in two-thirds of the normal blood volume. Although the hemorrhage was severe and carefully controlled, one cannot translate the results of an animal study to the clinical arena. Based upon these findings, however, controlled studies in man are needed to define the proper role of FFP therapy for restoration of coagulation proteins after clinical hemorrhagic shock.

This study does not fully address the question of FFP supplement for potential colloid or immune affects.[15] Further studies on hemodynamic and immune responses and sequential protein changes in serum and lymph after either plasma or Ringer's resuscitation are needed. Despite these limitations, these data demonstrate that supplemental FFP in this setting does not enhance the coagulation picture. During extensive plasma exchange without hypovolemic shock, removal of the total circulating plasma volume does not reduce the coagulation protein activity below an effective level.[16] Maintenance of coagulation proteins after exchange results from interstitial fluid space relocation of these factors. A similar restoration likely occurs after a severe hemorrhagic insult of one circulating blood volume; the main difference would be delayed liver synthesis of all proteins due to the shock insult.[16] Pending controlled studies in man, the routine use of plasma supplementation in the resuscitation regimen for hemorrhagic shock should be abandoned. Moreover, the use of FFP should be restricted to those individuals who have a bleeding insult that surpasses circulating one volume or to those patients with continued oozing due to a defined defect in the coagulation cascade.[16] Finally, more clinical studies are needed to better define the total role, if any, of FFP therapy in hemorrhagic shock. The lack of a defined benefit in such studies may curtail the precipitous use of FFP and abolish the exorbitant cost of unwarranted FFP therapy.[15]

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Discussion

DR. ROBERT J. BAKER (Chicago, Illinois): Dr. Martin has presented an extremely important paper because fresh frozen plasma has become the second most commonly used blood component, exceeded only by packed red cells, in surgical practice in the last decade. In actuality, the only clotting factor that is provided by fresh frozen plasma exclusively is factor 5, or labile factor. Factor 5 is also present in bank blood less than 7 days old, although packed red cells, because they have only half as much plasma as whole blood, have half as much factor 5, and that is the usual initial blood component administered.

Factor 8 and fibrinogen are more efficiently provided as cryoprecipitate, and there is a current trend to a much wider use of cryoprecipitate than was true a number of years ago. This is largely due to the experience in cardiovascular surgery; there is now a lesser use of fresh frozen plasma in major hemorrhage, massive trauma, and other extensive operations.

There are really two cogent reasons to support the contention of the authors that there is too much fresh frozen plasma being infused, the first of which is the cost, between $35 and $50 a unit, and secondly, the serum hepatitis risk, which is essentially the same with fresh frozen plasma as it is with whole blood, approximately 0.2% per unit. If 5 units of fresh frozen plasma are given, the hepatitis attack rate, at least theoretically, would be 1%, 10 units 2%, and so on.

It is hard to disagree with the conclusions of this paper, but several questions need to be addressed if there is advocacy of stricter criteria for use of dangerous and very expensive treatment modalities.

First, I would like to ask the authors how applicable the conclusions drawn from this carefully controlled, canine modified Wiggers shock preparation are to the patient in shock from major hemorrhage and/or trauma. For example, shock patients often become significantly hypothermic either before or during operation, which affects both platelet function and the ability of the liver to generate procoagulants. Was the temperature modified in these animals to simulate more closely the clinical setting?

In addition, I would like to ask what happened to platelet numbers in these animals? We are seeing more thrombocytopenia now that we look for it, as a manifestation of subclinical or even overt disseminated intravascular coagulation. Usually this is evident first as a fall in platelets, so the question is did platelet function and numbers diminish in these experimental animals?

The vastly more complex clinical abnormalities resulting from shock, including hypoxic hepatic dysfunction, need to be entered into this equation as well to justify the basic change in treatment philosophy suggested by this model. I suppose that we could say that blood component therapy is akin to contraception; the safest and least expensive course is total abstention, but that is not ordinarily the course that is chosen.

DR. JAMES CARRICO (Seattle, Washington): I congratulate Dr. Lucas and Dr. Martin on their excellent presentation and thank them for the opportunity to review the manuscript.

Dr. Baker has raised several questions that make my job easier. We have been shown that, in the model used, virtually all the clotting factors appeared to be increased initially. However, resuscitation with packed cells and electrolyte solution resulted in a decrease, particularly of factors V and VIII, and addition of fresh frozen plasma at a dose of 22 cc per kilogram made no significant difference. The implication is that fresh frozen plasma (at least at that dose) is not sufficient to correct the abnormality in clotting factors or appropriate in the resuscitation of hemorrhage shock.

I have two technical questions and two brief comments. The first technical question relates to the use of heparin. You indicate that you corrected for the heparin with protamine. I wonder how you determined precisely how to correct for the heparin and how much protamine to give, since many of the time-dependent assays of clotting factor could be impacted.

The other technical question relates to the long-term clotting studies. As we all know, the dog develops hemorrhagic lesions in the intestinal tract following severe prolonged shock. I wonder if you examined the intestinal tract of these animals to see if they had significant hemorrhage and what impact that had on the late changes in clotting factors.

The first comment relates to the dose of fresh frozen plasma. Was it adequate? It certainly was more than the usual recommended 1 unit of fresh frozen plasma per 5 to 6 units of transfused blood. On the other hand, it probably was not enough to replace all the clotting factors removed, at least the initial 22 cc per kilogram.

The other comment relates to the problem of making blood components available and at the same time having whole blood available for appropriate patients. As Dr. Lucas is aware, the Puget Sound Blood Center in Seattle has addressed this issue by using "modified whole blood." This modified whole blood is produced by separating the cells and plasma, removing the platelets and cryoprecipitate from the plasma, then recombining the remainder of the plasma with the red cells from the same donor. This substance then contains all the clotting components except factor VIII and platelets and is used for administration to patients with acute blood loss.

Studies reported by Counts, Heimbach, and others using modified whole blood showed that the only significant abnormality in clotting components after massive transfusions was thrombocytopenia (Ann Surg 1979; 190:91-99). I wonder if you might comment on the applicability of such a blood product on a broader geographic basis.

DR. DONALD TRUNKEY (San Francisco, California): It seems to me that we are skirting the central issue and that is the desirability of giving whole blood in a patient who requires massive transfusions.

The original impetus to do blood banking and to give transfusions was instituted by surgeons. I believe that there is only one blood bank in the United States that has a surgeon as its director, so we are forced to use components because the pathologists and internists have found other uses for whole blood.

There was a study done in 1976 (J Trauma 16:694) by the Israelis following the Six-Day War. They showed that if you gave whole blood less than 24 hours old (they gave 46 patients an average of 15 units), there was no coagulopathy. It seems to me that if you give relatively fresh blood (less than 3 days old), you can minimize the problem that has been outlined here today. Is it desirable to give whole blood to the massively injured or is it desirable to give components? The only way we are going to decide that is to have a multi-institutional randomized study, using relatively fresh whole blood *versus* components. I dare say we will find that components are inferior, as shown in this study.

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): I have enjoyed this study. The problem I have is with the clinical situation.

The pure hypovolemic shock as was produced here really does not produce coagulation dysfunction problems. It is with the tissue injury, massive tissue injury or the presence of infection, that we see activation of complement and the utilization of coagulation factors to a far greater extent. I am not sure that we should go home and think that this animal experiment necessarily reflects what we have to do for the patients who come in following a big automobile accident or who are in septic shock on the ward.

DR. CHARLES E. LUCAS (Closing discussion): I wish to thank Drs. Baker, Carrico, Trunkey and Clowes for their comments. Anecdotally, I have been recommending the infusion of 1 unit of plasma for every five to six transfusions for the last 15 years. When I attended the Consensus Development Conference Planning Committee a year ago January, I was a bit disturbed to find out that there was general criticism of those individuals who were making such recommendations.

I said to my colleagues: "I recommend it. I think it is good. Do you have any data to show that I am wrong?" When I came back to Detroit, I decided we were going to do a study to show that my colleagues were wrong. I am now eating crow.

Regarding the technical aspects, the amount of plasma infused for the resuscitation would be the equivalent of 6 units of plasma in a 70 kg man, and if you include the amount given on the next day, it would be equivalent to 9 units given in the 70 kg man, which is more than any of us have ever recommended in the past.

The amount of protamine was calculated on the basis of half life and dose; confirmation that our calculations were correct was based on the thrombin times which were restored to normal.

We did not look at the gut to determine whether there were any changes of a hemorrhagic nature.

The question regarding the application of any animal study to man is difficult. If one can translate animal studies to man, one would have to limit the translation in this study to the clinical situation where a patient is being restored with the entire circulating blood volume or 10 units of blood in the average sized individual.

I certainly concur that a pure study of this nature does not take into account the clinical problems with tissue injury and subsequent sepsis, thus emphasizing the need for prospective, controlled, randomized studies. I would hope that, when such prospective, controlled, randomized studies are done, not only whole blood is used as part of one arm of the study but also modified whole blood, which has been used so nicely in the Northwest.