Massive Transfusion Protocols (MTPs) in Cancer Patients

85

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Contents

Introduction 1205

Definition 1206
Massive Transfusion 1206
Massive Transfusion Protocol at The University of Texas MD Anderson Cancer Center 1208

Summary 1210

References 1210

Abstract

The management of soldiers with massive injury in the battleground and the blood support needed for these patients is an area of constant progress and led to the development of protocols to correct the rapid changes leading to death after the battle trauma. As a result there has been a standardization and timely release of blood components in defined ratios which are called massive transfusion protocols (MTPs). The civilian hospitals learned from the military experience, and MTPs are currently used in the emergency centers and operating rooms of hospitals. However, not all MTPs are created equal, and there is institutional variation, according to the type of patients requiring MTPs. There is still controversy around the ratios of blood components to be used and what population of patients benefit from the activation of MTPs.

Keywords

Massive bleeding · Massive transfusion · Massive transfusion protocols

Introduction

It was at the beginning of the twentieth century that the field of transfusion emerged, and during World War I, the transfusion of blood revealed as a lifesaving measure [27]. During World War II, whole blood was the product for resuscitation in battle trauma. Simultaneously the fractionation of plasma opened the field for plasma derivatives [5]. The experience acquired led to the use of whole blood, plasma, and plasma derivatives to

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support surgical procedures and the treatment of specific deficiencies. After the development of plastic bags and the technology for component separation progressed, there was a transition to use blood component therapy and crystalloids as fluid replaced instead of whole blood. However in patients with trauma and massive bleeding, there is hypoperfusion, which results in a triad of hypothermia, coagulopathy, and acidosis. Trauma resuscitation was based on the administration of crystalloids and infusion of blood components in a non-defined ratio which increased the coagulopathy, produced hemodilution, decreased oxygen-carrying capacity, and further aggravated the clinical picture. The first decade of the twenty-first century produced a shift in management of massive transfusion in trauma patients after the experience of the military in the conflicts of Iraq and Afghanistan. This led to the early use of blood components in defined ratios for rapid hemorrhage control as part of damage control resuscitation [2]. The standardization of blood component ratios for rapid release in the treatment of intravascular volume deficits led to the conception of massive transfusion protocols (MTPs). As consequence of the implementation of MTPs, trauma patients had an improved oxygen-carrying capacity and reduced incidence of consumptive and dilutional coagulopathy which resulted in improved clinical outcomes [15]. Thus, the use of massive transfusion protocols facilitated the management of emergently bleeding patients using standardized blood component ratios and optimized delivery times. The experience in the military setting was taken to civilian setting, and massive transfusion protocols were adopted in trauma centers and emergency rooms, with different patient populations benefiting from adapted MTPs according to the clinical picture.

Definition

Massive transfusion can be defined in many ways. In adult patients, it has been historically defined as a transfusion of ten or more units of RBC (one blood volume) in 24 h [28]. For a more practical approach, other definitions have been proposed, such as transfusion of five units of RBC or more (or half of one blood volume) in 3 h and transfusion of four RBC units in 1 h with evidence of ongoing blood loss of >150 ml/min [24]. The latter definitions are directed at identifying the patients with ongoing need of transfusion earlier in order to improve outcomes.

Massive Transfusion

Massive transfusions can occur in a variety of settings such as trauma, obstetric complications, and cardiovascular, liver, or spinal surgery, but most studies have initially focused on its use in the trauma setting. Many studies have pointed to the importance of timely delivery of blood components to the exsanguinating patients to avoid or to correct early coagulopathy and prevent morbidity and mortality [9, 16, 22]. Many hospitals around the USA and outside the USA have implemented massive transfusion protocols in an attempt to expedite the delivery of blood components to the bleeding patient. MTPs are designed to increase efficiency of the delivery of blood and blood components to the bleeding patients by facilitating the delivery of blood in a predetermined ratio in an attempt to improve survival. There is not a consensus in the ratios of blood components to be used in the MTPs in trauma patients; similarly there are significant variations in the type of patients receiving blood components due to great differences in the extent and distribution of the injury to tissue. The mechanism of trauma produces a different damage resulting in a different magnitude of bleeding and metabolic changes. Blunt injury patients may present with multiple sites bleeding, coagulopathy, and a more complex presentation, while patients that have sustained a penetrating injury usually have a defined site of hemorrhage and may present with a lower injury severity score. Thus, the ratio of components such as fresh frozen plasma (FFP) and platelets to red blood cells (RBC) is a subject of ongoing debate [13, 14]. Most of the data comes from the trauma setting, but the characteristics of the patients may

require different MTPs, and more studies are needed in different patient populations.

In a large prospective observational multicenter study (PROMMT study), the authors concluded that low plasma/RBC ratio (<1:2) was associated with increased mortality only in the first 24 h. The risk of death at 30 days was not significantly different between a low ratio (1:2) and a high ratio (1:1) of plasma/RBC and platelets/RBC[13]. The largest randomized clinical trial (PROPPR study) attempting to establish the best ratio also showed no significant difference between those ratios in the co-primary outcomes of 24-h and 30 days mortality. They did however find some differences in secondary outcomes, such as exsanguination in the first 24 h as the primary cause of death, which favored the 1:1:1 (plasma/platelets/RBC) group [14]. There are few studies addressing the appropriate ratio in the non-trauma setting. In a study of surgical and critically ill patients at a tertiary medical center, it was found that greater than 1:2 ratios of FFP/RBC or platelets/RBC did not result in a difference in 30-day mortality in studied 601 massively transfused non-trauma patients [11]. In a retrospective review of 865 massive transfusion events in an urban academic hospital over the lapse of 4 years, the authors found that most of the transfusions were given to patients without trauma, accounting for 90% or all massive transfusion event; there was no difference in the 30-day survival rate between patients who receive a high FFP/RBC ratio and the patients that received a low ratio [21].

A recently published systematic review of clinical trials concluded that fixed higher ratios of FFP and platelets to RBC are associated with higher transfusion of FFP and platelets without documented evidence of clinical benefit compared to the standard care or 1:1:2 ratio [19]. Currently, there are no specific guidelines on the specific ratio of blood products in the setting of oncologic critical care patients due to the clinical complexity of these patients. It has been proposed to start resuscitation efforts with a fixed ratio strategy to aid in the timely delivery of the needed blood products to the patient and then move toward a goal-directed strategy utilizing laboratory and point-of-care testing parameters as guidance [18]. Since the turnaround time of certain laboratory tests such as PT, aPTT, and CBC might not be appropriate in the setting of a massive bleeding patient, there has been emphasis in the use of point-of-care tests such as viscoelastic tests (TEG, ROTEM) [8, 10, 12]. More importantly, each institution needs to establish an adequate ratio of blood components to suit the serving patient population. During the initial phases of massive transfusion, the American College of Surgeons' Trauma Quality Improvement Program (ACS-TQIP) recommends transfusing RBC and plasma components in a ratio between 1:1 and 1:2, along with one apheresis platelets or a dose of whole blood-derived platelets for every six units of RBCs. The guidelines also recommend the MTP packages to be delivered in rounds taking no longer than 15 min until the MTP is terminated.

Massive bleeding and blood therapy are associated with several metabolic alterations that can further exacerbate the clinical condition of a critical patient [7, 17]. Other potential complications are hypothermia, acidosis, poor oxygen dissociation, hypocalcemia, and hyperkalemia. Many of these complications are related to the changes in blood products during storage, and at the same time, many of those derangements might already be present in critically ill oncologic patients. The clinical relevance of some of these effects remains unknown [6, 30].

When trying to establish a MTP in a specific patient population, it is important to take into consideration several factors such as the blood bank capabilities, proper education of all clinical and non-clinical teams and staff involved, and underlying clinical data. Since many blood banks have limited resources in regard to blood products and personnel, usually a physician needs to take responsibility regarding the appropriate indication of activation of an MTP as well as the appropriate endpoint considering the patient's underlying comorbidity and prognosis. Many times prognosis is reserved in patient with disseminated cancer in critical care units leading to ethical considerations in the use of such protocols (informing the blood bank when no more

components need to be issued as well as in recognizing the potential complications of transfusion during the intervention and after). Of vital importance for the success of a newly established MTP is the prospective gathering of data to ensure the proper monitoring of relevant outcomes. In certain cancer patients, namely, those in the ICU setting, attributing the MTP to a particular outcome might be more difficult since these patients have multiple other variables involved. A coordinated effort between the laboratory, the transfusion service, and treating team within a close, precise, and concise communication is key in the success of a MTP.

Currently, there are no established guidelines on the appropriate trigger of massive transfusion and the subsequent resuscitation strategy including the adequate ratio of blood components to be used in the critical care or perioperative setting of cancer patients.

Massive Transfusion Protocol at The University of Texas MD Anderson Cancer Center

At the University of Texas MD Anderson Cancer Center, patients that have a massive bleeding are supported under a massive transfusion protocol validated initially for patients in surgery and currently under validation for patients in interventional radiology and ICU. There are two MTPs activated by month as average at our institution; however patients that have a massive hemorrhage may be treated by selected blood components without activation of MTP. Because the ABO type of the patient is known, patients are supported with ABO identical or compatible blood components. However a cooler with O positive RBCs and plasma is always ready (emergency crate), and this is to be used if there is no enough time to release cross-matched units, activating immediately the MTP to follow up with coolers with cross-matched RBCs. A second emergency crate could be used if needed.

Operationally, there is a main transfusion service in charge of coordinating MTPs when needed, and there is a blood bank suite in the operating room where blood components and cross-matched red blood cells (RBCs) are in storage for patients scheduled for surgical procedures that may require RBC support. If a patient develops a massive bleeding and immediate transfusion is needed, a cooler is immediately available in the OR blood bank suite and in the transfusion service. This cooler has four units of O Rh-positive RBCs and four units of A plasma and is to be used first when there is no time to wait for cross-matched RBCs units. If a MTP is activated, a technologist is immediately placed in charge of the MTP and coordinates and communicates with the treating team. A second cooler with four units of ABO compatible or identical RBCs and four units of ABO compatible or ABO identical plasma will be provided; this will be cooler number one if the team considers that there is enough time for cross-matching RBC units (10–15 min) and the emergency crate will not be used. If the MTP is still active, then a third cooler with four units of RBCs, four units of plasma, and one unit of apheresis platelets will be released; the platelet unit is placed in a pouch externally attached to the cooler. The fourth cooler will have four units of RBCs, four units of plasma, one apheresis platelets, and five units of pooled cryoprecipitate; thus, cryoprecipitate will be added every other round until MTP is deactivated. Of great importance is the dynamic communication between the treating team and the transfusion service in order to deactivate the MTP once deemed appropriate. A working tool consisting of a table with the coolers and its contents was developed; the coolers are numbered, allowing for an easy identification of blood components attached and the time of release (see Form 1).

Cancer patients undergoing major oncologic surgery are at risk for massive transfusions [3]. Adding to the complexity of these patients, many of them have been diagnosed with chronic anemia, either due to the cancer itself or associated treatment [20]. One study by Ojima et al. found massive transfusion to be an independent prognostic factor. For shortened long-term survival in certain cancer patients [26]. Since the incidence of massive transfusion in cancer patients is largely unknown, more research is needed to provide

Patient Name:_____MRN:_____ or#_____
Date:_____

Cooler #	Round #	Units of RBC/ABO type	Units of FFP/ ABO type	Units of Platelets/ ABO type	Cryoprecipitate
	Emergency crate	4 O Rh Positive	4 A		
1	MTP round #1	4 ABO identical or compatible	4 ABO identical or compatible		
2	MTP round #2	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	5 pooled units
3	MTP round #3	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	
4	MTP round #4	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	5 pooled units
5	MTP round #5	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	
6	MTP round #6	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	5 pooled units
7	MTP round #7	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	
8	MTP round #8	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	5 pooled units
9	MTP round #9	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	
10	MTP round #10	4 ABO identical or compatible	4 ABO identical or compatible	1 ABO identical or compatible	5 pooled units

Form 1 Massive transfusion protocol working tool

recommendations for transfusion in the perioperative settings of patients undergoing major oncologic surgery. It is well known that immune surveillance is reduced in transfused cancer patients leading to potential dissemination of the disease. More specifically, transfusions are associated with poorer outcomes for colorectal, lung, and hepatobiliary cancer patients [4, 25]. A randomized controlled trial by Bergamin et al. favored using more liberal versus restrictive thresholds for RBC transfusions in severely ill oncology patients with septic shock since their overall reserve to respond to hypovolemia or normovolemic anemia is reduced [1, 29]. One retrospective study by Montange et al. that followed 21 patients who received a massive transfusion during an oncologic surgery found the overall death rate to be high, pointing toward the severity of the disease. Montange et al. [23] in interpreting their results, it is important to note that this study had a very low number of patients, most of which had ovarian cancer. Still, the debate toward perioperative

management of oncologic patients at risk for massive bleeding during major oncologic surgery and the appropriate activation and endpoint of a massive transfusion protocol needs to be further evaluated.

Summary

In summary, bleeding complications are seen in a large proportion of cancer patients due to several underlying mechanisms. Many cancer patients are also at increased risk of massive bleeding during major oncologic surgery, hence the importance of correcting risk factors prior to such procedures. A MTP has been developed and validated at MD Anderson Cancer Center geared toward surgery patients. A MTP specifically for other patient services such as ICU patients still needs to be developed and validated. Few studies on the outcome of massive transfusion protocols with specific ratios have been done in this vulnerable patient population, clearly highlighting the need for prospective studies at large academic centers with large volume of transfusions in this setting. The patients in oncology are different from trauma patients, and the bleeding is due to the therapy and morbid processes posing a unique challenge. Thus, MTPs in oncology are adaptations from the ones used in trauma, and the ratios of blood components for MTP in oncologic patients need further research. It is important, however, to emphasize the vital importance of optimal communication between direct patient providers and the transfusion service to provide directed blood component therapy or the use or MTPs in massive bleeding.

References

1. Bergamin FS, Almeida JP, Landoni G, et al. Liberal versus restrictive transfusion strategy in critically ill oncologic patients: the transfusion requirements in critically ill oncologic patients randomized controlled trial. Crit Care Med. 2017;45:766–73. https://doi.org/10.1097/CCM.0000000000002283.
2. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63:805–13.
3. Cata JP, Gottumukkala V. Blood loss and massive transfusion in patients undergoing major oncological surgery: what do we know? ISRN Anesthesiol. 2012;2012:918938, 11 pages. https://doi.org/10.5402/2012/918938.
4. Cata JP, Gottumukkala V. Blood transfusion practices in cancer surgery. Indian J Anaesth. 2014;58(5):637–42. https://doi.org/10.4103/0019-5049.144675.
5. Cohn EJ, Oncley JL, Strong LE, Hughes WL, Armstrong SH. Chemical, clinical, and immunological studies on the products of human plasma fractionation. I. The characterization of the protein fractions of human plasma. J Clin Invest. 1944;23:417–32.
6. Collins JA. Problems associated with the massive transfusion of stored blood. Surgery. 1974;75:274–95.
7. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ. Hemostasis in massively transfused trauma patients. Ann Surg. 1979;190:91–9.
8. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG(R)) and rotational thromboelastometry (ROTEM(R)) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care. 2014;18:518.
9. Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond). 2009;70:22–5.
10. Einersen PM, Moore EE, Chapman MP, Moore HB, Gonzalez E, Silliman CC, Banerjee A, Sauaia A. Rapid thrombelastography thresholds for goal-directed resuscitation of patients at risk for massive transfusion. J Trauma Acute Care Surg. 2017;82:114–9.
11. Etchill EW, Myers SP, Mcdaniel LM, Rosengart MR, Raval JS, Triulzi DJ, Peitzman AB, Sperry JL, Neal MD. Should all massively transfused patients be treated equally? An analysis of massive transfusion ratios in the nontrauma setting. Crit Care Med. 2017;45:1311–6.
12. Hanke AA, Horstmann H, Wilhelmi M. Point-of-care monitoring for the management of trauma-induced bleeding. Curr Opin Anaesthesiol. 2017;30:250–6.
13. Holcomb JB, Del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH, Group PS. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148:127–36.
14. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, Del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ, Cotton BA, Fabian TC, Inaba K, Kerby JD, Muskat P, O'Keeffe T, Rizoli S, Robinson BR, Scalea TM, Schreiber MA, Stein DM, Weinberg JA, Callum JL, Hess JR, Matijevic N, Miller CN, Pittet JF, Hoyt DB, Pearson GD, Leroux B, Van Belle G, Group PS. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313:471–82.

15. Johansson PI, Stensballe J. Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets – a review of the current literature. Transfusion. 2010;50:701–10.
16. Kutcher ME, Kornblith LZ, Narayan R, Curd V, Daley AT, Redick BJ, Nelson MF, Fiebig EW, Cohen MJ. A paradigm shift in trauma resuscitation: evaluation of evolving massive transfusion practices. JAMA Surg. 2013;148:834–40.
17. Leslie SD, Toy PT. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol. 1991;96:770–3.
18. Mcdaniel LM, Neal MD, Sperry JL, Alarcon LH, Forsythe RM, Triulzi D, Peitzman AB, Raval JS. Use of a massive transfusion protocol in nontrauma patients: activate away. J Am Coll Surg. 2013;216:1103–9.
19. Mcquilten ZK, Crighton G, Brunskill S, Morison JK, Richter TH, Waters N, Murphy MF, Wood EM. Optimal dose, timing and ratio of blood products in massive transfusion: results from a systematic review. Transfus Med Rev. 2018;32:6–15.
20. Mercadante S, Gebbia V, Marrazzo A, Filosto S. Anaemia in cancer: pathophysiology and treatment. Cancer Treat Rev. 2000;26(4):303–11. Review.
21. Mesar T, Larentzakis A, Dzik W, Chang Y, Velmahos G, Yeh DD. Association between ratio of fresh frozen plasma to red blood cells during massive transfusion and survival among patients without traumatic injury. JAMA Surg. 2017;152:574–80.
22. Meyer DE, Vincent LE, Fox EE, O'Keeffe T, Inaba K, Bulger E, Holcomb JB, Cotton BA. Every minute counts: time to delivery of initial massive transfusion cooler and its impact on mortality. J Trauma Acute Care Surg. 2017;83:19–24.
23. Montange F, Salm B, Godfrin PY, Dartois D, Carolus J. Massive transfusion in cancer surgery. A study of the survival of 21 patients. Cah Anesthesiol. 1996; 44(2):111–3. French.
24. Moren AM, Hamptom D, Diggs B, Kiraly L, Fox EE, Holcomb JB, Rahbar MH, Brasel KJ, Cohen MJ, Bulger EM, Schreiber MA, Group PS. Recursive partitioning identifies greater than 4 U of packed red blood cells per hour as an improved massive transfusion definition. J Trauma Acute Care Surg. 2015;79:920–4.
25. Odell DD, Bilimoria KY. Evaluating appropriate blood transfusion in cancer surgery. JAMA Surg. 2016; 151(6):525–6. https://doi.org/10.1001/jamasurg.2015.5104.
26. Ojima T, Iwahashi M, Nakamori M, et al. Anaemia in cancer: pathophysiology and treatment. J Gastrointest Surg. 2009;13:1821.
27. Primrose A, Ryerson ES. The direct transfusion of blood: its value in haemorrhage and shock in the treatment of the wounded in war. Br Med J. 1916;2:384–6.
28. Raymer JM, Flynn LM, Martin RF. Massive transfusion of blood in the surgical patient. Surg Clin North Am. 2012;92:221–34, vii.
29. Vincent J-L, Lelubre C. The sicker the patient, the more likely that transfusion will be beneficial. J Thorac Dis. 2017;9(12):4912–4. https://doi.org/10.21037/jtd.2017.11.102.
30. Wilson RF, Binkley LE, Sabo FM Jr, Wilson JA, Munkarah MM, Dulchavsky SA, Diebel LN. Electrolyte and acid-base changes with massive blood transfusions. Am Surg. 1992;58:535–44; discussion 544–5.