Chapter 11
Multiple Injury

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Abstract It is important to manage multiple injury patients so as not to experience the lethal triad of hypothermia, metabolic acidosis, and coagulopathy. The treatment method in patients with massive exsanguination is greatly different from that of elective surgery patients, and it is necessary to implement damage control surgery (DCS), based on the patient's general condition. The strategy is divided into DCS for controlling surgical bleeding and damage control resuscitation (DCR) for non-surgical bleeding. Damage control surgery consists primarily of abbreviated lifesaving surgery, and DCR consists of maneuvers to avoid the lethal triad and administer critical care such as permissive hypotension, resuscitative fluid administration, and hemostatic resuscitation. Managing multiple trauma with traumatic brain injury (TBI) is different from managing single torso injury and takes into account factors such as avoiding hypotension and abdominal compartment syndrome, the effect of resuscitative endovascular balloon occlusion of the aorta on intracranial pressure, adverse effects of colloids on hemostasis, and indications for higher platelet administration, which are introduced in this chapter, respectively. The management of patients with multiple trauma and TBI remains mostly unknown, although evidence has been steadily accumulated.

Keywords Multiple injury · Traumatic brain injury · Damage control · Permissive hypotension · Massive transfusion protocol

11.1 Introduction

Hypothermia, metabolic acidosis, and coagulopathy constitute a pathological condition that leads to a poor outcome in the treatment and management of patients with multiple injuries and is called the lethal triad [1]. In general, hypothermia

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refers to a core body temperature <34 °C, acidosis refers to pH <7.2, and coagulation disorder refers to the manifestation of nonmechanical bleeding (described later). In severe trauma, these factors adversely affect each other and can cause a bloody vicious cycle [2]. In recent years, it has been pointed out that hemodilution due to excess fluid resuscitation during trauma management may lead to further resuscitation-associated coagulopathy (RAC). Some authors consider RAC occurring with the lethal triad as "the lethal quartet" [3, 4]. In treating patients with severe multiple trauma and hemorrhagic shock, avoiding and/or recovering from the lethal triad is very important in management. However, curative hemostasis surgery at the injured site is not simple for patients who have collapsed vital signs, and opening the abdominal and/or thoracic cavity for a long time aggravates hypothermia and the collapse of the coagulation fibrinolytic cascade associated with increased exsanguination. Furthermore, these factors can cause severe lactic acidosis, which may result in opposite effects. Two decades ago, resuscitation by a large amount of crystalloids and packed red blood cell (RBC) transfusion were widely administered to maintain tissue perfusion and sufficient oxygen delivery against traumatic hemorrhagic shock [5]. Such large volume resuscitation enabled the withdrawal of hemorrhagic shock, reduced early death due to exsanguination after severe trauma injury, and reduced the risk of acute renal failure [5, 6]. However, on the other hand, acute heart failure, pulmonary edema, and abdominal compartment syndrome (ACS) [7] due to intestinal edema (as described later) had increased following massive crystalloid resuscitation. In addition, these pathophysiological alterations increase inflammatory cytokine production, reperfusion injury, and immunity decline, which increase sepsis and late death because of multiple organ dysfunctions [8]. Based on these findings, since the mid-1980s, instead of performing curative surgery as the initial treatment of severely traumatized patients with unstable vital signs, damage control such as gauze packing to the surrounding bleeding organs to suppress the insult was introduced and has contributed to the improvement in the survival rate [5, 6, 9].

The phrase "damage control" is a naval military term [9]. Damage control in the military field refers to maintaining preliminary buoyancy and restoring power while maintaining water tightness and airtightness; especially in a ship in which fire, collision, stranding, or explosion has occurred, it refers to removing inflammable material, extinguishing a fire, and eliminating gas smoke. Moreover, by preparing emergency equipment, the spread of damage can be stopped, injured people can be treated, and failures and power supply can be restored [10, 11]. Furthermore, as for the origin of the damage control concept, it was introduced at the beginning of the Napoleonic war in the early 1800s [10]. At that time, the idea was that it was necessary to perform amputation within 24 h when the patient's general condition was sufficiently stable to prevent death from severe extremity injury, which was difficult to treat.

Damage control surgery (DCS) is incorporated as part of the damage control strategy. This chapter details the damage control strategy of multiple injury and the influence and related issues that they have on neurocritical care.

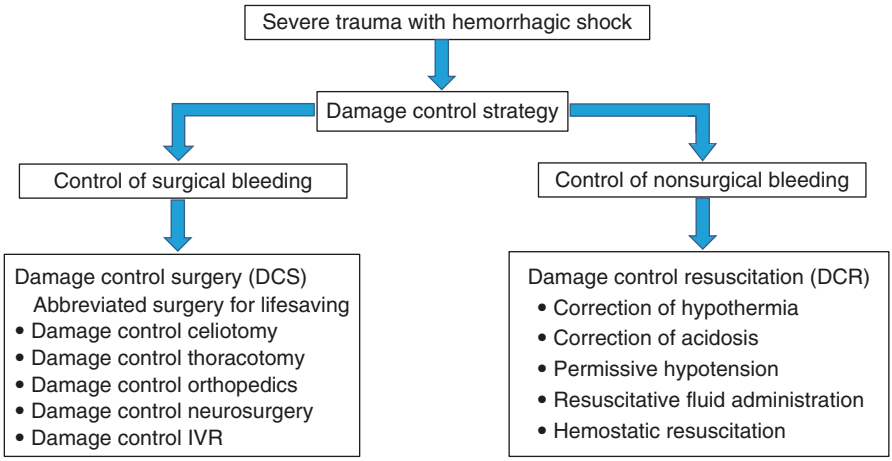

Fig. 11.1 Damage control strategy for severe trauma with hemorrhagic shock is divided into two methods. There are procedures for controlling surgical bleeding for a respective region and resuscitation for nonsurgical bleeding. *IVR* interventional radiology

11.2 Damage Control Strategy

Damage control strategy consists of two fundamental actions (Fig. 11.1). The first fundamental action is DCS, the objective of which is controlling surgical bleeding. It was initially applied to abdominal trauma; the concept has spread to celiotomy, thoracotomy, orthopedics, neurosurgery, and interventional radiology (IVR) [12–15]. The second fundamental action is trauma resuscitation, the purpose of which is controlling nonsurgical bleeding. The paradigm of management is shifting from the conventional high-volume resuscitation to low-volume resuscitation (i.e., damage control resuscitation [DCR]).

11.3 Damage Control Neurosurgery and Intracranial Pressure-Related Issues

In 2004, Rosenfeld [14] emphasized that rapid intervention of neurological treatment is equivalent to damage control of neurosurgery. They reported that the management of sustained bleeding in the torso is a priority in patients with multiple traumas accompanied by traumatic brain injury (TBI); if the patient's condition is stable, an intracranial pressure (ICP) sensor should be inserted in the emergency room or operating room in tandem with laparotomy and/or thoracotomy. The *Guidelines for the Management of Severe Traumatic Brain Injury* (third edition) published in 2007 recommended ICP should be monitored in TBI patients with Glasgow Coma

Score (GCS) of 3–8 and either an abnormal CT scan or a normal CT if two or more of the following features were noted: age >40 years, unilateral or bilateral motor posturing, or systolic blood pressure (sBP) <90 mmHg [16]. However, the latest (fourth edition) of the guidelines published in 2017 only recommends managing severe TBI patients by using information from ICP monitoring to reduce in-hospital and 2-week postinjury mortality. There was no mention of what condition of the patients for whom ICP should be monitored; however, if the value exceeds 22 mmHg, it is desirable to treat the patient because of increased mortality [17]. Also, as soon as the fourth edition of the guidelines was published, the results of the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial were reported, which could affect the recommendation. The RESCUEicp trial is a prospective randomly assigned study of 408 patients with intracranial hypertension (i.e., ICP >25 mmHg) that compared the effect of decompressive craniectomy versus that of ongoing medical care [18]. The results revealed that decompressive craniectomy patients have lower mortality, higher rate of persistent vegetative state, and severe disability. However, moderate disability and good recovery rate were similar between two groups. This finding was not contrary to the results of the 2017 guidelines. An article in which the guidelines indicated that mortality increases above ICP 22 mmHg was based on the report by Sorrentino et al. [19]. They conducted subgroup analysis of age and sex and concluded the mortality threshold did not change; however, the threshold of favorable outcome was 18 mmHg in female patients or an age >55 years. The guideline did not support subgroup analysis results of sex and age because of the small number of cases; thus, the desirable ICP may differ, depending on sex, and age is an interesting topic for the future research.

Abdominal compartment syndrome is also very important as a pathophysiological condition at a risk of elevating the ICP. The intra-abdominal pressure (IAP) is usually maintained at 0–5 mmHg, and an IAP ≥12 mmHg at rest in the supine position is defined as intra-abdominal hypertension (IAH) [20]. If the IAP rises because of abdominal trauma or intestinal edema caused by massive transfusion, the intrathoracic pressure (ITP) would also rise through the diaphragm [21]. Rising ITP decreases venous return, which increases ICP and diminishes cerebral perfusion pressure (CPP) [22]. Moreover, the worsening effect of ACS on whole body organs is substantial. The following may occur because of elevated IAP and ITP: reduced cardiac output and increased afterload in the cardiovascular system [22, 23], increased airway pressure and ventilatory failure in respiratory system [24], reduced urine volume because of hypoperfusion of the renal parenchyma and vein in the visceral organs [25], disordered mitochondrial function and energy metabolism in the liver [26], and further exacerbated edema and circulation in digestive organs [27]. Therefore, a diagnosis of ACS requires immediate intervention, and nonsurgical treatments and/or surgical management are available [20]. For primary ACS caused by abdominal trauma, decompressive laparotomy (DL) and an open abdomen are the indicated surgical treatments. For secondary ACS due to excessive volume resuscitation, nonsurgical treatment is the first-line approach [20, 28]. Nonsurgical treatment consists of five methods, as follows [20]:

1. To improve abdominal wall compliance, the use of sedatives, analgesics, muscle relaxants, and management with lowering the head to ≤30° may be considered.
2. To remove digestive tract contents, nasogastric tube insertion, colorectal drainage, and intestinal peristalsis should be administered.
3. Percutaneous drainage should be considered to remove abdominal cavity contents.
4. To control fluid balance, restricting excessive volume resuscitation and using diuretics may be considered.
5. To maintain organ function, ventilation and alveolar recruitment should be optimized.

If IAP persists at ≥20 mmHg and other organ disorders appear, despite the nonsurgical management, then it is desirable to consider DL [20, 28]. In 2018, a systematic review and meta-analysis of 286 patients with ACS who received DL was published [29]. According to the article, IAP was decreased on averate by 18.2 ± 6.5 mmHg and fell within the normal range. Moreover, heart rate, central venous pressure, pulmonary capillary wedge pressure (i.e., PCWP), and peak inspiratory pressure (i.e., PIP) were decreased; the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (i.e., P/F ratio) and urinary output were increased in adult patients. Nearly similar hemodynamic beneficial effects were also observed in pediatric patients, although the reported mortality rate was as high as 49.7% for adults and 60.8% for children. Based on the aforementioned findings, it was concluded that further validation is required to determine the severity and optimal timing for which DL is effective.

11.3.1 Damage Control Resuscitation

The DCR consists of the following five components [30]: (1) recovery from hypothermia, (2) correction of metabolic acidosis, (3) permissive hypotension, (4) restrictive fluid administration, (5) and hemostatic resuscitation. Each component and related issues are described below.

11.3.2 Correction of Hypothermia and Metabolic Acidosis

Hypothermia can occur for a variety of reasons such as tissue hypoperfusion, rapid infusion, transfusions, and skin exposure during surgery in patients with severe trauma. The risk of death increases to 41-fold when the core body temperature is less than 35 °C, the platelet function and all coagulation factor activities decrease when the temperature falls below 34 °C, and the mortality rate is nearly 100% when the temperature is ≤32.8 °C [31]. The supplementation of coagulation factors is ineffective, and temperature recovery is the only treatment in hypothermia-induced coagulopathy.

It is wandering away from the main subject; many discussions exist regarding the effect and complications of induced hypothermia in TBI patients. There are two methods for inducing hypothermia. Prophylactic hypothermia is administered before ICP elevation, and therapeutic hypothermia is used for treatment-resistant ICP elevation. These treatment effects have often conflicted in previous reports. In response to a report by Clifton et al. in 2011, indicating early 33 °C prophylactic hypothermia shows no difference in mortality and outcome, compared with normothermia [32]; the Brain Trauma Foundation guidelines published in 2017 do not recommend early (i.e., within 2.5 h) short-term hypothermia to improve outcomes in patients with diffuse injury [17]. Current study subjects of the therapeutic hypothermia management have shifted to duration, depth, rewarming, and which patient populations. Clinicians also need to pay attention to metabolic acidosis at trauma resuscitation. Tissue hypoperfusion due to hemorrhagic shock causes the accumulation of lactic acid and metabolic acidosis [33]. In addition, clinicians also need to pay attention because the administration of more than 2000 mL of normal saline (0.9%) at resuscitation may cause high chloride acidosis and subsequent coagulopathy [33].

11.3.3 Permissive Hypotension and Restrictive Volume Administration

Permissive hypotension is a strategy that allows the management of blood pressure lower than normal tissue perfusion pressure with the purpose of not exacerbating bleeding until surgical bleeding is controlled [34, 35]. This concept has had much focus in this decade, although it was described in 1918 by Cannon et al. [36]. They mentioned in the article for the first time the harmfulness of administering volume resuscitation before achieving hemostasis in patients with trauma injury and advocated maintaining an sBP of 70–80 mmHg until curative hemostasis is achieved. Permissive hypotension is indicated for patients with a penetrating torso injury not accompanied by severe TBI, and low-volume resuscitation, which restricts massive crystalloid administration, is used to control the sBP to 80–90 mmHg and the mean arterial blood pressure (mAP) to 50 mmHg [34]. Restrictive volume administration may provide many advantages such as mitigation of dilutional coagulopathy (i.e., RAC), suppression of "pop" a clot phenomenon, peeling off the thrombus of hemostasis by elevated blood pressure leading to rebleeding, and avoiding resuscitation injury by massive crystalloid administration, as mentioned previously [6]. However, care should be taken in sBP and infusion management in patients with severe TBI and in patients with brain injury and multiple trauma. It has long been important to avoid hypotension to reduce secondary injury and brain swelling of TBI [37], although how to manage blood pressure and volume resuscitation in patients with severe TBI and multiple injuries has not been determined. The 2005 American Heart Association's *Guidelines for Cardiovascular Care* reported that administering rapid infusion with an sBP target value of ≥100 mmHg is recommended only for blunt trauma or for penetrating trauma to the brain or extremities alone [38].

The *European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma* in 2016 states that the infusion volume should be limited with the aim of maintaining the mean arterial pressure (mAP) >80 mmHg in patients with severe TBI (GCS ≤8) and/or with spinal cord injury [34]. In the latest Brain Trauma Foundation guidelines in 2017, blood pressure management with TBI varies, based on age as follows: "maintaining sBP at ≥100 mmHg for patients 50–69 years old or at ≥110 mmHg or above for patients 15–49 or over 70 years old may be considered to decrease mortality and improve outcomes" [17]. As described previously, the reason the blood pressure management target cannot be set easily in patients with TBI is that it is difficult to evaluate and judge the cerebral blood flow (CBF). Monitoring the ICP is essential for accurate evaluation because CPP is included in the formula: mAP – ICP. However, in some environments it is difficult to initiate monitoring during the hyperacute phase, as well as establish high-quality research concerning blood pressure management in TBI, and comply with the research protocols. Moreover, CBF is theoretically preserved by autoregulation, even if blood pressure is reduced in a healthy person; however, this autoregulation may collapse in moderate to severe TBI, and CPP is not necessarily maintained only by blood pressure management. With regard to retaining CPP retention and decreasing ICP, attention should also be paid to the infusion fluid type for trauma patients. The use of mannitol or hypertonic saline at the time of increasing ICP is recommended [17], although hypertonic saline is recommended in DCR [39]. At present, it seems that there is no problem in choosing to administer hypertonic saline in patients with multiple trauma and TBI with the expectation that the ICP will decrease. The European guidelines in 2016 recommend avoiding hypotonic solutions such as Ringer's lactate in patients with severe head trauma to minimize fluid shift to damaged brain tissue [34]. Furthermore, caution is required for the administration of a colloid solution. Investigators in the Saline versus Albumin Fluid Evaluation (SAFE) study, which investigated in 460 patients with TBI, reported that the administration of albumin (4%) increases the mortality rate (RR, 1.62), compared with the administration of normal saline [40]. The SAFE-TBI study post hoc analysis revealed that the increase in mortality due to albumin administration in patients with severe TBI was associated with increased ICP [41]. The 2016 European *Guideline on Management of Major Bleeding and Coagulopathy Following Trauma* advocates "use of colloids be restricted because of the adverse effects on hemostasis" [34].

11.3.4 Resuscitative Endovascular Balloon Occlusion of the Aorta

Even if volume resuscitation is administered during the initial trauma management, it is possible for a crisis situation to occur in which the sBP cannot be maintained. If the uncontrolled hemorrhagic region is peripheral to the abdomen, an option is to maintain blood pressure through thoracic or abdominal aortic cross-clamping. The purpose of the procedure is to preserve blood flow and pressure in the heart and the central nervous system (CNS) by disrupting or reducing blood flow below

the clamp. Even if the method of aortic cross-clamping directly by thoracotomy or laparotomy is complete, blood flow below the clamping region is completely disrupted, and the insult caused by the procedure itself may worsen a patient's condition [42]. Resuscitative endovascular balloon occlusion of the aorta (REBOA), a method of blocking blood flow by inflating a balloon inserted in the aorta, is minimally invasive and can even be administered by a physician who is not learned in surgical procedures. Animal experiments of the REBOA procedure have data indicating that the mortality rate and lactic acid level increase when the blocking time exceeds 60 min [43]; therefore, a continuous cutoff time of 45 min or less is recommended. In direct cross-clamping, blood flow below a clamp is completely blocked, whereas REBOA can control the blood flow below the blocking region to some extent by the amount of normal saline injected into the balloon; this procedure is called partial REBOA [44]. Resuscitation is possible when the sBP is controlled to a 80–90 mmHg target as a permissive hypotension by partial REBOA in trauma patients without brain injury and is controlled to a 100 mmHg target in patients with multiple trauma and TBI. However, in actual practice, whether REBOA is beneficial or harmful for patients with TBI is inconclusive. It has been hypothesized that increased carotid artery blood flow by REBOA leads to deterioration by cerebral edema, elevation of ICP, and exacerbation of intracranial hemorrhage [45]. Some investigators report that the mortality of patients with multiple injuries and TBI requiring REBOA is as high as 50% [46, 47]. By contrast, there are animal experiments that such a supraphysiological response does not lead to hemorrhage exacerbation of brain CT. Johnson et al. [48] created hemorrhagic shock using a standardized brain trauma swine model and measured the mAP, carotid artery blood flow, and ICP and obtained brain CT imaging in the REBOA group, the partial aortic clamp group, and the control group. The mAP and carotid artery blood flow in the REBOA group was significantly high; however, the ICP was largest at the time of resuscitation due to the rapid transfusion in control group, which was contrary to expectation. There was no significant difference between the three groups in the proportion of hemorrhage exacerbations on the brain CT, and REBOA was not a factor that worsened TBI. Further study will be required for the effects and adverse effects of REBOA in patients with TBI and multiple injuries.

11.3.5 Hemostatic Resuscitation

As with other injuries, TBI was traditionally managed to maintain a high hemoglobin (Hb) level to prevent secondary brain damage due to reduced oxygen delivery [5, 49]. However, this concept has also changed in recent years. Robertson et al. [50] reported that neurological prognosis after 6 months did not change in a study of TBI patients when comparing the Hb transfusion thresholds of 7 and 10 g/dL. In a retrospective review of 1150 TBI patients, Salim et al. [49] concluded that blood transfusion is associated with high mortality (adjusted odds ratio [OR], 2.19) and high complication rate (OR, 3.67) in patients with or without anemia. Thus, it may

be that maintaining a Hb level higher than necessary is rather harmful; however, it is also a fact that there are circumstances in which massive transfusion must be administered rapidly in patients with multiple traumas. Hemostatic resuscitation in patients with multiple traumas is a strategy to minimize acute coagulopathy of trauma and shock (ACoTS) and RAC by the transfusion protocol and drug administration for massive hemorrhage [4]. Details of coagulopathy due to trauma and coagulopathy associated with massive fluid resuscitation such as ACoTS and RAC are discussed in Chap. 9 ("Coagulopathy and Brain Injury"). In this chapter, we describe the main treatment strategies for patients with multiple injuries.

11.3.5.1 Massive Transfusion Protocol

For the initial treatment of patients with severe multiple injuries and unstable vital signs, many trauma centers have adopted the massive transfusion protocol (MTP), which involves promptly administrating erythrocyte concentrate, fresh frozen plasma (FFP), and platelet concentrate (PLT) at an appropriate ratio without waiting for blood test results [4, 51]. In addition, massive transfusion is defined as the administration of more than 10 units of RBCs per 24 h, ≥150 mL/h, or 100% blood in less in 24 h; however, this definition is not evidence-based [52]. Many traumatic deaths due to exsanguination occur within 2–3 h of injury [53]. Therefore, in discussing massive transfusion in severe trauma, defining it as a transfusion volume per 24 h may not have a significant meaning [54]. Over the last decade, there have been discussions regarding whether the transfusion ratio of plasma to platelet to RBC is favorable at 1:1:1 in the MTP. Some investigators report that the survival rate increases when the proportion of plasma is increased [55–57], whereas other investigators indicate this finding is because of survival bias [58, 59]. Therefore, the appropriate ratio is of interest to researchers. Recent studies may have settled this discussion [53, 60]. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study published by Holcomb et al. [60] in 2013 was a prospective cohort study that observed 905 trauma patients who had required at least 3 units of transfusion within 24 h of admission [60]. They elucidated a significant decrease in 6-h mortality because of the early high rate resuscitation of plasma and PLT (plasma:PLT:RBC = 1:1:1), compared with patients with a ratio less than 1:2. Furthermore, a transfusion ratio less than 1:2 was associated with a three- to fourfold mortality rate. The Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) study published in 2015 was a multicenter prospective randomized control trial in which the plasma:PLT:RBC ratios of 1:1:1 and 1:1:2 were compared in 680 patients with severe trauma [53]. The 1:1:1 transfusion group had more hemostasis (86% vs. 78%) and less exsanguination (9% vs. 15%) in the first 24 h, but the 24-h mortality and 30-day mortality were comparable. The authors suggested that the reason the mortality was not significant was that most deaths due to exsanguination often do not occur after 24 h of injury, but within 2–3 h of injury. In addition, the 1:1:2 group eventually underwent many transfusions after the intervention and frequently used cryoprecipitate (described later) with a high hemostatic

effect (22% vs. 29%). This appeared an attempt to achieve the 1:1:1 strategy. Some current guidelines recommend a 1:1:1 strategy because of the aforementioned results and similarity of complication rate associated with transfusion [61, 62]. The subject of the PROMMTT and PROPPR studies was severe trauma in general; however, neither study differentiated TBIs. In 2011, a study that differentiated TBIs was reported by Brasel et al. [54]. They retrospectively examined patients who were divided into (1) TBI^+ patients with an abbreviated injury scale of ≥3 and (2) TBI^- patients with an abbreviated injury scale <3. To prevent survival bias, patients were excluded who died within 60 min. They found that a high PLT:RBC ratio improved 30-day survival in the TBI^+ group and a high plasma:RBC ratio was associated with an improvement in the 30-day survival in the TBI^- group. The reason the authors proposed for the favorable outcome of high ratio of PLT administration in the TBI^+ group is that PLT may activate oligodendrocyte precursor cells, which differentiate into oligodendrocytes in the damaged CNS and restore demyelinated areas; they also cited an experiment of blood-brain barrier damage in a rodent model [63]. For the platelet count, it is recommended to maintain the number of platelets ongoing bleeding with TBI at 100×10^9/L or more, based on the European guidelines 2016 [34]. At present, it appears that there is no problem in using the 1:1:1 protocol in patients with multiple traumas and brain injury. However, rapid transfusion may increase ICP, based on the animal experiment of REBOA cited earlier [48]. Further research is necessary to obtain conclusions.

11.3.5.2 Fibrinogen Concentrate and Cryoprecipitate

Fibrinogen is the final component of the coagulation cascade and an essential element for stable thrombus formation [64]. It is cleaved by thrombin into fibrin, which polymerizes to form a strong thrombus resistant to fibrinolysis [64]. In a prospective study of 517 trauma patients, Rourke et al. [65] reported that a low fibrinogen level was a predictor of 24-h mortality and 28-day mortality. The importance of fibrinogen is widely recognized in the treatment of multiple trauma. However, cryoprecipitate is purified by concentrating the coagulation factors contained in plasma and contains factor VIII, factor XIII, von Willebrand factor (vWF), and fibrinogen, which have a high hemostatic effect [66]. The European guidelines in 2007 recommended supplementation at a fibrinogen level of 1 g/L or less in patients with trauma [67]. However, the 2016 guidelines recommend supplementation of fibrinogen concentrate or cryoprecipitate at 1.5–2.0 g/L or less. The initial desirable fibrinogen administration is 3–4 g, which is approximately 15–20 units for cryoprecipitate or approximately 20–25 units for FFP [34].

In 2017, Innerhofer et al. [68] announced early cancelation of the Reversal of Trauma Induced Coagulopathy Using Coagulation Factor Concentrates or Fresh Frozen Plasma (RETIC) trial because of futility and safety reasons, which was verifying the effects of FFP or coagulation factor concentrates (CFCs) for patients with severe trauma and coagulopathy (including TBI patients). The CFCs

administered in this trial consisted of fibrinogen and/or prothrombin complex concentrate and/or factor XIII. The reason for the trial cancelation was that more rescue therapy is required in the FFP group (OR, 25.3) and the necessity for massive transfusion was increased (OR, 3.0). Based on these results, they concluded that first-line CFCs outperformed FFP administration, and they emphasized the importance of early effective fibrinogen supplementation for clotting failure with severe trauma. Prospective studies are being conducted to determine whether supplementation of urgent cryoprecipitate will improve the outcome. In 2015, the CRYOSTAT pilot study [69] examined cryoprecipitate supplementation within 90 min of arrival, and, in 2018, the Early-Fibrinogen in Trauma (E-FIT 1) pilot trial [70] aimed to administer cryoprecipitate within 45 min of arrival for patients undergoing MTP for hemorrhagic shock. A prudent interpretation of E-FIT 1 trial is required because administering cryoprecipitate supplementation within 45 min is difficult. However, the early supplementation group had no significant difference in all-cause mortality at 28 days, compared with the normal administration group in either trial. It is not reasonable to administer cryoprecipitate immediately after admission. However, the accumulation of further research results is required because the efficacy for TBI is unknown.

11.3.5.3 Antifibrinolytic Agents

Tranexamic acid (TXA) has a leading role in antifibrinolytic therapy. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial is a randomized controlled trial involving 20,111 injured patients with massive exsanguination, which includes TBI, within 8 h, or hypotension and/or tachycardia [71]. The TXA group, which received loading 1 g of TXA over 10 min, followed by 1 g infusion of TXA over 8 h, was compared with the placebo group (0.9% saline). The all-cause mortality (relative risk [RR], 0.91) and the risk of death from hemorrhage (RR, 0.85) decreased because of TXA administration. There were no significant differences in vascular occlusion complications and amount of transfusion. Furthermore, in an additional report in 2011, the risk of hemorrhage was significantly decreased when TXA was administered within 1 h (RR, 0.68) or 1–3 h postinjury (RR, 0.79) [72]. By contrast, the risk of hemorrhagic death was increased by administering TXA 3 h postinjury (RR, 1.44). Based on the results of the CRASH-2 trial, the 2016 European guidelines recommended TXA administration within 3 h, based on the method used in the trial [34]. In addition, the CRASH-3 trial is in progress [73]. The CRASH-3 trial is an international, multicenter, pragmatic randomized, double-blind, placebo-controlled trial for patients with intracranial hemorrhage on CT or with a GCS $\leq$12 among adults with single brain injuries within 8 h of injury and uncertainty as to whether TXA should be administered. The method of administration of TXA is similar to that in the CRASH-2 trial. The research results are pending regarding the extent an effect can be obtained for patients with single brain trauma.

11.3.5.4 Ionized Calcium (iCa)

Ionized calcium (iCa) is indispensable for the formation and stabilization of fibrin polymerization; a reduction in cytosolic iCa concentration decreases all platelet activity [74]. Giancarelli et al. [75] reported that, among 156 trauma patients who underwent massive transfusion in 2009–2013, 97% had hypocalcemia and 71% had severe hypocalcemia (iCa <0.9 mmol/L). The mortality was significantly higher among the severe hypocalcemia group than among the hypocalcemia group (49% vs. 24%), when compared with normal limit. The 2016 European guidelines recommend that iCa levels be monitored and maintained within the normal range during massive transfusion [34].

11.3.5.5 Factor VIIa

Boffard et al. [76] in their prospective study reported on the effect of factor VIIa in reducing the transfusion amount in patients with blunt trauma, even though it did not decrease mortality. Since that report, recombinant factor VIIa (rFVIIa) administration has been included in the MTP in many trauma centers [77]. The CONTROL trial in 2010 was a randomized, assignment, prospective study to verify the efficacy of rFVIIa in patients with torso or femoral trauma and refractory hemorrhage [78]. This study unfortunately resulted in less than one-half of the anticipated mortality reduction, and enrollment was censored. In 2018, Lombard et al. reported a propensity score analysis of rFVIIa administration in TBI, although it is a level III evidence [79]. This investigation covered 4284 TBI patients with GCS ≤13 who were diagnosed with brain CT and treated at 11 level 1 trauma centers. Of 129 patients were administered rFVIIa which is not involved in the risk reduction of mortality or morbidity as a result of comparison with the non-administered group. The results of prospective studies will be required to determine the effect of FVIIa administration.

11.4 Summary

As mentioned previously, some treatment strategies for patients with multiple traumas have undergone major transformations in recent decades. However, some treatment strategies also include revival of treatments that had been conducted in the past. In multiple trauma, including brain injury, there are many parts so that management is different for the torso and/or extremity injury and many factors that remain unknown. With cutting-edge treatment technology and development, we hope that the knowledge and experiences abandoned in the past will be integrated and renovate conventional trauma management, and thus many patients will be saved.

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