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Impact of Additional Administration of von Willebrand Factor Concentrates to Thrombocyte Transfusion in Perioperative Bleeding in Cardiac Surgery

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Keywords

Blood loss · Blood products · Coagulation factor VIII · Haemate® · Platelets · Von Willebrand factor

Abstract

Background: Von Willebrand factor (vWF) is an important part of blood coagulation since it binds platelets to each other and to endothelial cells. In traumatic and surgical haemorrhage, both blood cells and plasmatic factors are consumed, leading to consumption coagulopathy and fluid resuscitation. This often results in large amounts of crystalloids and blood products being infused. Additional administration of vWF complex and platelets might mitigate this problem. We hypothesize that administration of vWF concentrate additionally to platelet concentrates reduces blood loss and the amount of blood products (platelets, red blood cells [RBC], fresh frozen plasma [FFP]) administered. ***Methods:*** We conducted a monocentric 6-year retrospective data analysis of cardiac surgery patients. Included were all patients receiving platelet concentrates within 48 h postoperatively. Patients who additionally received vWF concentrates were allocated to the intervention group and all others to the control group. Groups were compared in mixed regression models correcting for known confounders, based on nearest neighbour propensity score matching. Primary endpoints were loss of blood (day one and two) and amount of needed blood products on day one and two (platelets, RBC, FFP). Secondary endpoints were intensive care unit (ICU) and in-hospital length of stay, ICU and in-hospital mortality, and absolute difference of platelet counts before and after treatment. ***Results:*** Of 497 patients analysed, 168 (34%) received vWF concentrates. 121 patients in both groups were considered for nearest neighbour matching. Patients receiving additional vWF were more likely to receive more blood products (RBC, FFP, platelets) in the first 24 h after surgery and had around 200 mL more blood loss at the same time. ***Conclusion:*** In this retrospective analysis, no benefit in additional administration of vWF to platelet concentrates on perioperative blood loss, transfusion requirement (platelets, RBC, FFP), length of stay, and mortality could

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be found. These findings should be verified in a prospective randomized controlled clinical trial (www.clinicaltrials.gov identifier NCT04555785).

Background

Perioperative bleeding is a common challenge in cardiac surgery. Bleeding is associated with increased intraoperative and in-hospital morbidity and mortality, thus a higher need of blood product transfusions, which itself is again associated with risks and a total increase in healthcare costs [1–5]. A proposed universal definition of postoperative bleeding classifies severity of bleeding after cardiac surgery in five degrees, based on the following risk factors: delayed sternal closure, postoperative chest tube output, packed red blood cell (RBC) transfusion, fresh frozen plasma (FFP) transfusion, platelet transfusion, cryoprecipitate transfusion, use of coagulation factor concentrates, use of recombinant activated factor VII, and surgical re-exploration [6].

Underlying causes of bleeding are often multifactorial. The following factors are discussed to be adversely involved [1, 2, 7–9]: advanced age [7], low body mass index [7], preoperatively impaired renal function [7], previous sternotomy [7], high urgency of surgery [7], extended degree of surgical procedure [7], use of extracorporeal circulation circuits [1, 7, 10], preoperative use of anticoagulatory or thrombocyte inhibitory drugs [1, 7–9], residual heparin effect [1], thrombopenia [9], platelet dysfunction [1, 9], consumption of coagulation factors [1, 9], low fibrinogen [7], increased fibrinolysis, respectively [1, 7], and haemodilution [1, 7]. As all these factors are closely intertwined, the exact correlations are not yet fully understood.

It is assumed that platelet dysfunction induced by the extracorporeal circuit system is one of the main reasons of bleeding [2]. Adequate platelet functioning includes plasmatic activation, platelet adhesion and aggregation. Von Willebrand factor (vWF) plays a crucial role therein. vWF is a glycoprotein that is produced in endothelial cells and megakaryocytes. It is stored in Weibel-Palade bodies and released as high molecular weight (HMW) molecules. A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (ADAMTS13) regulates the levels of vWF and cleaves it into smaller multimers, which circulate in a coiled and an inactive form. With high shear stress, as it occurs in vascular damage, vWF uncoils and exposes binding sites for the platelet surface receptor glycoprotein Ibα (GPIbα) which enhances platelet aggregation [11]. The longer vWF multimers are, the stronger the platelet aggregation to vascular damage. VWF also binds to exposed subendothelial collagen and hence adheres platelet clots to the endothelial walls [12–15]. Moreover, coagulation factor VIII is bound to vWF and thus protected [16].

In vitro research states that vWF only uncoils and turns into active polymers under high shear rates [11]. The A2 domain of the molecule seems to function as a shear sensor within the inactive vWF polymer and serves as a region for further cleavage by ADAMTS13 [14]. In vivo studies confirmed decreased polymer length in pathophysiological settings with increased shear stress, such as severe aortic stenosis [17], hypertrophic cardiomyopathy [16], or non-endothelized extracorporeal circulation circuits [9] like intraoperative cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO) [18], or left ventricular assist devices [19]. This quantitative loss of HMW molecules is also known as acquired von Willebrand syndrome (AVWS).

Objectives

Different mechanisms impact perioperative bleeding [20]. Platelet function can be affected by decreased platelet count and impaired activation of vWF. In vitro flow chamber models suggest evidence for enhancing platelet adhesion independent from platelet count, by addition of vWF to normal or supra-normal levels [21]. This benefit of adding vWF to improve platelet adhesion was especially seen in haemodilution (haematocrit <30%). This might result in a better haemostatic effect and a lower need for transfusions (RBC, FFP, platelets), especially in clinical conditions with low platelet counts and low vWF activity (e.g., after cardiac surgery with help of extracorporeal circuits). To the best of our knowledge, no investigations on the effect of platelet concentrates administered in combination with vWF complex concentrates in major bleeding have yet been performed. We hypothesize that the additional administration of vWF complex concentrate to platelet transfusion reduces blood loss and decreases needed blood transfusions (platelet concentrates, RBC, FFP). To address this, we compared cardiac surgery patients who got platelet concentrates to patients who got platelet concentrates and additional vWF complex concentrate.

Methods

Approval for this study was given by the responsible Ethics Committee of Northwestern and Central Switzerland (EKNZ, project ID: 2016-02081). This retrospective observational single-centre study was conducted at the Surgical Intensive Care Unit of the University Hospital Basel. Time frame of observation was between January 2011 and December 2016. Data were extracted from the local patient data management systems MetaVision® 5 and ISMed®).

Patients

All adult patients who underwent cardiac surgery at the University Hospital Basel between January 2011 and December 2016 and received one or more thrombocyte concentrates within 48 h postoperatively were included. Exclusion criteria were

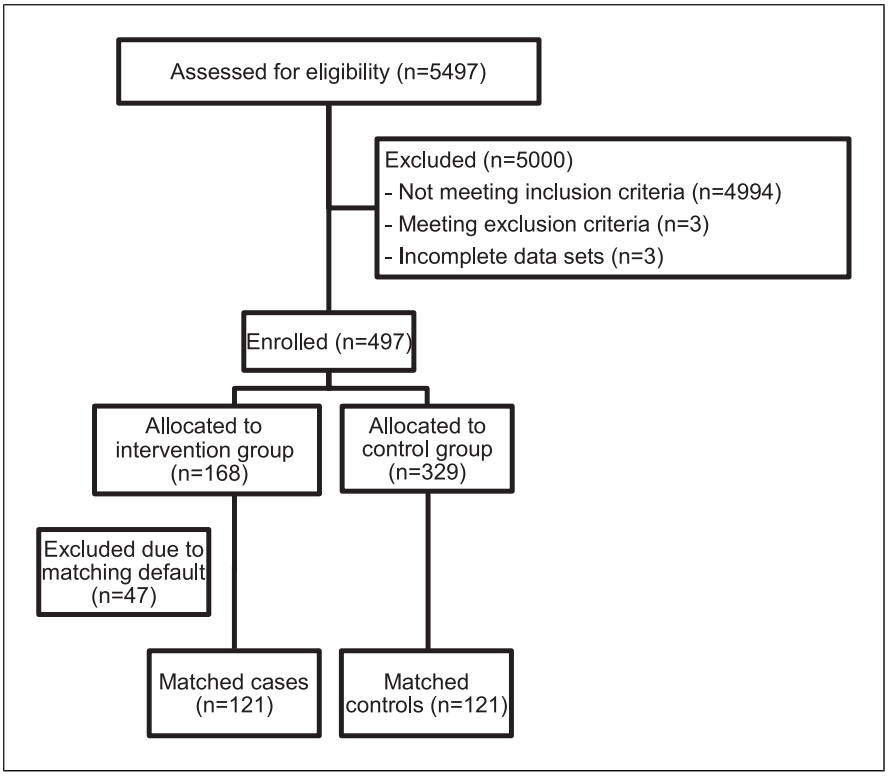

Fig. 1. Flow diagram.

documented general denial of research consent, innate bleeding disorders, or missing data affecting primary endpoint evaluation. All patients who received thrombocyte concentrates and vWF complex concentrates additionally were allocated to the intervention group; all patients who received thrombocyte concentrates only were assigned to the control group (shown in Fig. 1).

Intervention

Administration of vWF complex concentrates was based on the decision of the responsible attending physician. There was no existing protocol at the time of application. Official rule of thumb for application of vWF was severe blood loss (around 200 mL) in combination with low platelets (lower than 100 G/L). Therefore, dosage and time point of application (in relation to application of corresponding platelet concentrate or further platelet concentrates) differed. Used preparation was a vWF complex concentrate (Haemate®) containing vWF and coagulation factor VIII. A single dosage varied between 500/1,200E and 1,000/2,400E and was repeated in certain cases. Testing of vWF levels before administration was not feasible due to costly and lengthy analysis, and the need for a quick therapeutic reaction before results would have been obtainable.

Protocol

To observe effects of vWF complex concentrate transfusion on the defined endpoints, the two groups were compared according to the following aspects: amount of administered blood products (packs of platelets 200 mL, RBC 300 mL, and FFP 200 mL); fibrinogen and prothrombin complex concentrate (PCC; coagulation factors II, VII, IX, X); and measured blood loss (amount of chest tube drainage), each within the first (1–24 h) and second (25–48 h) day after surgery. Moreover, intensive care unit (ICU) and in-hospital length of stay, ICU and in-hospital mortality, and absolute difference in platelet counts before and after administration of treatment (platelet concentrates vs. platelet concentrates plus vWF complex concentrate) were investigated. To the best of our knowledge, transfusion packs are not of universally standardized size, which is why the actual pack volumes were stated.

To minimize bias, the following parameters were defined as potential confounders of perioperative bleeding: pH [22], international normalized ratio [9], partial thromboplastin time [9], haemoglobin and platelet count before transfusion [9], the amount of administered fluids [7], the amount of administered catecholamines, the use of other inotropic drugs, the amount of administered fibrinogen [7] and PCC [1], preoperative use of platelet aggregation inhibitors or anticoagulants [1], the medical condition leading to surgery [7], EuroSCORE II (European System for Cardiac Operative Risk Evaluation Score) that includes age [7], renal function [7] as well as type and urgency of surgery [7] among other factors [23], wherein a score of less than 4% equals a low and a score of 4–9% an intermediate risk. Lastly, for better comparability of the two groups, the SOFA score (Sequential Organ Failure Assessment) to quantify the patient's postoperative condition [24] was considered. Regarding all laboratory values "before intervention," we chose to consider the last obtainable value before application of platelets or platelets and vWF.

For description of the population, other variables were obtained: age, sex, priority of surgery (elective, urgent <48 h, emergency <12 h, salvage), type of surgery (coronary artery bypass grafting [CABG], valves, aortic dissection, combinations of these, other), medical issue leading to CABG surgery (angina pectoris, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction), parameters for SOFA score on day one and two after surgery (worst ratio of PaO2/FiO2; worst score on Glasgow Coma Scale [GCS]; worst mean arterial pressure; maximum dose of dobutamine,

epinephrine, or norepinephrine; highest count of bilirubin; lowest count of platelets; highest count of creatinine), body weight, total fluid amount and balance on first and second day after surgery, and use of vasoactive drugs other than epinephrine or norepinephrine.

Statistical Analysis

Descriptive data are presented as median with interquartile range. Due to significant differences in baseline parameters, nearest neighbour propensity score matching (1:1) was then performed (using R function "MatchIt" with default settings). Considered factors for propensity score matching were age, gender, EuroSCORE II, body weight, urgency, type of procedure, preoperatively used type of thrombocyte aggregation inhibitors or anticoagulation used preoperatively, and preoperative laboratory values (creatinine, pH, international normalized ratio, partial thromboplastin time, haemoglobin, thrombocyte count). Basic comparison of groups was done in *t* tests and χ^2 tests. For in-depth analysis, all surrogate variables were modelled (mixed-effect regression) using all available confounding variables and vWF application. In addition, a stepwise variable elimination based on Akaike information criterion was performed to obtain more generalized models. Missing data affecting the analysis of primary endpoints led to exclusion of patients. Level of significance was set at $p < 0.05$. All statistical analyses were performed using R Studio® Desktop, version 1.1.423.

Results

Description of Population

A total of 5,497 patients were screened, and 503 (9.2%) patients with perioperative platelet transfusion were included. Three had to be excluded due to missing data affecting primary endpoints and another three due to preexisting coagulation disorders (immune thrombocytopenic purpura, vWF disease type 1, severe myelodysplastic syndrome). Datasets of 497 patients were considered for analysis. Out of 497 patients, 168 (33.8%) received vWF complex concentrates. 47 patients had to be further excluded due to missing data, which led to 242 patients (121 in each group) that were considered for nearest neighbour propensity score matching. We were able to achieve an adequate balance of covariates in a matching ratio of 1:1 (reducing standard mean difference of propensity scores between groups by 64%).

Baseline characteristics before matching revealed relevant differences among groups (shown in Table 1). Intervention group showed a slight deviation towards higher urgency of procedure. Type of procedures was unequally distributed as well: there were significantly fewer valve surgeries in the intervention group than in the control group ($p = 0.02$) and also significantly ($p < 0.00$) more combined procedures (CABG and valve replacement and other procedure) in the intervention group than in the control group ($p < 0.00$). Since coronary heart disease (angina pectoris, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction) was more prevalent in the intervention group, the prevalence of use of dual antiplatelet therapy was also higher in intervention group. Information on distribution of surrogate parameters can be found in Table 2.

Primary Endpoints

Baseline analyses (*t* tests and χ^2 tests) revealed that amounts of platelet concentrates and FFP within the first 24 h were significantly higher in patients who received vWF ($p < 0.05$, shown in Tabel 3). Blood loss ($p = 0.06$) and thus the use of RBC concentrates ($p = 0.06$) was higher within the first 24 h. Within the second day, the same endpoints (need of blood products [platelets, FFP, RBC] and blood loss) did not show any significant differences.

In-depth analyses (mixed-model regression with stepwise variable elimination) substantiated significantly increased use of RBC concentrates, platelet concentrates, and FFP concentrates in vWF group within 24 h but not on the second day. Fibrinogen was significantly more frequently administered in vWF group. Use of PCC did not significantly differ among groups (shown in online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000530810). *p* values of baseline analyses (*t* tests and χ^2 tests of matched groups) are listed in Table 2–4 in column "Basic matching analysis" and *p* values of in-depth analyses (mixed-model regression with stepwise variable elimination) are listed in Table 2–4 in column "Modelled matching analysis."

Secondary Endpoints

In length of stay at ICU and in hospital, application of vWF did not show a significant effect (shown in Table 4). It also had no additional effect on in-hospital mortality. Rise in platelet count after administration of thrombocyte concentrates (plus vWF in intervention group) was equally adequate in both groups.

Other Surrogate Markers

Urine output was significantly lower in vWF group on day one and two ($p = 0.05$ and $p = 0.01$, respectively) in baseline analyses and remained significant in in-depth analyses, despite the higher fluid input, which was also reflected in a higher fluid balance on day 2. Use of catecholamines, particularly norepinephrine, was significantly higher in vWF group within first day and tended to stay elevated on second day. Looking at subsequent (within timespan of study) revision surgery, there was no significant effect with application of vWF.

Discussion

This retrospective study on the impact of additional administration of vWF to platelet concentrates showed no reduction in perioperative blood loss, need for

Table 1. Baseline characteristics

	Total (n = 497)		With vWF (intervention group)				Without vWF (control group)			
			unmatched (n = 168)		matched (n = 121)		unmatched (n = 329)		matched (n = 121)	
	median	IQR	median	IQR	median	IQR	median	IQR	median	IQR
Age, years	68	60–75	68	59–74	69	60–76	68	60–75	67	61–76
EuroSCORE II	4	2–13	4	2–13	4	2–13	4	2–13	5	2–16
Body weight	76	68–85	78	69–87	78	70–87	75	68–85	76	69–87
	N	%	*n*	%	*n*	%	*n*	%	*n*	%
Female sex	113	22.9	35	20.8	25	20.7	78	23.7	25	20.7
Aspirin	305	61.4	112	66.7	80	66.1	193	58.7	84	69.4
DAPT	125	25.1	55	32.7	40	33.1	70	21.3	37	30.6
Anticoagulation	115	23.1	38	22.6	31	25.6	77	23.4	32	26.5
Urgency	*N*	%	*n*	%	*n*	%	*n*	%	*n*	%
NA	3	0.6	1	0.6	1	0.8	2	0.6	0	0
elective	273	54.9	90	53.6	66	54.6	183	55.6	57	47.1
Urgent (<48 h)	44	8.9	11	6.5	10	8.3	33	10.0	13	10.7
Very urgent (<24 h)	42	8.5	16	9.5	12	9.9	26	7.9	15	12.4
Emergent (<12 h)	97	19.5	35	20.8	25	20.7	62	18.8	25	20.7
Salvage	38	7.6	15	8.9	7	5.8	23	7.0	11	9.1
Procedure group	*N*	%	*n*	%	*n*	%	*n*	%	*n*	%
CABG only	159	32.0	56	33.3	39	32.3	103	31.3	45	37.2
Valve(s) and other	85	17.1	23	13.7	17	14.1	62	18.8	17	14.1
Valve(s) only	74	14.9	16	9.5	13	10.7	58	17.6	12	9.9
CABG and valve(s)	69	13.9	26	15.5	20	16.5	43	13.1	19	15.7
CABG and valve(s) and other	52	10.5	28	16.7	21	17.4	24	7.3	18	14.9
Other	58	11.7	9	5.4	11	9.1	49	14.9	10	8.3
Reason for surgery	*N*	%	*n*	%	*n*	%	*n*	%	*n*	%
Angina pectoris	77	15.5	29	17.3	21	17.4	48	14.6	21	17.4
STEMI	42	8.5	19	11.3	12	9.9	23	7.0	11	9.1
NSTEMI	97	19.5	33	19.6	24	19.8	64	19.5	30	24.8
Dissection of aorta	59	11.9	22	13.1	14	11.6	37	11.2	15	12.4
Aortic prosthetics	13	2.6	3	1.8	0	0	10	3.0	2	1.7
Valve vitium	126	25.4	33	19.6	27	22.3	93	28.3	27	22.3
Combination	62	12.5	25	14.9	19	15.7	37	11.2	15	12.4
Other	21	4.2	4	2.4	4	3.3	17	5.2	0	0

EuroSCORE II, European System for Cardiac Operative Risk Evaluation Score II; DAPT, dual antiplatelet therapy; NA, not applicable; CABG, coronary artery bypass graft; STEMI, ST-segment elevating myocardial infarction; NSTEMI, non-ST-segment elevating myocardial infarction; IQR, interquartile range.

transfusions (platelets, RBC, FFP), length of stay (ICU and hospital), and mortality (ICU and hospital). Quite the contrary, vWF group received significantly more blood products (platelets, RBC, FFP) in the first 24 h after surgery and had higher blood loss at the same time. There was no more remaining difference on day two, which could imply a beneficial late effect of vWF.

Higher blood loss in the intervention group could be explained by an indication bias: improvement of haemostasis based on clinical decision-making of the responsible attending physician as there was no applicable guideline (neither official nor in-house). Administration of vWF improved platelet function mostly in cases of severe bleeding. This assumption is supported by the following: the intervention group tended to be older, underwent more complex procedures, had higher demand of fibrinogen and PCC, suggesting more extensive coagulopathy, catecholamines, and fluids and tended to be more often surgically revised, suggesting increased bleeding rates. Astonishingly, platelet counts before administration of vWF were higher in this

Table 2. Overview of confounders and surrogate markers (for details, see online suppl. Table 3)

	With vWF (intervention group)		Without vWF (control group)		Basic matching analysis	Modelled matching analysis
	matched (n = 121)		matched (n = 121)			
	median	IQR	median	IQR	p value	p value
Day 1 (1–24 h)						
SOFA score	8	6–10	8	6–10	0.96	n/a
Fluids, mL	12,192	9,245–17,105	12,739	9,769–16,660	0.94	n/a
Urine, mL	2,505	1,960–3,150	2,870	2,060–3,965	0.05	0.02
Fluid balance, mL	7,086	5,110–12,161	8,148	5,845–10,960	0.84	0.98
Epinephrine, µg/min	3	0.1–7	3	0–8	0.84	n/a
Norepinephrine, µg/min	7	3–12	5	2–9	0.03	<0.00
Catecholamines total, µg/min	11	5–19	8	4–15	0.10	<0.00
	N	%	*N*	%		
Vasoactive drugs					0.19	n/a
None	58	47.9	49	40.5	n/a	n/a
Milrinone	31	25.6	46	38.0	n/a	n/a
Dobutamine	19	15.7	11	9.1	n/a	n/a
Nitroprusside	12	9.9	13	10.7	n/a	n/a
Levosimendan	1	0.8	2	1.7	n/a	n/a
	median	IQR	median	IQR		
Day 2 (25–48 h)						
SOFA score	6	4–8	6	4–9	0.97	n/a
Fluids, mL	2,366	1,398–3,756	2,131	1,595–2,971	0.22	n/a
Urine, mL	1,822	1,265–2,400	2,126	1,440–3,155	0.01	0.01
Fluid balance, mL	−357	−1,117–1,222	−733	−1,641–515	0.02	0.01
Epinephrine, µg/min	0	0–0	0	0–2	0.48	n/a
Norepinephrine, µg/min	0	0–6	0	0–4	0.12	n/a
Catecholamines total, µg/min	1	0–8	0.1	0–6	0.47	n/a
	N	%	*N*	%		
Vasoactive drugs					0.07	n/a
None	58	48.0	75	62.0	n/a	n/a
Milrinone	31	25.6	29	24.0	n/a	n/a
Dobutamine	19	15.7	6	5.0	n/a	n/a
Nitroprusside	12	9.9	10	8.3	n/a	n/a
Levosimendan	1	0.8	1	0.8	n/a	n/a
	median	IQR	median	IQR		
Other						
pH before intervention	7.34	7.27–7.37	7.33	7.28–7.36	0.84	n/a
INR before intervention	1.4	1.3–1.6	1.5	1.3–1.7	0.70	n/a
PTT before intervention, s	38	32–49	40	34–54	0.61	n/a
Hb before intervention, g/L	86	78–95	87	77–98	0.83	n/a
Tc before intervention, 10^9/L	110	75–156	105	71–146	0.91	n/a
	N	%	*N*	%		
Surgical revision	39	32.2	31	25.6	0.32	0.93
ECMO	5	4.1	5	4.1	>0.99	n/a

SOFA score, Sequential Organ Failure Assessment score; INR, international normalized ratio; PTT, partial thromboplastin time; Hb, haemoglobin count; Tc, thrombocyte count; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

Table 3. Overview of primary endpoints (for details, see online suppl. Table 1)

	With vWF (intervention group)		Without vWF (control group)		Basic matching analysis	Modelled matching analysis
	matched (n = 121)		matched (n = 121)			
	median	IQR	median	IQR	p value	p value
Thrombocyte concentrates d1, mL	400	200–600	400	200–400	0.02	0.01
Erythrocyte concentrates d1, mL	1,200	300–2,100	900	300–1,500	0.06	<0.00
FFP d1, mL	400	0–1,200	0	0–800	0.03	<0.00
Blood loss from chest drainages d1, mL	1,450	1,000–2,050	1,300	910–1,900	0.06	0.03
Thrombocyte concentrates d2, mL	0	0–0	0	0–0	0.79	n/a
Erythrocyte concentrates d2, mL	0	0–300	0	0–300	>0.99	0.85
FFP d2, mL	0	0–0	0	0–0	0.15	n/a
Blood loss from chest drainages d2, mL	200	0–400	220	0–500	0.26	0.23
Fibrinogen, g	5	2–8	4	0–6	<0.00	<0.00
PCC (IE)	600	0–1,800	600	0–1,200	0.22	0.15

d1, day 1 (1–24 h); d2, day 2 (25–48 h); PCC, prothrombin complex concentrate (coagulation factors II, VII, IX, X); IQR, interquartile range.

Table 4. Overview of secondary endpoints (for details, see online suppl. Table 2)

	With vWF (intervention group)		Without vWF (control group)		Basic matching analysis	Modelled matching analysis
	matched (n = 121)		matched (n = 121)			
	median	IQR	median	IQR	p value	p value
Length of stay on ICU, d	4	2–8	4	2–7	0.83	0.50
Length of stay in hospital, d	11	8–22	13	9–18	0.68	0.31
Delta of platelet count after-before treatment, G/L	26	−4–45	23	4–46	0.92	0.98
	n	%	n	%		
Death in ICU or in hospital	15	12.4	12	9.9	0.68	0.74

IQR, interquartile range.

group, especially in unmatched group (see online suppl. Table 3). This could also be an indication of uncontrolled bleeding situations, as laboratory counts can lag at least 30 min. Lower urine output in vWF group could also indicate a more severe bleeding situation due to renal hypoperfusion, as blood creatinine levels did not differ significantly between groups. Distribution of performed surgeries tended to be more complex in intervention group, which would partially explain higher blood loss as well. Valve surgeries were significantly lower in the intervention group. Use of dual antiplatelet therapy was higher in the intervention group as well, which supports the theory of more severe bleedings in the intervention group. Furthermore, the time point of administration of vWF complex concentrates has not been observed in timely relation to application of blood products, volume resuscitation, and blood loss. This could have limited a possible benefit of our intervention as well. Indication and time bias could only be accounted for in a standardized, randomized trial.

Additional administration of vWF to platelet concentrates in regard to bleeding and need for transfusion has not yet been studied. Previous literature is scarce. There are several methods and parameters for analysis of platelet function and vWF levels; thus, diagnostic work-up, especially in acute perioperative setting, remains difficult [25] and is not recommended by default [26]. Therapy of acute bleeding in cardiovascular surgery is mainly about substitution of vWF/FVIII and antifibrinolytics [27]. It has been suggested that preoperative correction of impaired primary haemostasis resulted in a reduced need for

blood transfusion [28]. It was also described that severity of AVWS varies depending on underlying causes, which is therefore sometimes difficult to analyse in detail. HMW multimers of vWF in patients on ECMO are generally more destroyed than in patients with aortic valve stenosis [29]. In patients undergoing valve replacement due to aortic valve stenosis, no higher perioperative blood loss in patients with AVWS could be found [30]. In a recent small trial (n = 10), bleeding patients on ECMO, diagnosed with AVWS and treated with vWF, were observed. Bleeding ceased within 1–4 days in all patients [31]. Three out of 10 patients showed thrombotic events that could be related to vWF administration. Decrease or rather cessation of bleeding within a few days could be the natural course as bleeding significantly decreased on day two in both our groups. Our results do not allow for clinical or even therapeutical implications and only mark the very first step in what needs to be further pursued. Although vWF concentrate is an expensive blood product, we hope to decrease overall costs by reducing need for other costly products and interventions. This could be globally interesting for different healthcare sectors, especially those not supplying cryoprecipitate components.

Limitations

This study is clearly limited by its retrospective, non-randomized, non-standardized design. Sample size was based upon obtainable variables and not on power calculation beforehand. Administration of vWF concentrate happened upon clinical evaluation of numerous different clinicians and did not follow a strict protocol. Although statistical correction for different baseline characteristics and multiple confounders was attempted, we could not completely emend this limitation. Time frame was 6 years, in which therapy regimes changed. For instance, during the first period of observation, colloid fluids have been used more broadly. It is known that vWF activity is lower in colloid or hypertonic fluids [32]. Furthermore, there are other known factors that can impair vWF functioning and hence confound our endpoints. In this study, we did not include time on cardiopulmonary bypass [1] and hypothermia [1, 2], AB0 blood group and thromboelastography, or administration of desmopressin. Desmopressin is standard in therapy of VWS type 1 and enhances the release of HMW multimers of vWF [33]. Efficacy in VWS type 2 is controversial. Desmopressin is rarely used in cardiac surgery patients on our ICU and has thus not been included in our study. Also, thromboelastography was not routinely used on our ICU, so we did not include it in analysis. AB0 blood groups affect primary haemostasis as well. VWF plasma levels were reported to be approximately 25% lower in blood group 0 than in blood groups A, B, and AB [34]. A recent study showed an association of blood group 0 with more severe bleeding, independent of vWF and FVIII [35]. Blood groups were not included in the analysis. Due to preserved capacity to genetically produce, release, and increase vWF in situations of stress, the pre-existing difference is likely to be masked. Hypothermia was induced in operating room and did not timely coincide with application of vWF, which is why we did not include it in our analysis. Time on cardiopulmonary bypass was not included in analysis because we assumed that the difference in time would be explained by more complex surgery or more complications which are all parameters we included. Furthermore, antifibrinolytic agents (tranexamic acid or very rarely aprotinin) were applicated by default during surgery, which is why we did not include this variable in our analysis either. From pharmacological point of view, applicated dosage of 10 mg/kg body weight followed by 5 mg/kg body weight/hour is adequate to exert an antifibrinolytic activity for at least 24 h.

Moreover, time relations between administration of vWF and platelets were not considered. Supposedly, there needs to be a minimal lead time of vWF to platelets to unfold full effect. Inversely, administrations have to be within a certain time frame as half-life of vWF is approximately 16 h [36]. Underlying mechanisms are subject to further research. Furthermore, dosage was not standardized. In persuasion of our hypothesis, accounting for these confounders will be pivotal.

These retrospective findings might arise from unstandardized indications for vWF and time of drug administration. This suggests a more standardized approach, e.g., in form of a prospective randomized controlled trial, as, to the best of our knowledge, this is the first study concentrating on this therapeutic approach. This retrospective study served to obtain background information to plan a prospective randomized controlled trial.

Conclusion

This retrospective, non-randomized study could not clearly show a benefit in administration of vWF in addition to platelet concentrates regarding perioperative blood loss within 48 h and transfusion rates (platelets, RBC, FFP) in patients after cardiac surgery. However, platelet concentrates and administered vWF were not given in a standardized time frame, which could have impaired full effect. Moreover, the decision to add vWF to platelets could be based on excessive bleeding in most cases. Adding vWF concentrate could have curtailed even greater blood loss. Thus, the data used by the authors do not allow the authors' hypothesis to be adequately tested. Recruitment for our prospective, randomized, controlled trial has recently started (clinicaltrials.gov identifier NCT04555785) and may help clarify the results of this retrospective cohort study.

Statement of Ethics

Ethics approval was given by the Ethics Committee of Northwestern and Central Switzerland (EKNZ, project ID: 2016-02081). The study has been granted an exemption from written informed consent due to being an observational trial only. This was approved by the EKNZ.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Alexa Hollinger, Katrin Ledergerber, and Martin Siegemund designed the study. Katrin Ledergerber and Sibylle Zimmermann collected all data. Katrin Ledergerber and Atanas Todorov performed statistical analysis. Alexa Hollinger and Katrin Ledergerber wrote the primary draft of this article. All authors contributed to revision and approved the final version of this manuscript.

Data Availability Statement

The datasets used and analysed during the current study are available from the corresponding author upon request. The clinical data are stored electronically in the intensive care clinical information system software (MetaVision, iMDsoft®) provided in the intensive care unit of the University Hospital Basel.

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