The current status of autologous blood transfusion in Japan – The importance of pre-deposit autologous blood donation program and the needs to achieve patient blood management

Nelson Hirokazu Tsuno, Yutaka Nagura, Michiru Kawabata, Mika Matsuhashi, Shinji Sone, Toshiyuki Ikeda, Naoko Okochi, Koki Takahashi

Department of Transfusion Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

ABSTRACT

Background: Autologous blood transfusion (ABT) is currently considered the safest transfusion, since the risks of allogeneic immunological reaction and viral transmission are theoretically null. Although its use has declined in Western countries in the recent decade, it has been progressively expanded in Japan. With the widening of the concept of patient blood management (PBM), which aims to prevent the harmful adverse effects of the exposure to allogeneic blood, the importance of the ABT has once again gained interest.

Study design and methods: Here, we retrospectively analyzed the cases pre-depositing autologous blood for an elective surgery in the period of January 2000 to December 2010 in our hospital, where a pre-deposit autologous blood donation (PAD) program has been established in 2006, in an attempt to analyze the improvements achieved, and the problems remaining to achieve patient blood management.

Results: The PAD program contributed for the further improvement of ABT, and the number of participating patients increased, especially in the period 2002–2003, when the idea of PAD program implementation came out. By simple extrapolation of the ABT data to allogeneic blood, ABT was found to be superior in terms of cost-effectiveness. However, problems such as the high wastage rate, and the inappropriate transfusion triggers remain to be solved.

Conclusion: ABT plays the central role in PBM, but to achieve the real PBM, there is need to indicate ABT appropriately, according to the individual needs, and use it adequately, without discarding. Our present data reflect the present status of the ABT performance in Japan, and will serve as the basis for the development of strategies to achieve safe and appropriate performance of ABT, and consequently, achieve PBM.

1. Introduction

Recently, the patient blood management (PBM) or blood conservation, which aims to fully evaluate the patient’s condition to assess for factors predictive of preoperative and postoperative anemia and the need for transfusion, in an attempt to prevent the harmful adverse effects of the exposure to allogeneic blood [1–7] have gained especial interest. ABT is an important approach to achieve PBM [8]. Although, theoretically, autologous blood has low risk of immune-mediated adverse events, and has been shown to be superior to the pre-storage leukoreduced allogeneic one in terms of the risk of transfusion-related immunomodulation [9], the risk of adverse effects caused by soluble...
factors, such as cytokines and chemokines, accumulating during the storage period, still remain. Whereas many studies, including randomized controlled trials, have shown that autologous blood is not superior to allogeneic one in terms of transfusion-related immunomodulation (TRIM) [10–12] the use of ABT has been suggested as an alternative to prevent TRIM [13].

In the United States, hospital-based autologous whole blood donation programs were implemented in the 1980s, at the time there was a great threat related to transfusion-transmitted disease, especially with the advent of the HIV infection [14]. Although these programs continued into the 1990s, it has progressively declined in the 2000s [14], when a significant decline in the risk of transfusion-associated disease was achieved, and reports have shown that PAD might increase the performance of transfusion, including the autologous one [14]. More recently, however, with the increasing interest in the PBM, in which ABT plays the central role, it seems that interest is increasing.

In Japan, however, the situation is completely different due to the different circumstances, such as the social features, the governmental incentives, and the historical background of transfusion medicine. Instead of the increasing safety of allogeneic blood, after the tragic incidents that have led many people to be infected by HCV or HIV, there is a tendency of the Japanese population to opt for the own blood in the process of informed consent. It is a consensus in Japan that patients have the right of “informed choice”, i.e., based on the information provided by the doctors, they can choose which transfusion to receive. And the surgeons also believe that it is the best alternative. Also, based on the fact that the Japanese society is a super-graying society, bearing the risk of blood shortage in the near future, the Japanese government strongly encourages ABT. In this context, for more than 20 years ABT is largely performed in Japan. Although considered the safest transfusion, in most institutions dealing with ABT in Japan, the pre-deposit autologous blood donation program (PADP) is not established, thus the real safety of ABT remains to be confirmed. Also, the concept of patient blood management is not generalized in Japan, therefore, autologous blood may be over-collected and over-transfused.

Here, we present the data on the ABT performance during 10 years in a large university hospital in Japan, where a hospital-based PAD program was established, and show the improvements achieved, the cost-effectiveness of ABT compared to the allogeneic one, and discuss the problems remaining, and the future challenges for the achievement of safety and appropriateness of ABT in the context of PBM.

2. Methods

2.1. Patients

Patients pre-depositing autologous blood for elective surgery in the period between January 2000 and December 2010 were retrospectively analyzed. All patients received informed consent on blood transfusion, and have opted for the use of pre-deposited autologous blood.


The autologous transfusion fee includes the pre-deposit fee, which is paid to the hospital when autologous blood is pre-deposited, and the transfusion fee, which is paid at the time autologous blood is transfused. The outgo of PAD, shown in Table 1, includes the materials and reagents necessary for the blood group typing of the patient and the collected blood, the cost of the blood bags, and the treatment fees of nurses, transfusionists and medical technologists, giving a total of 410.74 dollars per 2 units (400 mL). The cost of the medical staff (treatment fee) is difficult to estimate. In this study, the mean average salary of all professionals of the hospital, according to the job category, was used for the calculation. The mean annual salary was divided by the mean working hours per year, and this value was applied for the calculations. Cross-match test is not indicated, but the blood group typing of the autologous blood product is checked prior to provision, to confirm the compatibility with the patient. The Japanese insurance system, presently, does not pay the use of autologous fresh frozen plasma (FFP) or autologous cryoprecipitate.

On the other hand, for the calculation of the income of the autologous collection program, the price of the blood product (2 units = 400 mL), the blood group typing of the patient, the screening test for irregular antibodies, the cross-match test, and the transfusion fee are used, giving a total of 372.93 dollars. Blood group typing is performed at least twice, as described for ABT. The outgo was calculated as the price of the blood products, obtained from the JRCBC, the materials and reagents for the blood group typing, screening test of irregular antibodies, and the cross-match test, which includes the fee of the medical technologist for the testing. It is calculated similarly to the treatment fee of ABT.

### Table 1

<table>
<thead>
<tr>
<th>Dollar ($)</th>
<th>Income</th>
<th>Outgo</th>
</tr>
</thead>
<tbody>
<tr>
<td>The outpatient medical fee (/l time)</td>
<td>8.75</td>
<td>–</td>
</tr>
<tr>
<td>Blood typing (/2 times)</td>
<td>12.00</td>
<td>9.93</td>
</tr>
<tr>
<td>Infusion (/1 time)</td>
<td>–</td>
<td>3.50</td>
</tr>
<tr>
<td>Infusion fee (including iron and ranger lactate)</td>
<td>–</td>
<td>305.50</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>–</td>
<td>303.50</td>
</tr>
<tr>
<td>Autologous blood transfusion fees (/2 units)*</td>
<td>–</td>
<td>30.50</td>
</tr>
<tr>
<td>Pre-deposit fee</td>
<td>50.00</td>
<td>–</td>
</tr>
<tr>
<td>Transfusion fee</td>
<td>187.50</td>
<td>–</td>
</tr>
<tr>
<td>Bag (/2 units, 400 mL)</td>
<td>–</td>
<td>20.00</td>
</tr>
<tr>
<td>Treatment fee</td>
<td>–</td>
<td>8.68</td>
</tr>
<tr>
<td>Doctor (/30 min/1 patient)</td>
<td>–</td>
<td>38.90</td>
</tr>
<tr>
<td>Nurse (/30 min/1 patient)</td>
<td>–</td>
<td>25.93</td>
</tr>
<tr>
<td>Technologist (/10 min/1 bag)b</td>
<td>–</td>
<td>8.68</td>
</tr>
<tr>
<td>Blood typing to autologous blood bag (/1 bag)</td>
<td>–</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td>565.25</td>
<td>410.74</td>
</tr>
<tr>
<td>Balance of payments (for the hospital)</td>
<td>+154.51</td>
<td>–</td>
</tr>
</tbody>
</table>

* The fee is doubled in the case of the frozen-preservation.
* In case of frozen preservation, the fees are calculated as follows: technologist (/l bag/120 min): $104.22; freezing procedure: $83.68; thawing procedure: $31.7.

### Table 2

<table>
<thead>
<tr>
<th>Dollar ($)</th>
<th>Income</th>
<th>Outgo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cell concentrate (/2 unit)</td>
<td>215.42</td>
<td>215.42</td>
</tr>
<tr>
<td>Type and screening test</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Blood type test (/2 times)</td>
<td>12.00</td>
<td>9.93</td>
</tr>
<tr>
<td>Irregular antibody test (/1 time)</td>
<td>25.00</td>
<td>11.27</td>
</tr>
<tr>
<td>Cross-match test</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reagents and materials (/l bags)</td>
<td>8.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Technologist (10 bags/1 h)</td>
<td>–</td>
<td>5.21</td>
</tr>
<tr>
<td>Transfusion fee (/2 units)</td>
<td>112.5</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>372.93</td>
<td>246.03</td>
</tr>
<tr>
<td>Balance of payments (for the hospital)</td>
<td>+126.89</td>
<td>–</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Dollar ($)</th>
<th>Income</th>
<th>Outgo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin</td>
<td>303.50</td>
<td>303.50</td>
</tr>
</tbody>
</table>
| Infusion fee, which is paid to the hospital when autologous blood is pre-deposited, and the transfusion fee, which is paid at the time autologous blood is transfused. The outgo of PAD, shown in Table 1, includes the materials and reagents necessary for the blood group typing of the patient and the collected blood, the cost of the blood bags, and the treatment fees of nurses, transfusionists and medical technologists, giving a total of 410.74 dollars per 2 units (400 mL). The cost of the medical staff (treatment fee) is difficult to estimate. In this study, the mean average salary of all professionals of the hospital, according to the job category, was used for the calculation. The mean annual salary was divided by the mean working hours per year, and this value was applied for the calculations. Cross-match test is not indicated, but the blood group typing of the autologous blood product is checked prior to provision, to confirm the compatibility with the patient. The Japanese insurance system, presently, does not pay the use of autologous fresh frozen plasma (FFP) or autologous cryoprecipitate.

On the other hand, for the calculation of the income of the autologous collection program, the price of the blood product (2 units = 400 mL), the blood group typing of the patient, the screening test for irregular antibodies, the cross-match test, and the transfusion fee are used, giving a total of 372.93 dollars. Blood group typing is performed at least twice, as described for ABT. The outgo was calculated as the price of the blood products, obtained from the JRCBC, the materials and reagents for the blood group typing, screening test of irregular antibodies, and the cross-match test, which includes the fee of the medical technologist for the testing. It is calculated similarly to the treatment fee of ABT.

### 3. Results

#### 3.1. Performance of the autologous blood collection program

After the idea of the implementation of PAD program came out in 2003, and efforts to implement it were started, the number of patients donating autologous blood, as well as the number of donated bags started increasing progressively, and also after the full implementation of the program in 2006, continued increasing, especially dependent on the orthopedic patients, followed by gynecology & obstetrics, neurosurgery and urology (Fig. 1). According to the preservation method, in 2003 and 2005, almost half of the autologous blood was preserved as whole blood, but after 2006, there was a tendency for the increase of red cell concentrate (RCC) in relation to whole blood. On the other hand, the number of cases of other departments, such as plastic surgery, otolaryngology, and liver and bone marrow transplant donors, decreased after the implementation of the program. The total number of collected bags, which was 885 in the fiscal year 2000, increased to 1069 in 2003, achieving the peak of 1355 in 2007, 1 year after the full implementation of the program, and slightly decreasing to 1318 in 2010. According to the preservation method, in 2000, the rate of whole blood was 43.6% (386/885), increasing to 49.8% (532/1069) in 2003, but decreased to 43.2% (585/1355) in 2007, and increased again to 48.9% (645/1318) in 2010. Among the RCC, in 2000, 50.1% (250/499) was frozen-preserved, decreasing to 15.8% (85/537) in 2003, 18.7% (144/770) in 2007, and slightly increasing to 21.7% (146/673) in 2010.

Cryoprecipitate was prepared in 30.0% among those in which the RCC was separated from FFP (150/499) in 2000, in 31.8% (171/537) in 2003, increasing to 37.7% (290/770) in 2007, and slightly decreasing to 33.7% (227/673) in 2010.

#### 3.2. The allogeneic transfusion avoidance rate and the ABT rate

The avoidance rate of allogeneic transfusion, which represents the rate of patients who pre-deposited autologous blood for an elective surgery, and could be operated on
without the need of an additional allogeneic blood use, to-
gether with the wastage rate, may be an indicator of the
appropriateness of the autologous blood indication and
the collection volume. The percentage of patients requiring
additional use of allogeneic blood, which was about 11% in
2002, decreased to 5% in 2003, oscillating between 5% and
8% thereafter, as shown in Fig. 2. Thus, the avoidance rate
of allogeneic is relatively good, keeping values over 90%,
which means, the necessary volume of autologous blood
is not underestimated in more than 90% of the cases. Also,
the ABT rate, which represents the percentage of elective
surgery patients, who required blood transfusion and re-
ceived only autologous one, has increased progressively
from approximately 35% in 2002 to approximately 50% in
2010. These values are also indicators of the good perfor-
mance of our PAD program.

3.3. Wastage rate of autologous blood

The wastage of autologous blood is an important indica-
tor of the appropriateness of the indication of PAD. The
higher the wastage rate, the more inappropriate is the in-
dication of PAD. As shown in Table 4, the wastage rate varies
according to the preservation method, the highest rate
being observed with cryopreserved red cells, followed by
the RCCs preserved separately from FFP, and the lowest
rate observed with whole blood. As a total, there was a ten-
dency for the increase of the wastage rate after 2008, but
according to the preservation method, that of the cryopre-
served RCC achieved maximal levels surpassing 50% in
2003, and progressively decreased thereafter. However, it
is still high, reaching values over 30% in 2010. The wastage
rate of RCCs preserved refrigerated is still over 20%, and
that of the whole blood products is around 10%. Therefore,
those products preserved as whole blood are more appro-
priately used, followed by the refrigerated RCCs and the
cryopreserved ones. The method of preservation is decided
by the surgeons, and there is a preference according to the
specialty. And those cryopreserved products have the low-
est possibility of use. Usually, cryopreservation is indicated
due to the postponement of the surgery, which can be
sometimes cancelled, eliminating the need of blood trans-
fusion. The wastage rate of the cryoprecipitate achieved a
peak of 35.2% in 2004, and is oscillating between 8% and
16% thereafter.

3.4. The cost-effectiveness of autologous blood vs. allogeneic
blood transfusion

The gross profit of 2 units (400 mL) PAD, calculated
according to the parameters shown in Table 1, is +154.51
dollars. On the other hand, the gross profit of 2 units
allogeneic blood transfusion, calculated based on the parameters of Table 2, is +126.89 dollars. Taking these values, we obtained the total gross profit for ABT, as shown in Table 3, and the profit that would be obtained in case the same amount of allogeneic blood was used instead.

As shown in Table 5, the total profit of ABT, which was 72,838 dollars in the fiscal year 2000, increased to approximately 130,000 dollars in 2007, 1 year after the establishment of the PAD program. In case the same amount of allogeneic blood was used, these values should be 50,793 and 82,224 dollars, respectively. In 2010, the profit of ABT was 133,635 dollars, whereas in case allogeneic blood was used, it would be 80,182 dollars. Thus, autologous blood is superior to the allogeneic blood transfusion in terms of the profit to the hospital. However, considering the costs for the patient, as well as the burden for them, dependent on the need of multiple visits to the hospital for the PAD, and the need of prevention or treatment of the PAD-associated anemia, it may be more onerous. The costs of the outpatient medical fee, the infusion of crystalloids and iron preparations, the blood tests, and the ABT fees are charged to the patients...
receiving ABT, who have to pay between 10% and 30% of the costs, depending on the type of insurance. On the other hand, in case allogeneic blood is to be used, the patients pay 10–30% of the cost of the blood product, the blood tests, and the transfusion fee, giving an approximately 30 dollars difference compared to autologous blood for every 2 units (400 mL).

4. Discussion

With the implementation of the PAD program, in addition to the increase in the number of patients pre-depositing autologous blood for elective surgery, other important improvements were achieved. The patients received more detailed and appropriate information related to PAD, participating more actively and making decisions on the planning of the collection schedule, and all patients had the “informed consent for PAD” obtained by the transfusionist during the first consultation. In addition, the appropriate control of the patients’ anemia prior to starting the blood donation, as well as the adequate control of the PAD-associated anemia, became feasible. This preoperative control of anemia is an important intervention for the achievement of PAD [8,14,15].

Whole blood preservation is the ideal method, since the recovery of red cells is not affected by the manipulation, avoiding bag leakage and contamination. The whole blood rate is influenced by the preferences of the surgeons, and also by the need of cryoprecipitate preparation, and thus, is not a good indicator of the appropriateness of PAD. Frozen-preservation is indicated only for those patients unable to make frequent visits to the hospital for PAD, for those who will need more frequent blood drawings, and for those the surgical procedure has to be postponed after the PAD program is started. In this aspect, the frozen-preservation rate may be used as an indicator of the appropriateness of the PAD, also because the wastage rate of frozen-preserved autologous blood is higher compared to other preservation methods, as discussed below. In our hospital, the rate of frozen-preserved RCC decreased after 2003, and it may be attributed to the interference of the transfusionists in the scheduling of blood collection.

Another important intervention of PBM is the use of autologous fibrin sealant [16], which is prepared from blood collected in the program. It is used to control bleeding of the surgical field, especially in neurosurgery, oral surgery, and orthopedics (spinal cases). The number of cryoprecipitate bags progressively increased, but it is noteworthy that the wastage rate of autologous cryoprecipitate ranges between 5% and 16.8% (a maximum of 35% was observed in 2004), as shown in Table 4. Thus, it seems that autologous cryoprecipitates are over-produced. And the increase of the RCC observed in recent years may be partly dependent on preparation of cryoprecipitates.

In terms of cost-effectiveness, by the simple comparison of the costs of autologous vs. allogeneic blood usage, the autologous one gives a higher profit for the hospitals, dependent on the relatively high medical fees of the autologous blood collection and transfusion. As shown in Table 5, the profit of the ABT is higher compared to that in case the same amount of allogeneic blood was used. Although of the different medical or insurance systems, the advantageous benefit of autologous vs. allogeneic blood transfusion has also been reported by others [17]. However, others have emphasized the small health benefit, with a considerable additional cost, depending on the high discarding of the donated but not transfused autologous units and a more labor-intensive donation process [18], and the need to avoid over-collection and over-transfusion of autologous blood to improve the cost-effectiveness [19]. Compared to these reports, although higher rate of allogeneic blood avoidance and the lower wastage rate were observed in our series, it may be dependent on the inappropriate indication of transfusion. Once autologous blood is pre-deposited, surgeons may feel that it should be transfused, independent of the hemoglobin levels, consequently raising the transfusion triggers, as shown in Table 6. The transfusion trigger was significantly higher in the group of autologous blood than the group of allogeneic one (P < 0.01). Also, we used the ABT data to extrapolate on the costs of allogeneic blood transfusion, but it does not mean that the same amount of allogeneic blood would be used in case the transfusion triggers are followed. Prospective studies using appropriate transfusion triggers will be necessary to confirm the real benefit of ABT. In our program, also there is a temporal and economical burden of the frequent visits to the hospital for the blood collection for the patients. And the real cost-effectiveness at a national level can be achieved only when the really necessary volume of autologous blood is collected pre-operatively, avoiding unnecessary transfusions, strictly following transfusion triggers, and reducing discarding.

In terms of PBM, the future perspective for the blood collection programs would be the achievement of the appropriateness of autologous blood usage, including efforts to reduce the transfusion rate itself, as well as to reduce the high wastage rate of PAD. In our service, the wastage rate ranges between 16% and 28% (Table 4), and has not improved even after the implementation of the PAD program. In special, the wastage rate of frozen-preserved blood is

<table>
<thead>
<tr>
<th>Group</th>
<th>Autologous blood</th>
<th>Allogeneic blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cases (transfused)</td>
<td>115 (115)</td>
<td>41 (16)</td>
</tr>
<tr>
<td>Male/female rate</td>
<td>1.4:1</td>
<td>1:1.5</td>
</tr>
<tr>
<td>Average age (range)</td>
<td>53 (17–87)</td>
<td>65 (10–90)</td>
</tr>
<tr>
<td>No. transfusion bags</td>
<td>236</td>
<td>25</td>
</tr>
<tr>
<td>Transfusion rate (%)</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td>The rate of Hb test before transfusion (%)</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Transfusion trigger (Hb, g/dL)</td>
<td>9.7 ± 1.4*</td>
<td>7.6 ± 0.8</td>
</tr>
</tbody>
</table>

*The statistical significance of the difference between two groups was determined the Mann–Whitney U test.
extremely high, ranging between 19% and 51.5%, followed by those preserved as RCC, which ranges between 19% and 30%. The wastage rate of whole blood autologous blood is around 10%. According to a study by Billote et al. [20], 41% of the collected autologous blood units were discarded, with a significantly high rate. In another study [21], the wastage rate of approximately 90% (369/416), with only 38 patients among 214 (17.8%) using the pre-deposited autologous blood, was reported; and among the transfused patients, four (10.5%) needed additional allogeneic blood transfusion, leading the authors to suggest the need of a good selection of the patients for the indication of PAD in elective orthopedic surgery. In elective cardiac surgery, pre-operative autologous blood donation was found effective in reducing exposure to allogeneic blood, but autologous blood was not used in more than 50%, and the allogeneic blood avoidance rate was 84%. [22] Therefore, the appropriateness of blood usage, also preconized by others [23,24], is required not only for allogeneic, but also autologous blood. There is urgent need to preoperatively analyze the individual volume need of autologous blood, and the strict control of the anemic state prior to surgery, to allow the appropriateness of autologous blood usage, based on the transfusion triggers, without waste. The best indicators would be the allogeneic blood avoidance rate, which should be as high as possible, and the waste rate, which should be as low as possible.

In Japan, historically, the spreading of hepatitis C through contaminated non-heated fibrinogen products for massive postpartum hemorrhage, led the population to be scared about blood transfusion [25–27]. Thus, regardless of the increasing safety of the allogeneic blood, there is a tendency for choosing the use of own blood for transfusion. Also, the Japanese society is a super-graying society, bearing a high risk of blood shortage in the near future. Taking these facts, in 2003, the government (The Ministry of Health, Labor and Welfare) enacted the Law for the Stable Provision of Safe Blood Products [28], which stipulates the domestic self-sufficiency of blood products through blood donation, including the autologous ones, and the guarantee of stable provision. Also, in 2005, the “Guide-lines of Transfusion Practice” [29], where the general outline for the performance of PAD are defined, describing ABT as “the safest transfusion practice to avoid the possible adverse effects of allogeneic blood transfusion, in case the internal management system for its performance is well-established, and should be actively promoted for patients receiving elective surgery”. Additionally, the Japanese Universal Health Insurance stipulated medical fees for the collection and the transfusion of autologous blood, which were upgraded in the revision of April 2012. Thus, from the societal, historical and political backgrounds, it is understandable why autologous blood is the most preferred in Japan. However, at the same time, it is leading to over-indication and over-transfusion. This is the reality we found in our service, which is one of the leading hospitals in Japan, in which the PAD system was fully-established. Thus, the situation would be not better in small hospitals and clinics, where the system is not established. It will be very important to critically review this scenario, and analyze the role of PAD from the societal, economical and medical viewpoints in Japan, which are completely different from Western societies. Also, it will be essential to make efforts to achieve the real safety of ABT, appropriately indicating it in the context of PBM, and we are confident our present data will serve as the basis to achieve these goals.

References


