Safe Management of Blood Products for Transfusion in Japan

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Problems in Transfusion Therapy

In recent years, the safety of blood products used for transfusion has increased considerably. The previous year has seen no reports of death from post-transfusion hepatitis or graft-versus-host disease (GVHD). However, the risk of ABO incompatible transfusion errors remains, and the adverse reaction of acute respiratory failure termed “transfusion-associated acute lung injury”, which is attributable to leukocyte antibodies, has been attracting increased attention. As a result of these problems, the Law to Secure the Stable Supply of Safe Blood Products, the so-called “New Blood Law,” was enacted in 2003, stipulating the obligations of doctors in implementing blood transfusion. Under the law, doctors are required to have knowledge of the complications of transfusion therapy and the measures to be taken against them.

Safe Blood Transfusion

To implement safe blood transfusions, proper blood transfusion practices are indispensable. Proper blood transfusion involves the minimum necessary transfusion. Because the function of the immune system is to recognize “self” and “non-self”, and because viruses have been incorporated into human genes during the course of human evolution, it is theoretically impossible for exogenous blood to be completely innocuous. Since there is no possibility of securing zero risk, it is important to avoid blood transfusion unless the situation is critical and to supply only components necessary for life support. However, because patients undergoing blood transfusion are at high vital risk, doctors are likely to provide excessive transfusion for fear the patient might otherwise die. Although extensive clinical experience is necessary to overcome the strong fear of the patient’s life being lost, not all doctors are able to acquire such experience. Therefore, education in transfusion medicine is of great importance.

Types of Blood Products Used for Transfusion

At present, Japanese Red Cross Society (JRCS) blood centers supply medical institutions with the following four types of blood products for transfusion: 1) banked whole blood, 2) red cell concentrates, 3) platelets, and 4) fresh frozen plasma. Among these, types 2–4 are the main ones used. Each type of blood product needs to be stored at a specific temperature. Red cell concentrate units, which are almost completely devoid of plasma components, contain mannitol-adenine-phosphate (MAP) solution as a preservative for the extended storage of red cells, and

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should be kept at 4 degrees Celsius. Such cells can be stored for up to 21 days. All platelet concentrates have been obtained by apheresis techniques since November 2004. Platelet concentrates are prepared by removing leukocytes, with the guarantee that the number of residual leukocytes does not exceed 1,000,000 per bag. Platelet concentrates are kept at 22 degrees Celsius while being shaken horizontally. They remain suitable for use only 72 hours after collection. Fresh frozen plasma is prepared by rapidly freezing the plasma component isolated from whole blood or obtained by component collection. Fresh frozen plasma units are kept at –20 degrees Celsius or colder and can be used for up to one year. In the event that the red cells isolated from the same whole blood unit are infected, the new quarantine system requires that delivery of the products be withheld for six months. The six-month quarantine period of the current fresh frozen plasma units terminated at the end of July. Because of the quarantine stipulation, the period of validity is, therefore, effectively 6 months.

Why is Component Transfusion Necessary?

Blood components targeted for transfusion show great variety in distribution and concentration in blood (Table 1). Therefore, it is important to use only the necessary component. Component transfusion is also important from the viewpoint of safety. Although the greatest problem involved in blood transfusion is incompatibility, platelets and fresh frozen plasma do not cause hemolysis as a result of incompatibility even if an improper blood type is used by mistake. If red cells in MAP solution are used, no adverse reaction due to anti-A and anti-B antibodies present in the plasma (minor incompatibility reaction) will occur.

<table>
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<tr>
<th>Temperature Control of Blood Products</th>
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<tr>
<td>Because the red cells and platelets used for transfusion are living cells, the following storage conditions should be strictly observed to maintain cell function outside the body until just before use.</td>
</tr>
<tr>
<td>Red cells: 4 ± 2 degrees Celsius</td>
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<td>Platelets: 22 ± 2 degrees Celsius</td>
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<tr>
<td>Although fresh frozen plasma units contain no cell components, the function of coagulation factors rapidly deteriorates, and therefore strict temperature control to –20 degrees Celsius is required.</td>
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<th>Preparation Prior to Blood Transfusion</th>
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<td>Informed consent</td>
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<td>Informed consent should be obtained from the patient or his or her family before implementing blood transfusion. In case of emergency bleeding, written informed consent based on the provision of sufficient information may be obtained after transfusion. Information provided to the patient and family includes the need for blood transfusion, its possible adverse effects, and the blood component to be used. If the option of autologous blood transfusion is available, it should be included in the information given.</td>
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<tr>
<td>“Type and screen” and cross match</td>
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<td>The patient’s blood type must be tested before transfusion. ABO and RhD blood typing is routine. In order to detect ABO abnormality (ABO subtypes), two tests, i.e., cell grouping and reverse grouping, are carried out. Next, the patient is examined for the presence of irregular antibodies against red cell antigens other than ABO antigens. Irregular antibodies are known to exist in about 1% of patients. Whereas 99% of patients are negative for irregular antibodies, blood</td>
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<th>Table 1 Body distribution of the blood components</th>
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<td><strong>In blood vessel</strong></td>
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<tr>
<td>Red cells</td>
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product units that are associated with negative reactions should be chosen for positive patients from among the stock in JRCS blood centers. In rare cases, only several suitable units may be available in Japan, and thus sufficient time should be allowed before use. The above process is called “type and screen (T & S)”. In addition, the cross match test, by which the patient’s blood and the blood product to be transfused are mixed to check their compatibility, is carried out just before use. When all the test results are favorable, the blood transfusion can be performed safely. Platelet and fresh frozen plasma units, which contain no red cells, can be used after ABO typing without cross matching.

**Practical Aspects of Blood Transfusion**

To implement a blood transfusion, a blood product unit maintained under proper conditions should be taken from the shelf together with a cross match test voucher just prior to use, by two individuals (doctor or nurse). The patient’s name and blood type (ABO, Rh), and the lot number of the blood product unit should be confirmed. One of the two individuals reads out every item, and the other confirms that the cross match test voucher agrees with the information on the blood bag. If the patient is conscious, it is also recommended that the patient give his or her own name and have the doctor or nurse confirm it with the patient name mentioned in the voucher. Most transfusion errors occur at the bedside, and thus due caution is necessary in this process.

**Observation of Patients Just after Blood Transfusion**

The doctor and nurse should not leave the patient immediately after the blood component unit is connected to the intravenous drip, but should stay at the bedside for at least 5 minutes and observe the patient. Thereafter, the patient should be observed at 15 and 30 minutes, at the end of transfusion, and 24 hours after transfusion. Since fever and urticaria occur in 5% of patients, antihistaminics and antipyretics should always be available. Steroids tend to be used frequently, but their overuse should be avoided.

**Preservation of Transfusion Records**

In cases of blood transfusion, the lot number of the blood product units used should be recorded and maintained for 21 years. The need for such a prolonged period of record keeping is due to the
risk of transfusion-mediated infection of variant Creutzfeldt-Jakob disease, a prion infection, which cannot be eliminated at present.

**Confirmation of Transfusion-transmitted Infectious Diseases**

Medical institutions in Japan currently are not obliged to keep patient sera. However, if the patient’s blood is kept in the institution prior to transfusion, it can be determined whether the origin of post-transfusion infection such as post-transfusion hepatitis, if any, is a result of the transfusion or of other causes. Ideally, it is desirable to keep pre-transfusion patient sera in a frozen state for at least one year. On this issue, the Japanese Ministry of Health, Labor and Welfare gave notice to approve pre-transfusion hepatitis B and C virus marker tests under the name of the chief of the Pharmacy and Food Safety Bureau in September 2004. The approved tests include three types of hepatitis B test, i.e., HBs antigen, HBs antibody, and HBe antibody tests, and two types of hepatitis C test, i.e., HCV antibody and HCV core antigen tests. Administration of the nucleic acid amplification test 3 months after transfusion is approved for hepatitis B, and administration of the HCV core antigen test 1–3 months after transfusion is approved for hepatitis C.

**Institutional Transfusion Therapy Committee**

Each medical institution should have a transfusion therapy committee to improve the safety of transfusion. Each committee is required to nominate a doctor who assumes overall responsibility for transfusion. It is important that the doctor responsible be an executive of the hospital who is able to provide guidance to doctors from other fields. The tasks of this doctor are shown in Table 2.

The primary purpose of this committee is to facilitate the proper use of blood products; its second purpose is to provide measures against transfusion errors; and its third purpose is to restrain excessive transfusion expenditures by decreasing abandoned blood products through determining the actual situation of blood product use in hospitals. If each aspect of transfusion management were left to different sections, e.g., ordering of blood products to the attending doctor, blood testing to the laboratory, and irradiation to the radiology department, it would not be possible to control blood products in terms of the validity period. When these procedures are unified into a single well-organized transfusion department, abandoned blood products can be reduced dramatically. This kind of system is known as unification of transfusion management (“one refrigerator for one hospital”).

**Assessment of the Hospital Management System**

An accrediting system to certify that a particular medical institution has developed such a management system is necessary. The US has had an inspection and accreditation (I & A) system for more than 20 years. This system seems to correspond to the medical inspection (on-the-spot inspection) system used in Japan.

Although the American Association of Blood Banks (AABB) initially took the lead in the I & A system, the Food and Drug Administration (FDA), the organization corresponding to the Ministry of Health, Labor and Welfare in Japan, began this type of inspection a decade ago.

Since no medical institution can practice blood transfusion without this accreditation, only about 3,000 institutions in the US are allowed to perform blood transfusions. According to a survey by the JRCS in 2004, Japan had approximately 15,000 medical institutions in which at least one unit of blood had been used for transfusion. Adjusting for the populations of the two countries, ten times more medical institutions in Japan provide blood transfusions than do in the US.

Under the national health insurance system of Japan, transfusion therapy has been handled as a general treatment, and, as a result, many institutions have been allowed to perform blood transfusions. However, if the strict I & A program of the US were applied to Japan, few Japanese medical institutions, including even some university hospitals, would obtain accreditation. Therefore, great confusion could occur if the same system were abruptly introduced to Japan.

**I & A system of the Japan Society of Blood Transfusion**

Taking its cue from the US AABB program, the
Japan Society of Blood Transfusion set up the I & A Committee, divided the country into 8 blocks, and proposed separate activities for each block. At present, several accredited doctors and technicians in charge of blood transfusion are volunteering in I & A activities in the Kanto and Kyushu areas. It is by no means easy for the limited number of executive transfusion staff to inspect other institutions, with some using their own paid vacation time. An inspection checklist is available at the URL of the Japan Society of Blood Transfusion (http://www.yuketsu.gr.jp).

Mutual Collaboration among Neighboring Institutions (Joint Conference of the Prefectural Transfusion Therapy Committees)

In 1998, the Fukuoka prefectural government took the lead in holding the first joint conference of prefectural blood transfusion therapy committees. This support by a local government was advantageous in encouraging a large number of medical institutions to participate. At that time, a questionnaire survey was carried out to determine the situation regarding the use of blood products in each institution. From the results, it became apparent that red cell concentrates were in use in a large number of institutions, whereas the use of platelets and fresh frozen plasma tended to be centered in large hospitals. In addition, the amount of blood products used in the 20 hospitals with the highest consumption accounted for about 80% of all blood product consumption. The most useful finding from the survey was a large variation in the consumption of blood products per bed among different medical institutions. Knowledge of such variation in blood product use makes it easier to set standards for blood transfusion as a therapeutic procedure. If a 3-fold difference in the consumption of fresh frozen plasma is noted between institutions A and B, the reason for the discrepancy needs to be clarified. A comparison among different institutions would highlight improper use of blood products that otherwise might remain unrecognized in individual institutions, and could help to curtail excessive use. Currently, it seems that some form of guidance in the proper use of blood products based on such data would be suitable for the situation existing in Japan.

Concluding Remarks

The safety of blood products used for transfusion was improved to a great extent by the development of the hepatitis C test in the late 1980s and the subsequent introduction of nucleic acid amplification into the test.

Current blood products are at least 1000-fold safer than they were around 1990. However, this does not constitute perfection, because there has been no change in the risk of morbid patients undergoing blood transfusion. The survival rate at 1 year after the first transfusion is 75%. In other words, as many as 25% of patients die within 1 year. Patient death is always a concern for the attending physician, and he or she may be prone to excessive blood transfusion in the hope of somehow saving the patient’s life. This may create a situation in which emotions interfere with the scientific wisdom on blood transfusion.

Consequently, it may lead to improper blood transfusion, such as combined use of red cells and fresh frozen plasma at a ratio of 1:1, transfusion of fresh frozen plasma without pre-transfusion coagulation test, and the use of banked whole blood for the treatment of bleeding, thereby imposing excessive risk on the patient.

Safe blood transfusion can be achieved when the doctor directs proper transfusion and the nurse implements it accurately. Serious attention needs to be paid to the important role of institutional transfusion therapy committees in implementing a system of safe blood transfusion.