Chapter 44
Management for Massive Hemorrhage During Surgery

Eiichi Inada

Abstract Although the incidence of massive hemorrhage during surgery is low, the prognosis of massive hemorrhage is poor. When we encounter massive hemorrhage, systematic approach is mandatory. Physicians, nurses, and technicians at the scene, staff in the transfusion department, and the staff in the blood center work as a team. Achieving hemostasis by surgical maneuvers and restoration of blood volume to maintain organ perfusion and oxygenation is essential. If the patient requires vasopressors and lack of crossmatched red cell concentrate (RCC), type-specific RCC should be used. When the situation is life-threatening, un-crossmatched type-compatible RCC should be used. To correct coagulopathy, judicious use of blood components such as fresh frozen plasma and platelet concentrates is mandatory. It may require cryoprecipitate, a fibrinogen product, when fibrinogen level is very low. To improve patient's outcome, understanding of current blood transfusion guidelines and institutional simulation is important.

Keywords Platelet concentrate • Fresh frozen plasma • Cryoprecipitate • Fibrinogen • Crossmatch • Massive transfusion protocol

44.1 Introduction

Blood loss due to bleeding is a reversible process as long as the amount of blood loss is compensated by physiological mechanisms, fluid resuscitation, and blood transfusion. However, the amount and rate of bleeding far greater than compensatory mechanisms lead to a vicious cycle which worsens bleeding tendency and impairs major organ dysfunctions (Fig. 44.1) [1]. It may result in permanent neurological damage and death.

Annual survey of the critical incidents related to anesthesia by the Japanese Society of Anesthesiologists (JSA) repeatedly demonstrated that critical bleeding is one of the major causes of intraoperative cardiac arrest [2, 3]. The JSA studies

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H. Uchino et al. (eds.), *Neuroanesthesia and Cerebrospinal Protection*,
DOI 10.1007/978-4-431-54490-6_44

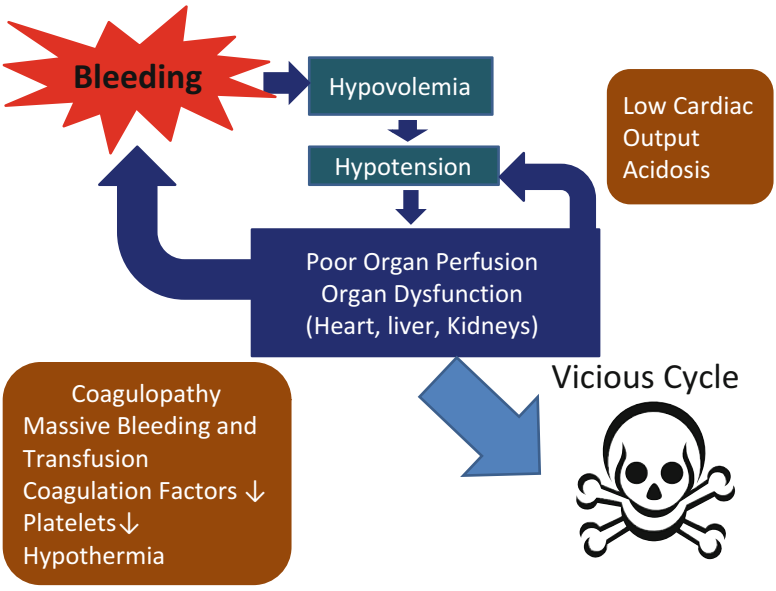

Fig. 44.1 Vicious cycle due to critical bleeding. A simple problem may go into a complex, catastrophic problem

demonstrated that critical bleeding in the perioperative period was the leading cause of the perioperative death in the first week postoperatively [4, 5]. About a half of perioperative critical bleeding was related to preoperative hemorrhagic shock by multiple traumas, rupture of the large blood vessels, and so on. The rest were related to intraoperative bleeding associated with surgical manipulation. Although the possibility of massive and rapid bleeding was usually anticipated and some preventive and treatment measures were taken to deal with critical bleeding, prognosis was still grave.

The Subcommittee on Surveillance of Anesthesia-Related Critical Incidents of the JSA analyzed the data. Contributing factors included far greater rate and amount of bleeding than anticipated, delay in decision to start blood transfusion and to order additional blood products, hesitation to use ABO-compatible red cell concentrates (RCC) including group O blood without crossmatching, delayed transportation of the blood products from the Red Cross blood centers, and inadequate manpower. In patients with critical bleeding, blood loss was greater than 12 L/60 kg (body weight) in 35.2 % of the patients, and the maximal estimated bleeding rate was greater than 240 ml/60 kg (body weight)/min in 44.9 % of the patients (Fig. 44.2). Despite shortage of blood products in the hospital, crossmatching test was waived in 13.4 % of the patients, and ABO-compatible blood products including type O blood were used only in 1.3 % of the patients. It suggests that risks of using un-crossmatched blood might be a major concern in the physicians in Japan even in the life-threatening situation.

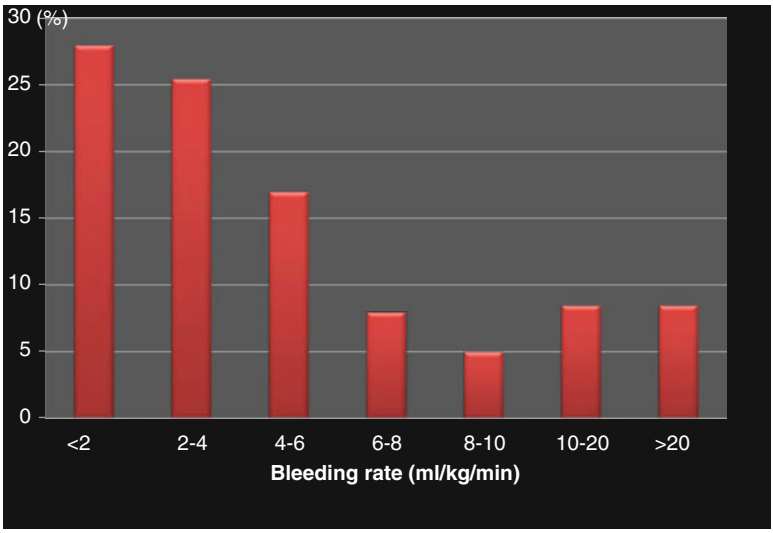

Fig. 44.2 Estimated rate of bleeding in patients with critical bleeding

Although the national guidelines for blood transfusion made by the Japanese Ministry of Health, Labour and Welfare exist, the issues on critical bleeding were not fully discussed, and clear guidelines were not described. Massive bleeding is commonly defined as the loss of one blood volume within a 24 h period. A variety of definition of critical bleeding has been used such as a rate of blood loss of 150 ml/min or more than 50 % loss of circulating blood volume within 3 h. The JSA has arbitrarily defined the critical bleeding as acute bleeding which is very likely to result in life-threatening situation in a short period of time, i.e., within a few minutes to a few hours. Immediate and appropriate therapy to stabilize the patient and to avoid secondary damages is required. The JSA and the Japan Society of Transfusion Medicine and Cell Therapy made the guidelines for treatment of critical bleeding to improve patient outcome in 2007.

44.2 "Guidelines for Actions Against Intraoperative Critical Hemorrhage"

44.2.1 Outlines of the "Guidelines for Actions Against Intraoperative Critical Hemorrhage"

The JSA established "Guidelines for Actions Against Intraoperative Critical Hemorrhage" (Guidelines) in collaboration with the Japanese Society of Blood Transfusion and Cell Therapy in 2007. Fundamental concept is that lifesaving measure is

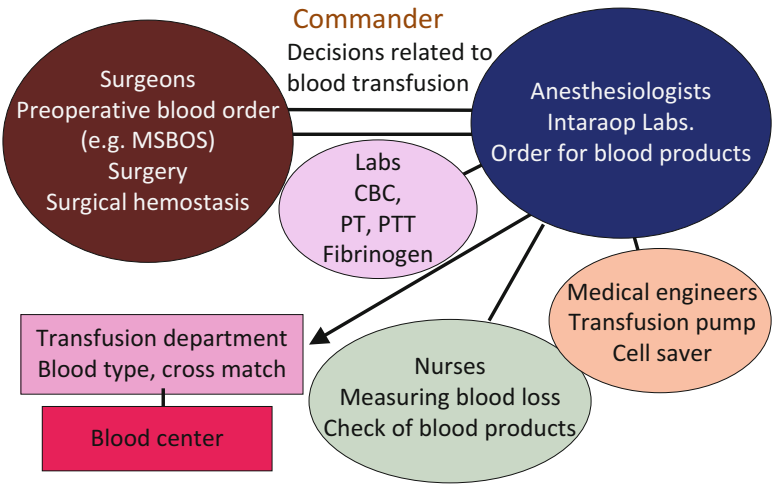

Fig. 44.3 Work as a team when critical bleeding occurs

much more important than theoretical complications in the setting of life-threatening critical bleeding.

There are a few basic strategies as follows:

1. Physicians and nurses, medical engineers in the operating room and emergency room, staff in the blood transfusion department, and staff in the blood center work as a team (Fig. 44.3). Intense communication between them is mandatory.
2. The nominated commander is in charge of the important decisions related to blood transfusion strategies and patient management (Table 44.1).
3. Surgeons concentrate on hemostasis rather than on proceeding the planned procedure. Damage control surgery should be considered.
4. Anesthesiologists insert a few large-bore intravenous lines; draw serial blood samples for blood cell counts, electrolytes, and coagulation studies; and request blood products according to the amount and rate of hemorrhage, vital signs, laboratory data, the prospect of hemostasis, and the patient's preoperative general status.
5. The commander determines the urgency of blood transfusion in accordance with the situation and notifies the transfusion department using the code (Fig. 44.4). Un-crossmatched ABO-compatible blood products should be used without hesitation if necessary.
6. Euvolemic status should be maintained to keep adequate perfusion pressures of major organs and to maintain their functions.
7. Hypothermia should be best avoided because hypothermia worsens bleeding tendency and increases the risk of disseminated intravascular coagulation. Devices such as warming blankets and efficient blood warmer should be used.
8. Electrolyte imbalance such as hyperkalemia and hypocalcemia should be aggressively treated.

Table 44.1 Roles of the commander

Declarations of critical bleeding
Call for help
Notify the transfusion department
Know the amount of blood products in storage
Declaration: critical bleeding, resolution
In the OR
Communicate with the surgeons
Decide to proceed or to change the procedure to damage control surgery
Assess bleeding/hemostasis
Take blood samples for CBC, electrolytes, and coagulation studies and fibrinogen levels
Get ready to use equipments including cell saver and blood transfusion pumps

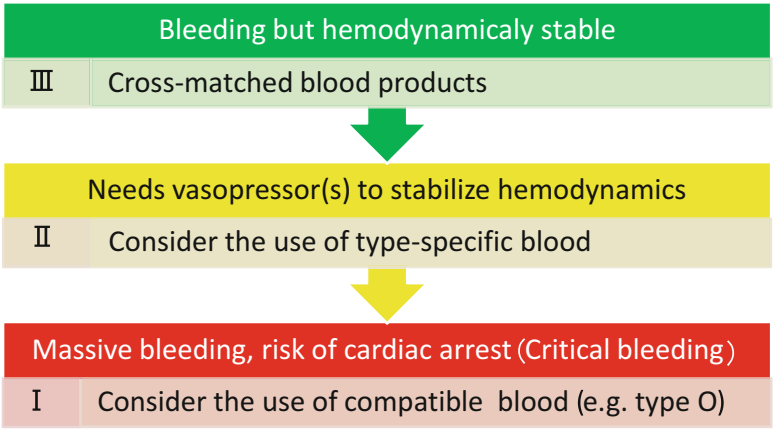

Fig. 44.4 Emergency blood transfusion codes

9. The institutional structure of the blood transfusion system and transport time from the blood center should be understood by the staff concerning blood transfusion.
10. The institutional guidelines for critical and massive bleeding should be established according to the Guideline.
11. Simulation training involving all departments related to blood transfusion should be performed.

44.2.2 Commander and the Team

When critical bleeding occurs, one single physician should become the commander who will direct and organize the overall therapy including blood transfusion. The commander declares a state of emergency. Most often, the anesthesiologist will

become the commander in the operating room (OR) because the anesthesiologist knows the general condition of the patient and is aware of the situation around the OR including diagnostic laboratory data, storage of blood products in the institution, and transport of blood products from the Red Cross blood center. After the life-threatening condition was evaded, the commander declares the end of emergency.

The personnel in the OR, the emergency room (ER), diagnostic laboratories, the department of blood transfusion, and the Red Cross blood center work together as a team in the setting of critical bleeding (Fig. 44.3). Close communication among all departments is essential. Anesthesiologists would start new large-bore intravenous lines (16 or 14 gauge catheters) for fluid resuscitation and blood transfusion, take blood samples for blood gases, and complete blood cell count, electrolytes, coagulation studies, and crossmatching. Arterial and central venous lines may be inserted if the situation permits. The commander requests blood products according to the general condition of the patients, laboratory data, and availability of blood products. Surgeons concentrate on hemostasis rather than on completing the planned procedure. Damage control surgery should be considered. Medical engineers prepare for intraoperative autologous blood transfusion devices and rapid infusion pumps. Nurses measure the amount of blood loss and keep contact with the blood bank and check blood product bags.

Postoperative management in the intensive care unit is probably required. Postoperative mechanical ventilation may be required.

44.2.3 Fluid Resuscitation Using Crystalloids and Colloids

It is important to maintain tissue perfusion by appropriate volume status and vasopressors if necessary. Restoration of circulating volume is initially achieved by rapid infusion of crystalloids such as lactated, acetated, or bicarbonate Ringer's solution and normal saline. Artificial colloids such as hydroxyethyl starch (HES) are usually indicated when blood loss is greater than 20 % of one blood volume. HES is indicated in critically bleeding patients. The amount of HES is commonly limited to 1,000 ml or 20 ml/kg of body weight because HES potentially induces platelet inhibition and renal dysfunction. HES is known to interfere with coagulation according to molecular weight. Because the currently available HES in Japan contains relatively low and medium molecular weight, interference with coagulation may not be significant. Duration of plasma volume expansion may be short-lived. The upper limit of HES is not described in the Guideline.

The use of albumin solution has been controversial [6, 7]. Currently 5 %, 20 %, and 25 % albumin solutions are available in Japan. Plasma protein fraction is also available. The Guideline did not prohibit the use of albumin solutions in the setting of critical bleeding. It should be kept in mind that the use of albumin may worsen the prognosis of patients with head injury [8].

44.2.4 Blood Transfusion

44.2.4.1 Red Blood Cell Transfusion

Fully crossmatched RCC is used in the routine cases. However, in the critical bleeding, there would not be enough time to prepare crossmatched RCC. Lifesaving is far important than to avoid remote risk of delayed hemolysis and other minor blood transfusion reactions. It is important to consider the risks and benefits of specific blood products in terms of availability and timing.

If blood typing and screening is performed preoperatively, RCC would be available within 10–15 min after blood typing or computer crossmatching (Table 44.2). The ABO group type-specific RCC can be used. If the ABO group type-specific RCC is not available in a short period of time, ABO-compatible RCC including group A or type B, then type O RCC should be used. If the patient's blood type is AB, either type A or type B, RCC should be used if available.

Distribution of ABO and Rh types varies from country to country. In Japan, the distribution of blood types is different from European countries. The blood types of Japanese roughly consist of type A 40 %, type O 30 %, type B 20 %, and type AB 10 %. The ratio of Rh-D(+) is over 99 % in Japan. The population of people with type AB, Rh-D(−) is less than 1/2,000 population.

Even the existence of alloantibody to red blood cells is known, the risk of hemolysis needs to be assessed against the risk of withholding blood transfusion until compatible RCC can be provided. The Guidelines recommend that un-crossmatched blood should be used when time does not allow for waiting the crossmatched RCC even in patients with red cell antibody. Rh-D(+) blood is most safely used even in the patient with Rh-D(+). Use of anti-Rh-D immunoglobulin in patients with Rh-D(−) should be considered postoperatively.

There is a risk of delayed hemolysis when un-crossmatched type-specific RCC is used. Overall risk of delayed hemolysis due to alloantibody and Rh incompatibility is up to 1 %. The patient with alloantibody to red cell who received un-crossmatched blood products should be observed closely for a few weeks to

Table 44.2 Approximate time for expedited release of red cell concentrate

ABO group	Crossmatch	Approximate preparation time in blood bank (min)	Risk of incompatibility
O	None	5	RBC alloantibody
ABO specific	None	10–15	RBC alloantibody
ABO specific	Abbreviated	30	Screen negative = none
			Screen positive = RBC alloantibody
ABO specific	Full	45–60	None

find signs of hemolysis promptly. Delayed hemolysis occurring after a few days to a few weeks can be managed without difficulty.

Irradiation is indicated to the RCC and platelets to prevent transfusion-related graft-versus-host disease (GVHD). Even in the setting of critical bleeding, irradiated blood products should be used.

44.2.4.2 Autologous Blood Transfusion: Intraoperative Blood Salvage

Use of preoperative autologous blood donation is limited. Effectiveness of preoperative autologous blood donation has been controversial. Preoperative autologous blood donation is encouraged in patients with rare blood type undergoing major surgery with the possibility of large blood loss. Our studies suggested that in obstetric patients with placenta previa and other factors, leading large blood loss may be benefited from the preoperative autologous blood donation. The median amount of preoperative autologous blood donation was 800 ml.

Use of intraoperative autologous blood salvage is encouraged when the contraindications for this method do not exist. Contraindications include contamination of malignant tumor cells and infectious organism. The help of medical engineers may be required. This technique may be quite useful in patients with ruptured major blood vessels.

44.2.4.3 Fresh Frozen Plasma

The major recommended indication of fresh frozen plasma (FFP) is to supplement multiple coagulation factors for bleeding tendency due to deficiencies in coagulation factors. Trigger levels are prothrombin time (PT) activity equal to or less than 30 % or prothrombin time-international normalized ratio (PT-INR) equal to or greater than 2.0, activated partial prothrombin time (aPTT) greater than two times the upper limit of the institutional standard level or activity equal to or less than 25 %, or fibrinogen level less than 100 mg/dl in Japan.

The indications for FFP are similar in other countries. The practice guidelines for perioperative blood transfusion by the American Society of Anesthesiologists state that FFP transfusion is indicated for (1) correction of excessive microvascular bleeding (coagulopathy) in the presence of PT greater than 1.5 times normal or INR greater than 2.0 or an aPTT greater than two times normal and (2) correction of excessive microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and aPTT cannot be obtained in a timely fashion [9].

In bleeding patients, these criteria may be fulfilled when the blood loss is greater than one blood volume. Fibrinogen concentration may become less than 100 mg/dl before other coagulation factors fall below the minimum hemostatic levels by bleeding [10, 11]. PT may not reflect decreased level of fibrinogen.

The fibrinogen concentration which causes microvascular bleeding is considered 50–80 mg/dl. It should be avoided to let fibrinogen concentration fall below this level in actively bleeding patients.

However, performing these coagulation studies may not be practical in actively bleeding patients with unstable hemodynamics. It also delays administration of FFP because of preparation time. Therefore, it is recommended to draw blood samples for later coagulation studies and to give FFP without waiting the final results.

Cryoprecipitates are useful to increase fibrinogen level efficiently with small amount of volume. Each unit of cryoprecipitate contains 150 mg of fibrinogen in about 15 ml of plasma. Unfortunately, cryoprecipitates are not commercially available in Japan. The only current indication for fibrinogen concentrates is congenital fibrinogen deficiencies with bleeding tendency. Fibrinogen products were approved for treatment of acquired low fibrinogenemia in the past. An estimated 10,000 cases of hepatitis C infection have been attributable to the use of inappropriately heated fibrinogen in Japan. It became a social issue, and citizens may hesitate to receive fibrinogen products even though the currently available products are properly produced and safe.

Recombinant activated factor VII concentrates are indicated with the specific factor deficiency with antibodies and are very expensive. Some anecdotal cases indicated the usefulness of factor VII products in patients with massive bleeding. Although some people recommend to use recombinant activated factor VII when other ordinary hemostatic measures have failed, one retrospective study suggested last-ditch recombinant activated factor VII therapy was ineffective to rescue the patients who were resistant to conventional treatment [12]. Recent review by Johannsson did not support the routine use of recombinant activated factor VII concentrates for patients with massive bleeding [13]. It may increase risk of thromboembolic events. Therefore, the use of recombinant activated factor VII was not mentioned in the Guideline.

ABO-compatible FFP can be used when type-specific FFP is not available.

44.2.4.4 Platelet Concentrates

Platelet concentrates are indicated when platelet count is less than 50,000 associated with bleeding tendency in usual surgical patients. The minimum level of 100,000/mm^3 is recommended for ophthalmologic and intracranial surgery. In the critical bleeding, platelet concentrates should be administered to maintain platelet count greater than 50,000/mm^3. The trigger of platelet transfusion may be higher than usual (e.g., 75,000/mm^3) in patients with critical bleeding. ABO-compatible platelet concentrates can be used when type-specific platelet concentrates are not available.

Serial and frequent measurements of blood cell count are necessary because platelet count changes rapidly in the setting of critical bleeding.

44.2.4.5 Avoidance of Adverse Effects and Complications of Rapid Blood Transfusion

Although blood transfusion may save lives in patients with critical bleeding, it presents risks to the patients. The potential risks include accidental transfusion of the incompatible unit of blood; transmission of viral, bacterial, and other microbial infections; graft-versus-host disease (GVHD); transfusion-related acute lung injury (TRALI); transfusion-associated circulatory overload (TACO); and so on. These complications can be fatal either in a short term or in a long term. Correct identification of the recipient blood group and use of compatible blood products are of paramount importance. It is strongly recommended to check the recipient blood group twice before blood transfusion. In an emergency situation, some physicians often check blood type only once. To avoid blood transfusion-related GVHD, irradiation to the blood products is highly recommended. Some institutions receive only irradiated blood products, and some receive nonirradiated blood products and irradiate blood products immediately before blood transfusion to avoid the risk of hyperkalemia [14]. Sometimes, there is no time to irradiate blood products in life-threatening situation. It is helpful to store irradiated blood products and to order irradiated blood products from the blood center for emergency.

Acute complications related to rapid blood transfusion including hypothermia, acid-base abnormalities, and electrolyte imbalance should be considered and appropriately treated.

It is important to avoid hypothermia. Hypothermia reduced platelet aggregation and vascular reactivity, leading to increased blood loss [15]. Efficient blood warmer should be used. Warm forced-air system and other devices should be used to keep normothermia.

Hyperkalemia due to the old RCC and irradiated blood can be fatal in massive blood transfusion [16]. Although it is rare to see life-threatening hyperkalemia due to blood transfusion, it may occur in the presence of impaired renal function and severe acidosis. It may also occur in infants and small children. Serial measurements of blood samples are necessary. Electrocardiogram changes including tall T wave may not be sensitive and often overlooked. Hyperkalemia should be treated by alkalization of the blood by hyperventilation and administration of sodium bicarbonate, furosemide, and calcium chloride (or calcium gluconate). After massive blood transfusion, hypokalemia may occur.

Hypocalcemia may occur with rapid transfusion of the RCC and FFP which include citrate. In the usual setting, hypocalcemia can resolve spontaneously in 10 min. However, in massive and rapid blood transfusion, severe hypocalcemia resulting in cardiac depression and circulatory collapse is a real possibility. Hypocalcemia should be treated by calcium products such as calcium chloride.

Use of rapid transfusion device is optional. Although these devices are capable of transfusing blood rapidly in the critically bleeding patients, these are not designed for this purpose. Some fatal accidents have occurred because of lack of

experience and neglect of the proper use. These rapid transfusion devices should be used by the experienced medical engineers or physicians.

44.2.4.6 Importance of Institutional Guidelines and Simulation

The guidelines set by the JSA and the Japan Society of Transfusion Medicine and Cell Therapy can be modified according to the situation of each institution. Our studies demonstrated that more than 80 % of the major institutions had their own blood transfusion guidelines. However, only one-third of the institutions performed simulations. Although these guidelines are well known and understood by the staff in the blood bank, these are not well understood by surgeons and obstetricians particularly working for the small institutions.

It is not clear how much blood products should be stored in each institution. The more the storage, the higher the amount of the wasted blood products. It is also important to know the transfer time from the Red Cross blood center. It takes more than 60 min to receive the blood products from the Red Cross blood center in the emergent situation in some institutions. It is also important to know how long it takes to determine blood types and to crossmatch. These factors should be taken into consideration when to order blood products.

44.3 Current Status

We have been following the situation of critical bleeding and blood transfusion in different departments including anesthesia, pediatric anesthesia, emergency medicine, obstetrics, and blood transfusion in Japan [17]. The study was supported by the Grant of the Ministry of Health, Labour and Welfare (H.19-MP-General-031) since 2007.

We performed a questionnaire survey regarding the present status of critical bleeding (≧5,000 ml) occurring in major hospitals in Japan in 2006 [18]. A total of 692,241 cases managed by anesthesiologists in 247 institutions were registered. There were 2,657 cases of massive hemorrhage over the circulating blood volume in the operating room, and 404 of them were considered critical. Thus, the number of patients with massive bleeding was 6.6 times that of patients with critical bleeding. In 1,257 patients with massive blood loss (≧5,000 ml), 196 patients (15.6 %) died within 30 postoperative days, and 160 patients (12.7 %) had major sequelae including permanent brain damage. While the amount of transfused RCC was 25.2 ± 24.2 units (one unit means RCC from 200 m of donated blood), the amount of RCC storage for emergency in the hospital was 12.7 ± 10.1 units for type A, 9.7 ± 7.3 units for type B, 11.9 ± 9.6 units for type AB, and 11.3 ± 11.0 units for type O. The un-crossmatched, type-specific blood transfusion and compatible, different blood type transfusion were performed in 8.2 % and 4.3 %, respectively. The lowest hemoglobin concentration was below 5 g/dl in 16.7 % of

the patients, but un-crossmatched, type-specific blood transfusion was performed only in 19.0 % and compatible, different blood type RCC transfusion in 5.2 %. Intraoperative blood salvage was performed in 5.7 % in patients undergoing noncardiac surgery.

The JSA performed the survey of massive blood loss defined as blood loss greater than 5,000 ml in the OR in 2011 [19]. One thousand and nine hundred cases were registered from 170 JSA-certified hospitals. A total of 643,999 cases managed by anesthesiologists in 186 institutions were registered. The number of the critical cases with blood loss greater than 5,000 ml was 1,900. The incidence of critical bleeding was 25.9 per 10,000 anesthetic cases. One-week mortality was 10.9 %. ABO type-compatible blood was used in 10.9 % of the cases. It seems that ABO type-specific blood was used more frequently in patients with massive bleeding. The 30-day mortality seems to be improved.

These surveys suggest recognition of the guidelines by the JSA was improved and timely judgment of blood transfusion was facilitated.

44.4 Massive Transfusion Protocol (MTP)

Recently, massive transfusion protocol (MTP) has been advocated in patients with massive bleeding and anticipated massive bleeding [20–22]. It is suggested that MTP improved the mortality of trauma patients during war. MTP includes not only blood transfusion but also general supportive measures.

General supportive measures should be taken to maintain oxygenation, cardiac output, tissue perfusion, and metabolic homeostasis. Hypothermia should be avoided, and body temperature should be kept over 35 °C. Significant metabolic acidosis should be aggressively treated to keep pH greater than 7.2, base deficit less than −6, and lactate levels below 4 mmol/L. Hypocalcemia should be corrected to keep calcium level greater than 1.1 mmol/L.

Permissive hypotension and minimal volume resuscitation are generally preferable, while active hemorrhage is being controlled. However, permissive hypotension is contraindicated in patients with traumatic brain injury, because hypotension decreases cerebral perfusion pressure (i.e., mean arterial pressure minus intracranial pressure) to the dangerous level. The safe low threshold for blood pressure is not clearly demonstrated.

Various MTPs have been used in different institutions. The effects of dilutional coagulopathy and hypovolemia may be minimized by using MTP. The optimal ratio of RCC to other blood components such as FFP and PC has not been determined yet. MTP often includes 1:1:1 ratio of RCC, FFP, and PC.

If the commander at the scene determines that the patient meets criteria for MTP activation, the commander notifies the blood bank and laboratories to activate MTP.

Once a patient is in the protocol, the blood bank is able to insure rapid and timely availability of blood components to facilitate resuscitation. A pack of RCC, FFP, and PC will be delivered to the OR or ER immediately. The pack of blood products

will be delivered to the OR or ER until bleeding is under control. If fibrinogen level is very low, cryoprecipitate will be delivered. Once definitive control of bleeding has been achieved, a restrictive approach to blood product transfusion is preferred because of the well-known risks and negative outcomes of transfusion.

There is no definitive data showing that MTP is useful in patients with intraoperative surgical bleeding.

Acknowledgment This article is supported by the Grant of the Ministry of Health, Labour and Welfare (H.19-Iyaku-General-031 and H.24-Iyaku-General-005).

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