BRIEF REVIEW

Pretransfusion Tests and Compatibility:
Questions of Safety and Efficacy

By S. P. Masouredis

PRETRANSFUSION TESTS, which currently include the crossmatch, are intended to guarantee the normal survival of transfused red cells at minimum cost. Tests designed to achieve these goals have undergone continuous modification since their introduction by Ottenberg in 1907.1 Recently, a series of events has led to a reexamination of what constitutes safe and cost effective compatibility testing, which provides blood in a timely fashion. Specifically, the question raised is: Can the crossmatch be abandoned, thereby relying only on the antibody screen of the recipient’s serum as the primary test of compatibility? It will be helpful to provide an overview of pretransfusion tests and their immuno-hematologic rationale to fully appreciate the issues involved.

Routine pretransfusion testing now in use in most blood banks2 involves the determination on both recipient and donor of the ABO group and Rh type (only the major Rh antigen, Rh0 (D)); performing an antibody screen on the recipient to determine if allo- or autoantibodies are present, and if so, identifying their blood group specificity; and finally, carrying out a major side crossmatch (recipient’s serum against donor’s red cells) using the antiglobulin reaction. Both the antibody screen and crossmatch are designed to detect in the recipient’s serum significant coating, hemolyzing, or agglutinating antibodies active at 37°C. Such testing, if done reliably by an experienced blood bank technologist, will in most instances verify ABO compatibility and detect most antibodies in the recipient’s serum directed against antigens on the donor’s red cells.

Unfortunately, these tests will not always guarantee the normal survival of the transfused cells, nor will they prevent untoward reactions to the transfusion. The routine methods in use are especially ineffective in preventing delayed hemolysis due to an anamnestic antibody response to donor antigens against which the patient has been previously sensitized and in whom the antibody concentration is undetectable due to the insensitivity of the tests now in use. Possibly up to 1 in 4000 (0.025%) recipients may be at risk for delayed hemolysis.3 More sensitive methods are available but are unsuited for routine testing because they lack specificity and detect many clinically insignificant antibodies, thereby confusing the interpretation of the results. There are other complications of transfusion therapy that are not prevented using routine testing. They will not prevent immunization of the recipient to other blood group antigens; since only the Rh0 (D) antigen is matched, they will not detect incompatibilities that may be due to non-red-cell elements such as plasma proteins (anti-IgA), platelets, or granulocytes; and they will not prevent graft-versus-host disease. Furthermore, pretransfusion testing of donor blood for hepatitis B surface antigen has not prevented the transmission of hepatitis due to the current inability to detect non-A non-B virus. Finally, in spite of rigorous requirements for specimen identification, current compatibility procedures do not always guarantee ABO compatibility because of clerical and human errors. Analysis of the FDA data on transfusion-related fatalities over a 3-yr period reveals that 22 of 25 deaths involving hemolytic reactions were due to clerical identification errors.4

It may appear paradoxical that proposals are under

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Submitted December 24, 1981; accepted January 11, 1982.
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0006-4971/82/5905--0001$01.00/0

Blood, Vol. 59, No. 5 (May), 1982 873
discussion to dispense with the antiglobulin crossmatch when it is generally recognized that current pretransfusion testing, including the crossmatch, fails to assure red cell compatibility. Part of the reason for this debate is historical and part is due to considerations of cost-effectiveness.

Some 5 yr ago in an effort to deal with chronic shortages of blood, it was recognized that there was a tendency to overorder crossmatched blood for elective surgical procedures. Surgeons, and particularly surgical house-staff, would order blood in excess to be on the safe side should an emergency demand for blood develop during surgery. The blame for overordering, in part, was due to the delay in the immediate availability of blood because of the time (usually in excess of 1 hr) required to carry out the pretransfusion tests that were always being modified and expanded to maximize their specificity and sensitivity. It became evident that the excessive number of crossmatches, defined as the ratio of units crossmatched to units transfused, was an unnecessary expense, and a high crossmatch to transfused ratio aggravated blood shortages and increased outdating. To remedy this problem, the concept of a blood ordering schedule for elective surgical procedures was introduced. Using previous experience and in consultation with the surgical staff, a schedule was agreed upon for each institution that listed for each procedure the number of crossmatched units that would be set-up. A different approach was devised for those surgical procedures in which blood was infrequently used. For such procedures in which the average number of units transfused per case is 0.5 or less (cholecystectomy, spinal fusion, transurethral prostatectomy, etc.), blood would not be crossmatched and only the ABO group, Rh type, and an antibody screen would be carried out. If an emergency request for blood develops in such cases, ABO and Rh-compatible blood would be released without a crossmatch if the antibody screen was negative. An additional back-up option for emergency requests was the introduction of low ionic strength media for the crossmatch, which permitted the use of a 10–15-min procedure instead of the 60-min saline ionic strength crossmatch. As experience confirmed the relative safety of using uncrossmatched blood with reliance only on the antibody screen for these situations, it was natural to ask: Can the same approach be used for all pretransfusion testing?

An historical precedent exists for reviewing and redefining the tests used for red cell compatibility. In the early 1960s, many blood banks carried out a minor side crossmatch (donor's serum against recipient's red cells) in addition to the major side reaction. The clinical significance of the minor-side crossmatch was debated, and it was finally abandoned, not so much on a critical evaluation of its merits but because blood banks had adopted the policy of routine screening of donors for antibodies that in effect substituted for the minor crossmatch. Even though most blood banks continue to screen donors for antibodies, the necessity for continuing this practice on all donors has been questioned. A more significant problem during the late 1960s was an over-zealous effort by blood bankers to expand pretransfusion testing by introducing methods designed to detect all antibodies in both recipients and donors. This resulted in a situation in which testing revealed phenomena with little relevance to clinical problems, complicated the interpretation of compatibility testing results, and invariably delayed the release of blood. Although it was generally appreciated that antibodies reacting at temperatures below 37°C were of little clinical significance, it was not until Giblett's report, based on a vast experience, convincingly demonstrated that room temperature reacting antibodies do not represent a clinical problem.

It is understandable that the need to reassess pretransfusion testing has surfaced in view of this historical pattern of sometimes unnecessary and enthusiastic testing. As a result, proposals are now being discussed that recommend the abandonment of the antiglobulin crossmatch and relying on only the antibody screen of the recipient for compatibility testing, but continuing to match donor and recipient for ABO and Rh. There are vocal advocates for the retention of both the antibody screen and antiglobulin crossmatch, and there are others equally convinced that the crossmatch is unnecessary. To gain a perspective on this debate requires some assessment of both the risks and benefits involved in doing away with the crossmatch.

A potentially serious risk is the inability to verify ABO compatibility. It is difficult to determine how frequently an ABO incompatibility error occurs as a result of inaccurate patient typing or accidental selection of the incorrect donor blood. Although such occurrences should be rare events, they are presently detected and prevented by the major crossmatch. Should the antiglobulin crossmatch be abandoned, it would be prudent to substitute an immediate spin of donor cells and recipients serum to verify ABO compatibility.

Another risk is that the antibody screen alone may miss clinically significant antibodies that would be detected in the antiglobulin crossmatch. This may be due to either poor expression of the antigen on the reagent red cells used for screening or to the absence of a low frequency antigen on the screening red cells. In a recent study, 99 of 32,339 patient samples had a reactive major antiglobulin crossmatch following a
nonreactive antibody screen (0.31%). Of these, however, only 4 antibodies were unequivocally clinically significant (0.01%). Two of these antibodies were to relatively high frequency antigens and could have resulted in hemolysis, but the other two were against very low frequency antigens and the chance that the patient would receive an antigen-positive unit was extremely remote. Similar figures have been reported by others, although it is difficult to compare such data because of differences in techniques and reagents. The risk of eliminating the crossmatch, therefore, is real but relatively small. The risk can be reduced further by using four carefully selected reagent red cells in the panel instead of two, but this solution defeats any cost advantage of eliminating the crossmatch.

Another risk consideration is the level of experience and sophistication of the technologists in small nonurban hospitals, which account for a significant amount of blood transfused. The technologists in such institutions do not spend full-time in the blood bank and may have difficulty in interpreting the results of the antibody screen and using the information to select the appropriate uncrossmatched blood.

Why consider abandoning the crossmatch if the level of safety, even though quite low, will be reduced. The argument advanced is that cost, both in terms of reagents and personnel, will be significantly reduced. With about 10 million transfusions per year, an average cost of $20 for the crossmatch, and the fact that on the average each unit of blood transfused is crossmatched 8 times, the cost per year for crossmatches in this country adds up to $1.6 billion.

It is obvious from this brief overview that the decision to abandon the crossmatch is a complex problem and will be difficult to resolve. Current FDA regulations require an antiglobulin crossmatch for all blood transfused. The Bureau of Biologics, FDA, convened a meeting in December 1981 to develop a consensus concerning the role of compatibility tests and to examine the consequences of eliminating the antiglobulin crossmatch and relying only on the antibody screen. It was the impression of some in attendance that the FDA may liberalize the current requirement for the antiglobulin crossmatch.

In summary, it appears to this reviewer that the issues are so complex that expression of a personal opinion does not appear warranted. Rather, I have elected to provide the reader with the appropriate background to allow him to intelligently follow the debate. Probably, the most significant conclusion, clearly expressed more than 15 yr ago, is that there would be no need to have this debate if we had more reliable and effective in vitro methods for predicting in vivo red cell survival.

REFERENCES

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