Chinese Expert Consensus on the Management of Non-Blood Hemostatic Drugs During Perioperative Period

The Pharmacovigilance Committee of GuangDong Pharmaceutical Association

ABSTRACT: The use of hemostatic drugs during perioperative period is an important measure to reduce blood loss and promote postoperative rehabilitation. Meanwhile, the improper use of hemostatic drugs may increase the risk of thromboembolic disease and disseminated intravascular coagulation. This consensus aims to regulate the use of hemostatic drugs during perioperative period. Based on the latest evidence of evidence-based medicine and suggestions from pharmaceutical and clinical experts, this consensus states the mechanism, clinical application suggestions and pharmaceutical care of commonly used non-blood hemostatic drugs during perioperative period, which contain no blood products. The purpose of this work is to provide reference for clinicians and surgical pharmacists to rationally use hemostatic drugs during perioperative period.

KEY WORDS: perioperative period; hemostatic drugs; rational drug use; pharmaceutical monitoring; expert consensus

As one of the primary risks of surgery, perioperative bleeding is related to high postoperative mortality and postoperative complications[1-2]. The use of hemostatic drugs during perioperative period is an important measure to reduce blood loss and promote postoperative rehabilitation[3-4]. Meanwhile, the improper use of hemostatic drugs may increase the risk of thromboembolic disease and disseminated intravascular coagulation (DIC). Therefore, it is necessary to evaluate the bleed risk of patients, select appropriate hemostatic drugs, strictly control the timing, usage and dosage of these drugs, and monitor their adverse reactions during perioperative period.

Since 2015, Guangdong Pharmaceutical Association has proposed the establishment of "surgical pharmacists" to construct surgical pharmacy, so that pharmacists can be part of the perioperative medication management and improve the rationality and safety of perioperative medication[3]. As one of the main measures to reduce perioperative blood loss, the rational use of hemostatic drugs needs the joint management of medicine, pharmacy and other disciplines. This expert consensus aims to provide reference for the rational use of hemostatic drugs by clinicians and surgical pharmacists during perioperative period through joint discussion between doctors and pharmacists. This consensus emphasizes that for special patients, the use of hemostatic drugs should be decided by doctors, anesthesiologists and clinical pharmacists according to the specific clinical conditions when necessary.

Steps and methods to formulate this consensus include: (1) Setting up an expert group to prepare the consensus; (2) Literature retrieval in PubMed, Cochrane Library, CNKI and Wanfang; (3) Summarizing and analyzing the literature, and drawing up the first draft of recommendations based on clinical experience. This consensus is not graded for evidence quality as it is not an evidence-based guide based on systematic review; (4) Conducting expert investigation and voting on the initial recommendations, and modifying or supplementing the recommendations according to the feedback from experts after each investigation. In the final vote, there are three options: agree, disagree and uncertainty. If the agreement rate (that is, the proportion of experts who choose "agree") is $\geqslant$75%, a consensus has been reached on this recommendation. The agreement rate of > 90% indicates a strong recommendation, and 75%~90% a weak one.

1 Hemostatic drugs used in perioperative period and their mechanism of action

The normal hemostasis mechanism of the body depends on the structural and functional integrity of coagulation system, fibrinolysis system, vascular walls and platelets, as well as their physiological adjustment and mutual balance. Hemostatic drugs refer to medicines that act on one or more of the above links and can promote hemostasis. They are mainly used to treat bleeding or hemorrhagic diseases caused by various reasons. The commonly used hemostatic drugs in clinic are shown in Table 1. This consensus focuses on seven non-blood hemostatic drugs that are widely used in perioperative period, including tranexamic acid, aminocaproic acid, hemocoagulase from snake venom, vitamin K, desmopressin (DDAVP), etamsylate and carbazochrome sodium sulfonate (CCSS). Coagulation factor

preparation, protamine for bleeding caused by heparin overdose and other hemostatic drugs that are less used during perioperative period are not detailed in this consensus.

Table 1 Hemostatic drugs commonly used in clinical practice

Drug category	Drug name
Drugs acting on fibrinolytic system	Tranexamic acid, aminocaproic acid, aminomethylbenzoic acid, etc.
Drugs acting on coagulation system	Hemocoagulase from snake venom [hemocoagulase bothrops atrox, haemocoagulase agkistrodon, hemocoagulase and hemocoagulase agkistrodon halys (pallas)] Vitamin K Coagulation factor preparations (human coagulation factor VIII, human coagulation factor IX, fibrinogen, recombinant human activated coagulation factor VII, prothrombin complex, etc.)
Drugs acting on vascular walls and platelets	Desmopressin (DDAVP), pituitrin, terlipressin Etamsylate Carbazochrome sodium sulfonate (CCSS), carbazochrome
Others	Protamine, Yunnan Baiyao, etc

1.1 Drugs acting on fibrinolytic system

Drugs acting on fibrinolytic system mainly include tranexamic acid (transamin), aminocaproic acid, aminomethylbenzoic acid (PAMBA) and ethylenediamine diaceturate. These drugs are synthetic derivatives of lysine, which can inhibit the activation of plasminogen into plasmin by reversibly blocking the lysine binding site on plasminogen molecules, and play an anti-fibrinolytic role, and also have a direct inhibitory effect on plasmin at high concentration. They have a good effect on the treatment of bleeding caused by increased fibrinolytic enzyme activity.

1.2 Drugs acting on coagulation system

1.2.1 Hemocoagulase from snake venom

Hemocoagulase from snake venom mainly includes hemocoagulase bothrops atrox for injection, haemocoagulase agkistrodon (HCA) for injection, hemocoagulase agkistrodon halys (pallas) for injection and hemocoagulase injection. The active components, titer and usage of different hemocoagulase are different, as shown in Table 2. These drugs are extracted from snake venom, which can accelerate the hydrolysis of fibrinogen to fibrin, and promote the formation of fibrin complex, which is easy to degrade in vivo and not easy to cause DIC. Some hemocoagulase [hemocoagulase agkistrodon halys (pallas) for injection and hemocoagulase injection] contain phospholipid-dependent coagulation factor X activator, which can activate coagulation factor X into Xa and promote thrombosis. This activation depends on vascular endothelial damage, platelet adhesion and aggregation and exposure of platelet phospholipids, which determines that this kind of hemocoagulase can target vascular damage, promote and strengthen thrombosis. It should be noted that this kind of hemocoagulase can indirectly activate coagulation factor XIII, which increases the risk of DIC[5-7].

Table 2 Comparison of the characteristics of hemocoagulase commonly used in clinical practice

Drug category	Hemocoagulase bothrops atrox for injection	Haemocoagulase agkistrodon (HCA) for injection	Hemocoagulase agkistrodon halys (pallas) for injection	Hemocoagulase injection
Venom source	Brazilian spearhead viper	Chinese agkistrodon acutus	Chinese agkistrodon halys ussuriensis	Chinese python
Active ingredient	Batroxobin	Agkistrodon acutus hemagglutinase, a single-component dipeptide chain	Thrombin-like and thromboplastin-like	Batroxobin and phospholipid-dependent coagulation factor X activator
Valence	60s	88s	60s	53s
Usage	Intravenous injection, intramuscular injection, subcutaneous injection, or local medication	Intravenous injection	Intravenous injection, intramuscular injection, subcutaneous injection, or local medication.	Intravenous injection, intramuscular injection, subcutaneous injection, or local medication
Executive standard	*Chinese Pharmacopoeia*, 2020 Edition, Part II	YBH11052008	WS-447(X-398)-2001	YBH24932005

1.2.2 Vitamin K

Vitamin K is a coenzyme necessary for the activation of vitamin K-dependent coagulation factors [including factors II (prothrombin), VII, IX and X]. Vitamin K-dependent coagulation factors can be fully combined with negatively charged phospholipids on the surface of platelets after γ-carboxylation, thus promoting blood coagulation. In the process of carboxylation, vitamin K, as an active coenzyme, provides energy for the reaction through oxidation. Vitamin K deficiency can himder the activation of the above coagulation factors, causing bleeding tendency and prolonged prothrombin time.

1.3 Drugs acting on vascular walls and platelets

1.3.1 Desmopressin (DDAVP)

Desmopressin (DDAVP), a synthetic vasopressin analogue, can promote the release of von willebrand factor (vWF) from vascular endothelial cells. VWF is synthesized in vascular endothelial cells, which can mediate platelet adhesion to vascular injury site and improve platelet adhesion and aggregation function. As a carrier of coagulation factor VIII, vWF can stabilize plasma coagulation factor VIII, which can participate in the endogenous activation of coagulation factor X after activation. Therefore, DDAVP can play a hemostatic role by increasing the activity levels of vWF and coagulation factor VIII in plasma and improving platelet adhesion and aggregation.

1.3.2 Etamsylate

Etamsylate, also known as dicynone, can increase the number of platelets in the blood, promote platelet aggregation and adhesion, release thromboactive substances from platelets, and shorten coagulation time. Meanwhile, it can enhance capillary resistance, reduce capillary permeability and reduce blood exudation.

1.3.3 Carbazochrome sodium sulfonate (CCSS)

Carbazochrome sodium sulfonate (CCSS) can stabilize acidic mucopolysaccharides in blood vessels and their surrounding tissues, enhance the resistance of capillaries to injury and the retraction of damaged capillaries, and reduce the permeability of capillaries, thus shortening the hemostasis time.

2 Suggestions on the application of hemostatic drugs in perioperative period

2.1 Bleed risk assessment

It is important to evaluate the bleed risk of patients before operation for the rational use of hemostatic drugs during perioperative period. The risk of perioperative bleeding is mainly determined by the type of operation or invasive operation. In general, any long-term (> 45 min) surgical operation, operation or invasive operation in important parts (the central nervous system and heart), organs with abundant blood supply (liver and spleen) or parts with active fibrinolysis (urogenital system) should be regarded as having high risk for bleeding[8-9]. Classification of bleed risk for different types of surgery or invasive procedures is different at home and abroad. According to *Multidisciplinary Expert Consensus on Perioperative Management of Antithrombotic Drugs* in China in 2020, which referred to relevant literature and the characteristics of five common non-cardiac operations, the surgery/procedure-related bleed risk is divided into “high-bleed-risk” or “low-bleed-risk” categories[8]. In the guideline of *Perioperative Management of Antithrombotic Therapy* by the American College of Chest Physicians in 2022, the surgery/procedure-related bleed risk separates patients into "high", "low-to-moderate" or "minimal" bleed risk categories (high-bleed-risk ≥2%, low-to-moderate-bleed-risk 0%-2%, and minimal-bleed-risk approximately 0%)[10-11] based on the guideline consensus of the International Society of Thrombosis and Hemostasis (ISTH). This consensus grades the surgery/procedure-related bleed risk as shown in Table 3 according to the above-mentioned literatures[8, 10, 11].

Table 3 Risk stratification for operation

Type of operation	High-risk	Low-risk
Thoracic surgery	Lobectomy, pneumonectomy on one side, pneumonectomy on pleura, lymph node dissection, esophageal surgery, pleural stripping, etc.	Simple pulmonary wedge resection, simple pulmonary bullae resection, pleural biopsy (no pleural bleeding or oozing), mediastinal tumor resection, chest wall tumor resection, etc.
Urological surgery	Adrenal related surgery, renal related surgery, ureteral related surgery (non-calculus surgery), percutaneous nephrolithotomy, cystectomy/partial	Cystoscopy, double pig tail tube (DJ tube) insertion/replacement/removal, ureteroscopy, transurethral

	resection, radical prostatectomy, transurethral resection of bladder tumor, transurethral prostatectomy, partial testicular resection/resection, partial penis resection/resection, tension-free transurethral suspension, retroperitoneal tumor resection, ileal bladder surgery, etc.	cystoscope/ureteroscope lithotripsy, sacral nerve stimulation electrode implantation/adjustment/removal, prostate particle implantation, prostatic urethral metal stent implantation, cystoscopy, urethral dilatation, urethral tumor resection, etc.
Orthopedic surgery	Femoral neck fracture surgery, hip replacement, knee replacement, open reduction and internal fixation of pelvic and long bone fractures, major spinal surgery, artificial shoulder replacement, bone tumor surgery, secondary revision surgery, etc.	Hand surgery, foot surgery, minor spine surgery, arthroscopy and surgery of shoulders, hands, knees and feet, etc.
General surgery	Thyroid related surgery, stomach related surgery (except perforation repair), weight loss surgery, splenectomy, pancreatic related surgery, gallbladder surgery, biliary related surgery, duodenal related surgery (except perforation repair), small intestine related surgery, colon related surgery, rectal related surgery, liver surgery, etc.	Breast surgery, hernia surgery, digestive tract perforation repair, colostomy, colostomy, appendix surgery, skin tumor resection, etc.
Others	Cardiac and intracranial surgery, any major surgery (operation duration > 45 min)	

In addition, patients themselves can also have an impact on the risk of bleeding. Before operation, it is necessary to systematically evaluate the risk factors of bleeding, especially the use of anticoagulants and antiplatelet drugs, and make corresponding interventions. If necessary, hemostatic drugs should be used preventively to reduce the risk of bleeding during and after operation, which mainly includes the following aspects[9, 12]:

(1) Physical examination: Focus on the general nutritional status of patients and related signs of hemorrhagic diseases, including but not limited to purpura, ecchymosis and subcutaneous hematoma;

(2) Hemorrhage history: Ask the patient if there are any abnormal bleeding manifestations, including epistaxis, gingival bleeding, ecchymosis, hematuria or hematochezia, joint or soft tissue bleeding; Whether there is spontaneous bleeding or significant bleeding after minor trauma;

(3) Past medical history: Ask about the patient's surgical history (including minor operations such as tooth extraction, foreskin excision and tonsillectomy) or foreign injury history; Whether there is massive postoperative bleeding, including immediate or delayed occurrence; Previous blood transfusion history; History of menorrhagia or iron deficiency anemia in female patients; Whether there are other diseases, such as chronic liver and kidney diseases, connective tissue diseases or amyloidosis; Family history of hemorrhagic disease;

(4) Drug use history: Ask about the patient's history of oral antiplatelet drugs or anticoagulant drugs; Whether the medication has been stopped and when;

(5) Coagulation function examination: Blood routine examination to evaluate the number of platelets; Coagulation function examination evaluated prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). If conditions permit, viscoelastic hemostasis test can be combined to obtain more information. At present, the available viscoelastic hemostasis tests include thromboelastography and rotational thromboelastography.

In conclusion, to evaluate the bleed risk of patients before operation, the possible bleed risk should be determined first according to the type of operation and the surgeon's own proficiency. The second is to analyze whether the patient may have coagulation dysfunction and determine whether to give corresponding intervention or treatment before operation on the basis of physical examination, bleeding history, past medical history and medication history, and the results of coagulation function examination.

Recommendation 1: Before operation, it is necessary to systematically evaluate whether the patient has any risk factors that cause bleeding, and intervene accordingly according to the risk factors. If necessary, hemostatic drugs should be used preventively to reduce the risk of bleeding during and after operation.

(Recommended level: strongly recommended)

2.2 Application of hemostatic drugs

2.2.1 Drugs acting on fibrinolytic system

Before clinical application of antifibrinolytic drugs, factors such as patients' age, renal function, operation mode and time should be considered. It is especially recommended for patients with damaged tissues with high fibrinolytic activity (such as oropharynx, prostate and endometrium) and patients with traumatic coagulopathy. Viscoelastic hemostasis test can be used to evaluate whether patients have hyperfibrinolysis and guide anti-fibrinolytic therapy and blood transfusion. Late administration of anti-fibrinolytic drugs (such as more than 3 hours after the start of bleeding) can lead to poor hemostasis[13]. Among these drugs, tranexamic acid has the strongest efficacy, about 10 times that of aminocaproic acid. If tranexamic acid is not available, aminocaproic acid can be used instead[14].

In cardiac surgery with cardio pulmonary bypass (CPB), it is suggested that tranexamic acid be used preventively, and its total amount be within 70-150 $mg \cdot kg^{-1}$. In any dosage regimen, it is necessary to reach the effective blood concentration before CPB begins. Take tranexamic acid as an example, at least $mg \cdot kg^{-1}$ should be given intravenously before CPB, and the effective blood concentration should be maintained in CPB, and the administration can be stopped after CPB[12, 15]. There is no uniform standard for the specific dosage of tranexamic acid. For heart surgery with low bleed risk (such as simple valvuloplasty, valve replacement and coronary artery bypass grafting), the recommended load is 10 $mg \cdot kg^{-1}$ with a maintenance load of 1-2 $mg \cdot kg^{-1} \cdot h^{-1}$; For patients with high risk of bleeding in heart surgery, the recommended load is 30 $mg \cdot kg^{-1}$ with a maintenance load of 16 $mg \cdot kg^{-1} \cdot h^{-1}$. It is not recommended that the total dose exceed 50 $mg \cdot kg^{-1}$ for patients with no high risk of bleeding[16]. If there are contraindications to the systemic application of tranexamic acid (for example, intractable seizures), topical application of tranexamic acid is suggested[14].

For patients with major orthopedic surgery at risk of bleeding, it is also recommended to prevent the use of tranexamic acid to reduce the amount of bleeding and the need for blood transfusion[14]. Administration strategies are generally divided into single-dose, multi-dose and local administration. The single-dose administration is generally to give tranexamic acid 20-60 $mg \cdot kg^{-1}$ or 1-5 g intravenous drip 5-30 minutes before skin incision; The first dose of multi-dose administration is the same as single-dose administration, and additional dose is given within 24 hours after operation; Local administration is generally used during operation. The specific method, dosage and timing of administration are recommended in Table 4[17]. For orthopedic surgery, intravenous administration can be combined with local administration, except for knee joint replacement, which needs to be combined with multi-dose and local administration, the rest are recommended to be combined with single-dose administration.

Table 4 Recommendation of the application of tranexamic acid in orthopedic surgery

Type of operation	Single-dose intravenous administration	Multi-dose intravenous administration	Local administration	Intravenous and local administration
Hip replacement	Tranexamic acid of 10-50 $mg \cdot kg^{-1}$ or 1-3 g is given intravenously 5-10 min before incision.	The first dose is the same as a single dose (10 $mg \cdot kg^{-1}$or 1 g each time) at an interval of 3-6 hours for 24 hours after surgery.	Intraoperative local application of 1-3 g tranexamic acid.	Intravenous method is the same as simple intravenous application, combined with local application of tranexamic acid 1-2 g before incision closure.
Knee joint replacement	Tranexamic acid of 20-60 $mg \cdot kg^{-1}$ or 1-5 g is given intravenously 5-10 min before incision (if tourniquet is not applied) or tourniquet release.	The first dose is the same as a single dose, with 10 $mg \cdot kg^{-1}$ or 1 g at an interval of 3-4 hours for 24 h after surgery. Tourniquets are not recommended for multi-dose.	For local application of tranexamic acid ≥2 g or concentration ≥20 $mg \cdot mL^{-1}$ before and after incision closure, 10% tranexamic acid is preferred because of the relatively small content of knee joint cavity.	Intravenous method is the same as multiple administration method, combined with local application of tranexamic acid 1-2 g before closing the incision.

Spinal surgery	Tranexamic acid of 15-30 mg·kg^{-1} or 1-2 g is given intravenously 15 min before incision.	The first dose is the same as a single dose, with 2-3 doses (15 mg·kg^{-1} or 1-2 g each time) at an interval of 3-8 h after surgery.	Before closing the incision, the operation area is soaked with tranexamic acid, with a dosage of 1 g and a soaking time of 5 min.	Intravenous drip of tranexamic acid 15 mg·kg^{-1} 15 min before skin incision, combined with local immersion of tranexamic acid 1 g for 5 min before incision closure.
Traumatic orthopedic surgery	Tranexamic acid of of 10-20 mg·kg^{-1} or 1-2 g is given intravenously 15-30 min before incision.	The first dose is the same as a single dose, with one additional dose (10-20 mg·kg^{-1} or 1-2 g each time) after 3 h or before incision closure.	Before closing the incision, 2-3 g of tranexamic acid is applied locally, and injected under the fascia and intramuscularly around the fracture end.	Intravenous drip of tranexamic acid 1 g 10 min before skin incision, combined with subcutaneous and intramuscular injection of tranexamic acid 3 g before incision closure.

Prophylactic administration of tranexamic acid can reduce the blood loss during gynecological surgery if the patient who intends to undergo gynecological surgery due to benign indications has no history of thrombotic events. 10 mg·kg^{-1} tranexamic acid can be given intravenously for 10 minutes 20 minutes before incision.[18-22]. Prophylactic use of tranexamic acid may also be considered in patients at high risk for cesarean section, vaginal delivery, or prenatal bleeding; For patients with postpartum hemorrhage, 1 g tranexamic acid can be injected intravenously as soon as possible within 3 hours, and repeated administration can be given if the hemorrhage continues[14].

For other non-cardiac perioperative patients, tranexamic acid should be used (unless contraindicated) in all patients with estimated blood loss of >500 mL or moderate blood loss, generally with 1 g intravenous injection for 10 minutes, and patients with traumatic bleeding can also be given 1 g intravenous drip in the following 8 hours[23-24].

Recommendation 2: For patients undergoing CPB heart surgery, major orthopedic surgery, partial gynecological surgery and other operations with estimated blood loss of >500 mL or moderate blood loss (such as liver transplantation, hepatectomy, trauma surgery and some neurosurgical operations, etc.), it is suggested to prevent the use of tranexamic acid before operation (unless contraindicated) to reduce the amount of blood loss and blood transfusion requirements. (Recommended level: strongly recommended)

2.2.2 Drugs acting on coagulation system

(1) Hemocoagulase from snake venom: Hemocoagulase is suitable for all kinds of surgical operations to prevent bleeding. For surgical patients with high bleed risk, especially those who are undergoing heparin or low molecular weight heparin and need emergency surgery, low-dose hemocoagulase can be used before and during surgery, and if necessary, it can be used after surgery[16, 25-29]. For adults, the usual dose is 1-2 units each time, and the maximum daily dose is 8 units. Among them, haemocoagulase agkistrodon (HCA) for injection is only approved for hemostasis of superficial wound bleeding in surgery. Except that, the usage and dosage of other hemocoagulase are almost the same, and they can be injected intravenously, intramuscularly or subcutaneously, and can also be used locally[30] For example, in endoscopic mucosal dissection, 4-6 units of hemocoagulase bothrops atrox for injection can be used, dissolved in 40-60 mL physiological saline, and sprayed locally on the wound surface for 20 mL every 30 seconds[31]. For bleeding related to bronchoscopy, besides local perfusion with iced saline, epinephrine or thrombin and intravenous injection of pituitrin, 1-2 units of hemocoagulase can also be injected intravenously[32]. It is not recommended to use hemocoagulase for a long time (> 7 days), and the fibrinogen level should be monitored if it is used continuously for more than 5 days; For DIC patients, it is not recommended[28, 33].

Recommendation 3: For surgical patients with high bleed risk, especially those who are undergoing heparin or low molecular weight heparin and need emergency surgery, low-dose of hemocoagulase can be used before and during surgery, and if necessary, it can be used after surgery. (Recommendation level: weak recommendation)

(2) Vitamin K: Vitamin K is an essential substance for the conversion of prothrombin precursor into thrombin, which can prevent bleeding caused by vitamin K deficiency; For patients with decreased synthesis of coagulation factors II, VII, IX and X caused by liver dysfunction, vitamin K can be supplemented to enhance coagulation function[33]. Generally, it is 10 mg intramuscular injection or slow intravenous injection, once or twice a day. In 2018, the guidelines of American College of Surgeons pointed out that, for patients who have been using vitamin K antagonists (VKA) for anticoagulant therapy for a long time, it is suggested to be stopped 5 days before surgery and testing INR before surgery. If the INR is still prolonged (> 1.5) 1 day before surgery, they can take a small dose of vitamin K (1-2 mg) orally and re-test INR the next day. On the day of operation, intravenous injection of vitamin K (1 mg once) can make INR return to normal as soon as possible[34]. Although the ACCP guidelines in 2022 also agreed to stop using VKA ≥5 days before elective surgery, it is not recommended that patients with prolonged INR (> 1.5) before surgery be given vitamin K routinely[10]. For emergency surgery with high risk of bleeding, it is recommended to give vitamin K before operation until INR returns to normal[8]. For patients with bleeding, if it is suspected that coagulation dysfunction induced by VKA is one of the causes of bleeding, it is suggested that 5-10 mg of vitamin K should be intravenously given combined with prothrombin complex to stop bleeding[14].

Recommendation 4: For patients with decreased synthesis of coagulation factors II, VII, IX and X caused by liver dysfunction, vitamin K can be supplemented to enhance coagulation function; For patients who have been using VKA for anticoagulant therapy for a long time, it is suggested to be stopped 5 days before operation, and INR should be detected before operation. If INR is > 1.5, vitamin K should be supplemented to restore INR to normal. (Recommended level: strongly recommended)

2.2.3 Drugs acting on vascular walls and platelets

(1) Desmopressin (DDAVP): DDAVP is for patients with platelet dysfunction (such as hemophilia and uremia) and those who use antiplatelet drugs before operation. Due to its limited hemostatic effect, its combined use with other blood components is recommended for patients with high bleed risk or severe bleeding. For patients with von Willebrand or mild hemophilia A who have been proved to be effective in the treatment of DDAVP and have no contraindications, DDAVP can be used as a first-line drug to prevent minor surgery or treat minor bleeding[14]. It is suggested that DDAVP be used in high-risk uremia patients to reduce bleeding during invasive operation and manage acute bleeding[14].

DDAVP may be beneficial to perioperative conditions such as hypothermia, acidosis, refractory microvascular hemorrhage caused by aspirin or cardiopulmonary bypass, but some studies have shown that the use of DDAVP can only slightly reduce the amount of red blood cell transfusion[35-37]. It is not recommended to use DDAVP generally in perioperative period[35,38-39].

DDAVP takes effect 1 hour after intravenous injection, and the action time is about 6 hours. To prevent bleeding from operation or invasive operation, the drug should be given 30-60 min in advance. The usage of DDAVP is usually 0.3 $\mu g \cdot kg^{-1}$ at a time, dissolved in 50-100 mL of normal saline, and intravenous infusion is completed within 15-30 min. Because the mechanism of DDAVP is to promote endothelial cells to release stored vWF, the hemostatic effect will be reduced after repeated administration. DDAVP is also the only drug that can treat bleeding caused by abnormal platelet function after CPB heart surgery. It is for patients undergoing coronary artery bypass grafting who take antiplatelet drugs within 7 days before operation or CPB＞140 min. The medication is suggested to be given about 1 hour before the CPB operation is stopped, and it can be ineffective at the beginning of or before the operation[12, 14, 40].

Recommendation 5: For patients with platelet dysfunction (such as patients with von Willebrand, mild hemophilia A or uremia without contraindications) and those who used antiplatelet drugs before operation, it is recommended to prevent the use of DDAVP to reduce bleeding during invasive operation; DDAVP is recommended for patients with bleeding caused by abnormal platelet function after CPB heart surgery. (Recommended level: strongly recommended)

(2) Etamsylate: Etamsylate can be used to prevent and treat bleeding before and after various operations [41-42]. The blood concentration reached its peak at 1 hour after intravenous injection, and it should be used 15-30 min before operation, which was beneficial to hemostasis during operation[33]. 0.25~0.5 g

can be injected intravenously or intramuscularly 15-30 min before operation, and 0.25 g can be injected 2 hours later if necessary, 0.5-1.5 g a day. When used for bleeding treatment, the usage is intramuscular injection or intravenous injection, 0.25-0.5 g once and 0.5-1.5 g a day; Intravenous drip, 0.25-0.75 g once and 2-3 times a day; There are also tablets to choose from. Adults take 0.5-1 g orally once, three times a day.

(3) Carbazochrome sodium sulfonate (CCSS): CCSS is often used for various hemorrhagic diseases caused by increased capillary permeability, such as urinary system, respiratory tract, upper digestive tract and gynecological diseases. It can also be used for trauma and surgical bleeding, and it can be used in the perioperative period of urology, obstetrics, otolaryngology and other operations[43]. In recent years, studies have shown that CCSS combined with tranexamic acid can reduce the perioperative blood loss more effectively than tranexamic acid alone, without increasing the incidence of thromboembolic complications[44-45], but CCSS can not effectively prevent postoperative bleeding after endoscopic submucosal dissection[46].

CCSS is usually injected intramuscularly, 20 mg once , twice a day, or added to infusion for intravenous drip, 60-80 mg once.

3 Pharmaceutical care

For perioperative patients, rational use of hemostatic drugs is the key to reduce blood transfusion, improve hemostatic effect and reduce adverse drug reactions. Clinical pharmacists need to evaluate and monitor related drug treatment, which can usually be divided into two stages: patient assessment before treatment and pharmaceutical care during treatment.

First, the patient should be evaluated before the operation to determine whether he/she has indications for hemostatic drugs, and the appropriate hemostatic drugs should be selected according to the type of operation and the bleeding risk of the patient. It is also necessary to evaluate whether the patient has contraindications and whether it is necessary to adjust the dosage of hemostatic drugs. In addition, pharmacists should ask patients about the drugs they are taking, analyze whether there is interaction with the proposed hemostatic drugs, and ask patients about their allergic history to drugs, food or other substances. For perioperative patients, the most important thing to prevent postoperative bleeding is to stop bleeding completely during operation. Therefore, hemostatic drugs are generally advocated for preoperative and intraoperative use, and in principle, they are not used after operation. Perioperative use of one hemostatic drug is generally advocated. There is less evidence-based medical evidence to support the repeated use of drugs or the combined use of drugs with different mechanisms.

Pharmaceutical care in perioperative hemostatic drug therapy mainly includes the evaluation of the safety and effectiveness of drug therapy, communication with the competent doctor according to the evaluation results, provision of individualized drug administration suggestions when necessary, and continuous dynamic evaluation and follow-up. The contents of pharmaceutical care mainly include: (1) Safety care: Planned observation of various short-term and long-term adverse reactions that may occur with hemostatic drugs. For the hemostatic drugs mentioned in this consensus, except aminocaproic acid, the incidence of adverse reactions of other drugs is low, mainly immune reactions, which are often related to rapid injection. Therefore, it is necessary to control the dripping speed during the medication, closely observe the patient's condition changes, and stop taking the drug immediately in case of adverse reactions. In addition, if the intake of water is not restricted during the use of DDAVP, it may cause water retention, hyponatremia and its complications. (2) Effective monitoring: Observe the bleeding of patients during and after operation. After operation, the patient's condition should be closely observed, especially the changes of vital signs, including blood pressure, heart rate, ventilation state, oxygen saturation and urine volume, so as to determine whether the patient has hypovolemia or early shock. Meanwhile, attention should be paid to the observation of the color and drainage volume of the patient's drainage fluid.

3.1 Precautions for the use of hemostatic drugs

Table 5 Precautions for the use of hemostatic drugs

Drug name	Contraindications	Drug interactions	Incompatibility	Medication for special population	Adverse reaction	Others
Tranexamic acid	Forbidden for patients with acquired color vision deficiency, subarachnoid hemorrhage, and active intravascular coagulation or those allergic to tranexamic acid or any component.	(1) It may increase the risk of thrombosis of human prothrombin complex concentrate, human anticoagulant complex and human factor VII complex, and it is forbidden to use them together. (2) Estrogen derivatives may enhance the thrombogenic effect of tranexamic acid, and their combination is prohibited. (3) The combined use of thrombolytic drugs (alteplase, streptokinase, urokinase, etc.) and tranexamic acid can affect each other, and their combined use is prohibited.	Incompatibility with penicillin or blood transfusion.	The excretion of tranexamic acid is highly dependent on renal function. For patients with renal insufficiency, the administration interval should be obviously prolonged or the dosage should be reduced.	Compared with aminocaproic acid, its adverse reactions are rare, and the main adverse reactions include nausea, vomiting and loss of appetite.	(1) Patients with thrombosis (cerebral thrombosis, myocardial infarction, thrombophlebitis, etc.) and those who may cause thrombosis and those with wasting coagulation disorders should be carefully administered. (2) As this medicine can lead to secondary pyelonephritis and obstruction of ureteral blood clots, it should be used with caution when hemophilia or renal pelvis parenchymal lesions cause massive hematuria. (3) It is generally not used alone for secondary fibrinolytic bleeding caused by DIC. If necessary, this medicine should be used on the basis of heparinization. (4) Heparin is safer than this medicine in the treatment of low fibrinogen bleeding caused by intrauterine stillbirth. (5) Tranexamic acid may induce epilepsy, and the risk of epilepsy may be greater in patients with end-stage renal disease or moderate to severe renal insufficiency. (6) If the injection speed is too fast, there can be occasional symptoms of nausea, chest discomfort, palpitation and blood pressure drop. So when in use, intravenous injection should be slow for 2-5 min, or slow to 5-10 min according to clinical needs.
Aminocaproic acid	Forbidden for patients with thrombosis tendency or past history of vascular embolism.	(1) It may increase the risk of thrombosis of drugs such as human prothrombin complex concentrate, and their combined use is prohibited. (2) Its combined use with oral contraceptives and estrogen can increase the risk of thrombosis.	Incompatibility with phenethylamine.	It is easy to form thrombus and damage heart, liver and kidney function, so pregnant women should use it with caution (grade C); Forbidden for lactating women (L4 level); Use with caution in patients with renal insufficiency; This medicine contains benzyl alcohol, and giving drugs containing benzyl alcohol as preservative to premature infants is related to fatal wheezing syndrome.	Adverse reactions are common, mainly including nausea, vomiting and diarrhea, followed by dizziness, itching, dizziness, tinnitus, general malaise, nasal congestion, rash, erythema, non-ejaculation, etc., especially when the daily dose exceeds 16g. Rapid intravenous injection can cause hypotension, tachycardia and arrhythmia, and a few people can have convulsions and heart or liver damage. High dose or course of treatment for more than four weeks can cause myalgia, weakness, fatigue, myoglobinuria, and even renal failure, which can be relieved and recovered after stopping taking the medicine.	(1) It is excreted quickly, so continuous administration is needed, otherwise it is difficult to maintain a stable effective blood concentration. (2) Its effect of immediate hemostasis is poor, and it should be used in combination with other hemostatic drugs for acute massive hemorrhage. (3) It cannot prevent arteriole bleeding. Ligation is needed to if there is active arterial bleeding during operation. (4) In the absence of heparin, it should not be used in the presence of DIC. (5) It should not be injected too fast, otherwise it will cause obvious blood pressure reduction, tachycardia and arrhythmia.
Hemocoagulase	Forbidden for patients with a history of thrombosis and those who are allergic to this kind of drugs.	—	—	Not for pregnant women unless there is an emergency.	The incidence of adverse reactions is low. It does not increase the risk of thrombosis, and occasionally allergic reactions occur. If allergic reactions occur, antihistamines or/and glucocorticoids can be given timely	(1) It is not suitable for bleeding caused by DIC and hematological diseases. (2) It has no compensatory effect if blood lacks platelets or some coagulation factors (such as prothrombin), so it should be applied on the basis of supplementing platelets or the lack of coagulation factors or transfusion of

					and symptomatic treatment according to the general anti-allergic treatment methods. Before clinical use of this drug, patients should be asked in detail whether they have a history of similar drugs, whether they are allergic, in order to adjust a reasonable drug administration program.	fresh blood. (3) In the case of primary fibrinolysis (such as endocrine gland and cancer surgery), it should be combined with anti-fibrinolytic drugs. (4) Care should be taken to prevent overdose, otherwise its hemostatic effect will be reduced. (5) Considering the higher risk of adverse reactions caused by intravenous injection than intravenous infusion, intravenous infusion is recommended for hemocoagulase (including haemocoagulase agkistrodon (HCA) for injection, hemocoagulase agkistrodon halys (pallas) for injection, and hemocoagulase injection).
Vitamin K	Forbidden for patients with severe liver diseases or poor liver function and those who are allergic to any component of the drug.	(1) The effects will cancel each other out if it is used together with VKA. (2) Salicylic acid, sulfanilamide, quinine, quinidine, sucralfate, coleenamine, actinomycin D, etc. can affect the effect of vitamin K, so attention should be paid when using it.	Incompatibility with vitamin C, vitamin B12, dextran, phenytoin sodium, ranitidine and minocycline.	—	There are few adverse reactions, and occasionally allergic reactions, such as dizziness, rapid pulse, weakness and excessive sweating. If the intravenous injection is too fast, exceeding 5 $mg \cdot min^{-1}$, it may cause facial flushing, sweating, bronchospasm, tachycardia, hypotension, etc. There have been reports of death caused by rapid intravenous injection. Intramuscular injection of this medicine can cause local redness and pain.	(1) It has no effect on the bleeding tendency caused by heparin, and there is no need to use it for traumatic bleeding. (2) It decomposes rapidly when exposed to light, and should be protected from light during use. (3) It should be injected slowly in intravenous administration, with an administration speed not exceeding 1 $mg \cdot min^{-1}$.
Desmopressin (DDAVP)	Forbidden for patients with habitual or mental polydipsia (urine volume exceeding 40 $mL \cdot kg^{-1} \cdot 24\ h^{-1}$), those with cardiac insufficiency or other diseases who need to take diuretics, those with moderate and severe renal insufficiency (creatinine clearance rate $<$ 50 $mL \cdot min^{-1}$), those with syndrome of abnormal secretion of antidiuretic hormone, those with hyponatremia, and those who are allergic to desmopressin acetate or other components of drugs.	It can increase water retention or antidiuretic effect when combined with diuretics, corticosteroids, tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, non-steroidal anti-inflammatory drugs, chlorpromazine, clomipramine, clofibrate and carbamazepine, so their combined use should be avoided.	—	Patients with renal dysfunction (eGFR $<$50 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) are prohibited from using nasal spray and sublingual buccal tablets; Elderly patients should start taking drugs from the lower limit of the dose range.	Common adverse reactions include headache, fatigue, transient hypotension, reflex tachycardia, facial flushing, stomachache and nausea. Occasional side effects include allergic reaction, emotional disorder, dizziness caused by high-dose use, and water retention, hyponatremia and its complications if water intake is not restricted during use.	(1) Due to the danger of water poisoning, it should be used with caution in the following situations: children and elderly patients; Patients with imbalance of body fluids or electrolytes; Patients at risk of increased intracranial pressure. (2) It may cause changes in blood pressure and heart rate, and patients with coronary insufficiency and/or hypertension and cardiovascular diseases should use it with caution. (3) It should not be used to treat patients with type IIB hemophilia, as it may induce platelet aggregation.
Etamsylate	Forbidden for patients allergic to etamsylate.	Combined use with dextranum can reduce its curative effect. If their combined use is necessary, it should be used at certain intervals and try to use etamsylate first.	It contains phenolic hydroxyl group, which is easy to be oxidized and discolored when it is compatible with alkaline	As a preventive measure, it is best to avoid using it during pregnancy; Breastfeeding is not recommended during treatment; Patients with renal insufficiency should use it with caution.	Low toxicity. Symptoms may include nausea, headache, rash, temporary hypotension, with occasional reports of anaphylactic shock after intravenous injection.	(1) Patients with thromboembolic diseases or those with this history should use it with caution. (2) Several cases of isolated fever have been reported. During the use of this medicine, the drug should be stopped permanently if fever occurs.

			drugs, and its discoloration point pH is 6.7, so it should not be used together with sodium bicarbonate injection or aminocaproic acid.			
Carbazochrome sodium sulfonate (CCSS)	Forbidden for patients with hereditary fructose intolerance. Fructose produced by D-sorbitol in this medicine can not be metabolized normally, which may induce hypoglycemia, liver failure, renal failure, etc. Forbidden for patients with allergic history to the ingredients of this medicine .	—	Incompatibility with cefoxitin, and the chemical stability can be affected when the two drugs coexist.	The dosage should be reduced as the physiological function of elderly patients decreases; There is no information about medication during pregnancy, so use it carefully during pregnancy.	It is mainly the reaction of the immune system, including local pain, redness, itching and drug eruption at the injection site, occasional nausea and dizziness, and no serious adverse reactions. Occasionally, there are reports of urticaria, skin mottle and maternal systemic muscle spasm after treatment with carbazochrome sodium sulfonate.	(1) The metabolites of this medicine can sometimes make the urine bilirubin test positive. (2) Sometimes there can be lumps and pain at the site of administration; Avoid nerves and blood vessels when injecting subcutaneously or intramuscularly. (3) If the drug is given repeatedly, it should be carried out on the left and right sides, especially for children.

3.2 Precautions for monitoring perioperative hemostatic drugs

3.2.1 Tranexamic acid (1) cannot be used for patients with acquired color vision defect, those with subarachnoid hemorrhage, those with active intravascular coagulation and those allergic to tranexamic acid or any component. (2) Patients with thrombosis and epilepsy should use it with caution. (3) It interacts with human coagulation factor preparations, estrogen derivatives and thrombolytic drugs, so their combined use is forbidden. (4) Intravenous injection should be slow to avoid nausea, chest discomfort, palpitation, blood pressure drop and other symptoms. (5) Fibrinolysis indexes such as D-dimer and fibrinogen degradation products should be detected in a large number of intravenous applications.

3.2.2 Aminocaproic acid (1) is forbidden for patients with thrombosis tendency or vascular embolism in the past. (2) Forbidden to be used together with drugs such as human prothrombin complex concentrate; Avoid oral contraceptives or estrogen. (3) Incompatibility with etamsylate. (3) Use with caution for pregnant women, premature infants and patients with renal insufficiency; Prohibited during breastfeeding. (4) Medication should be administered continuously. (5) Do not inject too fast to avoid adverse reactions such as lowering blood pressure.

3.2.3 Hemocoagulase (1) is forbidden for patients with a history of thrombosis and those allergic to this kind of drugs; This medicine is not for bleeding caused by DIC and hematological diseases. (2) Pregnant women should not use it unless there is an emergency. (3) Beware of overdoses, otherwise its hemostatic effect can be reduced. (4) Long-term use is not recommended (> 7 days), and the fibrinogen level should be monitored after continuous use for over 5 days. (5) Intravenous infusion is recommended for intravenous injection of haemocoagulase agkistrodon (HCA) for injection, hemocoagulase agkistrodon halys (pallas) for injection and hemocoagulase injection .

3.2.4 Vitamin K (1) is forbidden for patients with severe liver diseases or poor liver function and allergic to any component of the drug. (2) Avoid its combined use with VKA. (3) Incompatibility with vitamin C, vitamin B12, dextran, phenytoin sodium, ranitidine and minocycline. (4) It decomposes rapidly when exposed to light, and should be protected from light during use. (5) It should be injected slowly when giving drugs by intravenous injection.

3.2.5 Desmopressin (DDAVP) (1) is forbidden for patients with habitual or mental polydipsia [urine volume > 40 $mL \cdot kg^{-1} \cdot (24\ h^{-1})$], those taking diuretics, those with moderate and severe renal insufficiency (creatinine clearance rate < 50 $mL \cdot min^{-1}$), those with syndrome of abnormal secretion of antidiuretic hormone, those with hyponatremia, and those allergic to DDAVP acetate or other components of drugs. (2) Avoid its combined use with diuretics, corticosteroids and tricyclic antidepressants. (3) Elderly patients should start taking drugs from the lower limit of the dose range. (4) It should not be used to treat patients with type IIB hemophilia. (5) Water intake should be restricted when using it.

3.2.6 Etamsylate (1) is forbidden for patients allergic to it. (2) Incompatibility with alkaline solutions such as sodium bicarbonate injection and aminocaproic acid. (3) Use with caution during pregnancy, lactation and for patients with renal insufficiency. (4) During the use of this medicine, it should be stopped permanently if fever occurs.

3.2.7 Carbazochrome sodium sulfonate (CCSS) (1) is forbidden for patients with hereditary fructose intolerance and those with allergic history to the ingredients of this medicine. (2) Incompatibility with cefoxitin. (3) Elderly patients should reduce the dosage; Use with caution during pregnancy. (4) Avoid nerves and blood vessels when injecting subcutaneously or intramuscularly; If the drug is given repeatedly, it should be carried out on the left and right sides, especially for children.

4. Conclusion

Perioperative use of hemostatic drugs is an important measure to reduce blood loss in surgery, and the management of related drugs has received increasing clinical attention. The use of hemostatic drugs in perioperative period should be individualized, and the advantages and disadvantages should be fully

weighed. It is necessary to decide whether to use hemostatic drugs according to the type of operation and bleed risk factors of patients, and choose the proper hemostatic drugs according to the indications, mechanism of action and precautions in use. This consensus summarizes the mechanism of action, precautions and adverse reactions of commonly used non-blood hemostatic drugs during perioperative period, and provides suggestions for perioperative management of hemostatic drugs based on existing guidelines, clinical practice and multi-professional expert opinions. However, the perioperative use of some drugs is still controversial, and it is hoped that more high-quality clinical studies will provide evidence support in the future.

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