Cytosorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding

Kambiz Hassan, MD, Jochen Kannmacher, MD, Peter Wohlmuth, PhD, Ulrich Budde, MD, Michael Schmoeckel, MD, and Stephan Geidel, MD

Department of Cardiac Surgery, Asklepios Klinik St. Georg, Hamburg; Department of Anesthesiology and Intensive Care Medicine, Asklepios Klinik St. Georg, Hamburg; Asklepios ProResearch Institute, Hamburg; and Section of Hemostaseology, Medilys Laborgesellschaft, Hamburg, Germany

Background. **The purpose of this study was to analyze the results of Cytosorb (CytoSorbents, Monmouth Junction, NJ) adsorption during emergency open heart operations in patients at high risk of bleeding due to treatment with coagulation-active substances.**

Methods. **We investigated 55 consecutive patients (median age 70 years; interquartile range: 60 to 77) who underwent emergency cardiac surgery at our institution between June 2016 and June 2018. All patients were receiving therapy with either ticagrelor (n = 43) or rivaroxaban (n = 12). In 39 of 55 cases, we routinely installed standardized Cytosorb adsorption into the heart-lung machine. Bleeding complications during and after surgery were analyzed in detail and compared with 16 patients without adsorption.**

Results. **In the Cytosorb adsorption group, no rethoracotomies had to be performed. Drainage volumes in 24 hours were only 350 mL (interquartile range: 300 to 450 mL) after ticagrelor administration and 390 mL (interquartile range: 310 to 430 mL) after rivaroxaban therapy. In the majority of patients, transfusions of blood products were not needed. Compared with that group, among the group of patients without adsorption, multiple bleeding complications occurred. These were associated with longer total operation ($p = 0.0042$), higher drainage volumes ($p = 0.0037$), more transfusions of red blood cells ($p = 0.0119$) and platelets ($p = 0.0475$), a significantly higher rethoracotomy rate ($p = 0.0003$), significantly prolonged stay in the intensive care unit ($p = 0.0141$), and a longer hospital stay ($p = 0.0244$).**

Conclusions. **The intraoperative use of Cytosorb adsorption of ticagrelor and rivaroxaban in emergency open heart operations is reported for the first time. The data show that the strategy is safe and is an effective method to reduce bleeding complications. We recommend the use for safety in patients with ticagrelor or rivaroxaban undergoing emergency cardiac surgery.**

(Ann Thorac Surg 2019;108:45–51)

Excessive bleeding under the coagulation-active substance rivaroxaban or the antiplatelet drug ticagrelor impairs the outcome of open heart surgery [1–3]. The aim of the present analysis was to assess the results of sorbent hemadsorption using the Cytosorb system (CytoSorbents, Monmouth Junction, NJ) during emergency cardiac operations in patients at high risk of bleeding due to treatment with ticagrelor or rivaroxaban.

Patients who present for emergency cardiac surgery have increasingly been treated with these drugs for the following reasons: antiplatelet treatment with ticagrelor is a recommended therapy for coronary artery disease but it should be discontinued whenever possible before elective coronary artery bypass graft surgery (CABG) to reduce bleeding complications [4, 5]; conversely, rivaroxaban—which belongs to the group of novel oral anticoagulants—is frequently being given to prevent thromboembolic events, for example, in patients with concomitant atrial fibrillation. Interestingly, the risk of bleeding complications under coagulation-active substance therapy in emergency open heart operations has not previously been investigated sufficiently in large patient cohorts.

Recently, however, removal of coagulation-active substances has been demonstrated in vitro with the use of a cytokine adsorber [6, 7]. Currently, the extracorporeal cytokine adsorber Cytosorb is commonly given for patients with severe infections and sepsis. In our investigation, we used sorbent hemadsorption with Cytosorb during emergency cardiac operations in an attempt to reduce bleeding complications. The intraoperative use of Cytosorb adsorption in patients with ticagrelor or rivaroxaban treatment undergoing emergency open heart operations is reported for the first time. The analysis summarizes the experience of a single center with a high case load of emergency cardiac operations.

Accepted for publication Dec 10, 2018.

Address correspondence to Dr Hassan, Department of Cardiac Surgery, Asklepios Klinik St. Georg, Lohmuehlenstr 5, Hamburg 20099, Germany; email: k.hassan@asklepios.com.

0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2018.12.032

Patients and Methods

The Hamburg General Medical Council Ethics Committee approved the protocol for this study.

We investigated 55 of 217 (25.3%) consecutive patients (median age 70 years; interquartile range [IQR]: 60 to 77), who underwent emergency open heart operations at our institution between June 2016 and June 2018. In contrast to the other 162 cases, these 55 patients were receiving therapy with either ticagrelor (n = 43) or rivaroxaban (n = 12). The calculated risk, using the European System for Cardiac Operative Risk Evaluation II, was 3.23% (IQR: 2.25% to 4.49%). In 39 of 55 cases, we routinely installed standardized Cytosorb adsorption (CA) into the heart-lung-machine (CA group), treated since June 23, 2017. Bleeding complications during and after surgery were analyzed in detail and retrospectively compared with 16 patients without adsorption (WA group), treated between June 2016 and June 2017. For this retrospective anonymous study (according to the valid legal situation in Germany), no specific signed declaration of consent was necessary. There was no general change of treatment regimen in the observation period beside Cytosorb adsorption. Furthermore, comparison of demographic data demonstrated no relevant difference between groups.

The Cytosorb adsorpter was included in the cardiopulmonary bypass (CPB) circuit between the oxygenator and the venous reservoir (Fig 1). The filter is made of biocompatible porous polymer beads able to remove substances from whole blood based on pore capture and surface adsorption. Cytosorb is CE Mark approved under the Medical Devices Directive (ISO 10993 biocompatible, manufactured in the United States under ISO 13485 certification). Safety of the method was defined as follows: use of an approved and tested medical device with freedom from unacceptable risks. Furthermore, the handling of installation by trained staff should be straightforward and guarantee optimal flow conditions. The dose of heparin should not be reduced with such drugs, because incomplete inhibition of thrombin may lead to secondary platelet activation and consumption [8].

Before surgery, we noted the functional status of each patient using the New York Heart Association criteria and all relevant comorbidities. Our exclusion criteria for the study were ongoing resuscitation or severe sepsis. No other level of selection was performed. None of the patients was receiving clopidogrel, 6 patients were receiving acetylsalicylic acid. Demographic data are presented in Table 1.

Outcome variables assessed were the incidence of major bleeding complications, blood or blood products applied, and operation-related times. We further analyzed the 24 hours drainage volume, days in the intensive care unit (ICU), total length of stay, and cardiac/noncardiac deaths within 30 days. Rates, severity, and management of periprocedural bleeding complications were recorded in detail. Our surgical strategy for rethoracotomies was high drainage volume without tendency for improvement (more than 1,000 mL over 6 hours) or a suspicion of arterial bleeding. In our center, protocols recommend transfusion of red blood cells with hemoglobin less than 6 g/dL independent of individual compensability, and hemoglobin of 6 g/dL or more with symptoms of anemia or ongoing bleeding. Platelet transfusion is generally given to patients with bleeding and documented or suspected platelet dysfunction or low

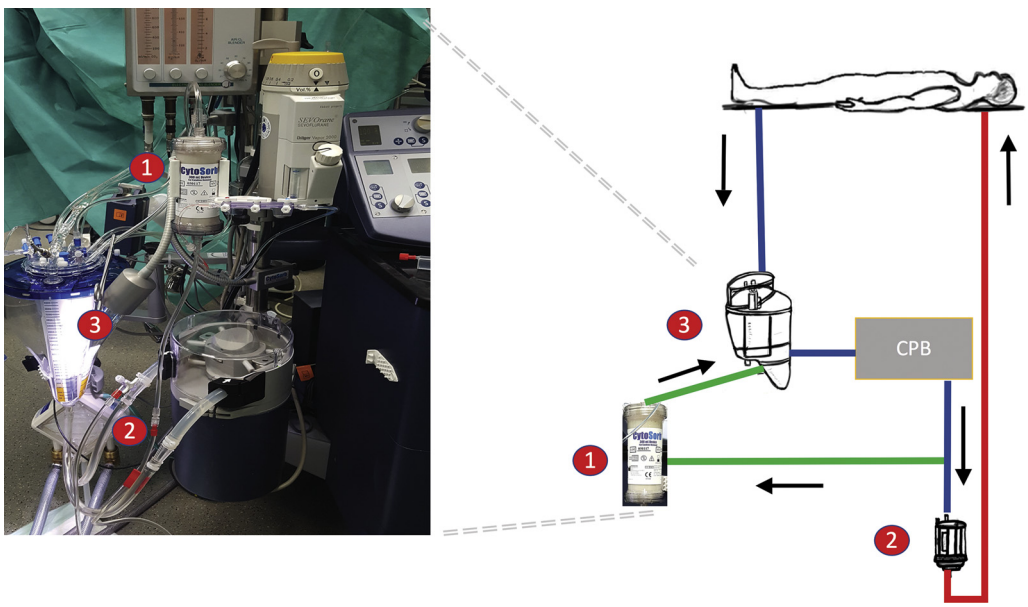

Fig 1. The Cytosorb adsorber (CytoSorbents, Monmouth Junction, NJ) (1) is included in the cardiopulmonary bypass (CPB) circuit of the heart-lung machine between the oxygenator (2) and the venous reservoir (3). The adsorber is made of biocompatible porous polymer beads able to remove substances from whole blood based on pore capture and surface adsorption, and needs a blood flow rate of approximately 100 to 700 mL/min for optimal filter performance.

Table 1. Patient Baseline Data

Variables	CA Group		WA Group		*p* Value
	Ticagrelor (n = 32)	Rivaroxaban (n = 7)	Ticagrelor (n = 11)	Rivaroxaban (n = 5)	
Demographics					
Age, years	66 (55–77)	77 (76–80)	69 (60–73)	72 (71–74)	0.3310
Female	6 (18.8)	4 (57.1)	2 (18.2)	1 (20)	0.2163
Body mass index, kg/m^2	27 (25–29)	26 (24–29)	27 (26–29)	27 (25–27)	0.7935
NYHA class					
II	18 (56.3)	4 (57.1)	4 (36.4)	3 (60)	NA
III	12 (37.5)	3 (42.9)	7 (63.6)	2 (40)	NA
IV	2 (6.2)	0 (0)	0 (0)	0 (0)	NA
Comorbidity					
Hypertension	29 (90.6)	6 (85.7)	11 (100)	5 (100)	0.9971
Peripheral vascular disease	9 (28.1)	2 (28.6)	2 (18.2)	2 (40)	0.6800
COPD	12 (37.5)	4 (57.1)	5 (45.5)	3 (60)	0.9212
Renal impairment					0.9517
Normal, cc >85 mL/h	9 (28.1)	0 (0)	3 (27.3)	0 (0)	
Moderate, cc >50, <85 mL/h	13 (40.6)	5 (71.4)	6 (54.5)	4 (80)	
Severe, cc <50 mL/h	10 (31.3)	2 (28.6)	2 (18.2)	1 (20)	
LVEF					0.7314
Good >50%	15 (46.9)	4 (57.1)	4 (36.4)	2 (40)	
Moderate 31%–50%	15 (46.9)	1 (14.3)	7 (63.6)	2 (40)	
Poor 21%–30%	2 (6.2)	2 (28.6)	0 (0)	1 (20)	
Pathology of heart disease					
Coronary artery disease	32 (100)	7 (100)	11 (100)	5 (100)	NA
Aortic valve disease	3 (9.4)	0 (0)	0 (0)	0 (0)	NA
Mitral valve disease	1 (3.1)	0 (0)	1 (9.1)	0 (0)	NA
Aortic dissection	1 (3.1)	0 (0)	0 (0)	0 (0)	NA
Atrial fibrillation	4 (12.5)	7 (100)	2 (18.2)	5 (100)	NA
EuroSCORE II	3.1 (1.2–5.1)	3.9 (2.9–9.1)	3.1 (2.9–3.6)	3.3 (3.3–4.2)	0.5602
Emergency	32 (100)	7 (100)	11 (100)	5 (100)	NA

Values are median (interquartile range) or n (%).

CA = Cytosorb adsorption; cc = creatinine clearance; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NA = not available; NYHA = New York Heart Association; WA = without adsorption.

platelet count. Our common standardized surgical strategies and procedural details have been described in detail elsewhere [9].

In 8 CA group patients, we measured the drug effect before and after CPB. Blood was taken by the anesthesiologist before and after the operation in the operating room. That was done for ticagrelor patients by Multiplate (DiaPharma, West Chester, OH) analysis (n = 5) and rivaroxaban patients by anti-factor Xa assay (n = 3). The Multiplate analyzer offers the possibility of rapid determination of platelet function. For the purinergic receptor P2Y, G protein–coupled 12 ($P2Y_{12}$) receptor, the agonist adenosine diphosphate test was performed. Clinical practice guidelines suggest that platelet function testing is necessary for patients who are being treated with antiplatelet therapies and are undergoing surgery with a high bleeding risk [10]. A high risk of major bleeding in CABG patients undergoing a cutoff of less than 30 in the adenosine diphosphate test has been shown by other investigators [11]. Cutoff values were established in a Hirudin-treated blood sample.

Patients who underwent CABG received acetylsalicylic acid postoperatively. For all other patients who needed anticoagulation therapy to protect them from embolism, heparin was given under the control of partial thromboplastin time. Heparin was also administered after removal of tubes in patients with nonvalvular atrial fibrillation or other novel oral anticoagulant indications. Patients with mechanical valves or contraindications for novel oral anticoagulants were given coumadin.

The aim of this study was to examine effects of Cytosorb adsorption on patients compared with patients without adsorption, and rivaroxaban versus ticagrelor on baseline, procedural, and outcome data. Data were summarized as means and SDs or medians as well as 25th and 75th percentiles (interquartile range [IQR]) in the case of continuous data. Discrete and categoric data were shown as frequencies and percentages. Categoric

Table 2. Details of Surgery and Early Postoperative Data

Variables	CA Group		WA Group		*p* Value
	Ticagrelor (n = 32)	Rivaroxaban (n = 7)	Ticagrelor (n = 11)	Rivaroxaban (n = 5)	
Surgical procedure					
CABG[a]	27 (84.4)	7 (100)	10 (90.9)	5 (100)	NA
CABG+AVR	3 (9.4)	0 (0)	0 (0)	0 (0)	NA
CABG+MVP	1 (3.1)	0 (0)	1 (9.1)	0 (0)	NA
Aortic dissection treatment	1 (3.1)	0 (0)	0 (0)	0 (0)	NA
Concomitant surgery					
Standardized AF ablation	3 (9.4)	3 (42.9)	1 (9.1)	2 (40)	NA
LAA occlusion	2 (6.3)	1 (14.3)	1 (9.1)	2 (40)	NA
Time-related outcomes					
CPB time, minutes	115 ± 39	80 ± 15	108 ± 34	97 ± 22	0.4119
Cross-clamp time, minutes	77 ± 31	81 ± 47	64 ± 26	70 ± 10	0.5373
Procedure duration, minutes	288 ± 63	184 ± 97	353 ± 84	309 ± 50	0.0042
Blood product transfusion, units					
Red blood cells					0.0119
0	25 (78.1)	6 (85.7)	6 (54.5)	0 (0)	
1	3 (9.4)	1 (14.3)	1 (9.1)	2 (40)	
2	1 (3. 1)	0 (0)	3 (27.3)	2 (40)	
>3	3 (9.4)	0 (0)	1 (9.1)	1 (20)	
Platelets					0.0475
0	21 (65.6)	5 (71.4)	0 (0)	0 (0)	
1	10 (31.3)	2 (28.6)	6 (54.5)	3 (60)	
2	1 (3.1)	0 (0)	4 (36.4)	2 (40)	
3	0 (0)	0 (0)	1 (9.1)	0 (0)	
Desmopressin treated	21 (65.6)	4 (57.1)	11 (100)	5 (100)	0.4780
Rethoracotomy rate	0 (0)	0 (0)	4 (36.4)	2 (40)	0.0003
Drainage volume in 24 hours	350 (300–450)	390 (310–430)	890 (630–1,025)	600 (590–1,000)	0.0037
Intensive care, days	2 (1–3)	2 (2–3)	3 (2–4)	6 (5–6)	0.0141
Total length of stay, days	11 (9–12)	11 (10–13)	14 (10–16)	18 (18–20)	0.0244

[a] Coronary artery bypass graft surgery (CABG) in 49 of 55 (89.1%); in the CABG procedure, both thoracic arteries were used in 31 patients (56.4%) for complete arterial revascularizations.

Values are median (interquartile range), n (%), or mean ± SD.

AF = atrial fibrillation; AVR = aortic valve replacement; CA = Cytosorb adsorption; CPB = cardiopulmonary bypass; LAA = left atrial appendage; MVP = mitral valve replacement or repair; NA = not available; WA = without adsorption.

data are presented as number (percent). The models were composed of two-factor variables and their interactions. For continuous variables, we used an analysis of variance setting; for count data, we investigated a Poisson model; and for dichotomous data, we applied a logistic regression model. The column filter presents *p* values comparing the mean proportions of the variables in the column Label between adsorption/no adsorption. An analogue procedure was carried out for the column group (rivaroxaban versus ticagrelor) and the variables in the column Label. The last column presents *p* values for the interaction effects. It addresses the question of whether there was a difference in adsorption depending on the group (rivaroxaban versus ticagrelor). No variable selections were performed; effects of the response were expressed as parameter estimates and *p* values. Comparisons among groups for rethoracotomy were also calculated with Fisher's exact test. All *p* values were two-sided, and *p* less than 0.05 was considered significant. All calculations were performed with R version 3.3.2 (R Core Team 2016, R Foundation for Statistical Computing, Vienna, Austria).

Results

Emergency procedures included CABG in 49 patients (89.1%), 5 patients (9.1%) underwent combined CABG and valve surgery, and 1 patient (1.8%) had replacement of the ascending aorta; all relevant details of surgery and early postoperative data are outlined in Table 2. All 55 patients underwent operation on CPB. Mean cross-clamp time was 78 ± 33 minutes in the CA group patients and 66 ± 22 minutes in the WA group ($p = 0.5373$). Total operation time was longer in the WA group (269 ± 80 minutes versus 339 ± 76 minutes, $p = 0.0042$). The mean CPB time

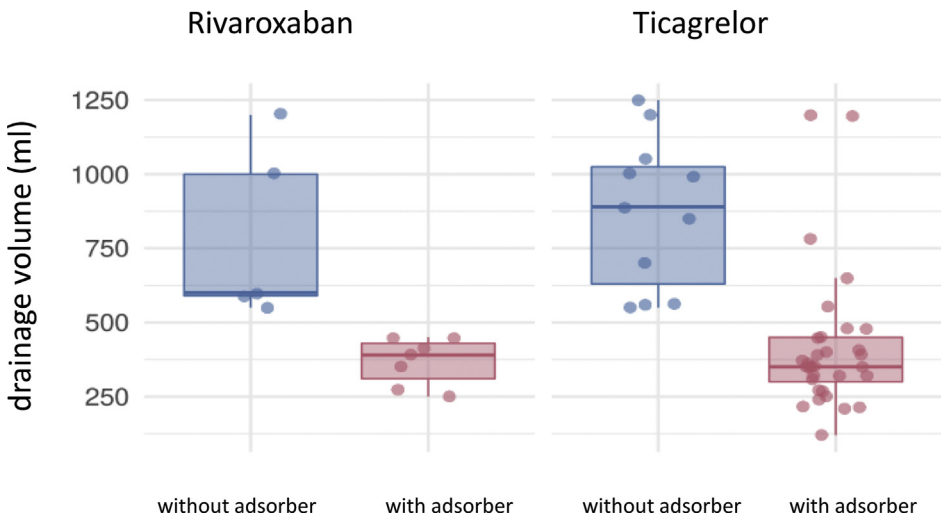

Fig 2. Drainage volume over 24 hours in patients treated with ticagrelor or rivaroxaban, with or without an intraoperative adsorber.

was 109 ± 38 minutes in CA group patients and 104 ± 30 minutes in WA group patients ($p = 0.4119$).

Safety of the Cytosorb adsorption method could be guaranteed in all cases. The handling of installation had been straightforward, and optimal flow conditions could be achieved.

Generally, the use of adsorption influenced the postoperative 24-hour drainage volume ($p = 0.0037$). Mean drainage volume over 24 hours was only 350 mL (IQR: 300 to 450 mL) after ticagrelor in the adsorber group compared with 890 mL (IQR: 630 to 1,025 mL) in patients treated with ticagrelor and without adsorber (Fig 2). After rivaroxaban therapy it was 390 mL (IQR: 310 to 430 mL), and without adsorber, 600 mL (IQR: 590 to 1,000 mL).

Compared with the CA group, the WA group patients had multiple bleeding complications. In the majority of patients of the CA group, transfusions of blood products were not needed. The difference in transfusion of red blood cells between groups was $p = 0.0119$, and for transfusion of platelet between groups, it was $p = 0.0475$ (Table 2). After ticagrelor administration and intraoperative adsorption, in 21 cases (65.6%) transfusions of platelets were not needed, and in 25 cases (78.1%) transfusions of red blood cells were not needed. In contrast, all patients without adsorption and prior ticagrelor therapy had transfusions of platelets. Five of 11 patients without adsorption and prior ticagrelor therapy needed more than 2 units of platelets. After rivaroxaban therapy and adsorption, 6 of 7 patients (85.7%) did not need transfusion of red blood cells, and 5 of 7 patients (71.4%) did not need transfusion of platelets (Table 2).

Six of 16 WA group patients (37.5%) needed rethoracotomy because of relevant bleeding within 10 hours of surgery. All these patients had been administered ticagrelor. In contrast to this, in the CA group, no rethoracotomies had to be performed ($p = 0.0003$).

In the CA group, there was one noncardiac death, of a 70-year-old man on postoperative day 16, with death due to severe sepsis caused by serious pneumonia. In the WA group, one cardiac and two noncardiac deaths occurred: a 71-year-old woman with ventricular perforation caused by acute myocardial ischemia died on postoperative day 60 with low cardiac output. Two cases of severe intestinal ischemia (in an 80-year-old woman and a 76-year-old man) led to noncardiac death on the second and 10th postoperative day, respectively.

Cytosorb adsorption significantly influenced the length of hospital stay and duration in the ICU: the total length of postoperative stay in the ICU was only 2 days (IQR: 1 to 3) in the CA group and 4 days (IQR: 2 to 5) in the WA group ($p = 0.0141$). The total length of hospital stay was 11 days (IQR: 9 to 13) for the CA group and 16 days (IQR: 13 to 18) for the WA group ($p = 0.0244$).

In 4 of 5 ticagrelor patients, the adenosine diphosphate test value after CPB was above the cutoff. Patient number 5 showed a reduced value and needed transfusion of blood products (1 unit of platelets and 3 units of red blood cells) with high drainage volume, but rethoracotomy was not needed. All patients treated with rivaroxaban and the use of adsorption demonstrated a substantial decrease of the drug concentration in the anti-factor Xa assay.

Of the other 55 of the 162 emergent patients without ticagrelor or rivaroxaban, rethoracotomies were performed in 14 cases. The 24-hour drainage volume was 540 mL (IQR: 380 to 650 mL). Most of these patients had been treated with novel oral anticoagulants other than rivaroxaban or other antiplatelet drugs (these 162 patients represent a very heterogeneous group receiving medication before surgery).

Comment

Administration of coagulation-active substances is known to be a relevant risk factor for bleeding complications and therefore increased morbidity and mortality concomitant with emergency cardiac operations [1–3]. The primary outcome of the described study was to analyze bleeding complications after administration of ticagrelor or rivaroxaban among patients scheduled for emergency open heart surgery at our institution. Generally, patients

receiving ticagrelor or rivaroxaban treatments have more bleeding and bleeding complications. That has also been shown in other major studies. We examined and reflected on patient-specific outcomes. As a secondary outcome, we investigated the effects of intraoperative Cytosorb adsorption in some of these cases. We observed that patients without adsorption had multiple bleeding complications, with a high rethoracotomy rate, high 24-hour drainage volume, and the need for more transfusions. That was associated with a prolonged ICU stay and long total hospital stay [12]. In addition to earlier studies, we confirmed that bleeding is an important risk factor for increased transfusion of blood products, and poor morbidity and mortality among cardiac surgical patients [13–15]. The rate of reoperation because of high bleeding volume was significantly higher in the group without Cytosorb adsorption. Interestingly, all patients who had rethoracotomies were receiving ticagrelor.

In the past, some trials have shown that the incidence of surgery-related major bleeding was high when ticagrelor was discontinued less than 24 hours before surgery [16]. During emergency operations, however, there is no time for waiting. The higher incidence of bleeding because of ticagrelor is a reflection of its characteristic pharmacologic property. Ticagrelor is a direct-acting $P2Y_{12}$-receptor antagonist that binds reversibly and noncompetitively to the $P2Y_{12}$ receptor at a site distinct from that of the endogenous agonist adenosine diphosphate. Transfusion of platelets is not a definitive solution because of the remaining amount of ticagrelor in the circulation that can inhibit the new platelets. Our criteria for platelet transfusion over the described period in emergency situations and for patients receiving ticagrelor or rivaroxaban were low platelet count and bleeding problems. We now believe that, normally, there is no need for platelet transfusions in patients with normal platelet count values when the adsorber is used.

Rivaroxaban belongs to a new class of drugs that successfully prevent thromboembolisms. In several randomized trials, superior performances of the substance were demonstrated [17]. There is no valid clinical experience with an antidote called Andexanet Alfa (Portola Pharmaceuticals, San Francisco, CA) for rivaroxaban in heart surgery patients. Therefore, the only possibility is to reduce or try to eliminate the medication from the patient's bloodstream using an adsorber. However, both drugs have in common a high protein-binding capacity. Ticagrelor and rivaroxaban are both "nondialyzable" drugs that have a high degree of protein binding. That is used for successful adsorption. Hemoadsorption with Cytosorb is, therefore, a quite simple method to rapidly remove or eliminate drugs and reduce cytokines from a patient's blood under the conditions of CPB [18].

Among patients with adsorption, there was only one inevitable noncardiac death. Compared with cases without adsorption, with the intraoperative use of Cytosorb, the postoperative course of our study patients was almost uneventful and normal; none of 39 patients showed relevant postoperative bleeding. That led to a significantly improved remaining time in the ICU and a shorter hospital stay. We observed a lower 24-hour drainage volume after adsorption; furthermore, the adsorption group needed significantly fewer transfusions of red blood cells and platelets. We interpret these favorable results as a successful adsorption of ticagrelor or rivaroxaban during the emergency cardiac operations.

The question arises, however, whether there is a different approach than the traditional adsorption to remove coagulation-active substance from a patient's blood. Considering patients who cannot undergo surgery with CPB, Buchanan and associates [19] developed an antigen-binding fragment with high ticagrelor-binding potential. This antidote can neutralize the free fraction of ticagrelor and reverse its antiplatelet activity. It was effective in human platelet plasma in vitro, and in mice in vivo. Whether this experimental approach can be used in cardiac surgery is unclear. We believe adsorption with Cytosorb remains the only way to increase patient safety and to reduce bleeding complications.

We believe that Cytosorb adsorption with the described indication also helps to reduce the costs of emergency open heart surgery. The use of adsorption was associated with an operation time reduced by almost 1 hour and the decreased use of blood. Furthermore, we could save costs by faster discharge of patients from the ICU. However, it remains uncertain which blood tests should validate the effectiveness of adsorption. A direct measurement of ticagrelor or metabolites can demonstrate the effectiveness of the adsorber. That can be done at only highly specialized centers. The effectiveness of reducing rivaroxaban can be demonstrated directly using the anti-factor Xa assay.

Study Limitations

The study was not undertaken to evaluate the results of coagulation-active substance administration in general. Instead, we focused on patients receiving ticagrelor or rivaroxaban medication who were scheduled for emergency open heart operations so that we could learn about effects on bleeding complications and the clinical situation. We present a nonrandomized observational study over a timeframe of 2 years. The adsorption patients were from June 2017 onward, and the control group comprised patients without adsorption between June 2016 and June 2017. The total number of patients we dealt with was only 55, with 39 in the Cytosorb group and only 16 in the group without adsorption, thus limiting the breadth of conclusions. We therefore wanted to reduce exogenous confounders that are associated with the period of investigation such as modified patient blood management or the use of different surgical material. The statistical models were composed of two-factor variables and their interactions; difficulties of this examination were multiple group comparisons of more than 20 variables but only 55 patients and different group sizes with small subgroups. It still remains unclear how much adsorption time is needed to fully eliminate both drugs from the body. Only 8 patients had measurements of drug effects because we did not have the option to carry out point-of-

care testing. The data relate only to a single center, thereby limiting the conclusions. Therefore, prospective randomized investigations of larger cohorts and follow-up investigations are required to confirm these preliminary data.

Conclusion

The intraoperative use of the Cytosorb hemadsorption in patients with ticagrelor or rivaroxaban treatment undergoing emergency open heart operations is a safe and effective method to reduce bleeding complications and to improve the postoperative outcome. We recommend the use of Cytosorb adsorption for safety in patients undergoing emergency cardiac surgery and medication with ticagrelor or rivaroxaban.

References

1. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg 2014;147:1458–63.
2. Vivacqua A, Koch CG, Yousuf AM, et al. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? Ann Thorac Surg 2011;91:1780–90.
3. Fröjd V, Jeppsson A. Reexploration for bleeding and its association with mortality after cardiac surgery. Ann Thorac Surg 2016;102:109–17.
4. Windecker S, Kolh P, Alfonso F. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541–619.
5. Kikkert WJ, van Geloven N, van der Laan MH, et al. The prognostic value of Bleeding Academic Research Consortium (BARC)-defined bleeding complications in ST-segment elevation myocardial infarction: a comparison with the TIMI (Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and ISTH (International Society on Thrombosis and Haemostasis) bleeding classifications. J Am Coll Cardiol 2014;63:1866–75.
6. Angheloiu GO, Gugiu GB, Ruse C, et al. Ticagrelor removal from human blood. J Am Coll Cardiol Basic Trans Sci 2017;2:135–45.
7. Koertge A, Wasserkort R, Wild T. Extracorporeal hemoperfusion as a potential therapeutic option for critical accumulation of rivaroxaban. Blood Purif 2018;45:126–8.
8. Levy JH. Pharmacologic preservation of the hemostatic system during cardiac surgery. Ann Thorac Surg 2001;72(Suppl):1814–20.
9. Schlingloff F, Oberhoffer M, Quasdorff I, et al. Oral anticoagulation after successful atrial fibrillation ablation surgery: is it necessary? Ann Thorac Surg 2016;101:1471–6.
10. Ferraris V, Saha SP, Oestreich JH, et al. 2012 Update to The Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg 2012;94:1761–81.
11. Ranucci M, Baryshnikova E, Soro G, et al. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. Ann Thorac Surg 2011;91:123–30.
12. Hassan K, Bayer N, Schlingloff F, et al. Bleeding complications after use of novel oral anticoagulants in patients undergoing cardiac surgery. Ann Thorac Surg 2018;105:702–8.
13. Moulton MJ, Creswell LL, Mackey ME, et al. Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996;111:1037–46.
14. Dixon B, Santamaria JD, Reid D, et al. The association of blood transfusion with mortality after cardiac surgery: cause or confounding? (CME). Transfusion 2013;53:19–27.
15. Stone GW, Clayton TC, Mehran R, et al. Impact of major bleeding and blood transfusions after cardiac surgery: analysis from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Am Heart J 2012;163:522–9.
16. Hansson EC, Jidéus L, Åberg B, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. Eur Heart J 2016;37:189–97.
17. Patel MR, Mahaffey KW, Garg J, et al. for the ROCKET-AF Steering Committee and Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–9.
18. Nemeth E, Kovacs E, Racz K, et al. Impact of intraoperative cytokine adsorption on outcome of patients undergoing orthotopic heart transplantation—an observational study. Clin Transplant 2018;32:e13211.
19. Buchanan A, Newton P, Pehrsson S, et al. Structural and functional characterization of a specific antidote for ticagrelor. Blood 2015;125:3484–90.