU	0.99	0.96	1.02	0.46	0.99	0.97	1.03	0.92	1.01	0.99	1.03	0.52	1.01	0.99	1.04	0.24
Hunt and Hess grade																
1 = Asymptomatic, headache, or meningismus	Reference Category								Reference Category							
2 = Moderate to severe headache, nonfocal examination	1.08	0.42	2.75	0.88	0.92	0.35	2.41	0.87	1.30	0.56	3.01	0.54	1.15	0.49	2.71	0.75
3 = Drowsiness, confusion. or mild deficit	3.68	1.47	9.19	<0.01	3.41	1.36	8.56	<0.01	3.11	1.29	7.47	0.01	2.93	1.21	7.11	0.02
4 = Stupor, hemiparesis	27.24	5.30	139.94	<0.01	19.30	3.66	101.76	<0.01	17.35	3.45	87.22	<0.01	12.06	2.31	62.89	<0.01
5 = Deep coma and decerebrate rigidity	11.43	4.10	31.89	<0.01	5.62	1.87	16.86	<0.01	6.90	2.60	18.30	<0.01	3.11	1.09	8.94	0.03
Transfusion	1.41	0.57	3.51	0.46	1.42	0.57	3.53	0.45	1.43	0.62	3.31	0.41	1.51	0.65	3.55	0.34

SAH, subarachnoid hemorrhage; LOS, length of stay; neuro-ICU, neurologic intensive care unit; OR, odds ratio; CI, confidence interval.
[a]Model 1; [b]model 2. Models were calculated using binary logistic regression analysis. Model 2: Outcome of all patients with complete outcome data excluding patients who died in the neurologic intensive care unit (neuro-ICU) within 3 d, regarding unfavorable outcome in terms of mRS 2–6 (n = 217).

lower threshold HGB value for patients with SAH, because analysis of transfusion was only conducted retrospectively and, therefore, a possible selection bias may be discussed. Identifying the optimal HGB and threshold for transfusion should be approached in a prospective manner, randomly assigning target HGB values and transfusion protocols.

In Austria, only leukocyte-depleted RBC units are allowed for routine clinical use. Thus, a possible negative effect attributed to leukocytes is very unlikely.

Neuro-ICU mortality was slightly elevated in patients without transfusions, although this difference did not reach statistical significance. This might be attributable to the fact that patients who die early in the course of the disease are less likely to receive blood transfusions, thus, being included in the nontransfusion group. In fact, in our study, almost half (49%, n = 24) of the patients in the nontransfusion group died within 3 days after admission in contrast to only 18% (n = 2) in the transfused patients. Facing this possible bias, we have excluded all patients who died early in the neuro-ICU in the outcome and mortality analysis (model 2, Tables 4 and 5). However, this approach did not alter levels of significance, thus, we believe in the stability of our statistical model.

Spontaneous SAH is still considered a life-threatening disease often leading to neurologic sequelae and prognostic uncertainties even in professional intensivists, especially when dealing with relatives of the patients (28, 29, 16). Our analysis revealed that >41% of all patients have recovered fully and present themselves in an excellent functional health status (resembling mRS 0–1), approximately 3 years after discharge. This is, to the best of our knowledge, the first study evaluating GOS and mRS in patients with spontaneous SAH after >3 years post-neuro-ICU treatment. Most studies addressing this question have only measured functional outcome between 3 months and 1 year post-ICU (29–31). We believe that correct assessment of long-term function outcome should be examined later because neurorehabilitation is often prolonged in such patients and may lead to a surprisingly good outcome as in our cohort.

Binary logistic regression analysis showed that age ($p < 0.01$) and higher Hunt and Hess grade ($p < 0.01$) are independently associated with unfavorable long-term outcome (i.e., GOS 1–3 and mRS 2–6). Interestingly, LOS did not show a significant correlation with outcome, indicating that even prolonged ICU care does not additionally harm patients. This is of utmost importance because prolonged ICU care is often necessary in patients developing delayed complications, such as vasospasm. In addition to that, the development of specialty ICUs, such as neuro-ICUs or neurosurgical ICUs, experienced in dealing with such complications may be enforced as this might be beneficial for patients treated in such units.

Our study was not designed to draw conclusions on vasospasm possibly being triggered or enhanced by transfused blood, because we were lacking a predefined angiographic protocol. This should be addressed in a future study prospectively scanning for symptomatic vasospasm or new hypodensity on cerebral computed tomography scans.

This study has important limitations that must be considered when interpreting the results. First, the retrospective collection of some of the data may have introduced bias. However, the fact that the major outcome parameters (mortality, GOS, and mRS) were collected prospectively gives strength to our data. A second limitation is the possibility of temporal trends in treatment strategies to bias our results. We believe this source of bias may be small because there were no major changes in physician staffing or introduction of novel technologies in our hospital during the study period. Through the retrospective approach of the study, data on preexisting conditions or rate of infectious complications could not be evaluated statistically reliable and were, therefore, not included in outcome analysis. Strengths of our data include electronic retrieval of all HGB data points and RBC transfusions as well as a preexisting verified clinical database. Some patients were lost to follow-up between neuro-ICU discharge and long-term outcome evaluation, but the bias analysis comparing baseline characteristics of patients with long-term follow-up and those classified as lost to follow-up did not reveal any difference. However, loss of patients to follow-up can lead to bias among patients who do well and move away from the area without leaving forwarding information, as well as patients who die without leaving someone who has appropriate information.

CONCLUSION

We have presented a study evaluating the effect of RBC transfusion on mortality and long-term functional outcome in patients with spontaneous SAH. RBC transfusions were mainly infunded at HGB levels between 7 and 9 g/dL and were not associated with ICU mortality or unfavorable long-term outcome. Factors independently associated with unfavorable outcome were higher Hunt and Hess grade as well as age but not LOS, possibly indicating that even prolonged treatment in a specialty ICU and successful control of in-hospital complications may lead to favorable outcome in these patients. Complete resaturation of pre-SAH health status could be achieved in >41% of the patients.

Future studies should prospectively evaluate the optimal HGB value in patients with spontaneous SAH and the interactions of RBC transfusions or even synthetic drugs stimulating erythrocytes regeneration on outcome.

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