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Management of Blood Loss in Hip Arthroplasty: Korean Hip Society Current Consensus

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The volume of hip arthroplasty is stiffly increasing because of excellent clinical outcomes, however it has not been shown to decrease the incidence of transfusions due to bleeding related to this surgery. This is an important consideration since there are concerns about the side effects and social costs of transfusions. First, anemia should be assessed at least 30 days before elective hip arthroplasty, and if the subject is diagnosed as having anemia, an additional examination of the cause of the anemia should be carried and steps taken to address the anemia. Available iron treatments for anemia take 7 to 10 days to facilitate erythropoiesis, and preoperative iron supplementation, either oral or intravenous, is recommended. When using oral supplements for iron storage, administer elemental iron 100 mg daily for 2 to 6 weeks before surgery, and calculate the dose using intravenous supplement. Tranexamic acid (TXA) is a synthetic derivative of the lysine component, which reduces blood loss by inhibiting fibrinolysis and clot degradation. TXA is known to be an effective agent for reducing postoperative bleeding and reducing the need for transfusions in primary and revision total hip arthroplasties. Patient blood management has improved the clinical outcome after hip arthroplasty through the introduction and research of various agents, thereby reducing the need for allogeneic blood transfusions and reducing the risk of transfusion-related infections and the duration of hospitalizations.

Key Words: Transfusion, Blood management, Hip arthroplasty

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INTRODUCTION

Among surgical techniques introduced in the 20th century, hip arthroplasty has demonstrated some of the best treatment results and its use is becoming more frequent as the population ages. However, a considerable amount of blood loss is unavoidable during hip arthroplasty. Park et al.[1] have reported that approximately 1,500 mL of blood is lost during the surgery. Even though knowledge is increasing and blood management techniques are gradually progressing, the incidence of allogeneic blood transfusions in the field of orthopedics has not decreased. Considering the side effects and social costs of transfusions (e.g., immune suppression, acute and delayed hemolytic reaction, anaphylaxis, transfusion-related acute lung injury, host response and postoperative infection), studies on the needs and methods of patient blood management are warranted.

The authors of this study reviewed recent published methods designed to minimize bleeding and transfusion and guidelines for appropriate transfusion protocols during hip arthroplasty.

PREOPERATIVE ANEMIA ASSESSMENT

Even mild degree of anemia can contribute to the risk for postoperative transfusions and mortality rates in hip surgery[2]. Therefore, the presence of anemia should be evaluated at least 30 days before surgery in patients undergoing hip surgery[3]. When a patient is diagnosed with anemia, an additional examination should be carried out to determine the cause of the anemia and to correct this condition, and surgery should be postponed until the anemia is resolved[3]. For preoperative evaluation, detailed history taking, including gastrointestinal-related symptoms especially in elderly patients, and assessment of complete blood count (CBC), iron studies including ferritin, C-reactive protein, renal function and others is required.

Serum hemoglobin is the level of hemoglobin in the blood and measured in g/dL (normal ranges, male: 13-17 g/dL, female: 12-15 g/dL), and hematocrit measures the percentage (%) of red blood cells (RBC) in the serum (normal ranges, male: 39-50%, female: 36-45%). Among RBC indices, the mean corpuscular volume (MCV) is a measure of the average volume of a RBC in femtoliter (fL) (normal range, 62-96 fL) and the mean corpuscular hemoglobin (MCH) is the average amount of hemoglobin per RBC and the unit of measurement is picogram (pg; normal range, 20-31pg). The mean corpuscular hemoglobin concentration (MCHC) is the average concentration of hemoglobin in RBCs. The MCHC is often decreased in microcytic anemia, mostly normal in macrocytic anemia, and elevated in hereditary spherocytosis or sickle cell disease (normal range, 27-38 g/dL).

Tests for iron studies include CBC, peripheral smear, serum iron, total iron binding capacity (TIBC), serum ferritin, reticulocyte hemoglobin content and others. Ferritin is a universal intracellular protein that stores iron and releases it in a controlled fashion. Normal ferritin levels range between 15-200 ng/mL (males) and 12-150 ng/mL (females). A decrease in serum ferritin is the most specific lab test to determine iron-deficiency anemia. A low preoperative hemoglobin level before surgery is an independent risk factor of transfusion, and in cases of malnutrition, insufficient nutrients need to be supplemented[4]. The goal of correction before surgery is to elevate hemoglobin concentration to normal levels established by the World Health Organization[3,5]. Since erythropoiesis takes about 7-10 days, oral or intravenous (IV) iron supplementation is recommended for preoperative iron supplementation in cases of iron deficiency[3]. When using oral supplements for iron storage, a daily dose of 100 mg elemental iron is recommended for 2 to 6 weeks before surgery. When using IV iron supplementation, requirements can be estimated using the Ganzoni equation below[6].

Total iron deficit (mg)=[target Hb–actual Hb (mg/dL)] $\times$ weight (kg) $\times$ 0.24+500 mg

The dose of iron supplementation used for treatment purpose should be adjusted according to the formulations of iron supplements administered.

The best way to prevent postoperative anemia and the need for transfusion is to screen and correct anemia before surgery. The diagnosis and correction of anemia are very important because 74% of patients undergoing surgery experience anemia before and after surgery[7].

Since surgical manipulations induce inflammatory responses and inhibit erythropoiesis, oral iron supplementation after surgery is ineffective and generates side effects[8]. For this reason, IV iron supplementation is recommended to correct postoperative anemia and prevent transfusion following surgery[3].

The recommended dosage of IV iron supplementation after surgery is a dose of 200 mg of elemental iron per 500 mL of blood loss[3]. Since IV iron supplementation increases the risk of hypersensitivity reactions, it is recommended that this form of supplementation is administered in a clinical setting capable of managing anaphylactic or anaphylactoid reaction[9]. Thus, patients need to be thoroughly monitored

for 30 minutes after completion of IV iron supplementation[9]. In addition, iron supplements should be given in accordance with administration instructions written on product labels.

Preoperative erythropoietin can be used for adults who deposit more than 3 units of whole blood through pre-deposit program prior to hip surgery or for those who cannot pre-deposit despite of an estimated blood loss of greater than 1,000 mL intraoperatively[3]. For patients requiring facilitated production of maximum RBCs, IV administration is recommended at a dose of 600 IU/kg twice a week for 3 weeks. To prevent the reduction of iron stores associated with the use of erythropoietin, IV iron supplementation is advised[10,11].

STRATEGY TO MINIMIZE BLOOD LOSS

Preoperative tests for bleeding tendencies in patients should be performed. When patients have risk factors for anemia or intraoperative bleeding, surgeons should correct bleeding tendencies in order to avoid unexpected bleeding. Preoperative anemia is a risk factor that increases postoperative morbidity and mortality, and is known as a cause of iron deficiency in more than 1/3 of cases[12,13]. After evaluating the conditions and causes of anemia according to serum hemoglobin and ferritin concentrations, correction of anemia status is recommended from 4 weeks prior to surgery using iron, vitamin B12, folic acid, erythropoietin and others[14-16]. Adjustment of antiplatelet or anticoagulant agents such as aspirin, heparin, warfarin and clopidogrel are suggested for reducing intra- and post-operative bleeding. Furthermore, the possibility of transfusion caused by unexpected bleeding and associated complications can be lowered by determining family history of coagulopathy or presence of liver disease[17-21]. Although preoperative autologous blood donation is not thought to be cost effective and does not lower transfusion rates, it is considered as an option for those patients with rare blood types[22].

Since inappropriate positioning during surgery may influence intraoperative bleeding by generating venous engorgement, surgical positioning should be carefully considered and implemented. Moreover, the pressure and tidal volume of ventilator should be adjusted to decrease the mean intrathoracic pressure because positive pressure ventilation under general anesthesia may have an adverse effect on venous return[23].

Since intraoperative hypothermia may increase bleeding by reducing platelet function and enzyme activity in the coagulation cascade, the maintenance of normal body temperature is required[24]. Controlled hypotension technique reduces blood loss by decreasing blood extravasation and local wound blood flow, but consistent hemodynamic monitoring is required and this technique is not permitted in patients with coronary artery disease[25].

Central neuraxial blocks such as spinal and epidural anesthesia are known to have blood saving effects by decreasing sympathetic tone and venous tone, and their effects last until postoperative period[1,26-28]. Local anesthesia can reduce the need for transfusion and complication rates (e.g., postoperative mortality, thromboembolic events, pneumonia, respiratory depression, myocardial infarction, renal dysfunction)[27].

Intraoperative shed blood can be collected and processed for re-use using RBC salvage and reinfusion system[23]. Cell saver, one intraoperative auotologous transfusion technique in which drained blood is collected, washed, and reinjected, can also be considered. Cell saver is a reinjection technique in which the drained blood is filtered to remove hemolyzed cells, free hemoglobin and other impurities and washed for reinjection[29,30]. The use of cell saver protects patients and decreases the need for total RBC transfusions since the patient' s own blood is being transfused by collecting intraoperative blood loss[31].

The early diagnosis and treatment of intraoperative coagulopathy is crucial in order to reduce blood loss. Point-of-care testing appears to be useful for early diagnosis because several hemostasis-related factors can be identified at the bed side; fresh frozen plasma or fibrinogen concentrate can be used for treatment as needed[23].

The administration method and intraarticular injection of tranexamic acid (TXA) can significantly reduce bleeding volume[32]. In addition to TXA, the appropriate use of topical hemostasis agents can also be effective at reducing bleeding.

TRANEXAMIC ACID

TXA is one of the most important agents among a variety of intraoperative blood management protocols[33,34]. TXA is a synthetic derivative of the lysine component, and was discovered in 1962 by two independent research groups[35,36]. This agent reduces blood loss by inhibiting fibrinolysis and clot degradation. Intraoperative surgical trauma generates fibrinolysis and elevated fibrinolytic activity increases bleeding volume[37]. TXA inhibits the interaction of protease and activated plasmin on the surface-binding sites of fibrin by competitively and reversibly binding to the lysine-binding sites of plasminogen. This

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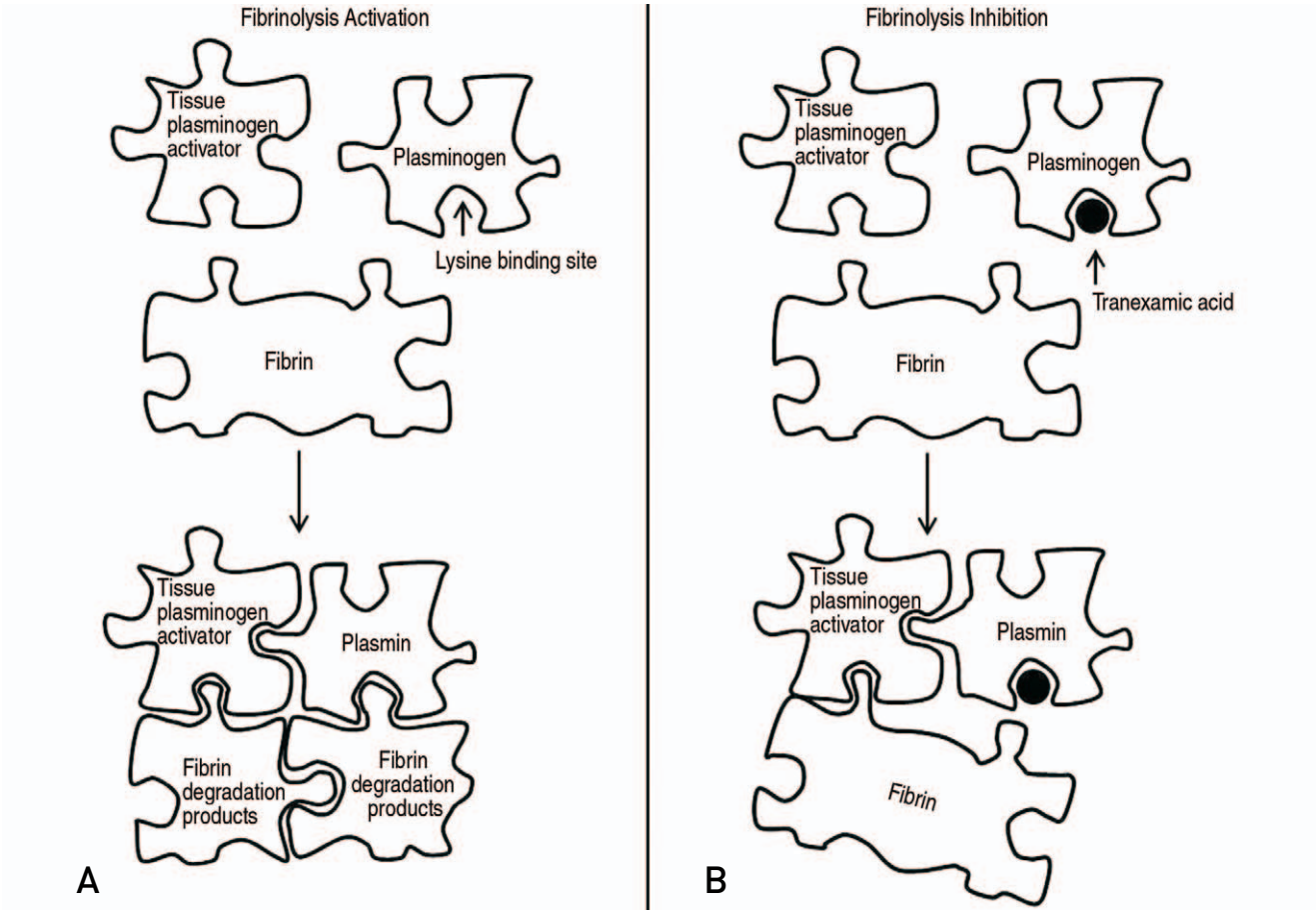

Fig. 1. Schematic representation of the mechanism of action of tranexamic acid. (**A**) Activation of fibrinolysis. (**B**) Inhibition of fibrinolysis. Due to structural similarity of lysine, tranexamic acid competitively inhibits binding of fibrin to plasminogen.

mechanism blocks plasmin-induced degradation of the fibrin clot (Fig. 1). As documented by several authors, the use of TXA effectively and safely reduces the amount of postoperative bleeding and the need for transfusions in primary total hip arthroplasty and revision hip arthroplasty[38-46]. However, the appropriate route (IV versus topical), correct dose and time of administration of TXA still remain unclear. Though a larger number of studies on IV administration of TXA in hip arthroplasty have been reported, a recent meta-analysis has revealed that the mean transfusion rate was 2.56 times lower than the non-TXA group and that the incidence of venous thrombosis was comparable among these two groups[47,48]. A variety of previous studies have suggested correct dose, administration time, frequency, etc; the general usage is as follows:

In IV TXA administration for total hip arthroplasty, 10-20 mg/kg or 1 g of TXA is given immediately before surgery[39]. Due to the pharmacokinetic properties of TXA, at least one IV administration is recommended postoperatively[49]. For topical TXA use, doses of higher than 2 g are more effective than low-doses[39]. A comprehensive analysis of systematic reviews and meta-analyses has not suggested that either IV or topical administration of TXA generates postoperative systemic thrombosis. However, recent clinical studies on the use of TXA in total hip arthroplasty have provided insufficient evidence on serious complications[38].

HEMOSTATIC MEDICAL DEVICES

Appropriate surgical techniques and minimally invasive approaches are fundamentally important to minimize intraoperative blood loss. Although suture, Bovie, clips and others are primarily used for hemostasis, hemostatic agents are used as adjuvants when hemostasis fails with primary methods[50].

Hemostatic agents are mainly divided into systemic and topical agents. Systemic hemostatic agents include lysine analog, protease inhibitor, aprotinin and others. Since one potential adverse event related to the use of these agents is the systemic activation of hemostatic factors, some

authors have described that the morbidity of cardiovascular disease, mortality, and long-term mortality may increase[51]. Efficacy, safety, fast adsorption to the tissues, absorbability, biocompatibility and ease-of-manipulation are required for topical hemostatic agents to be used at bleeding sites, and hemostatic agents having no side effects such as infection should be used.

Topical hemostatic agents are mainly divided into the following groups: i) mechanical, ii) chemical, iii) physical, and iv) physiological depending on their compositions and mechanisms[52]. Physical agents include bone wax, Ostene and others, and they limit blood loss by forming a physical barrier that compresses the bleeding site. Physical agents are commonly used as a primary option because of their cost effectiveness.

Chemical agents are caustic substances composed of zinc, silver nitrate or aluminum chloride. These agents precipitate proteins necessary for hemostasis and facilitate blood coagulation by blocking small vessels and producing thrombi by destroying adjacent tissues.

Physical agents include gelatin, cellulose, microfibrillar collagen and hydrophilic polymer. These hemostats induce hemostasis by facilitating thrombus formation by forming a three-dimensional meshwork where platelets aggregate to form a clot. Furthermore, their hygroscopic property leads to the accumulation of coagulation factors by absorbing blood.

Physiologic agents promote hemostasis by activating the coagulation cascade that naturally occurs at the vasoconstriction and bleeding sites. Physiologic agents can be based on pharmacology (e.g., epinephrine, TXA) or natural biology (e.g., thrombin, fibrin).

CURRENT CONSENSUS FOR APPROPRIATE AND SAFE TRANSFUSION AFTER HIP SURGERY

Pre- and post-operative anemia is very common, and "the 10/30 transfusion trigger rule" was empirically applied in the past. Transfusion is given when there is a transfusion trigger (i.e., hemoglobin level below 10 g/dL or a hematocrit level below 30%). However, this rule does not always apply in clinical practice since it is outdated and lacks clear evidence. Carson et al.[53] suggested that there is no need to use this conventional rule since there was no difference in mortality and morbidity of cardiovascular disease between a group of patients undergoing transfusions at hemoglobin levels of less than 10 g/dL compared with those undergoing transfusions at a hemoglobin level of 8 g/dL.

According to the National Institute For Health and

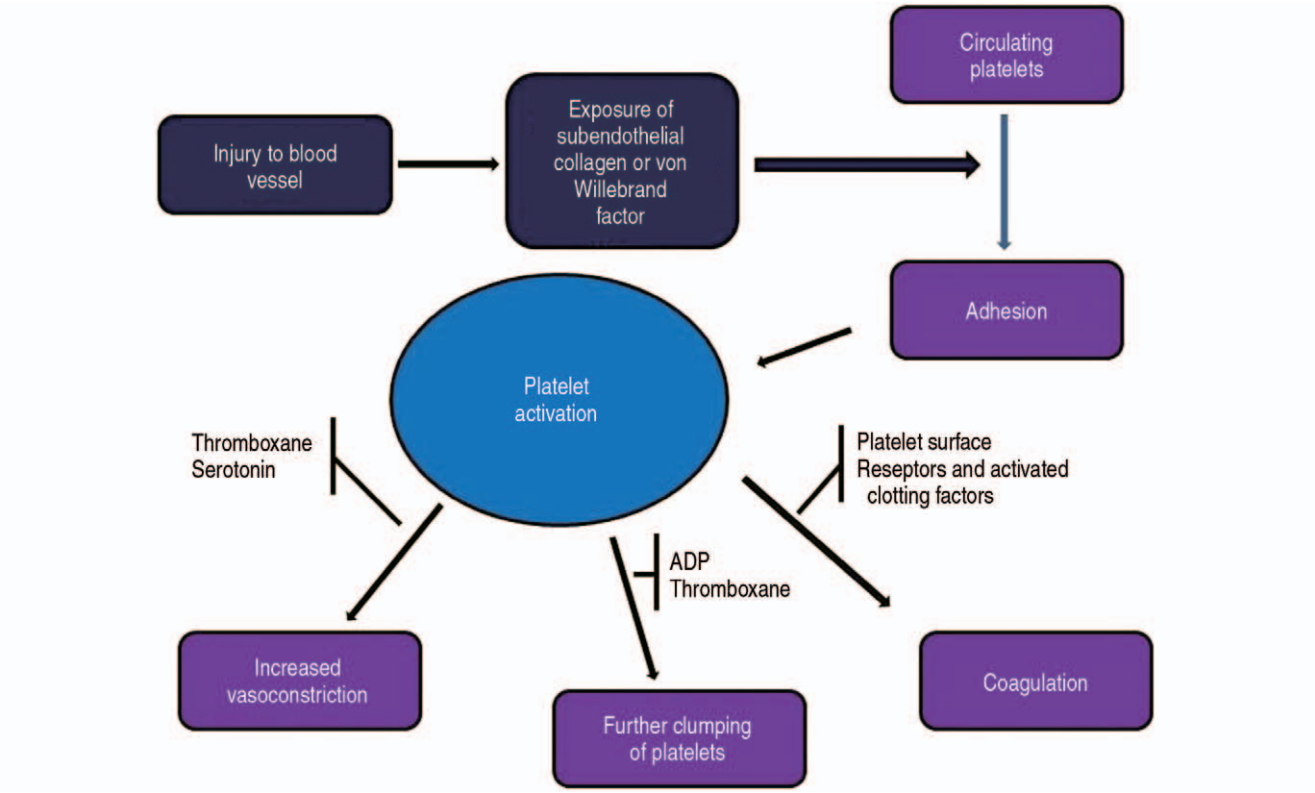

Fig. 2. Platelet activation system. ADP: adenosine diphosphate.

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Clinical Excellence (NICE) guidelines, an RBC transfusion should be considered when hemoglobin levels are less than 7 g/dL; transfusions are also permitted in patients with cardiovascular disease if their hemoglobin concentration is less than 8 g/dL. However, patients with chronic anemia should be assessed individually. Platelet transfusion is considered for patients who are associated with severe bleeding or a platelet count of less than 50×10^9/L and undergoing surgery expected to have blood loss. Fresh frozen plasma should only be used to replace a single coagulation factor deficiency when abnormal findings are confirmed in coagulation tests and heavy bleeding occurs.

DRUGS THAT INCREASE BLEEDING RISK

Blood vessel coagulation involves the exposure of subendothelial collagen or von Willebrand factor following vessel injury and the subsequent activation of platelets circulating in the injured area, and eventually vasoconstriction and platelet aggregation (Fig. 2). Medications that may increase bleeding risks include anticoagulants, antiplatelet, novel oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), selective norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) (Table 1).

Anticoagulants inhibit thrombosis by activating clotting mechanism on different areas; common anticoagulants include heparin, hirudin, warfarin and drotrecogin alfa. Thrombolytic agents degrade fibrinogen and fibrin and increase the conversion of plasminogen to plasmin, thus removing blood clots. The most common thrombolytic drugs are anistreplase, streptokinase, urokinase, tissue plasminogen activators (tPAs) (Fig. 3). Common antiplatelet

Table 1. Classification of Drug that Increase Bleeding Risk

Drug class	Specific agents
Anticoagulants	Argatroban, bivalirudin, desirudin, heparin, lepirudin, warfarin
Antiplatelets	Aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine
NOAs	Apixaban, dabigatran, edoxaban, rivaroxaban
NSAIDs	Low risk: celecoxib, etodolac, ibuprofen, meloxicam, nabumetone, salsalate
	High risk: flurbiprofen, indomethacin, ketorolac, meclofenamate, naproxen, oxaprozin, proxicam
SNRIs	Desvenlafaxine, duloxetine, venlafaxine
SSRIs	Citalopram, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline

NOA: novel oral anticoagulant, NSAID: nonsteroidal anti-inflammatory drug, SNRI: selective norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor.

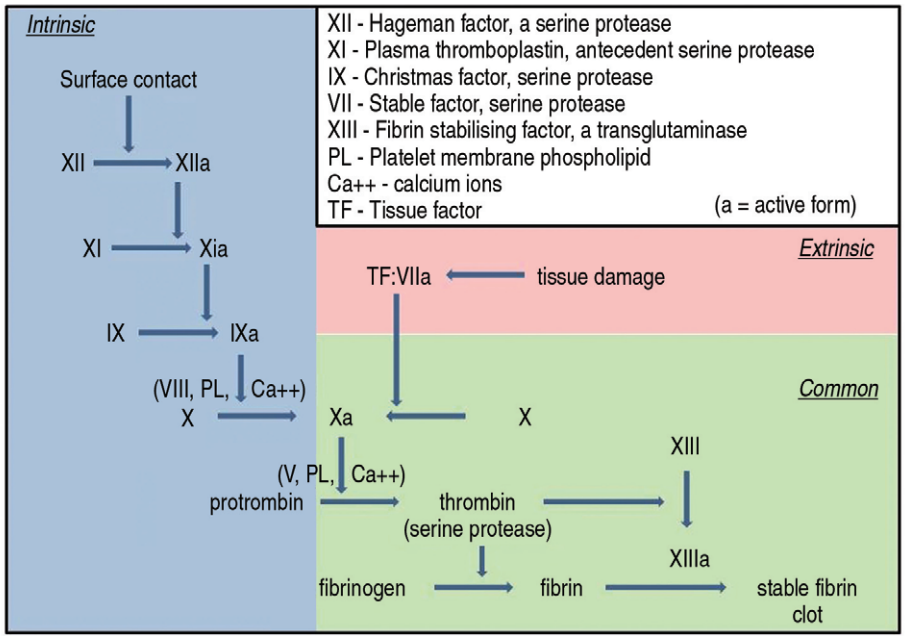

Fig. 3. Coagulation pathway.

Table 2. European Intravenous Iron Product Comparison

	CosmoFer® (low Mw iron dextran)	Ferrlecit® (iron gluconate)	Venofer® (iron sucrose)	Ferinject® (iron carboxymaltose)	Monofer® (iron isomaltoside 1000)	Rienso® (ferumoxytol)
Manufacturer	Phanrmacosmos	Sanofi Aventis	Vifor	Vifor	Phanrmacosmos	Takeda
Carbohydrate	LMW Dextran (branched polysaccharides)	Gluconate (monosaccharides)	Sucrose (Disaccharides)	Carboxymaltos (branched polysaccharides)	Isomaltoside 1000 (unbranched liner oligosaccharides)	Polyglucose soribitol-carboxymethylether (branched polysaccharides)
Therapeutic area	Broad	HD+EPO	Broad	Broad	Broad	CKD
Maximum single dose	20 mg/kg	125 mg	200 mg	20 mg/kg Single dose limit: 1,000 mg	20 mg/kg	510 mg
Maximum single dose administration in a 80 kg man	1,600 mg	125 mg	200 mg	1,000 mg	1,600 mg	510 mg
One dose iron repletion (TDI)	Yes	No	No	No	Yes	No
Infusion within 1 hour	No	NA	NA	Yes	Yes	Yes
Test dose required	Yes	No	Yes/No	No	No	No
Iron concentration (mg/mL)	50	12.5	20	50	100	30
Vial volume (mL)	2 and 10	5	5	2 and 10	1, 2, 5 and 10	17

LMW: low molecular weight, HD: hemodialysis, EPO: erythropoietin, CKD: chronic kidney disease.

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Table 3. Hypersensitivity Due to Immune Reaction

	Skin	Resp.	GI	CV	CNS
Immediate	Pruritis, extended flush, urticaria, angioedema	Dyspnea, tachypnea, cough, bronchospam, stridor	Nausea, emesis, colic, diarrhea	Hypo and hypertension, tachy and bradycardia, palpitations, chest pain, shock	Dizziness, syncope, LOC
Delayed	Fever, athralgia, myalgia, lymphadenopathy, exanthems				

Resp.: respiratory, GI: gastrointestinal, CV: cardiovascular, CNS: central nervous system, LOC: loss of consciousness.

agents include aspirin, NSAIDs, clopidogrel, and SSRIs, and these drugs prevent initial clot formation by inhibiting platelet adhesion and aggregation through slightly different mechanisms. Some herbal drugs (e.g., ginko, garlic, ginger, ginseng) have been shown to increase the risk of bleeding.

Since the combined use of different drugs may create drug-drug interactions, it is recommended to monitor patients closely for the first 5 days after prescribing antibiotics and antifungal agents[54]. Moreover, bleeding may be associated with concurrent use of clopidogrel and proton pump inhibitors (PPIs) due to the inhibition of CYP2C19. Therefore, the presence of bleeding should be detected through blood tests[55].

ROLE OF IV IRON

Gombotz et al.[56] suggested that the need for allogeneic transfusion was predictable in 97.4% of cases by the following factors: 1) level of anemia prior to surgery, 2) volume of perioperative blood loss and 3) transfusion trigger; therefore the assessment of preoperative hemoglobin level was most important of all. A preoperative hemoglobin level has been identified as the strongest predictor of the need for transfusion and is related with an increase in mortality. According to a study undertaken by Lasocki et al.[57], on 1,534 patients who underwent orthopedic surgery, of all 217 patients with a preoperative anemic state, 97.7% maintained an anemic state postoperatively, whereas all 1,317 patients with a non-anemic state preoperatively, 83.8% were switched to an anemic state postoperatively. Furthermore, in a study on 7,759 patients who received non-cardiac surgery, Beattie et al.[58] reported that preoperative anemia increased the risk of allogeneic transfusion and 90-day mortality.

When anemia is detected in when testing preoperative hemoglobin levels, the cause of anemia should be identified. Though malnutrition, chronic renal failure and others should be considered, iron-deficiency is the leading cause of anemia, accounting for the largest percentage. Iron therapy is leveraged to treat iron deficiency anemia, and a comparative studies on oral iron replacement and parenteral iron replacement described the safety, convenience and effective benefits of parenteral iron replacement[59].

IV iron therapy reduces the risk of perioperative anemia by conveniently and rapidly supplementing iron stores and also lowers the risks of mortality and need for allogeneic transfusions. Currently, a variety of iron supplements exist, and because each medication has unique molecular structures and varies in their iron content and absorption, instructions for the proper use of each product should be taken into account (Table 2). Potential adverse events following IV iron injection are temporary hot flashes, chest compression, headache, nausea, vomiting, mild fever, arthralgia and myalgia associated with free iron toxicity, and hypersensitive reaction caused by an immune response may occur[60,61] (Table 3). Multiple recent studies have demonstrated that preoperative IV iron therapy significantly lowers the risk of allogeneic transfusions and shortened the length of hospital stay[62,63].

CONCLUSION

Patient blood management has improved clinical outcomes following hip arthroplasty through the introduction of various treatment options including preoperative assessment of patients, anesthetic techniques, the use of TXA and others, thereby reducing the need for allogeneic blood transfusion, the risk of transfusion-related infection and the duration of hospitalization. Further research is warranted in the field of orthopedic surgery.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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