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Consensus Report / Konsensus Raporu

Consensus Report on Patient Blood Management in Cardiac Surgery by Turkish Society of Cardiovascular Surgery (TSCVS), Turkish Society of Cardiology (TSC), and Society of Cardio-Vascular-Thoracic Anaesthesia and Intensive Care (SCTAIC)

Kalp Cerrahisinde Hasta Kan Yönetimine ilişkin Uzlaşı Raporu

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ABSTRACT

Anemia, transfusion and bleeding independently increase the risk of complications and mortality in cardiac surgery. The main goals of patient blood management are to treat anemia, prevent bleeding, and optimize the use of blood products during the perioperative period. The benefit of this program has been confirmed in many studies and its utilization is strongly recommended by professional organizations. This consensus report has been prepared by the authors who are the task members appointed by the Turkish Society of Cardiovascular Surgery, Turkish Society of Cardiology (TSC), and Society of Cardio-Vascular-Thoracic Anaesthesia and Intensive Care to raise the awareness of patient blood management. This report aims to summarize recommendations for all perioperative blood-conserving strategies in cardiac surgery.

Keywords: Cardiac surgery, patient blood management, transfusion, bleeding.

ÖZ

Anemi, transfüzyon ve kanama kalp cerrahisinde bağımsız olarak komplikasyon ve mortalite riskini artırır. Hasta kan yönetiminin başlıca amacı perioperatif dönemde aneminin tedavisi, kanamanın önlenmesi ve kan ürünü kullanımının optimize edilmesidir. Bu programın yararı birçok çalışmada kanıtlanmış olup, kullanımı birçok mesleki dernek tarafından önemle önerilmektedir. Bu uzlaşı raporu, Türk Kalp Damar Cerrahisi Derneği (TKDCD), Türk Kardiyoloji Derneği (TKD) ve Göğüs-Kalp-Damar Anestezi ve Yoğun Bakım Derneği'nin çalışma grubu üyeleri tarafından hasta kan yönetimine ilişkin farkındalığı artırmak amacıyla hazırlanmıştır. Bu raporda, kalp cerrahisinde perioperatif dönemde kan koruyucu stratejilerin tümüne ilişkin öneriler özetlenmiştir.

Anahtar sözcükler: Kalp cerrahisi, hasta kan yönetimi, transfüzyon, kanama.

Cardiac surgery constitutes a high risk for bleeding and transfusion due to multiple causes such as procedures, patient characteristics, medications, and cardiopulmonary bypass (CPB). Anemia, transfusion, and bleeding independently increase the risk for complications and mortality.[1] The term patient blood management (PBM) includes strategies to increase patient's red cell mass, to prevent bleeding, and to optimize the use of blood products. Its main benefit has been confirmed by many studies and its utilization is strongly recommended by professional organizations.[2] The success is only achieved, if it is applied in a multidisciplinary manner by a team including a surgeon, cardiologist, anesthesiologist, perfusionist, and nurse.

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Abbreviations:

AAP ..... Antegrade autologous priming
ASA..... Acetylsalicylic acid
ACT..... Activated clotting time
aPTT ..... Activated partial thromboplastin time
ACS ..... Acute coronary syndrome
ANH..... Acute normovolemic hemodilution
ATACAS ..... Aspirin and tranexamic acid for coronary artery surgery
AF ..... Atrial fibrillation
BMS ..... Bare metal stent
CPB ..... Cardiopulmonary bypass
CHF..... Congestive heart failure
DM ..... Diabetes mellitus
DOACs ..... Direct Oral Anticoagulants
DES ..... Drug-eluting stent
DAPT ..... Dual antiplatelet therapy
FFP..... Fresh frozen plasma
GVHD..... Graft-versus-host disease
Hct..... Hematocrit
Hb..... Hemoglobin
HIT..... Heparin-induced thrombocytopenia
HES ..... Hydroxyethyl starch
INR..... International normalized ratio
LMWH..... Low-molecular-weight heparin
MiECC ..... Minimally Invasive Extracorporeal Circulation
MUF..... Modified ultrafiltration
PBM ..... Patient blood management
PCI ..... Percutaneous coronary intervention
PAD..... Preoperative autologous donation
PCC ..... Prothrombin complex concentrate
PT..... Prothrombin time
RAP..... Retrograde autologous priming
RBC..... Red blood cell
RCC..... Red cell concentrate
ROTEM..... Rotational thromboelastometry
SCT ..... Standard coagulation test
SCTAIC ..... Society of Cardio-Vascular-Thoracic Anaesthesia and Intensive Care
TACO ..... Transfusion-associated circulatory overload
TAVI..... Transcatheter aortic valve implantation
TEG..... Thromboelastography
THAs..... Topical hemostatic agents
TIA..... Transient ischemic attack
TRALI..... Transfusion related acute lung injury
TRIM ..... Transfusion related immummodulation
TXA ..... Tranexamic acid
TSC ..... Turkish Society of Cardiology
TSCVS ..... Turkish Society of Cardiovascular Surgery
UF ..... Ultrafiltration
UFH ..... Unfractionated heparin
VETs ..... Viscoelastic tests
VKA..... Vitamin K antagonist
vWF..... von Willebrand factor

Blood management during cardiac surgery starts with risk identification of bleeding and thrombosis, treatment of anemia, and optimizing antithrombotic treatments. Preoperative consultation of the patient for PBM in clinics may provide excellent care in these patient populations. Subsequently, intraoperative blood-conserving strategies including a meticulous surgical technique, optimal management of anticoagulation, and appropriate use of hemostatic agents would serve to protect patient's blood. Finally, the optimal treatment of coagulopathy and bleeding with an appropriate use of blood products would definitely decrease the risk for complications.

This consensus report is an extended summary of the book prepared by the authors who are the task members assigned by the Turkish Society of Cardiovascular Surgery, Cardio-Vascular-Thoracic Anaesthesia and Intensive Care Society, and Turkish Society of Cardiology. This book has been recently published to raise the awareness of PBM and to educate members of the Heart Team in cardiac surgery.[3] This book, written in Turkish, is a synopsis of information in the latest literature and international guidelines.

In this report, you can find recommendations about all blood-conservation strategies using expressions such as 'should be used', 'is reasonable', 'may be used' or 'it is not recommended'. This judgment is achieved by assessing the effectiveness of the treatment according to the latest literature and guidelines.

CLASSIFICATION OF STRATEGIES FOR BLOOD CONSERVATION

In this report, each technique is classified according to the application period. This classification provides a better understanding and systematic approach for clinicians. Table 1 shows the classification of techniques.

RISK IDENTIFICATION FOR TRANSFUSION AND BLEEDING

Transfusion

Transfusion, related to bleeding or not, carries a risk for infective (viral diseases, pneumonia, wound infection) and non-infective (renal failure, TRALI, TACO, TRIM) complications. This effect on morbidity and mortality is strongly confirmed by many studies.[4] Therefore, transfusion should be applied for the appropriate target at the right time. Instead of laboratory tests (hemoglobin [Hb] or hematocrit [Hct]), inadequate tissue oxygenation markers are suggested to make a decision for transfusion.[5] To date, many risk scoring systems have been developed, and the most recent one is the ACTA-PORT which is useful to predict the number of packed cells to transfuse during cardiac surgery.[6-9]

Bleeding

Bleeding after cardiac surgery is seen in 2 to 9% of cases and increases the risk for morbidity and mortality up to six fold.[10,11] The risk for bleeding should be identified and, then, preventive and blood

Table 1. Blood conservative strategies classified according to application period

Preoperative	Intraoperative	Postoperative
Risk identification for transfusion and bleeding	Blood conservative Surgical technique	Management of bleeding 1. Transfusion criteria 2. Viscoelastic test guided coagulopathy treatment 3. Re-exploration for bleeding
Preoperative anemia; diagnosis and treatment	The use of fresh whole blood	
Preoperative antithrombotic drug management	Antifibrinolytics	
Preoperative coagulation test	Acute normovolemic Hemodilution	Postoperative antithrombotic drug management
Autologous blood donation	Heparin-protamine management	
	Volume therapy	
	Minimally invasive extracorporeal circulation and techniques	
	Autotransfusion	
	Ultrafiltration	
	Hemostatic agents	

conservative strategies should be planned before the operation. Until present, different risk scoring systems for bleeding have been used, but have not been widely accepted. Therefore, the common causes for bleeding should be recognized by the Heart Team (Table 2).

Recommendations

1. The risk score for transfusion (ACTA-PORT) should be calculated (predicted number of packed cells) preoperatively, and preventive strategies should be applied during the whole perioperative period.
2. The risk factors for bleeding should be examined preoperatively. The level of bleeding risk should be identified, and all preventive strategies should be planned, when necessary.

PREOPERATIVE ANEMIA: DIAGNOSIS AND TREATMENT

Anemia is a common comorbidity which occurs in 25 to 40% of patients undergoing elective cardiac surgery.[13,14] Perioperative anemia and blood transfusion can be considered as preventable surgical risk factors, as both anemia and transfusion contribute to poor outcomes.[15] Preoperative anemia should be defined, evaluated, and managed to minimize the use of blood products in patients undergoing cardiac surgery. It is considered, with the treatment of anemia, complications such as transfusion-related mortality and morbidity are reduced and long intensive care and hospital stay are shortened.[16,17]

Table 2. Risk factors for bleeding and re-operation for bleeding

Patient related risk factors	Procedure-related risk factors	Risk factors for re-operation for bleeding
Age (>70 years)	Surgeon	Age (>70 years)
Female	Prolonged CPB time	Low BMI
Low BMI	Redo operation	High EuroSCORE
Preoperative anemia	Emergent surgery	Non CABG or combined procedures
Preoperative antithrombotic drug[12]		High creatinine levels
Chronic renal failure		
Liver failure		
Diabetes mellitus		

CPB: Cardiopulmonary bypass; BMI: Body mass index; CABG: Coronary artery bypass grafting.

Irrespective of male or female gender, Hb levels below 13 g/dL are considered anemia.[18] All patients undergoing a major elective surgery should be evaluated for anemia. Iron deficiency is the most common cause of anemia in the perioperative period. Intravenous iron should be used as the first-line treatment option in patients who do not respond to oral iron or have iron intolerance, or surgery is planned within 6 weeks after the diagnosis of iron deficiency.[18,19]

Recommendations

1. The laboratory testing for anemia (iron, ferritin, transferrin saturation) should be evaluated preoperatively and surgery needs to be scheduled in this context.
2. In untreated anemia patients, it is reasonable to postpone elective surgery for the diagnosis and treatment of anemia.
3. Investigation of ferritin levels, even if the patient is not anemic, may be used in high-risk patients for bleeding.
4. In the treatment of preoperative anemia, Hb level should be targeted as ≥13 g/dL for both genders.
5. Preoperative iron replacement:
   - Oral iron replacement therapy is reasonable in case of iron deficiency, either anemic or non-anemic, if the procedure can be postponed for 6 to 8 weeks.
   - Intravenous iron therapy should be used in patients who are scheduled for surgery less than 6 weeks or who do not respond to or tolerate oral iron therapy.
   - In case of iron sequestration (non-anemic), preoperative erythropoietin therapy may be used in selected high-risk patients for bleeding.
   - In case of anemia, combined iron replacement and erythropoietin treatment may be used preoperatively in selected patients.
6. Dietary supplements (such as vitamin B12, vitamin D, folic acid) may be used in selected patients.
7. Routine preoperative red blood cell (RBC) transfusion is not recommended in case of anemia.
8. Iron replacement and erythropoietin treatment may be used in groups of patients who are scheduled for preoperative autologous blood donation (rare blood groups, insufficient blood stock, and alloimmunization, etc.).

PREOPERATIVE ANTITHROMBOTIC DRUG MANAGEMENT

Recommendations for Antiplatelet Therapy

1. The risk for thrombosis following percutaneous coronary intervention (PCI) should be identified preoperatively to optimize antithrombotic drug management.[20]
2. The thrombotic risk following PCI should be identified, irrespective of the stent type (bare metal stent [BMS] or drug-eluting stent [DES]) according to the time to surgery after stent implantation, angiographic features of the coronary lesions, and clinical characteristics of every individual patient.[21-24]
3. High thrombotic risk group comprises the patients having balloon angioplasty within 2 weeks, stent implantation within 3 months (particularly within the past month), and acute coronary syndrome (ACS) or complex PCI within 6 months. Intermediate risk includes balloon angioplasty between 2 to 4 weeks, stent implantation between 3 to 6 months, and ACS or complex PCI between 6 to 12 months.[25]

Preoperative use of acetylsalicylic acid (ASA)[26,27]

4. If cardiac surgery is elective and the risk for bleeding is high (complex or redo surgery, severe renal insufficiency, hematological disease, and hereditary thrombocyte dysfunction); ASA may be interrupted at least 5 days before surgery.
5. If cardiac surgery is urgent or emergent, the risk for bleeding is low or moderate, or the risk for thrombosis is moderate or high, ASA should not be discontinued before surgery.

Preoperative use of dual antiplatelet therapy (DAPT)[26-29]

6. ASA should not be interrupted preoperatively.
7. Ticagrelor, clopidogrel and prasugrel should be interrupted 3, 5 and 7 days, respectively before surgery in patients who have an intermediate thrombotic risk (excluding low bleeding risk patients).
8. In case of a high thrombotic risk with a low bleeding risk, surgery can be performed without any interruption. If the bleeding risk intermediate or high, the patient should be evaluated by the Heart Team for the necessity of bridging therapy (Figure 1).

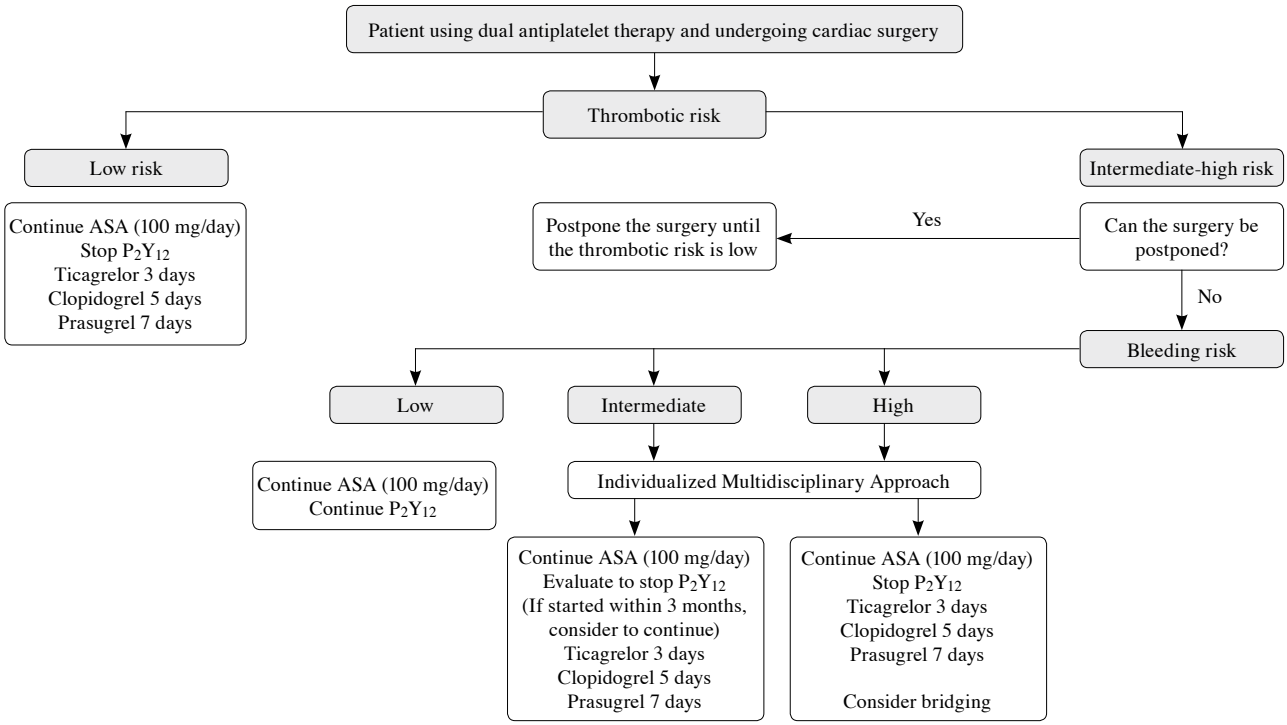

Figure 1. Preoperative management of dual antiplatelet therapy according to thrombotic and bleeding risk in cardiac surgery.
ASA: Acetylsalicylic acid.

9. Bridging therapy with eptifibatide, tirofiban, and cangrelor may be used in patients with a high thrombotic and bleeding risk for cardiac surgery which cannot be postponed (Figure 2).
10. It is reasonable to use platelet function test to analyze the residual effect of P_2Y_{12} inhibitors to optimize the time of surgery or to identify the risk for bleeding.[30-32]

Recommendations for Anticoagulant Therapy

1. The risk for thrombosis should be identified preoperatively to optimize anticoagulant drug management. The thrombotic risk assessment are based on the type of prosthetic heart valve, the position of valve, a history of cerebrovascular event due to valve thrombosis, CHA_2DS_2-VASc score, etiology of atrial fibrillation (AF) and thrombophilia.[29,33]
2. Thrombotic risk is associated with the indication of anticoagulation therapy.
3. Prosthetic mitral valve, tricuspid valve (including biological valve), aortic monoleaflet valve, and stroke/transient ischemic attack (TIA) within the past 6 months due to valve thrombosis constitute the high thrombotic risk for patients with prosthetic heart valves. The CHA_2DS_2-VASc score 7-9, stroke/TIA within the past 3 months and AF due to rheumatic mitral valve disease and new venous thromboembolism, severe thrombophilia comprise the high-risk group.
4. Prosthetic aortic valve plus one risk factor (AF, stroke/TIA >6 months, diabetes mellitus [DM], congestive heart failure [CHF], and age >75 years) for prosthetic heart valve, CHA_2DS_2-VASc score 5-6, and stroke/TIA history within the past 3 months due to AF and venous thromboembolism within the past 3 to 12 months, and non-severe thrombophilia for venous thromboembolism indicate an intermediate risk.
5. Prosthetic aortic valve without any risk factor, CHA_2DS_2-VASc score 1-4 without stroke/TIA, and venous thromboembolism more than 12 months prior constitute a low risk.

Preoperative use of Vitamin K antagonist (VKA)[26,34,35]

1. VKA should be stopped at least 5 days before cardiac surgery and bridged with low-molecular-weight heparin (LMWH) or unfractionated

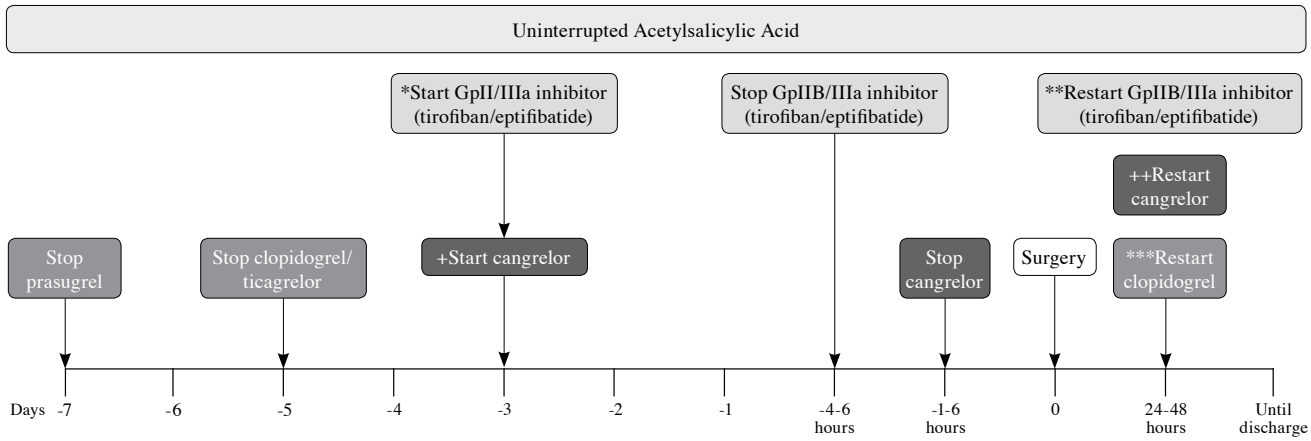

Figure 2. Perioperative management of dual antiplatelet therapy in cardiac surgery.

* After discontinuation of P_2Y_{12} within 72 hours without bolus dose;
Tirofiban: **0.1** µg/kg/min (If creatinine clearance <50 mL/min 0.05 µg/kg/min);
Eptifibatide: **2.0** µg/kg/min (If creatinine clearance <50 mL/min 1.0 µg/kg/min);
+ After discontinuation of P_2Y_{12} within 72 hours without bolus dose;
0.75 µg/kg/min (No need to dose adjustment in renal failure minimum 48 hours to maximum 7 days)
** If no oral intake
++ If no oral intake
*** Within 24-48 hours when oral intake starts, clopidogrel should be given in 75 mg/day maintenance dose following 300-600 mg bolus dose. Prasugrel and ticagrelor are not recommended.

heparin (UFH) in patients with a high thrombotic risk (Figure 3).

2. Patients with a prosthetic aortic valve plus at least one risk factor should be considered a high thrombotic risk and managed accordingly. Other patients in the intermediate- and low-risk group should undergo cardiac surgery with VKA interruption 5 days before surgery without bridging.
3. In case of an emergent surgery, prothrombin complex concentrate (PCC) can be preferred to fresh frozen plasma (FFP) to reverse the effect of VKA and to prevent complications due to transfusion.[36-38]

Preoperative Use of Direct Oral Anticoagulants (DOACs)[39]

4. DOACs are rapid-acting drugs, and bridging is not recommended, if the timing is optimal.
5. The time of discontinuation of dabigatran should be managed (48 to 96 hours) according to the creatinine clearance levels (Figure 3).
6. The time of discontinuation of rivaroxaban, apixaban, and edoxaban is 48 hours before cardiac surgery, irrespective of the creatinine clearance levels.
7. In case of an emergent surgery, it is reasonable to use idarucizumab to reverse the effect of dabigatran.[40,41]
8. In case of an emergent surgery, it is reasonable to use Andexanet Alfa to reverse the effect of apixaban and rivaroxaban.[38,42,43]

PREOPERATIVE COAGULATION TEST

An important component of preoperative preparation is the patient's coagulation status. The first and most important way to evaluate coagulation status is to question the standardized history of personalized or familial bleeding. Patients' history (including the patients' and the families' bleeding history) and a careful preoperative physical examination are essential to identify pre-existing hemorrhagic disorders.[44] Coagulation tests should be performed in patients with an acute pathology which may cause hemorrhage.[45] In addition to standard laboratory tests (prothrombin time [PT] and activated partial thromboplastin time [aPTT]), viscoelastic tests (VETs) have also an important role in perioperative (pre-, intra-, and postoperative) evaluation and treatment of coagulation status. Fibrinogen level is the only test which has been shown to be a predictor of bleeding in many recent guidelines.[2] Platelets should be functionally evaluated in selected patients besides thrombocytopenia.

Recommendations

1. The use of routine coagulation tests for the prediction of perioperative bleeding is not

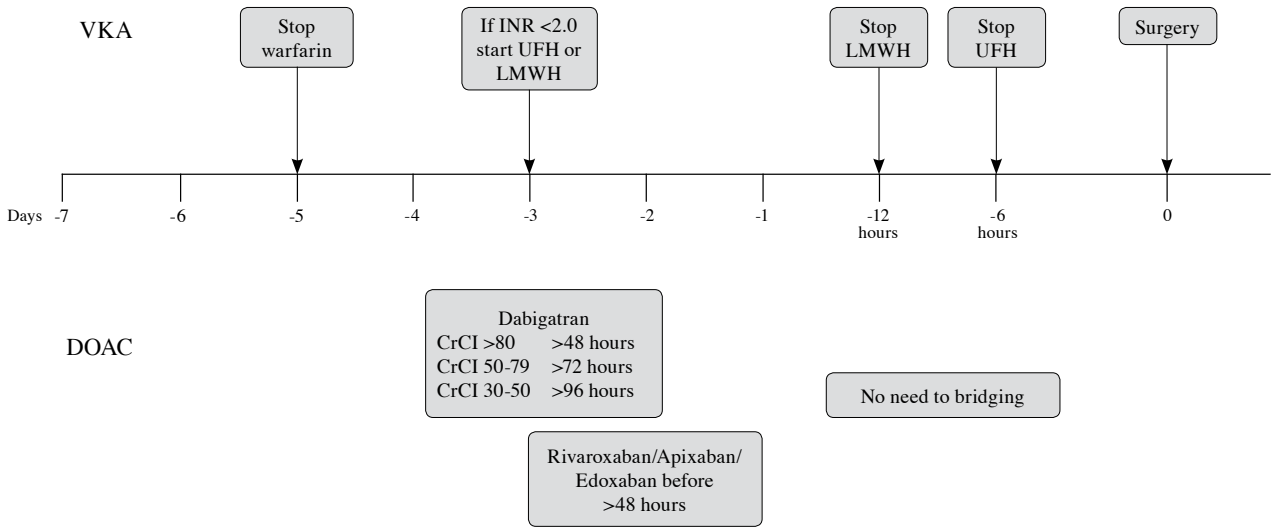

Figure 3. Perioperative management of oral anticoagulant therapy in cardiac surgery.

Bridging algorithm for the patients using oral anticoagulation and undergoing cardiac surgery.
VKA: Vitamin K antagonist; INR: International normalized ratio; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulant; CrCI: Creatinine clearance.

recommended in non-selected patients prior to surgery and other invasive procedures.

2. A standardized bleeding questionnaire should be used for screening the perioperative bleeding risk. It is reasonable to perform VET and/or standard coagulation test (SCT) in the following patients:
   i. Positive bleeding history
   ii. Surgical procedure with a high risk for bleeding
   iii. Presence of comorbidities with a high risk for bleeding (such as disseminated intravascular coagulation, sepsis, and liver disease)
3. Routine testing of platelet function is not recommended. It is reasonable to use if,
   i. Hemorrhage is not diagnosed by SCT and VET.
   ii. A potent (P_2Y_{12} inhibitors) antiplatelet drug is used.

AUTOLOGOUS BLOOD DONATION

Preoperative autologous donation (PAD) is known, but not commonly used as blood conservation strategy. Through the PAD, the patient is protected against febrile and non-febrile transfusion reactions, alloimmunization, and graft-versus-host disease (GVHD). However, the risk for infection or hemolysis persists, and the risk for transfusion due to anemia induced by donation and availability of autologous blood is increased with a high cost. On the other hand, PAD should be limited to healthy individuals with a long life expectancy requiring intense blood transfusion or those without cross-match compatible blood. The eligibility criteria for PAD are good health condition, being tolerant to iron replacement and surgery with the risk for bleeding more than 500 to 1000 mL. It is contraindicated in case of cardiovascular risk factors (unstable angina, recent myocardial infarction, heart failure, aortic stenosis, angina at rest, or TIA), organ dysfunction, and active infection.

Recommendations

1. Routine use of PAD is not recommended, as PAD is associated with lower preoperative Hb levels leading to higher amounts of transfusion.[46-48]
2. PAD may be used in case of rare blood type, or if identification of alloantibody is not possible and cross-match compatible blood is not available.[49,50]

BLOOD CONSERVATIVE SURGICAL TECHNIQUES

Operative technique is one of the most important steps in the prevention of morbidity related to bleeding and transfusion. The decision should be made by the multidisciplinary Heart Team. Hemodilution and coagulopathy due to CPB are prevented by off-pump cardiac surgery which may reduce transfusion.

However, meta-analyses and randomized trials have not reached a final judgment about this issue.[51,52] Therefore, it is recommended only in selected patients in accordance with the recent guidelines.[2] Minimally invasive approaches cause less surgical trauma which reduce bleeding. Most of studies have concluded that the use of blood products would be restricted by minimally invasive surgery.[53-55]

Recommendations

1. The decision of the multidisciplinary team (a surgeon, cardiologist, anesthesiologist, and perfusionist) is strongly recommended in terms of treatment strategy, incision, and operative technique to prevent complications due to bleeding and transfusion.
2. Off-pump surgery may be preferred to reduce perioperative use of blood products, if optimal surgical treatment is provided.
3. Minimally invasive techniques (mini-thoracotomy, mini-sternotomy transcatheter aortic valve implantation [TAVI], other transcatheter techniques) may be performed to reduce perioperative use of blood products, where applicable.

THE USE OF FRESH WHOLE BLOOD (FWB)

The FWB identifies the donor blood stored at room temperature less than 24 hours after donation.[56] Hemostatic properties of FWB gradually decrease by lowering FV and FVIII levels, and viable platelets yield in course of time. In addition, the increase in the extracellular potassium and lactate and the decrease in glucose and pH levels during the storage of whole blood result in metabolic imbalances after transfusion.[57,58]

Although, several clinical studies have demonstrated the superiority of FWB to reconstituted blood which is composed of FFP, RBC, and single donor platelet concentrate (dPC) units in terms of bleeding control, overall studies have concluded that the only advantage of FWB against reconstituted blood is less donor exposure.[57-59]

Recommendation

1. The use of FWB is not recommended in cardiac surgery, if blood components are avalibale.

ANTIFIBRINOLYTICS

Antifibrinolytics (tranexamic acid [TXA], Epsilon-aminocaproic acid [EACA], and aprotinin) are used to reduce blood loss, blood transfusion, and the need for reoperation in cardiac surgery.[60,61] This triple effect has been demonstrated for aprotinin and TXA.[60,62] However, the effect of EACA on the reduction of reoperation has not been demonstrated, yet.[60]

The multi-center Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) study showed that blood transfusion requirement ($p<0.001$) and reoperation rate (1.4% and 2.8%, $p=0.001$) were lower in the TXA group, despite increased neurological events such as convulsions.[62] Several meta-analyses also demonstrated that aprotinin reduced the need for reoperation and blood transfusion.[60] However, this drug has not been licensed, except for some countries, due to its adverse effect on cardiovascular events and mortality. Thus, care should be taken to ensure that it is approved by the local authority and the balance of benefit/harm should be considered. Although there is a limited number of studies comparing EACA to other antifibrinolytic agents, there are meta-analyses showing similar effects to other antifibrinolytic agents.[63]

Recommendation

1. Antifibrinolytics should be used to reduce bleeding and transfusion.[60,62,64]

ACUTE NORMOVOLEMIC HEMODILUTION (ANH)

Acute normovolemic hemodilution is one of the strategies to decrease the need for allogeneic blood transfusion in cardiac surgery. It is commonly used, reliable, easy-to-apply, and low-cost technique. The ANH has been shown to regulate microcirculation by reducing blood mass, blood cell damage, and preserving organ functions by reducing the inflammatory response.[65] The amount of transfusion has been reduced by 18 to 90% through ANH.[66]

Recommendations

1. ANH may be used to reduce perioperative transfusions in selected cases.[67]
2. It is reasonable to use ANH in patients with autologous blood transfusion, rare blood group, alloantibody positivity, and refusing allogenic transfusion for special reasons.[67]
3. ANH is not recommended:
   - In the presence of severe anemia (Hb <11 g/dL or Hct <33%) or platelet dysfunction.[67]
   - Coronary artery disease (critical stenosis, unstable angina, left ventricle dysfunction).[68]

- In the presence of severe pulmonary disease, impaired renal function and hepatic dysfunction.[68]

4. Each center should establish their own protocol (patient selection, vascular access, ANH volume, fluid to be replaced, blood collection, and storage) in ANH applications.

HEPARIN-PROTAMINE MANAGEMENT

Optimal anticoagulation during CPB and its adequate neutralization after CPB is important to maintain the balance between thrombosis and bleeding in cardiac surgery. Less anticoagulation may cause thrombi, more consumption of coagulation factors, and vice versa, it may cause bleeding and consumption of coagulation factors. For heparin, dosing, its application, measurement of anticoagulation, appropriate reversal by protamine, alternatives of heparin are the main challenges during CPB.

Recommendations

1. The bolus administration of UFH based on the body weight (300 to 400 IU/kg) is reasonable to ensure adequate anticoagulation.[69]
2. The efficacy of anticoagulation should be measured by therapeutic functional test or maximum activated clotting time (ACT) at regular intervals before and during CPB. The ACT should be kept for more than 480 sec during CPB.[69,70]
3. Heparin concentration analysis may be used in addition to ACT.[71]
4. If anticoagulation is inadequate before CPB, despite additional doses of heparin, FFP transfusion or antithrombin III infusion may be used.[72]
5. Protamine dose adjustment according to heparin level is reasonable to prevent bleeding and to minimize blood product use.[71]
6. It is reasonable to provide a protamine/heparin ratio of 1:1. The ratio above 2.6:1 is associated with platelet dysfunction, coagulopathy, and bleeding.[70]
7. In patients requiring high-dose UFH use, low-dose protamine infusion may be used for 6 hours after CPB to prevent heparin rebound.[73]
8. The adverse effects of protamine (i.e., vascular collapse, pulmonary hypertension, and anaphylaxis) should be recognized and resuscitative care should be planned.[74]
9. In case of heparin-induced thrombocytopenia (HIT) diagnosed based on functional serum tests, it is reasonable to postpone (about 2 to 3 months) elective surgery requiring CPB.
10. In case of an emergent surgery, it is reasonable to use bivalirudin as an alternative to heparin. Its efficacy can be monitored by the ecarin clotting time (ECT). The reversal of its effect by any antidote is not possible, which may cause bleeding after CPB and require additional hemostatic strategy.[70]

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia is an adverse drug reaction of heparin which may result in potentially fatal clinical entities. It is not uncommon and caused by risk factors similar to cardiac surgery.[75,76] It develops within 1 to 2 weeks after heparin, and antibodies to the heparin-platelet factor 4 complex play a key role in the clinical status of the patient.[2] The risk for HIT development is independent of the type, dose, and route of administration of heparin. Clinical picture includes thrombocytopenia and both arterial and venous thrombosis due to activation of platelets. The 4T score should be assessed for the likelihood of HIT by thrombocytopenia, time of platelet decline, presence of thrombosis, and other causes of thrombocytopenia.[77] Discontinuation of heparin alone is not sufficient to reduce the risk for thrombosis, and non-heparin anticoagulant treatment is necessary.[78-80]

If cardiac surgery cannot be postponed, bivalirudin or argatroban may be used as an alternative for anticoagulation during CPB. However, the use of non-heparin anticoagulants (bivalirudin, argatroban, danaparoid, fondaparinux, or DOACs) have not been approved for use in the treatment of acute HIT. The treatment agent and application amounts to be selected should be based on the patient-specific evaluation.

Recommendations

1. 4T score should be calculated in case of HIT suspicious clinical findings such as thrombocytopenia accompanied by a thrombotic event.[77]
   - If score is 0-3, heparin treatment is regulated according to the indication and non-heparin anticoagulants are discontinued, if possible.
   - If score is ≥4, heparin is discontinued and non-heparin anticoagulant is initiated.

If immunological assay yields negative results, it is treated as a low 4T score. Otherwise (in case of positivity), a functional assay may be performed to confirm.

- If the score is 6-8, the probability of the diagnosis is high, even the functional test is negative.

2. In case of elective cardiac surgery requiring heparin, it is reasonable to postpone the procedure until HIT antibodies become negative.
3. If cardiac surgery cannot be postponed, it is reasonable to use bivalirudin or argatroban as an alternative for anticoagulation during CPB.
4. In case of HIT, the use of heparin (UFH or LMWH) should be avoided in the perioperative period.
5. Non-heparin anticoagulants may be used in case of HIT, even if it is off-label use.

VOLUME THERAPY

The aim of fluid (crystalloid or colloid) therapy in cardiac surgery is to maintain adequate blood pressure, cardiac output, tissue perfusion, and oxygenation. A consensus has not yet been reached upon on the optimal choice of fluids, either crystalloid or colloid. However, it is known that hemodilution is caused by priming and volume resuscitation, and both increase the use of blood products.[81]

Crystalloid solutions are routinely used in cardiac surgery, since they cause lower rates of coagulopathy, infection, and anaphylaxis with a lower cost. However, high-volume normal saline solution (0.9%) has been shown to alter serum osmolarity, increase the blood product use, cause hyperchloremic acidosis, and postoperative acute renal failure. Stable isotonic solutions such as ringer lactate or ringer solution are therefore recommended.[82]

The most commonly used colloid solutions are hydroxyethyl starch (HES) solutions, albumin and gelatin which are more effective to expand intravascular volume.[83,84] However, the main disadvantages include impaired renal function, need for renal replacement therapy, tendency to bleed, and an increased risk for mortality. There are conflicting results in the literature and yet a single consensus has not been established for the use of colloid solutions.[85-87] Nonetheless, new-generation HES solutions seem to be safer in terms of coagulopathy and renal complications.[88]

Recommendations

1. The target is the hemodynamic stability in the perioperative period provided by volume therapy.[89]
2. Preoperative risk factors, hemodilution, high Hct values, and coagulation status should be considered during volume therapy in the perioperative period.[72]
3. In addition to fluid selection, timing, monitoring (particularly dynamic, transesophageal echocardiography), and evaluation of hemodynamics are crucial.[72]
4. There is no advantage in using HES as the prime solution to reduce bleeding and blood product use.[90]
5. Hemodilution should be avoided to reduce bleeding and blood transfusion.[81]
6. The use of new-generation HES solutions are not recommended to reduce hemorrhage, although limitation of hemodilution is reasonable to reduce bleeding and transfusion.[72]
7. The use of HES solutions in volume therapy should be restricted to prevent renal complications and reduce mortality.[91]
8. Stable and isosmotic electrolyte solutions may be used, if crystalloid solutions are preferred.[92]
9. The colloid solution use should not exceed 30 mL/kg per day; new-generation HES solutions or gelatin may be preferred, if colloids are to be used.[93]
10. In the postoperative period, balanced solutions (ringer, ringer lactate) should be preferred as the maintenance fluid therapy.[82]
11. FFP should not be used for volume extension.[72]

MINIMALLY INVASIVE EXTRACORPOREAL CIRCULATION AND STRATEGIES

Hemodilution, excess activation of coagulation system, loss of platelets, and its function are associated with systemic inflammatory syndrome caused by CPB which increase the risk for transfusion in the perioperative period.[94-96]

The Minimal Invasive Extracorporeal Minimally Invasive Extracorporeal Circulation (MiECC) defines essentially closed, shortened, biocompatible circuit without venous reservoir which requires less prime volume and anticoagulation.[97] Meta-analyses and studies have shown the beneficial

effect of the use of MiECC in terms of packed red cell transfusion.[98-100] Retrograde or antegrade autologous priming techniques are also used to reduce hemodilution during CPB. This beneficial effect has been confirmed in several studies and recommended by the recent guidelines.[72,101,102]

Recommendations

1. The use of MiECC is reasonable to decrease the risk for transfusion.
2. The RAP and AAP can be used to reduce hemodilution and to decrease the amount of transfusion.

AUTOTRANSFUSION

In cardiac surgery, blood taken from the mediastinal shed and remaining into the CPB circuit are collected, processed, and infused to the patient intra- and postoperatively through the autotransfusion techniques.[72,103] As a result, allogenic blood transfusion, particularly RBC transfusion, can be reduced by the cell-salvage system.[72,103] Besides, systemic inflammatory response related to CPB may cause postoperative organ dysfunction and complications which can be reduced by autotransfusion.[104] The use of autotransfusion system improve the anti-inflammatory cytokine/pro-inflammatory cytokine ratio.[105]

Recommendations

1. It is reasonable to use autotransfusion (cell-salvage system) to reduce transfusion, particularly in high-risk patients.

ULTRAFILTRATION (UF)

Hemodilution during CPB may result in an increased total body water, interstitial edema of vital organs, hypoxia, hypotension, coagulopathy, renal dysfunction, myocardial and cerebral ischemia, and even mortality. Ultrafiltration is a hemoconcentration technique which filtrates the plasma from blood via semi-permeable membrane which is used as a blood conversation strategy in cardiac surgery. The beneficial effects of UF in cardiac surgery patients are uncertain and, although some studies have shown a benefit, some others have provided controversial results.[106] Several studies have also demonstrated reduced RBC transfusions with the use of UF. In a randomized-controlled study from Brazil, modified ultrafiltration (MUF) groups had reduced chest tube drainage compared to control group after 48 hours and the Hct levels were higher and transfusion requirement was less in the MUF group.[107] Meta-analysis conducted by Boodhwani et al.[108] found a benefit of UF in lower rates of postoperative bleeding and blood transfusions. Mongero et al.[109] analyzed a total of 40,650 (propensity-matched) adult cardiac surgery cases for a 61-month period and concluded that UF was not associated with a reduction of risk for RBC transfusion during cardiac surgery.

Recommendations

1. There is no adequate evidence to recommend the routine use of UF as a blood conversation technique or to decrease postoperative bleeding in adult cardiac surgery.
2. The UF, particularly MUF, may be used in selected patients such as volume overload or excessive use of crystalloid cardioplegia.

HEMOSTATIC AGENTS

A. Fresh Frozen Plasma

Recommendations

1. FFP should not be used prophylactically to reduce blood loss or reduce the need for blood products in cardiac surgery.[110,111]
2. The use of FFP is reasonable to decrease bleeding due to coagulation factor deficiency and the need for blood transfusion, particularly by the VET guidance.
3. FFP may be used to reverse the effect of oral VKAs preoperatively.[110,111]

B. Factor XIII

Factor XIII (FXIII) is a coagulation factor acting at the end of the coagulation cascade, provide a tight and strong clot formation by cross-linking fibrin monomers. There is no evidence that the use of FXIII which reduces bleeding, the need for blood products, and reoperation for bleeding.[112]

Recommendation

1. Prophylactic use of FXIII is not recommended, but may be beneficial in selected patients with postoperative plasma FXIII level less than 70% of normal value.[112]

C. Fibrinogen

In cardiac surgery, hypofibrinogenemia is a common coagulopathy associated with CPB, hemodilution, and bleeding which strongly causes bleeding.[113]

Recommendations

1. Fibrinogen concentrate should not be used prophylactically to reduce bleeding or the need for transfusion.[114]

2. It is reasonable to use fibrinogen concentrate in case of bleeding related to hypofibrinogenemia (lower than 1.5-2 g/dL).[115]

D. Prothrombin complex concentrate

Prothrombin complex concentrate comprises coagulation factors (Factors II, VII, IX, X) whose production is vitamin K-dependent. It (4 factors or activated form) is used to treat bleeding related to VKA or coagulation factor deficiency, and to reverse VKA effect in case of an emergent surgery. In patients with elevated international normalized ratio (INR) values (>4-5) under VKA treatment, it is aimed to reverse the effect of VKA with PCC or FFP, when an urgent surgical intervention is required.[116]

Recommendations

1. It is reasonable to use PCC in case of bleeding associated with VKA therapy or coagulation factor deficiency.
2. PCC may be preferred to FFP with the intent of rapid and effective reversal of VKA to prevent complications related to FFP.[116]

E. Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) is a vasopressin analog which induces the von Willebrand factor (vWF) release from endothelial cells.[117] Although it has been argued that perioperative DDAVP use in cardiac surgery may lead to a slight decrease in the postoperative bleeding, this effect has been found to be more prominent in patients with platelet dysfunction or preoperative ASA use.

Recommendation

1. Desmopressin should not be used prophylactically to reduce blood loss. However, in patients with bleeding related to platelet dysfunction (inherited or acquired), the use of DDAVP is reasonable to reduce blood loss and transfusion requirements.[118]

F. Recombinant Factor VIIa

After tissue damage, Factor VIIa (FVIIa), formed by the effect of tissue factor, plays a role in the coagulation cascade by activating Factor X. Although it is suggested to use in the management of hemorrhages refractory to conventional methods in adult and pediatric cardiac surgery, there are some reports of increased thromboembolic events.[119-121]

Recommendation

1. FVIIa should not be used prophylactically to reduce bleeding in cardiac surgery.
2. FVIIa may be used in case of life-threatening hemorrhage refractory to conventional hemostatic methods.[120]

G. Topical hemostatic agents (THAs)

Topical hemostatic agents can be used to support the coagulation system in case of bleeding which cannot be controlled by conventional methods.[122] These agents are classified according to characteristics as active (containing anti-bleeding agents) and passive (without anti-bleeding agents), or both.

G.1. Active THAs

Active THAs induce coagulation system by stimulating conversion of fibrinogen to fibrin at the site of bleeding via a high concentration of thrombin.[123]

Recommendation

1. The use of human-derived thrombin is reasonable in case of a high risk for bleeding in surgical sites.[124]

G.2. Passive THAs

Passive THAs (collagen, cellulose, gelatin, and polysaccharides) do not contain coagulation factors, but have physical properties which lead to compression and platelet aggregation.[125]

Recommendation

1. The routine use of passive THAs in cardiac surgery is not recommended, although it may be used in case of bleeding from anastomosis and suture sites in patients with a high risk for transfusion.[126]

G.3. *Fibrin sealants*

Fibrin sealants contain fibrinogen and thrombin, leading to clot formation in the bleeding site.[127]

Recommendation

1. The use of fibrin sealants is reasonable in case of bleeding which arises from the needle hole in cardiac and aortic surgery.[126]

MANAGEMENT OF BLEEDING

Transfusion Criteria

Cardiac surgery carries a high risk for transfusion; however, transfusion should be administered for therapeutic, but not preventive purposes.[128] Transfusion criteria may vary according to personal approaches and decisions, which is not based on scientific evidence. The following transfusion principles should be adopted:

i. Transfusion should be applied in case of acute blood loss, hypoxia due to anemia, and coagulopathy causing bleeding.
ii. The balance between benefit/harm should be considered before transfusion.
iii. Laboratory values are not a trigger for transfusion.
iv. Transfusion should be applied, if there is a sufficient amount of knowledge and equipment to treat complications.
v. Patients need to be monitored during transfusion.

Triggers for Packed Red Cell

1. In case of Hb ≥10 g/dL or Hct ≥30%, transfusion should not be applied.[129]
2. In case of Hb ≥8 g/dL or Hct ≥24%, transfusion should be avoided unless;
   a. An emergent surgery
   b. Acute coronary syndrome
   c. The need for high-dose inotropes or mechanical circulatory support
   d. Venous oxygen saturation below 65%
   e. Arterial blood lactate level above 4.0 mmol/L
   f. Inadequate global body perfusion
   g. Massive bleeding
   h. End-organ ischemia (myocardial ischemia, stroke, or anuria)
3. In case of Hb 7 to 8 g/dL or Hct 21 to 24%, transfusion may be considered, if there is low oxygen delivery to tissues.[128]
4. In case of Hb below 7 g/dL, transfusion is reasonable.[129]
5. In case of Hb below 6 mg/dL, transfusion should be done.

Fresh frozen plasma

1. FFP should not be used to prevent bleeding or to expand intravascular volume.[130]
2. FFP should not be considered as the first-line therapy, if coagulopathy can be treated by VKA dose adjustment or vitamin K.
3. FFP should not be used in case of coagulopathy without bleeding.[131]
4. FFP may be used in case of coagulopathy due to massive transfusion or major surgery.[12,131,132]
5. FFP may be used in case of bleeding due to coagulation factor deficiency, when fractionated blood products are unable to be obtained.[12,131,132]
6. FFP may be used in case of bleeding due to VKA therapy, when PCC is not available.[12]
7. The use of PCC (4-factors or activated form) is reasonable, if emergent reversal of VKA is needed.[12]
8. FFP can be used empirically or level-guided, in case of antithrombin III deficiency.[72,131,133]
9. In case of bleeding, off-label use of PCC may be considered as an alternative to FFP.

Platelet

Transfusion is reasonable:

1. If the platelet count is below 50×10^9/L in patients with bleeding
2. If thrombocytopenia due to massive transfusion is present
3. If thrombocytopenia due to disseminated intravascular coagulopathy is present.[72,133,134]

Cryoprecipitate

1. The use of cryoprecipitate is reasonable in case of bleeding accompanied by low (below 1.5 to 2 g/dL) fibrinogen levels.[135]
2. VET-guided use of cryoprecipitate is reasonable in case of bleeding.
3. Fibrinogen concentrate can be used instead of cryoprecipitate, if available.

Viscoelastic test-Guided Coagulopathy Treatment

Bleeding due to coagulopathy has worse consequences than surgical causes.[136] The treatment of coagulopathy under the VET guidance may decrease the use of blood products and may improve clinical outcomes.[136-140]

Recommendations

1. VET-guided coagulopathy treatment is reasonable in case of bleeding or in selected patients with a high risk for bleeding.
2. The routine use of VET is not recommended in cardiac surgery.
3. Easy access, service 24/7, professional evaluation, and algorithmic application should be provided for effective use of VET.
4. Suggested treatment algorithms for thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are presented in the book.[3]

Re-Exploration for Bleeding

Bleeding, re-exploration and transfusion, alone or combined, affect the worst outcomes in cardiac

surgery.[1] The rate of re-exploration is about 2 to 8% and the major causes are surgical sites.[1,141,142] Therefore, early diagnosis of surgical bleeding, and emergent and appropriate correction is critical to prevent complications related to bleeding and blood products.

Recommendations

1. Meticulous surgery should be performed to prevent bleeding.
2. The team (a surgeon, intensive care specialist, and nurse) needs to be aware to keep chest tubes open. Active drainage systems may be used for this purpose.[143]
3. The team (a surgeon, intensive care specialist, and nurse) needs to be aware about hemodynamic changes related to bleeding.
4. Recommended amount of bleeding for re-exploration:
   - Over 300 mL/h within the first hour
   - Over 250 mL/h within the first 2 hours
   - Over 200 mL/h within the first 3 hours or total 750 mL
   - Massive bleeding
   - Cardiac arrest accompanied by bleeding
   - Cardiac tamponade.
5. Early re-exploration (within the first 12 hours) should be done in case of persistent drainage.[144,145]
6. In case of massive bleeding or bleeding associated cardiac arrest, re-exploration may be done in the intensive care unit.

POSTOPERATIVE ANTITHROMBOTIC DRUG MANAGEMENT

Medical treatment plays a key role for the success of perioperative and long-term care in cardiac surgery which reduces morbidity and mortality.[26] Postoperatively, antiplatelet and anticoagulant therapy is crucial to prevent ischemic events, arrhythmias and to manage thromboembolic risk factors.[146] However, these agents may increase the risk for late bleeding complications. Therefore, appropriate use of antiplatelet or anticoagulant agents should be recognized by the Heart Team.[147]

Recommendations

Acetylsalicylic Acid

1. Acetylsalicylic acid should be restarted within 24 hours (6 hours, if possible) after coronary artery bypass grafting (CABG), when early bleeding is not significant.[148]
2. It is reasonable to restart within 24 hours after surgery, when there is no concern about bleeding in patients undergoing non-coronary cardiac surgery with a preoperative indication for ASA.

Dual Antiplatelet Therapy

1. It is reasonable to restart DAPT after CABG as soon as it is considered safe in patients with ACS. In patients with a high risk for ischemia, P_2Y_{12} inhibitors should be restarted within 48 hours after surgery.[149-151]
2. It may be considered to restart P_2Y_{12} inhibitors within 3 to 4 days postoperatively, when the risk for ischemia is not high (e.g. recent stent implantation >1 month or ACS without stenting).[12,26,147,152-157]

Anticoagulant Therapy

Mechanical valve

1. Anticoagulant treatment with UFH and VKA should be started on the first postoperative day and maintained, until the INR is in therapeutic range.[158,159]
2. In case of bleeding risk, VKA may be restarted, whenever it is deemed safe, preferably within 48 hours.
3. In patients with an indication for postoperative therapeutic bridging, it is reasonable to start UFH 12 to 24 hours after surgery.
4. Low-molecular-weight heparin may be considered as an alternative bridging strategy to UFH 24 to 48 hours after surgery.[39,160]
5. It is reasonable to restart VKA on the first postoperative day, and lifelong oral anticoagulation with VKA is recommended for all patients.[2,158]
6. DOACs are not recommended in patients with a mechanical valve prosthesis.[161]
7. The addition of low-dose ASA (75 to 100 mg/day) to VKA should be considered in case of concomitant atherosclerotic disease or thromboembolism, despite an adequate INR.[161-165]

Bioprosthetic valve

1. VKA is reasonable on a lifelong basis for patients with a surgical or transcatheter bioprothesis who have other indications for anticoagulation.

2. VKA may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.[166]

Others

1. VKA should be considered for the first 3 months after mitral or tricuspid valve repair or valve-sparing procedures.
2. DAPT may be considered after TAVI, if any of anticoagulants are not indicated.[167]

BLOOD MANAGEMENT IN PEDIATRIC CARDIAC SURGERY

In congenital cardiac surgery, the indications and complications of transfusion show a considerable differences than in adults. These differences are predominantly related to the physiological and developmental factors, as well as pathophysiology of the diseases encountered in the pediatric population. Although developing an evidence-based algorithm is challenging, the basic principle of transfusion is always the same: transfusion of the right blood product to the right patient at the right time, and the right indication.

Unfortunately, many of the parameters in an infant/child undergoing cardiac surgery are not unique. More importantly, it is not possible to evaluate the algorithms of blood conservation on evidence-based implementations. Therefore, possible scenarios for low- and high-risk patients may be defined and flowcharts for blood conservation may be recommended.[168]

Preoperative Recommendations

1. Anemia, iron deficiency, and history of bleeding or coagulation disorders should be evaluated preoperatively.
2. A multidisciplinary approach for the diagnosis and treatment of preoperative anemia should be standardized.
3. The discontinuation of antithrombotic treatment should be optimized.
4. Autologous blood donation may be considered in selected cases.[17,169-172]

Intraoperative Recommendations

5. Meticulous surgical technique for minimizing blood loss should be provided. Cyanotic patients, those undergoing a reoperation, and newborns are at a higher risk for bleeding.
6. Factors related to CPB:
   - Hemodilution-optimal Hct level: Although there is no consensus about an optimal Hct level in pediatric cardiac surgery, 25% may be considered.[173]
   - Techniques for hemoconcentration: Conventional or MUF may be used in reversing the effects of hemodilution.[174] Optimal management of the composition of prime solution is recommended.
   - Optimal management of hypothermia during CPB is reasonable.
   - Cell-savers may be used in selected pediatric cases.[175]
   - Optimal algorithm for anticoagulation and neutralization during CPB should be provided.
   - Antifibrinolytics may be useful to avoid bleeding in pediatric population.[176]
   - To analyze coagulation system, VET can be used, particularly in case of bleeding.[177]
   - Recombinant coagulation factors may be administered in case of bleeding.[178]

ULTRA-BRIEF STEPS OF PBM

1. Identify the risk for thrombosis and bleeding.
2. Treat anemia.
3. Optimize cessation and bridging of antithrombotic drugs.
4. Use antifibrinolytics.
5. Optimize anticoagulation during CPB.
6. Optimize volume therapy.
7. Minimize hemodilution.
8. Diagnose and treat bleeding promptly.
9. Use an individualized and VET-guided approach for the use of blood products.
10. Choose the optimal timing to restart antithrombotic drugs.

In conclusion, patient blood management should be a philosophy for the Heart Team to improve the outcomes of surgical procedures and postoperative process. Each center should establish its own algorithm and train the whole team for a complete application. This is the first report in Turkey regarding this issue and will be updated and improved every two years. As a continuation of this report, a web-based, multi-center prospective study is planned to be initiated by the Turkish Society of Cardiovascular Surgery and Society of Cardio-Vascular-Thoracic Anaesthesia and Intensive Care. The analysis of this study would provide a great source of scientific data which would guide future applications and update current knowledge.

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