Transfusion Medicine

Provision of phenotype-matched blood units: no need for pre-transfusion antibody screening

Fun Yi Lau,* Raymond Wong,* Natalie Pui Ha Chan,°
Chung Hin Chui,*# Elaine Ng,@
Margaret Heung Ling Ng,° Gregory Cheng,*

*Department of Medicine and Therapeutics, The Chinese University of Hong Kong; °Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong; #Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University; @Department of Pathology, Ruttonjee Hospital, Hong Kong

Background and Objectives. The Hong Kong government is planning to introduce an electronic smart identity card for all seven million citizens in 2003. If the smart card contains the full red cell phenotype/genotype of the individual, it may be possible to transfuse phenotype-matched blood units without pre-transfusion antibody screening. We conducted a feasibility study.

Design and Methods. Red cell phenotype was determined for 407 donor blood units and 493 patients for whom an antibody screen had been ordered. The computer program selected phenotype-matched blood from the donor stock for the patients according to actual transfusion request. For patients with a positive antibody screen, full crossmatching was carried out with the computer-selected phenotype units. The frequencies of the various red cell phenotypes in the population were calculated from Red Cross data of antigen frequencies. The probabilities of finding at least one unit of phenotype-matched blood from a 300-unit hospital stock and a 4,000-unit Red Cross stock were determined for each phenotype. Cost analysis was performed.

Results. Ninety-two out of 493 patients received a total of 395 blood units. The required number of phenotype-matched blood units could be found for 92 patients using a 300-unit pool and for all patients using a 4,000-unit pool. We calculated that phenotype-matched blood could be provided for more than 98% of patients without antibody screening. The total cost of the project is US$ 98 million with potential savings of US$ 14 million per year.

Interpretation and Conclusions. It is feasible and cost-effective to transfuse patients with phenotype-

Correspondence: Prof. Gregory Cheng, 9/F Clinical Science Building, Prince of Wales Hospital, Ngan Shing Street, Shatin, N.T., Hong Kong. Fax: international +852-26375396. E-mail: gcheng@cuhk.edu.hk

matched blood without antibody screening using a smart card system.
©2001, Ferrata Storti Foundation

Pre-transfusion antibody screening is the adopted practice in many hospitals. Patients with negative results will be issued ABO compatible blood units following an immediate spin or electronic crossmatch procedure.[1,2] If the antibody screening test is positive, antibody identification should be performed and whenever possible, the patient should be transfused with red cells lacking the corresponding antigen. Many small hospitals may not have the resources to perform antibody identification and referral to a reference laboratory is necessary. This may result in delays in blood transfusion. Antibody investigation is very labor intensive and time-consuming for patients with multiple alloantibodies or autoantibodies. For patients with strong autoantibodies, phenotype-matched blood will be given even if such units are incompatible by direct crossmatch.

We wanted to test whether it is safe to issue phenotype-matched blood to patients without carrying out pre-transfusion antibody screening. The advantages and potential health care savings of such a transfusion practice are discussed.

Design and Methods

The Prince of Wales Hospital is a 1,360-bed general hospital with a busy 24-hour emergency department. It serves a population of one million people and is the regional referral center for major trauma,

burns and cancer patients. On average 300 patients are admitted daily, with half of these patients being admitted through the emergency department. Approximately forty operations are performed daily. The blood bank adopts an antibody screening–computer crossmatch procedure. It performs roughly 100 antibody screens and issues an average of 55 (range 30-186) blood units daily. The average blood bank stock is 300-400 units, and the Red Cross replenishes the stock daily except on Sundays. The Red Cross has an average stock of 4,000 units.

This pilot study was carried out during the first two weeks of August, 2000.

Red cell phenotypes

ABO, Rh, Duffy, Kidd, Kell, MNSs and Miltenberger phenotypes of study patients and donor cells were determined using the DiaMed gel card (DiaMed AG, Switzerland) and DIANA gel card (Diagnostic Grifols S.A., Spain) according to the manufacturers' instructions.

Donor blood units

Red cell phenotypes were determined for the 407 donor blood units in the blood bank stock.

Segments of red cells from each donor unit were cut and saved for further crossmatch.

Patients

The 493 patients from general medical and surgical wards for whom antibody screening was requested during the first two weeks of August were recruited into this study. Patients were to be issued blood units according to the current practice without delays, computer crossmatching being carried out for patients with negative antibody screen, and full crossmatch for patients with positive results. Patients actually requiring blood transfusion were to participate in the mock trial described below.

Computer program for issuing phenotype-matched blood units

The red cell phenotypes of the 407 donor blood units and 493 patients were entered into the computer. In the mock trial, the staff entered the ID of the patient actually requiring blood transfusion into the computer. The computer then selected phenotype-compatible blood units from the blood bank stock. Homozygous patients, e.g. MM would only be issued phenotype-identical blood units, while heterozygous patients, for example MN could be issued MM, MN, or NN blood units and so forth. The computer listed out the serial numbers of all suitable blood units currently available in the hospital stock according to expiry dates. The staff then

selected the requested number of units from the list. Therefore, rare units, e.g. Fy(a-,b-) , may be selected for transfusion into a Fy(a+,b+) patient rather than allowing such units to expire. The selected blood unit phenotype was counterchecked against the patient's phenotype in a separate electronic crossmatching procedure before mock issue. For patients with a positive antibody screen, a full crossmatch was performed using the saved blood segments from the corresponding computer-selected units to see whether the selected unit was also compatible by the current practice protocol.

Probability of finding phenotype-matched blood for the various phenotypes

From the gene frequencies of the various blood group antigens among Hong Kong Chinese, we calculated the predicted frequencies of the various red-cell phenotypes. We also estimated the odds of finding one or more units of phenotype-matched blood for each phenotype using a 300-unit hospital stock, and a 4,000-unit Red Cross stock. For example, according to a survey by the Hong Kong Red Cross,[3,4] the distributions of group O, CCDee, Fy(a+,b-), kk, Jk(a+,b-), MN, ss, Mi-, Le(a-,b+) were 40.6%, 55.1%, 90.6%, 99.94%, 29.2%, 49.1%, 94%, 93%, 59.5%, respectively. The frequency of the above red cell phenotype was calculated as 1.5% ($40.6\% \times 55.1\% \times 90.6\% \times 99.94\% \times 29.2\% \times 49.1\% \times 94\% \times 93\% \times 59.5\%$).

The percentage of compatible phenotypes among the donor population was calculated to be 3.05%, because this phenotype could be transfused with MM, MN and NN blood units. Therefore, among the 300-unit hospital stock, an average of nine units would be phenotype-compatible. Alternatively, the chance of finding at least one unit of suitable blood for this patient from a 300-unit and a 4,000-unit donor pool was 99.99% and 99.999%, respectively (Table 1). If the above phenotype was a very rare one, for example, Kk (0.06%) instead of kk (99.94%), then its distribution frequency became 0.0009%. However, because this phenotype could be transfused with Kk and kk blood, the percentage of compatible phenotypes among the donor population was also 3.05%, and the chance of finding at least one unit of suitable blood was also greater than 99%. Similar calculations were performed for all the other phenotypes.

Main outcome measures

1. To determine whether the phenotype-matched blood units selected for patients with a positive antibody screen were also compatible by the current practice protocol, so that transfusion safety is

Table 1.

Frequency of compatible donor phenotype in general population	Probability of finding at least one compatible unit from:	
	300-unit pool	4000-unit pool
3.0%	99.99%	99.999%
0.6%	*83.5%	99.999%
0.3%	59.4%	99.999%
0.2%	45.2%	99.966%
0.1%	25.9%	98.172%

For compatible donor frequency of 0.2%, the probability of finding at least.°

	1 unit	2 units	3 units
From 300-unit pool	45.2%	12.2%	2.4%
From 4,000-unit pool	99.966%	99.696%	98.596%

*If a compatible phenotype is found in only 0.6% of the general population, the probability that any unit is incompatible is 0.994. The probability that all 300 units are incompatible is $(0.994)^{300}$. Therefore, the probability that at least one unit is compatible is $1-(0.994)^{300} = 0.835$. °The calculations are based on the formula $(0.002 + 0.998)^{300}$ and $(0.002 + 0.998)^{4000}$ respectively. 98.5% of population will have donor frequency greater than 0.6%; 99.7% of population will have donor frequency greater than 0.2%.

not compromised.

2. To determine whether transfusion would be delayed for patients with a negative antibody screen due to absence of the appropriate phenotype-matched blood in the blood bank stock.

Cost analysis

The cost of performing red cell phenotyping on 7 million HKSAR citizens, the labor involved and the annual cost for red cell phenotyping for new immigrants and newborns were estimated. The potential savings in manpower and health care costs were also calculated.

Results

Among 493 patients recruited into the study, 46 were antibody screen positive, eight of them were transfused a total of 26 blood units. The computer program was able to find the requested number of phenotype-matched blood for these eight patients. All the selected phenotype-matched units were compatible by the full crossmatch. Two patients had anti-M and two patients had anti-E, the computer-selected blood units lacked the corresponding antigens. No specific antibodies could be identified in the other four patients.

Eighty-four out of 447 antibody-negative patients received a total of 369 blood units. The computer

was able to find phenotype-matched blood for all but one patient from the 407 hospital blood units. That patient did not require an urgent blood transfusion. His hemoglobin dropped from 12.2g/dL to 8.1 g/dL over five days and two units of blood were transfused 24 hours after typing and screening had been ordered. He was group B, his phenotype frequency was 0.0427% and the probability of finding the requested number of blood units from the Red Cross stock was 99.5%.

Probability calculations

For some uncommon recipient phenotypes, only 0.2% of the general population is phenotype compatible. The probabilities of finding at least one unit of phenotype-matched blood from the 300-unit hospital stock and the 4,000-unit Red Cross stock were 0.451 and 0.999 respectively (Table 1). Indeed, 99.7% of the population will have a compatible donor frequency greater that 0.2%. With a transportation time of 15-45 minutes between the Red Cross center and the hospitals, phenotype-matched blood could be provided for more than 98% of the admitted patients within an hour. The estimation had already considered the possibility of many patients requiring transfusion simultaneously in different hospitals.

Cost analysis

The cost of reagents to perform serologic red cell phenotyping in duplicate (HK$ 100 each) for 7 million citizens would be HK$ 700 million (US$ 90 million). A full time technician is able to perform 150-200 red cell phenotypes daily. Two hundred technicians working full-time for one year would be able to complete the task. Total salaries would be approximately HK$ 60 million (US$ 7.5 million). With a birth rate and immigrant rate of 50,000 and 60,000 *per annum*, respectively, the annual reagent cost for red cell phenotyping would be HK$ 11 million (US$ 1.4 million). Three technicians (total salaries HK$ 750,000 *per annum*) could handle the phenotyping for newborn citizens and new immigrants.

Patients with rare phenotypes, visitors or illegal immigrants without phenotype information may still require antibody screening. This should constitute less than two percent of the present workload. The number of blood bank staff at each hospital could therefore be significantly reduced by 50-90% (5 staff per hospital at an annual salary of HK$ 250,000-$ 400,000 each). For the forty government hospitals, the annual savings in salaries and reagent costs would be HK$ 110 million (US$ 14 million).

Discussion

Our study suggests that it is feasible and cost-effective to perform red cell phenotyping for all HKSAR citizens and transfuse patients with phenotype-matched red cells. With the exception of one case, the transfusion needs of all the studied patients could be met. Even for that patient, phenotype-matched blood could be obtained from the Red Cross during the regular daily delivery. For patients with a positive antibody screen, all the phenotype-matched blood units selected were also compatible by the full crossmatch and lacked the corresponding antigens. The 493 patients recruited accounted for about 75% of the patients for whom typing and screening were requested during the study period. The 395 units of blood transfused into the studied patients were comparable to the number of blood units issued weekly. Obstetric patients were not recruited because they usually have low transfusion rates. Therefore, our study reflects the weekly transfusion demand. Two hundred technicians will be able to complete the red cell phenotyping for the 7 million citizens in 12 months. If the red cell antigenic profile of each citizen is encoded in a personal electronic smart card, then the red cell phenotypes of all admitted patients and donor red cell units will be readily available. The total salary and reagent costs for the smart card project are estimated to be US$ 98 million. The recurrent cost is about US$ 1.4 million annually for phenotyping newborn subjects and new immigrants. However, the annual savings in manpower and blood bank budget amount to at least US$ 14 million and it would take only seven years to recover the expenses. This does not include the savings in venipunctures and repeated blood samplings. The above cost analysis is based on performing red cell phenotyping serologically in duplicate using semi-automated methods. The genes encoding all major blood group antigens have been identified and cloned. It is therefore possible to determine red cell phenotype accurately by molecular techniques with full automation.[5-9] The cost benefit may be even greater.

Once the project is completed, there will be no need for any further antibody screening, antibody identification or other pretransfusion test for the majority of patients. Whenever a blood request is made, the blood bank will know immediately whether the demand could be met with the hospital stock. For non-urgent transfusion, the required phenotype-matched units will be delivered from the Red Cross during the regular daily replenish-ment. If such units are not readily available from the Red Cross 4,000-unit pool, a standard pre-transfusion antibody screen will be performed. If a patient with an uncommon phenotype requires emergency or massive transfusion, it may be impossible to provide a sufficient number of units of phenotype-matched blood. In emergency transfusion, it is currently acceptable to transfuse group O or ABO specific unmatched blood before completion of the antibody screen. With the smart card system, one can select the best-matched blood units for the patient according to the frequency of the clinically significant alloantibodies detected in the local population. For example, anti-Le^a occurs exclusively in Le(a$^-$b$^+$) patients, while anti-E is the most commonly encountered alloantibody. Therefore in a ee, Le(a$^-$b$^+$) patient, ee, Le(a$^+$b$^-$) blood would be a safe phenotype-match. This should be a better and safer transfusion practice than the current protocol of unmatched transfusion. In massive transfusion during liver transplant or exsanguination, even if the recipient has known alloantibodies (e.g. anti-D), it is currently acceptable to transfuse antigen positive (D$^+$) blood first and save the antigen (D) negative blood units until the patient's bleeding is controlled. Similarly, with the smart card system, one could transfuse the second or third best-matched blood units first and reserve the perfectly matched units for transfusion after control of bleeding. Alternatively, one could transfuse with the best-matched units first and perform an antibody screen for selected patients in the meantime.

Hong Kong is a densely populated area, and average transportation time from the Red Cross center to all major hospitals is less than one hour. With a stock of 300 units for major hospitals with emergency departments and a 4,000-unit Red Cross stock, more than 98% of the patients requiring blood transfusion could be provided with phenotype-matched blood without delay and antibody screening.

The phenotype blood system has several potential advantages over the current antibody screening method:

a) the time from request for type and screening, drawing of blood sample by ward staff, delivery of the blood sample to the blood bank, processing of the sample by blood bank staff, to completion of the antibody screening tests, averages at least one and half hours, and often longer. With the smart card-phenotype system

there are no such delays;

b) for patients with a positive antibody screening test, there is even further delay. For patients with autoantibodies, or multiple alloantibodies, it may be days or even weeks, before alloantibodies can be excluded or identified. Determination of red cell phenotype in such patients is also difficult. With the smart card system, phenotype-matched blood will be readily available without delay;

c) according to current guidelines, once a transfusion is commenced, transfusion of further blood units must be completed within 72 hours, or the pretransfusion testing must be repeated on a new specimen.[1,2] There is no need for such repeat testing with the smart card system. Moreover, the 72-hour limit is not perfectly safe. Patients with previous sensitization may develop a secondary amnesic response within 24 hours, and the 72-hour recommendation will not prevent hemolysis of the subsequent blood units. Also, for patients who do not develop new alloantibodies, repeating the test after 72 hours would be wasteful;

d) the antibody-screening system is not able to detect all alloantibodies. If a patient has antibodies against an antigen missing from the screening cell panel, such antibodies will be missed. For example, anti-Mi is common among Chinese,[10-12] but most commercial screening cells are Mi negative. Also, if the screening cell panel is heterozygous, rather than homozygous for certain blood group alleles, weak antibodies or low titer antibodies against such an antigen will be missed. The smart card system may overcome the above problem. One may argue that if the red cell phenotype information on the card is incomplete, one may miss the rare antibodies against the antigens that are missing in the smart card. According to a Hong Kong Red Cross survey, antibodies against the Rh, Duffy, Kidd, Lewis, Miltenberger, MN, Diego and P systems account for 99.9% of the alloantibodies encountered. The risk of a patient with an antibody against an antigen missing from the smart card receiving a unit with the corresponding antigen is estimated to be less than 1/100,000. This is similar to the risk of antibody screening missing out some rare antibodies against rare antigens absent from the screening cell panel that are detectable only by the full crossmatch;

e) currently when the Red Cross stock for certain blood groups (e.g. group O) is low, the Red Cross makes a public appeal for volunteer donations. Many first-time volunteers come to donate blood, but many of them are of a different blood type (A, B etc), thereby wasting considerable resources. The first four digits of the smart card will represent a specific phenotype, for example, 1011 stands for O, CCDee, MN etc. The Red Cross can then specifically appeal for citizens with smart card numbers beginning with 1011 to donate if blood of such a phenotype is required, making the appeal much more efficient;

f) rare phenotypes such as RhD negative or O Bombay will be identified, and encoded in the smart card. Upon admission, the blood bank and Red Cross can be alerted immediately and potential donor units or donors can be called up much earlier. If such donors or units are not readily available, an antibody screen will be performed and blood units will be issued according to the current practice. For elective operations, sufficient numbers of blood units will be available within two days. As for the concern whether such rare phenotype units may expire before they are required by the patients with a rare phenotype and therefore wasted, such units can be safely transfused into patients with more common phenotypes just before expiry;

g) mismatched blood transfusion due to clerical error, for example a blood sample drawn from the wrong patient, or labeled as another person's specimen remains a common problem worldwide. Each donor blood unit collected at the Red Cross is labeled with the red cell phenotype directly transcribed electronically from the donor smart card. Upon admission to hospital, a wristband with the patient's ID number and barcode phenotype is attached to the patient. At the bed side, the nurse will use a portable barcode scanner to counter-check the red cell phenotype and patient's personal ID number on the blood unit against those on the patient's wristband and the patient's smart ID card. If all data match, the portable scanner will generate a go-ahead signal.

It is essential and crucial that the red cell phenotype on the smart card is correct. In one study, 2.3% of the ABO blood group data on the US army military tags were incorrect.[13] With modern techniques and sophisticated labeling systems, one can develop a foolproof system for the smart card. The

smart card will contain a unique personnel identity number and the fingerprint of an individual in digital form. When the specimen is collected from the individual for phenotype testing, the individual will scan his fingerprint into the computer. If the scanned fingerprint matches the digital fingerprint of the ID card in the database, the computer will then label the specimen with the unique personnel identity number corresponding to the matched fingerprint. Therefore, the result of phenotyping will be linked to the individual unique fingerprint and identity number in the computer database. ABO groupings of donor units and admitted patients may no longer be necessary with such a foolproof system. For patients with damaged cards or lost cards, one can either perform the standard antibody screen or, if the computer database is very good, one can use the individual fingerprint and ID number to select the phenotype blood without the card. If a patient carries a fake smart card, his fingerprint will not match the fingerprint on the card or that in the database.

The citizens of Hong Kong have accepted the concept of a personnel ID card with a photograph and digital fingerprint. There is still some debate on whether health data should be included on a voluntary basis only. Red cell phenotype in general is not considered as a personnel health problem and should not be a privacy issue.

We postulate that for places with good transportation networks and a dense and rather homogeneous population, the smart card phenotype system is feasible and cost effective. Antibody screening or full crossmatching may still be needed in some situations, for example patients with rare phenotypes, visitors or illegal immigrants without phenotype information. However, if over 95% of patients can benefit from the smart card system without the need of any pre-transfusion testing, the convenience and savings in health care are worthwhile. The extent of the red cell phenotype on the smart card depends on the frequency distribution of the various red cell antigens and alloantibodies encountered in the locality. In Hong Kong, matching for the Rh, Mi, MN, Fyb, Kidd, Lewis, P and Diego system will avoid 99.9% of the alloantibodies detected (Red Cross data). Even though our results are still preliminary, we feel that the system has great potential and will significantly change transfusion practice in the new century. We plan to conduct a larger study involving six major hospitals in Hong Kong. The study will give an accurate estimate of how often patients with a rare phenotype are encountered in daily practice, how often mas-sive transfusions are required, how often transfusion to non-alloimmunized patients is unnecessarily delayed because of lack of suitable phenotype blood, how often pre-transfusion screening is still required for some patients and how often the blood units need to be transported on an emergency basis from the Red Cross to the hospital. The data from this study will determine whether it is safe and ethical to transfuse patients with phenotype blood without pre-transfusion testing.

Potential implications for clinical practice

An electronic record of all blood phenotypes in a population may revolutionate transfusion practices.

References

1. American Association of Blood Banks. Standards for Blood Banks and Transfusion Services. 15th ed. The Association; 1993.
2. Australasian Society of Blood Transfusion Inc. Guidelines for pretransfusion testing. 2nd ed. The Society; 1993.
3. Mak KH, Yan KF, Cheng SS, Yuen MY. Rh phenotypes of Chinese blood donors in Hong Kong, with special reference to weak D antigens. Transfusion 1993; 33:348-51.
4. Mak KH, Cheng S, Yuen C, Chua E, Lin CK, Leong S. Survey of blood group distribution among Chinese blood donors in Hong Kong. International Society of Blood Transfusion, XXIII Congress. Amsterdam. Vox Sang 1994; 67(Suppl 2):50.
5. Olsson ML, Hansson C, Avent ND, Akesson IE, Green CA, Daniels GL. A clinically applicable method for determining the three major alleles at the Duffy (FY) blood group locus using polymerase chain reaction with allele-specific primers. Transfusion 1998; 38:168-73.
6. Maaskant-van Wijk PA, Faas BH, de Ruijter JA, et al. Genotyping of RHD by multiplex polymerase chain reaction analysis of six RHD-specific exons. Transfusion 1998; 38:1015-21.
7. Rozman P, Dovc T, Gassner C. Differentiation of autologous ABO, RHD, RHCE, KEL, JK, and FY blood group genotypes by analysis of peripheral blood

samples of patients who have recently received multiple transfusions. Transfusion 2000; 40:936-42.

8. Murphy MT, Fraser RH, Goddard JP. Development of a PCR-based diagnostic assay for the determination of KEL genotype in donor blood samples. Transfus Med 1996; 6:133-7.

9. Irshaid NM, Thuresson B, Olsson ML. Genomic typing of the Kidd blood group locus by a single-tube allele-specific primer PCR technique. Br J Haematol 1998; 102:1010-4.

10. Lin CK, Mak KH, Cheng G, et al. Serologic characteristics and clinical significance of Miltenberger antibodies among Chinese patients in Hong Kong. Vox Sang 1998; 74:59-60.

11. Cheng G, Hui CH, Lam CK, et al. Haemolytic transfusion reactions due to Mi-antibodies; need to include Miltenberger III positive cells in pre-transfusion antibodies screening in Hong Kong. Clin Lab Haematol 1995; 17:183-4.

12. Mak KH, Banks JA, Lubenko A, Chua KM, Torres de Jardine AL, Yan KF. A survey of the incidence of Miltenberger antibodies among Hong Kong Chinese blood donors. Transfusion 1994; 34:238-41

13. Rentas FJ, Clark PA. Blood type discrepancies on military identification cards and tags: a readiness concern in the U.S. Army. Mil Med 1999; 164:785-7.