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PREHOSPITAL USE OF PLASMA: THE BLOOD BANKERS' PERSPECTIVE

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ABSTRACT—At the 2013 Traumatic Hemostasis and Oxygenation Research Network's Remote Damage Control Resuscitation symposium, a panel of senior blood bankers with both civilian and military background was invited to discuss their willingness and ability to supply prehospital plasma for resuscitation of massively bleeding casualties and to comment on the optimal preparations for such situations. Available evidence indicates that prehospital use of plasma may improve remote damage control resuscitation, although level I evidence is lacking. This practice is well established in several military services and is also being introduced in civilian settings. There are few, if any, clinical contraindications to the prehospital use of plasma, except for blood group incompatibility and the danger of transfusion-induced acute lung injury, which can be circumvented in various ways. However, the choice of plasma source, plasma preparation, and logistics including stock management require consideration. Staff training should include hemovigilance and traceability as well as recognition and management of eventual adverse effects. Prehospital use of plasma should occur within the framework of clinical algorithms and prospective clinical studies. Clinicians have an ethical responsibility to both patients and donors; therefore, the introduction of new clinical capabilities of transfusion must be safe, efficacious, and sustainable. The panel agreed that although these problems need further attention and scientific studies, now is the time for both military and civilian transfusion systems to prepare for prehospital use of plasma in massively bleeding casualties.

KEYWORDS—Plasma, hemorrhagic shock

INTRODUCTION

Consultants in transfusion medicine or "blood bankers" (BBs) are medical doctors whose primary role is to advise the acting clinician and oversee the provision of high-quality blood components and products. Blood bankers provide clinical oversight for the selection and care of donors and the prevention of infection transmission, for blood grouping and compatibility testing, and for the procurement and quality assurance of blood components and transfusion logistics. Activities should be underpinned by evidence-based practice and comply with current legislation. Whereas the decision to transfuse is the responsibility of the acting clinician, the BBs work closely with the clinicians to develop optimal transfusion guidelines and algorithms. It is important to remember that these statements are equally valid for emergency civilian and military situations. The expertise of BBs is therefore crucial to implementation and running of prehospital transfusion services, in civilian as in military settings.

At the 2013 Traumatic Hemostasis and Oxygenation Research Network's Remote Damage Control Resuscitation symposium, a panel of senior BBs, with both civilian and military background and experience, was invited to discuss their willingness and ability to supply prehospital plasma for resuscitation of massively bleeding casualties and which preparations would be optimal in such situations from the blood bank perspective. All panel participants afterward provided a written summary of their viewpoints, and the current article is a synthesis of these contributions and available literature.

CURRENT SCIENTIFIC AND CLINICAL RATIONALE FOR PREHOSPITAL USE OF PLASMA

The BBs panel acknowledged that several retrospective clinical studies as well as basic physiological ones provide data to indicate that aggressive and early administration of plasma may improve the initial care of the bleeding, critically injured patient (1–7). Plasma provides all coagulation factors, especially if fresh frozen plasma (FFP) is used, and may therefore prevent or compensate dilutional (or secondary) coagulopathy. Interestingly, though, no indications exist that the administration of fibrinogen alone will improve survival (8). This suggests that transfusion of plasma acts through other mechanisms than merely providing fibrinogen. Plasma also provides hemostatic regulating factors, for example, protein S, buffering capacity, and colloidal pressure; contains inhibitors of excess fibrinolysis and coagulation; and may modulate the function of the endothelium in a favorable way (9). Thus, transfusion of plasma may influence favorably the development of functional (or primary) coagulopathy. This is dealt with extensively elsewhere in this issue of *Shock* (11). On the other hand, not all studies show improvement of survival by transfusion of plasma in such situations (12–15), but this could be because the effect is marginal in many settings. Clearly, transfusion is only one aspect of a larger trauma resuscitation

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bundle, and if most other factors are optimal, plasma transfusion may provide only marginal benefit, except in special yet undefined cases (5). It should be noted, though, that no negative effect of plasma transfusion on survival in massively bleeding casualties has been reported. The PROMMT (Prospective, Observational, Multicenter, Major Trauma Transfusion) (2) study is a randomized controlled trial that was just completed that will compare 1:1 to 1:2 ratios of plasma and platelets in adult trauma patients. Hopefully, this trial will provide some clarity to this issue in trauma care (16).

CHALLENGES AND OPTIONS IN PREHOSPITAL USE OF PLASMA

Adverse effects

Four potential adverse effects should be considered significant:

- *Anti-A/anti-B–induced hemolysis in the recipient*. In the prehospital setting, only one—a "universal"—plasma preparation should be used. This is difficult because only blood group AB plasma lacks the potentially harmful anti-A and anti-B antibodies. Group AB donors comprise only 4% to 5% of all donors, and this is too small a resource to provide "universal" plasma at a larger scale. A working solution may be to use single-donor group A plasma with low titers of anti-B. Such plasma is compatible with more than 85% of white recipients, and the transfusion of considerably more than one plasma volume (i.e., >>3 L) seems to be required to induce clinically significant hemolysis in group B and AB recipients (17). Another option would be to use plasma from pools of donor plasma, in which donations of various blood groups will neutralize anti-A and anti-B through reaction with soluble blood group antigens. The French military blood program uses FFP from pools of at least 10 AB, A, and B donors, in which the activity of anti-A and anti-B is neutralized by soluble A and B blood group antigens (18). In the prehospital setting, "universal" plasma or equivalents can be transfused without knowledge of the patient's blood group.
- *Respiratory complications including transfusion-induced acute lung injury*. The use of plasma may be complicated by the reactions common to all blood components. However, plasma-rich components are associated with a higher risk of allergic-type reactions. Safety concerns have also been raised regarding the risk of ARDS following resuscitation with plasma-rich transfusion protocols. These have not been realized in UK military practice (19). Transfusion-induced acute lung injury is a serious complication leading to reduced gaseous exchange. Although the problem may not be seen in the prehospital arena, it may need to be considered after transfer. This serious adverse effect is induced by anti-HNA (human neutrophil antigen) or anti-HLA (human leukocyte antigen) antibodies in donor plasma. Such antibodies are usually induced in pregnancy. If only male plasma is used, or plasma tested to show the absence of such antibodies, the danger of transfusion-induced acute lung injury is greatly reduced (20). Another option is to use plasma from pools, in which such antibodies will be diluted and neutralized. Transfusion-induced acute lung injury has never been reported with pooled, solvent-detergent–treated plasma (S/D FFP) (21).
- *Transmission of infectious agents*. Transfusion-transmitted infection is rare if blood is provided by a blood establishment. If proper selection of donors and infection testing are carried out, the danger of infection transmission by single plasma units is similar to that of single-donor cellular blood components. The danger can be further reduced by anti-infectious treatment of the plasma or by use of quarantine plasma. Such measures are usually deemed mandatory if plasma from pools is being used. No reports exist of infection transmission by such plasma. However, non–lipid-enveloped viruses and nonviral agents may persist despite all actions taken. Plasma will therefore never become 100% infection proof.
- *Hypocalcemia*. Plasma contains citrate, which may transiently bind calcium in the recipient. The impact is dependent on plasma volume, speed of transfusion, and patient metabolism. Calcium is rarely required in the prehospital arena but may need to be considered if large volumes of blood components are used. Treatment should be given to the transfused patient according to local algorithms.

Plasma source

Blood is a human tissue donated to support the survival and health of fellow human beings. Donors shall preferably be voluntary and nonremunerated (voluntary, nonremunerated blood donors [VNRBDs]), and countries are urged by the World health Organization and other international organizations to strive for self-sufficiency by such donors (22–24). Arguments for this attitude are ethical above all, but safety, economical, and organizational ones also apply (25–28), especially at the global level (25), and have been reaffirmed recently by the World health Organization (25). In the Netherlands and in Italy, paid donations of blood and plasma for transfusion are forbidden by law. Commercialization of parts of the human body is forbidden by international convention (29).

Currently, the global consumption of plasma is too big to be met by plasma from VNRBDs alone (30, 31). Many countries are dependent on paid donors in the United States, Germany, Austria, and the Czech Republic to satisfy their market demand. The development of new clinical capabilities that may lead to greater use of plasma should take into consideration the sourcing of plasma. Nations should be self-sufficient where possible. Further increase of consumption of plasma should be scrutinized extensively before general acceptance. Increased consumption, caused, for example, by prehospital transfusion, should preferably be covered through a national or regional plasma program based on VNRBDs (25, 30, 31). Improper use and wastage of plasma should be avoided, whichever plasma source is applied.

Blood grouping

In the prehospital setting, "universal" plasma or equivalents can be transfused without knowledge of the patient's blood group. The use of prehospital blood components may complicate subsequent ABO and RhD grouping. Ideally, the patient blood group should be pre-recorded. In civilian situations, consideration should be given to taking a blood sample for later blood grouping

before plasma is given. However, this must be weighed against the risks of errors during identification and sample labeling.

Transfusion safety and staff training

Traceability and hemovigilance are important. Clinical staff must be confident of the identification of the patient receiving blood and must be trained in the recognition and immediate management of acute transfusion reactions.

Logistics, transport, and storage

Each unit of plasma will have a reference number, which is a unique component number or a batch number. The fate of each unit must be documented. Documentation can be manual, but consideration should be given to the use of a laptop-based laboratory information system with bar-code printer and reader for semistatic medical facilities. Military and civilian experience has shown that plasma may be wasted if thawed and then not required. Wastage is in part determined by the postthaw shelf-life.

Fresh frozen plasma

Coagulation factors are well kept in FFP. Fresh frozen plasma should always be kept frozen during transport from the producing unit to the blood bank. However, after thawing, some will start to deteriorate after about 6-h storage at 4°C (32). Although the significance of these changes for use in acute trauma bleedings remains unknown, it seems natural to thaw FFP as close to the clinical use as possible. On the other hand, thawing of FFP may take 20 min, which may be quite long when plasma is needed urgently and may be impossible under field conditions. No agreement exists on maximum postthaw storage time. Current UK civilian practice is 24 h, whereas military practice is based on a postthaw period of 5 days stored at 4°C ± 2°C. Fresh frozen plasma such defined can be successfully delivered in an austere setting (5) as part of a massive transfusion capability. On the other hand, there are no results to indicate that the deterioration of some coagulation factors and thrombin generation (33) during up to 5 days of storage in the cold leads to reduced clinical effect of plasma transfusion. Thus, it is possible to keep a significant number of thawed FFP for immediate use, but the danger of growth of bacteria increases with increasing postthaw storage.

Frozen-thawed FFP is supplied in plastic bags, both as single donations and also as equivalent amounts of commercially available S/D FFP. The preparation has advantage of low weight and ease of administration; however, frozen bags may fracture and split unless protected during transit or handling.

Lyophilized (freeze-dried) FFP

With lyophilized (freeze-dried) (L-FFP), FFP without a postthaw period should be readily available for transfusion when needed. Reconstitution of the preparation is easy, and no thawing is necessary. The preparation can be reconstituted with less water than in the original plasma (down to 50%), thus reducing the weight of the equipment. However, L-FFP is so far available only in glass bottles.

A recent comparative study, done at the Netherlands Military Blood Bank, evaluated clotting factor and inhibitor activity in reconstituted lyophilized plasma, FFP thawed, and refrozen at −80°C and FFP after storage for up to 6 days at 2°C to 6°C and found that the coagulation factor activity met required quality standards (unpublished results).

In Europe, there are currently two ways of obtaining L-FFP. LyoPlas (German Red Cross) from single apheresis donors can be bought commercially and stored for 1.5 years at 2°C to 25°C. The preparation is used by both German civilian and military hospitals and is licensed by Paul Ehrlich Institute. According to the producer, the quality of the fresh reconstituted single-donor L-FFP (preparation time 5–7 min) is comparable to thawed FFP that has been stored for 7 days at 4°C. Whether the somewhat reduced coagulation activity compared with freshly thawed FFP is of clinical significance remains unknown. LyoPlas has a good safety profile, similar to FFP, with more than 200,000 U transfused (34).

The French military transfusion service produces "universal" L-FFP (FLyP) by pooling A, AB, and B plasma from at least 10 donors. The production plant has capacity to produce limited amounts of this preparation for other countries by contract, using plasma from the nation in question. A prerequisite is that the FFP delivered for production must be quarantined for 6 months or virus inactivated by amotosalen treatment. Some European countries are not readily able to supply such FFP. FLyP has been used in role 3 facilities during the conflicts in Iraq and Afghanistan with reports of more than 1,000 U being administered (18, 35).

Glassberg et al. (36) have published an extensive account of the evolution of the Israel protocol for the implementation of L-FFP under remote damage control resuscitation conditions. The article also includes data for the first 10 casualties following the new protocol. Lyophilized (freeze-dried) FFP is aimed to serve first as a resuscitation fluid for casualties in shock with life-threatening injuries. Although already implemented, questions remain concerning the use of L-FPP at point of injury without the benefit of level I evidence. Casualty selection is an important concern, and the possibility to use of point-of-care coagulation testing may be of value (37).

Lyophilized (freeze-dried) FFP is currently being used for remote damage control resuscitation in military medical services of several countries: LyoPlas in Germany, the Netherlands, United Kingdom, Norway, Sweden, and Israel and FLyP in France. LyoPlas is also used in the civilian emergency service in Bergen, Norway. Lyophilized (freeze-dried) FFP is not available in the United States, although it is used on a very limited basis in some US military units.

Costs

Prehospital use of plasma, whatever preparation is chosen, will increase immediate costs of treatment when compared with artificial volume expanders. Immediate costs will depend heavily not only on the price of the plasma preparation used, but also on wastage and improper use. The price per single unit of plasma increases the more production procedures are added to FFP. As an example, in Norway, the price of industrial S/D FFP from plasma pools is about four times that of raw FFP, whereas LyoPlas costs nearly twice as much as S/D FFP. Prices vary between countries, however. On the other hand, with lyophilized plasma, one may expect that wastage will be low, because plasma can be prepared ad hoc. Furthermore, results exist that

suggest that increased use of plasma in hospital settings may reduce the consumption of other blood components (13). If, in addition, prehospital use of FFP leads to improved results, this new treatment paradigm may prove highly cost-effective.

DISCUSSION

Although level I evidence is lacking, the BB panel agreed that now is the time for both military and civilian transfusion services to prepare for the introduction of prehospital transfusion of plasma for massive hemorrhage. As far as possible, plasma should originate from VNRBDs. It is not clear which plasma preparation is optimal for prehospital use, and this may change over time. Focus should continuously be on the selection of optimal plasma preparation, developing and maintaining robust supply and logistics chains, and the development of treatment. It is important to create robust systems for supply, logistics, and training of personnel that comply with all relevant national and international regulations and conventions.

Clinicians have an ethical responsibility to both patients and donors. The introduction of new clinical capabilities must be safe, efficacious, and sustainable. Plasma is not merely plasma, but is supplied in various forms that may or may not be clinically equivalent for prehospital transfusion. Prehospital transfusion of plasma represents extrapolation of data obtained in the hospital settings extended into the prehospital arena. Care for the bleeding patient, like most aspects of trauma care, is focused on the nature of the best available treatment, rather than the location in which it is provided. Plasma transfusion in the prehospital settings should be accompanied by meticulous data collection, analysis, and implementation of lessons learned.

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