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ORIGINAL ARTICLE

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Effectiveness of adherence to a preoperative antiplatelet and anticoagulation cessation protocol in cardiac surgery

Richard van Valen[a,*], Menno van Gameren[b], Mostafa M. Mokhles[a], Johanna J.M. Takkenberg[a], Maarten ter Horst[c], Jan Hofland[d] and Ad J.J.C. Bogers[a]

[a] Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, Netherlands
[b] Department of Cardiology, Erasmus MC, Rotterdam, Netherlands
[c] Department of Anesthesiology, Erasmus MC, Rotterdam, Netherlands
[d] Department of Anesthesiology, Radboud UMC, Nijmegen, Netherlands

* Corresponding author. Department of Cardiothoracic Surgery, Room Ad201, Thoraxcenter, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, Netherlands. Tel: +31-10-7035426; fax: +31-10-7034507; e-mail: r.vanvalen@erasmusmc.nl (R. van Valen).

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Abstract

OBJECTIVES: Reduction of blood loss after cardiac surgery remains challenging. The effectiveness of adherence to a protocol on cessation of anticoagulants and platelet-inhibiting medications was investigated together with the influence of protocol violations on blood loss after surgery, use of blood products, surgical re-explorations and 30-day mortality.

METHODS: Between 2009 and 2013, data were collected prospectively for all elective cardiac surgery procedures in adult patients ($n = 1637$). Two groups were distinguished: Group 1 adhered to the protocol for cessation or continuation of medication ($n = 1287$, 79%) and Group 2 violated the protocol ($n = 350$, 21%).

RESULTS: Median blood loss was 300 ml (interquartile range 175–500 ml). Eighty patients underwent re-exploration due to blood loss (5%). Thirty-day mortality was 2% ($n = 27$). Protocol violation was associated with increased blood loss [median 275 ml (175–475 ml) vs 350 ml (250–612); $P \leq 0.001$] and with increased average use of fresh frozen plasma (226 ml vs 139 ml; $P << 0.00001$), red blood cell transfusion (115 ml vs 87 ml; $P = 0.081$) and thrombocyte transfusions (52 ml vs 37 ml; $P = 0.0082$). The number of re-explorations (4% vs 6%; $P = 0.39$) and mortality risk (1% vs 2%; $P = 0.72$) did not differ.

CONCLUSIONS: Balancing the benefit of continuing platelet inhibitors or anticoagulants versus cessation before surgery remains challenging. Adherence to the protocol will lead to lower blood loss and in a lower consumption of blood products although the decision to go for re-exploration and 30-day mortality does not differ compared with the protocol violation. Stopping medication does not lead to thromboembolic events.

Keywords: Protocol adherence • Blood loss • Blood products • Re-explorations

INTRODUCTION

Blood loss after cardiac surgery is a burden for patients and institutions and increases the health care costs. Excessive blood loss most often results in prolonged intensive care stay and increased use of blood products [1]. The documented side effects of blood transfusions are the transmission of pathogens, immunological response and metabolic disorders [2]. Research into the prevalence, treatment and prevention of (excessive) blood loss has a long history in cardiac surgery. Despite ongoing research and improvements of protocols and perioperative care, the number of re-explorations for blood loss remains a concern [3–5].

Modifiable factors to reduce blood loss can be sorted into process-related, procedure-related and patient-related categories [2]. Current guidelines recommend a systematic multimodality and multidisciplinary approach to reduce blood loss and the number of re-explorations that are needed in patients undergoing cardiac surgery [6]. The objective of this study is to explore the effectiveness of implementing a protocol for the management of anticoagulants prior to cardiac surgery. Specifically, the association between adherence to a preoperative anticoagulation/antiplatelet therapy cessation protocol and the following outcomes was studied: (i) blood loss in the first 12 h after elective cardiac surgery, (ii) the amount of blood products used [red blood cells (RBCs), fresh frozen plasma (FFP)

and thrombocytes], (iii) the number of re-explorations for bleeding and (iv) mortality rate.

MATERIALS AND METHODS

Initial protocol

An initial protocol that aimed to reduce postoperative blood loss after cardiac surgery was introduced into clinical practice in January 2008 based on the literature and guidelines at that time and containing only those measures that were supported by the multidisciplinary team [7–9]. This protocol was presented to all medical professionals—nurses, perfusionists, anaesthetists, intensivists, residents and surgeons—in our centre who were attending cardiac surgery patients. In addition, referring centres were notified of the changes in the preoperative workup. The complete protocol is presented in Supplementary Material, S1.

The current study

This study was conducted in a university teaching hospital in the Netherlands and was approved by the institutional review board (MEC 2008-162). The need for informed consent was waived, as the protocol we used was the standard of care for our patients.

The main goal of this study was to investigate one particular aspect of the implemented protocol: the effectiveness of protocol implementation for the management of anticoagulant therapy prior to cardiac surgery (Preoperative section, Supplementary Material, S1). The ward nurse confirmed preoperatively whether the anticoagulant medication was stopped on time by asking the patient.

Study cohort

Between 2009 and 2013, data were collected prospectively for all elective adult cardiac surgical procedures, including procedural information, process characteristics and protocol adherence. During this period, the intention was to treat all included patients according to the protocol. Data collection started from the time a patient was accepted for surgery and continued up to 30 days after surgery. Patients undergoing emergency surgery, heart transplantation or implantation of cardiac support devices (e.g. left ventricular assist device) were excluded from the study. In addition, if a patient required a second cardiac surgical procedure during the admission, this patient was excluded from the study. For each patient, data for the amount of blood loss, need for reintervention due to blood loss, use of blood products and mortality were gathered.

The following two study groups were defined:

- Group 1: Protocol adherence comprising the following subgroups:
  - *Group 1a*: no use of anticoagulation/antiplatelet medication. This group contained 447 procedures.
  - *Group 1b*: patients who stopped anticoagulation/antiplatelet medication timely prior to surgery. This group contained 745 procedures.
  - *Group 1c*: patients who continued to use anticoagulation/antiplatelet therapy until the surgical procedure, based on the protocol. This group contained 76 procedures.
  - *Group 1d*: patients who partly stopped with anticoagulant medication [e.g. coumarins were stopped, but acetylsalicylic acid (ASA) was used until the day of the surgery] according to the protocol. This group contained 19 procedures.
- Group 2: Protocol violation comprised patients who violated the protocol with regard to timely cessation of anticoagulation/antiplatelet medication prior to surgery. This group contained 350 procedures.

Subgroup analyses and risk factor selection

Outcomes were measured for the complete cohort of patients, and subgroup analysis was performed for the following types of surgery: coronary artery bypass grafting (CABG), valve surgery, concomitant CABG and valve surgery and other types of cardiac surgery.

The variables that were considered as potential risk factors for the outcomes are presented in Supplementary Material, S2. These were the EuroSCORE 1® variables and variables thought to be of clinical importance. In addition to these variables, the effect of the individual surgeon was also examined as an independent variable.

Effect of protocol adherence on the use of blood products

The usage of different blood products was compared between Group 1 and Group 2. Data on the usage of FFP, thrombocytes and RBCs were gathered. Per group, the percentage of patients who actually received blood products was also compared. The cost for extra use of blood products was calculated by taking the mean usage of blood products per patient (total use of blood products divided by the number of patients in the particular group). The mean difference between the groups was subsequently used for calculating the extra costs due to excessive use of blood products.

Statistical methods

The unpaired *t*-tests were used for continuous data (range, median and standard deviation). Non-normally distributed data (the Kolmogorov–Smirnov test) were compared using the Mann–Whitney *U*-test. Categorical data were represented as frequencies and compared using the χ^2 test or the Fisher's exact test where appropriate. All tests were 2-sided, with an alpha level of 0.05. In addition to doing comparative statistics, we identified independent predictors for all the end-points. Multicollinearity of the considered potential risk factors was checked: there were no factors with significant collinearity (variance inflation factor <3). Linear regression analysis was used to identify predictors for continuous end-points (blood loss and used blood products). Logistic regression analysis was used to identify the predictors for binary end-points (re-explorations and 30-day mortality). This was done by performing univariate analyses for all the potential predictors and entering them into multivariate analyses, if *P*-value <0.10.

Table 1: Baseline comparison of the study groups

	Group 1: protocol adherence (*n* = 1287)	Group 2: protocol violation (*n* = 350)	*P*-value
Female gender, *n* (%)	425 (33)	69 (20)	<0.00001
Urgent surgery, *n* (%)	17 (1)	23 (7)	<0.00001
COPD, *n* (%)	159 (12)	41 (12)	0.76
PVD, *n* (%)	117 (9)	65 (19)	<0.00001
Previous cardiac surgery, *n* (%)	144 (11)	7 (2)	<0.00001
Active endocarditis, *n* (%)	23 (2)	3 (1)	0.22
Critical preoperative condition, *n* (%)	44 (3)	36 (10)	<0.00001
Unstable angina pectoris, *n* (%)	36 (3)	46 (13)	<0.00001
Recent myocardial infarction, *n* (%)	97 (8)	109 (31)	<0.00001
Diabetes mellitus, *n* (%)	249 (20)	93 (27)	0.0027
CVA history, *n* (%)	38 (3)	19 (6)	0.023
History of endocarditis, *n* (%)	14 (1)	0 (0)	0.051
Age (years), median (IQR)	65.0 (56–73)	66.0 (60–73)	0.040
Creatinine, median (IQR)	83.0 (72–98)	85.0 (74–99)	0.11
Logistic EuroSCORE®, median (IQR)	4.0 (2.1–7.7)	3.3 (1.7–6.9)	0.012
ASA use in group, *n* (%)	639	341	<0.00001
ASA continued	94 (15)	331 (97)	<0.00001
ASA violation	0 (0)	324 (98)	<0.00001
ASA timely stopped	545 (85)	10 (3)	<0.00001
Clopidogrel use in group, *n* (%)	141	155	<0.00001
Clopidogrel continued	40 (28)	111 (72)	<0.00001
Clopidogrel violation	0 (0)	108 (97)	<0.00001
Clopidogrel timely stopped	101 (72)	44 (28)	<0.00001
Coumarin group use in group, *n* (%)	220	26	<0.00001
Coumarin continued	0 (0)	5 (19)	<0.00001
Coumarin violation	0 (0)	5 (100)	<0.00001
Coumarin timely stopped	220 (100)	21 (81)	<0.00001
DAPT use in group, *n* (%)	162	184	<0.00001
DAPT continued	0 (0)	85 (46)	<0.00001
DAPT violation	0 (0)	85 (100)	<0.00001
DAPT timely stopped	162 (100)	99 (54)	<0.00001
Use of any anticoagulation/antiplatelet medication, *n* (%)	840 (65)	350 (100)	<0.00001

ASA: acetylsalicylic acid; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; DAPT: double antiplatelet therapy; IQR: interquartile range (25th and 75th percentile); PVD: peripheral vascular disease.

All analyses were performed with the SPSS statistical software, version 24.0, release 2016 (IBM, Armonk, NY, USA).

RESULTS

During the study period, 1617 patients underwent 1637 unique surgical procedures. Fourteen (0.9%) patients underwent 3 surgical procedures during the study period and 6 (0.4%) patients underwent 2 surgical procedures. Of the 1637 surgical procedures, 1287 (79%) patients adhered to the protocol (Group 1) and 350 (21%) patients violated the protocol (Group 2). The characteristics of both groups are presented in Table 1. The group of protocol violations presented significantly more often with a history of previous cardiac surgery or unstable angina and underwent more often urgent surgery (Table 1).

Use of anticoagulation/antiplatelet medication

In 1190 of the 1637 (72.7%) procedures, either platelet-inhibiting medication or coumarins (Groups 1b + 1c + 1d + 2) was used. Detailed information on the type of anticoagulation/antiplatelet medication for Groups 1 and 2 is presented in Table 1. Of these 1190 anticoagulation/antiplatelet users, 840 (71%) patients adhered to the protocol (Group 1). The total group of anticoagulation/antiplatelet users adhering to the protocol includes 745 (63%) patients who stopped anticoagulation/antiplatelet medication timely before surgery (Group 1b) and 95 (8%) patients who continued anticoagulation/antiplatelet medication according to the protocol (Group 1c and Group 1d). Furthermore, 350 (30%) patients violated the protocol with regard to anticoagulation/antiplatelet medication (Group 2).

Protocol violation was seen in all types of surgery, with the highest percentage of violation in the group of patients undergoing CABG surgery (38%, *n* = 289). Protocol adherence was the highest in the group of patients using coumarins (98%, *n* = 241) (Supplementary Material, S2).

Mortality, blood loss and re-explorations

Overall 30-day mortality in the entire cohort of patients was 2% (*n* = 27). The mortality was 2% (*n* = 22) in Group 1 (protocol adherence) and 1% (*n* = 5) in Group 2 (protocol violation). Data regarding blood loss in our patient population in the different subgroups are presented in Table 2.

No significant association was found between the individual surgeon and the amount of blood loss or the risk of re-exploration (Supplementary Material, S3).

Table 2: Blood loss per surgery group

	Total group	CABG	Valve surgery	CABG and valve surgery	Other[a]
Blood loss (ml), mean, median (IQR)	414, 300 (175–500)	411, 325 (225–500)	371, 225 (150–425)	590, 425 (275–700)	325, 200 (125-362)
Red blood cell use (ml), mean, median (IQR)	93, 0 (0–0)	76, 0 (0–0)	89, 0 (0–0)	181, 0 (0–275)	73, 0 (0–0)
Fresh frozen plasma use (ml), mean, median (IQR)	157, 0 (0–0)	115, 0 (0–0)	171, 0 (0–0)	295, 0 (0–325)	118, 0 (0–0)
Thrombocyte use (ml), mean, median (IQR)	40, 0 (0–0)	35, 0 (0–0)	40, 0 (0–0)	69, 0 (0–0)	27, 0 (0–0)
Re-exploration, *n* (%)	80 (5)	17 (2)	42 (7)	14 (7)	7 (8)
30-day mortality, *n* (%)	27 (2)	9 (1)	10 (2)	5 (3)	3 (3)

[a]Other refers to congenital surgery, aortic surgery, aortic valve and aortic surgery.
CABG: coronary artery bypass grafting; IQR: interquartile range (25th and 75th percentile).

Table 3: Effects of protocol violations on blood loss

	Group 1 (protocol adherence)	Group 2 (protocol violation)	*P*-value
Blood loss (ml), mean, median (IQR)	436, 275 (175–475)	485, 350 (250–612)	<0.00001
Red blood cell use (ml), mean, median (IQR)	87, 0 (0–0)	115, 0 (0–0)	0.081
Fresh frozen plasma use (ml), mean, median (IQR)	139, 0 (0)	226, 0 (0–325)	<0.00001
Thrombocyte use (ml), mean, median (IQR)	37, 0 (0–0)	52, 0 (0–0)	0.0082
Re-exploration, *n* (%)	66 (6)	14 (4)	0.39
30-day mortality, *n* (%)	22 (2)	5 (1)	0.72
Percentage of patients using blood products, *n* (%)			
Red blood cell	262 (20)	84 (24)	0.14
Fresh frozen plasma	240 (19)	101 (29)	<0.00001
Thrombocytes	168 (13)	65 (19)	0.0088

IQR: interquartile range (25th and 75th percentile).

ADULT CARDIAC

Effect of protocol adherence on blood loss and the use of blood products

Compared with the group of protocol adherence, patients who violated the protocol (Group 2) lost more blood [median 350 ml (interquartile range 250–612 ml) vs 275 ml (interquartile range 175–475 ml); $P < 0.00001$]. As presented in Table 3, there were significant differences in the use of blood products between Group 1 and Group 2. There is a trend for the use of RBC ($P = 0.081$) and a significant difference for the use of thrombocytes and FFP ($P = 0.0082$ and $P < 0.00001$, respectively).

As presented in Table 3, the average difference in RBC transfusion between the protocol adherers and the protocol violators is 28 ml per operated patient. With regard to 1000 elective cardiac surgery patients per year, the potential savings could be 30 000 euros per year. This is based on an average cost of 282 euros per unit of RBC (265 ml), as charged by Sanquin, the national blood bank of the Netherlands, in 2016.

Independent predictors for blood loss

Urgent surgery and surgery on the thoracic aorta were associated with increased blood loss. The use of clopidogrel and double antiplatelet therapy (DAPT) was also associated with increased risk of blood loss, even if it was stopped according to the protocol prior to surgery (Group 1b) (Table 4). A comparable result was observed in the group of patients who continued anticoagulation/antiplatelet medication according to the protocol (Group 1c). In Group 2, more blood loss was observed in patients using ASA, clopidogrel and DAPT (Table 4).

Thromboembolic events

During this study, no preoperative thromboembolic events were registered in our patient group.

DISCUSSION

This study shows that adherence to the preoperative part of our institutional blood loss reduction protocol is associated with a significant decrease in blood loss. This study also pinpoints that violations of the protocol are predominantly seen in the group of CABG patients, a group of patients in whom preoperative anticoagulation management can be challenging. These patients often require urgent or emergent surgery or have undergone recent implantation of drug-eluting stents that require continued use of platelet inhibitors. Furthermore, this study found that although blood loss was higher in patients with protocol violations, this did not affect patient mortality or the number of re-explorations needed due to blood loss.

Table 4: The effect of continuation of different types of anticoagulant medication on increased blood loss, increased use of RBC, thrombocytes, fresh frozen plasma and increased risk of re-exploration

Multivariate analysis	Blood loss		Use RBC		Use thrombocytes		Use FFP		Re-exploration	
	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
ASA use	0.108	<0.00001			0.125	<0.00001			0.51	0.073
ASA continued	0.066	0.030	0.056	0.046			0.078	0.004		
Clopidogrel continued	0.058	0.033	0.113	<0.00001	0.216	<0.00001				
Clopidogrel violation							0.113	<0.00001		
Coumarin use	0.108	<0.00001	0.071	0.004			0.096	<0.00001	0.51	0.093
Type of surgery			0.125	<0.00001			0.104	<0.00001		
Aortic surgery	0.106	<0.00001					0.110	<0.00001	2.03	<0.00001
Surgery other CABG					0.157	<0.00001			0.84	0.017
Urgent surgery			0.093	<0.00001			0.056	0.02	1.29	0.028
Critical preoperative condition					0.065	0.01				
Age			0.085	0.001			0.070	0.006		
Active endocarditis			0.099	<0.00001						

ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; FFP: fresh frozen plasma; RBC: red blood cell.

It has been well established that stopping anticoagulant/antiplatelet therapy leads to reduced blood loss during and after surgery [7–10]. For this reason, preoperative cessation of antiplatelet and/or anticoagulation therapy is included in the current hospital protocols. Most of the studies concerning this topic focus on mortality and re-explorations [8, 11–13]. The value of the current study is that it focuses on the daily clinical practice of working with such a protocol in which protocol violations will occur. Cessation of anticoagulants carries the risk of thromboembolic complications [7, 14]. During the investigated period, none of these complications were seen. This suggests that applying this protocol is safe and does not lead to a higher rate of thromboembolic complications. This knowledge, combined with the increased amount of blood loss and the use of blood products in patients who fail to follow protocol, suggests that applying and strictly enforcing the protocol is worthwhile.

The expected effect of new anticoagulant medication

In the investigated time frame, the protocol we used prescribed temporarily ceasing the use of clopidogrel as single agent or as part of DAPT 5–7 days before surgery (with an expected and accepted risk of 1% increase in myocardial infarction) [7]. Our current practice, which arose after the time frame of this study, is using new platelet inhibitors (P2Y12 inhibitors) such as ticagrelor. Our new protocol states that while most surgical procedures can be performed safely on DAPT or at least on ASA alone with acceptable rates of bleeding, ceasing P2Y12 inhibitors is not recommended in high-risk cohorts (high-risk anatomy or ongoing ischaemia) [6]. This more liberal protocol supposedly results in less ischaemia or infarction but is likely to lead to more postoperative blood loss, as shown in the recent literature. For example, Hansson *et al.* [3] showed that continuation of ticagrelor led to a markedly more blood loss and more blood transfusions than continuation of clopidogrel. This makes it reasonable to state that our findings will be even more outspoken if extrapolated to the current guidelines on myocardial revascularization [6].

The role of the surgeon

Of all the precautions and instructions incorporated in the introduced protocol, surgical aspects are almost absent. In general, surgeons are considered to already be doing everything they can to limit blood loss during surgery. It is self-explanatory that it is impossible to form consensus on each possible surgical technique and include it in a blood reduction protocol. To rule out that the surgeon is an independent predictor of blood loss, we performed multivariate analysis with all the surgeons as a predictor. Results showed that individual surgeons are not a predictor of more blood loss or more re-explorations. The role of the anaesthesiologist and the perfusionist was not examined in this study.

Anticoagulant/antiplatelet therapy and blood loss

Although the use of ASA, clopidogrel and DAPT leads to more blood loss, it does not result in an increased number of re-explorations. For DAPT, this was a surprising finding. The use of DAPT has been described to result in increased blood loss, usage of FFP and blood transfusion in other studies [15]. We were not able to confirm any increased blood loss from the continued use of DAPT in this cohort of patients. There is, however, an increased use of blood products as reported in other studies. The finding that more blood loss is not associated with more re-explorations (involved treatment team decision) appears to be in contradiction and is also not in line with other studies [12, 13, 16]. A possible explanation could be that more blood loss is expected and accepted by both the surgeons and the intensivists attending these patient groups. The decision to perform a re-exploration is probably postponed in these patients, which is reasonable because coagulation pathways are disrupted by protocol violations. Pharmacological optimization of coagulation is vital before deciding to perform surgical re-exploration. Point-of-care testing (bedside tests that give an accurate and swift result on, for example, platelet function) provides an important tool in the management of this kind of blood loss and should be an integral part of perioperative and postoperative care, especially in those with the continued use of platelet inhibitors [4].

Costs related to protocol violations

In light of increasing health care costs, cost-effectiveness is becoming an important aspect of health care. Patients undergoing cardiac surgery are at a higher risk of receiving blood products [17]. In the group of protocol violation, the amount of blood loss was higher as was the use of blood products. Reducing the amount of blood loss in these patients will not only result in a cost reduction for the hospital but also reduce the risk of potentially harmful effects of blood transfusions.

Strengths and limitations

The major strength of this study is that it shows how challenging it can be to implement and use a guideline-based protocol in daily clinical practice. Another strength is the relatively large number of patients included in this study. Furthermore, this study provides an insight into the health care costs related to excessive blood loss.

However, this study also has several limitations. It is a retrospective study based on patient data from a single-centre tertiary care university hospital. Furthermore, no data are available about the measures taken in addition to the protocol to reduce blood loss preoperatively. In addition, the reasons for protocol violations are unknown, so they cannot potentially contribute to a more effective protocol.

CONCLUSIONS

Balancing the benefit of continuing platelet inhibitors or anticoagulants versus cessation before surgery remains challenging. Adherence to the protocol will lead to lower blood loss and in a lower consumption of blood products although the decision to go for re-exploration and 30-day mortality does not differ compared with the procedures in which the protocol was violated. Stopping medication according to the protocol does not lead to thromboembolic events.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

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