

GUIDELINES FOR THE TRANSFUSION OF RED CELLS

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ABSTRACT

The following recommendations, which aim at standardising and rationalising clinical indications for the transfusion of red cells in Belgium, were drawn up by a working group of the Superior Health Council. To this end, the Superior Health Council organised an expert meeting devoted to "Guidelines for the transfusion of red cells" in collaboration with the Belgian Hematological Society. The experts discussed the indications for red cell transfusions, the ideal red cell concentrate, the practical issues of administering red cells, and red cell transfusions in patients in a critical condition. The recommendations formulated by the experts were validated by the working group with the purpose of harmonising red cell transfusion in Belgian hospitals.

INTRODUCTION

Since the year 2000, some 500,000 red cell units have been transfused on a yearly basis in Belgium. A series of large-scale studies conducted totally or in part in our country (i.e. the SANGUIS study (1990-91) and the Biomed I and II studies (1996 and 1999-2000) has shown that there has been a remarkable drop in the number of red cell transfusions performed for surgical patients in our country over the last 15 years (1- 5). The same studies revealed that there are wide discrepancies amongst hospitals concerning the amounts being transfused for similar interventions or pathologies. Instead of concentrating on selected samples of patients, a recent study commissioned by the Minister of Health

and Social Affairs, who was acting through the Belgian Health Care Knowledge Centre (6), covered all transfusions performed during the year 2000 in Belgium. It showed that transfusions not only tend to be restricted to a limited number of pathologies, but also to a limited number of patients suffering from these. This is the outcome of a continuous drop in the number of transfusions that have been carried out over the last few years. Nevertheless, many patients who still require transfusions need them in large quantities, often in emergency situations. This in turn has enhanced rather than levelled-out the discrepancies between centres, with transfusions being increasingly distributed at random, contrary to what used to be the case in the past, when the utilisation of transfusion resources used to be more predictable.

Two conclusions can be drawn from this study. First, there is still room for improvement in the use of transfusions in everyday practice, as far as patients receiving few red cell units are concerned. Second, with the bulk of the overall amounts being transfused to a small number of patients, including patients with a very long life expectancy, it becomes ever more important that the products being transfused and the transfusion process itself conform with the highest possible quality standards.

Therefore, the Superior Health Council (SHC) organised an expert meeting on red cell transfusion that was held on November 18th, 2005, in collaboration with the Belgian Hematological Society. This meeting was designed to collect recent knowledge on the issue of red cell transfusion and its alternatives in order to draw up recommendations for good transfusion practice in hospitals. It was based on the "evidence-based medicine" approach, with particular attention to meta-analyses, and aimed at contributing towards improving local transfusion procedures and policies, as well as providing a scientific basis to the transfusion committees.

Using the information available, it was possible to formulate a series of principles that need to be observed when transfusing red cells. The SHC working group "Blood and Blood Products" then discussed these principles and finalised them (7).

This document is not a statement of user requirements but may be used in the assessment of minimum standards of good clinical practice.

A. The objective of red cell transfusions

Red cells are transfused to prevent or to correct an imbalance between oxygen transport and demand. As is the case with any therapy, the transfusion of red cells has its risks. Any decision to carry out such a transfusion must therefore be taken under the assumption that the benefits for the patient are likely to exceed the risks.

Transfusing red cells without controlling tissue oxygen demand makes little clinical sense. In particular, pain, fever, tachycardia, shivering as a reaction to cold or anaesthesia, convulsions, agitation, exertion must be taken into consideration and treated whenever possible before deciding to carry out a transfusion. Septic shock may impede the uptake and use of oxygen by the tissues, despite the presence of a normal or even increased oxygen transport capacity. Aggressive etiologic and haemodynamic treatment must be initiated before considering red cell transfusion.

Increasing haemoglobin concentrations improves maximal oxygen delivery during exercise. Enhancing physical performance, however, does rarely constitute an acceptable indication for red cell transfusion, whether autologous or allogeneic.

Oxygen transport is determined by both cardiac output and the concentration of oxygen in the blood. Under normal circumstances, nearly all oxygen is carried by haemoglobin. The following discussion assumes that haemoglobin is fully saturated when leaving the lungs. Every instance in which haemoglobin fails to saturate requires treatment and should be corrected as far as possible before considering the transfusion of red cells. Moreover, the lower the haemoglobin concentration, the greater the extent to which dissolved oxygen contributes to tissue oxygen transport and consumption. In order to meet oxygen demands, low haemoglobin levels require a compensatory increase in cardiac output. Care should be taken that the cardiac function of anaemic patients is monitored and supported. Maintenance of adequate circulating blood volume is of paramount importance in this context.

RECOMMENDATION

- Red cell transfusion is only one part of a global therapy aimed at correcting an imbalance between oxygen transport and oxygen demand. Before carrying out a transfusion, it is necessary to address the question of oxygen demand as well as the other factors involved in oxygen transport, such as the oxygenation of arterial blood and cardiac output.

B. Stored red cells

All blood components that are issued in Belgium are prestorage leukocyte-depleted components.

There are a number of ways by which removing leukocytes (and platelets) from red cells prior to their storage have a positive effect on their further storage: the early removal of leukocytes, which are metabolically active, prevents them from consuming glucose and creating metabolites, as well as releasing bioreactive substances and leukocyte enzymes (8). It follows that any comparison of studies on the clinical impact of red cell transfusion should take into account whether or not the red cells were leukocyte-depleted.

The red cell storage lesion is best looked upon as the sum of all storage-induced damage to red blood cell units that reduces their rate of survival when returned to the circulation of a recipient, or their ability to deliver oxygen at the microcirculatory level (8). Alterations such as the depletion of red cell adenosine triphosphate (ATP) and 2,3 di-phosphoglycerate (2,3 DPG) levels, the reduction in deformability associated with the loss of membrane constituents, haemoglobin and K⁺ leakage, and the accumulation of bioreactive substances could have a profound effect on the recipient of a red blood cell concentrate. However, the clinical impact of the storage lesion remains largely unknown (8, 9).

There is conflicting evidence on whether the transfusion of a low number of stored (> 14 days) red cells could affect the outcome of a critically ill adult patient. In a recent double blind randomised, controlled trial (10), the transfusion of two units of leukocyte-depleted red blood cells that had been stored for 2 - 3 days in euvolemic, critically ill anaemic patients was compared with the transfusion of units that had been stored for 22 - 32 days. No difference could be found in any global or regional oxygenation parameter. These findings were confirmed in another recent pilot study (11). However, a large-scale but retrospective study showed that there is a strong relationship between the average and also the maximum storage time of transfused erythrocytes and mortality, morbidity and length of hospital stay in redo cardiac surgical patients (12). It should be noted that the median number of transfused units (4.1; range 2 - 48 units) was higher than in the other two studies. Another large retrospective study involving 2,732 cardiac surgery patients failed to disclose any difference in outcome when comparing patients having received buffycoat depleted red cells

stored for an average of 12.7 (+/- 2.8) days versus 24.3 (+/- 3.5) days: both relatively long storage times (13). However, given the limited evidence available, large clinical prospective trials comparing red cell storage times are needed in order to show whether there is any significant clinical effect, in particular under circumstances as trauma and shock. At this stage, it is impossible to draw any conclusions about the benefit to risk ratio of the transfusion of large quantities of red blood cells that have been stored for over 10 days (14, 15).

K⁺ plasma levels in stored red cell units increase rapidly. But, because of rapid dilution, redistribution into cells and excretion after transfusion, this rarely causes any problems in the adult recipient with normal renal function. However, hyperkalaemia may occur in neonatal recipients who have exchange transfusions or rapid transfusions with stored blood. Therefore, as a precaution, only red cells stored for at most five days or less should be used for intrauterine transfusions, as well as for large or exchange transfusions in neonates, especially when involving the irradiation of red cells (16, 17). In such cases too, irradiated red cells must be transfused within 24 hours because irradiation damages the red cell membrane and increases the leakage of potassium (18, 19). Red cells for small volume (10 - 20 ml/kg) top-up neonatal transfusions may be irradiated up to 14 days after collection, and stored for another 14 days after that (18).

2,3 DPG regulates the release of oxygen from haemoglobin. 2,3 DPG interferes with oxygen fixation onto the haemoglobin molecule. Low 2,3 DPG levels enhance oxygen affinity and result in a left shift of the oxygen dissociation curve. Intracellular 2,3 DPG levels fall rapidly to zero (~ 0 after 14 days) in stored red cells but regenerate (as ATP does) to normal after transfusion (50 % of normal levels within 3 - 8 hours) (20). Despite this, fresh red cells and red cells that have been stored for a relatively long time have been found to be equally efficacious in immediately reversing anaemia-induced brain oxygenation deficits in humans (21, 22).

RECOMMENDATIONS

- At this stage, it is impossible to make any recommendations about the transfusion of large quantities of red blood cells that have been stored for over 10 days.
- Neonatal patients should only receive red cells that have been stored for five days or less in case of massive or exchange transfusion. In such a setting,

erythrocytes that have been irradiated should not be transfused any later than 24 hours after irradiation.

- Optimal oxygen delivery does not seem to require fresh rather than stored red cells.

ATP is the primary energy carrier of red cells and there is a very close link between its concentration in the red cell and in vivo recovery of red cells. With the red cell additive solutions currently being used, the 24-hour post-transfusion in vivo recovery is generally reduced to 75 – 80 % after 5 – 6 weeks of storage at 4 °C, whereas a 75 % recovery is the internationally accepted requirement by the end of the shelf life (23).

Several research teams have been investigating how the storage time of red cells can be improved. This has led to the development of techniques to improve the quality of the red cells during storage (8, 23). However, because these new techniques involve complicated processes, such as removing compounds of the additive solution before the transfusion and reducing the volume of the solution, they are not ready for clinical use yet.

Furthermore, the potential growth of psychrophilic bacteria (bacteria still growing at relatively low temperatures: 5 °C – 30 °C) in the red cells during storage remains a problem.

C. The risks involved in not carrying out a transfusion

In France, epidemiological analyses carried out recently on the basis of death certificates have shown that approximately a hundred out of 8 million anaesthetised patients could die each year as a result of not receiving a transfusion in time, whether directly from uncompensated haemorrhage and hypovolemic shock, or indirectly from myocardial ischemia, prolonged hypotension or other effects of anaemia (24). These statistics show that the risks involved in not carrying out a transfusion are greater than those involved in administering a transfusion to anaesthetised patients (including child birth with anaesthetic support), as is apparent from the total number of deaths that can be attributed to these transfusions. Apart from any problems that might arise when an appropriate therapy is decided on, these data shed doubt on the way in which blood products are made available by the system and administered to the patient who urgently needs them.

RECOMMENDATION

- Any patient who needs a transfusion should receive sufficient quantities of the required blood component in time.

D. Trigger haemoglobin concentration

The total red blood cell mass constitutes a more reliable means of predicting physical performance and the way in which anaemia is tolerated than the concentration of haemoglobin in the blood (25). Unfortunately it cannot be measured easily. There are quite a number of circumstances under which circulating haemoglobin concentration does not reflect the red cell mass: acute haemorrhage, haemodilution and haemoconcentration, splenomegaly and cardiomegaly. As a result, there is no way of predicting for a given individual patient at which haemoglobin concentration oxygen transport will cease to meet oxygen demand. Besides, the aim is to prevent such a point from being reached.

There are no precisely defined values of the haemoglobin concentration on which the decision of transfusing red cells can be based. However, haemoglobin concentrations should be monitored after a transfusion to assess its efficacy.

Concordant physiological evidence gleaned from animal models (26, 27), from clinical observations (28) as well as from epidemiological studies that were conducted in countries in which transfusions are only available on an irregular basis (29) allows for a minimal (vital) haemoglobin concentration threshold to be set at about 45 grams per litre of blood. Below this threshold, the life of the patient is in immediate danger.

Below a concentration of 70 grams of haemoglobin per litre of blood, most healthy humans will experience symptoms such as a limited ability to carry out any physical or even mental tasks. All limitations associated with this level of anaemia can be compensated in healthy volunteers by means of a high inspired oxygen fraction. However, below 70 g/l, red cell transfusion is indicated under most *clinical* circumstances.

When anaemia has developed slowly, i.e. over a period of weeks, its tolerance is increased as a result of the combined effect of normovolaemic dilution, peripheral vasoconstriction and metabolic changes in the red cells. However, under those circumstances, there is also a risk of acute circulatory volume overload during trans-

fusion. Well-tolerated chronic anaemia may only be treated by means of an etiological treatment, even in severe cases.

Above a concentration of 100 grams of haemoglobin per litre of blood, cases of significant physiological compromise are exceedingly rare and red cell transfusions should only be considered under exceptional circumstances.

Evidence gathered from large numbers of surgical patients who refuse transfusion therapy (30, 31), from epidemiological surveys of health insurance data banks (32), and from non-randomised clinical studies suggest that the mortality rate of patients with cardiac compromise increases when their haemoglobin concentration drops below 100 grams per litre of blood. However, it is important to bear in mind that in these studies a pathological process that was not related to the cardiac condition caused the anaemia. It would therefore be more correct to assume that a cardiac patient who also suffers from an unrelated, anaemia-inducing condition exhibits an increased risk of a cardiovascular complication. In addition, there is no clear evidence from the available literature that transfusion of coronary artery disease patients to haemoglobin concentration above 100 grams per litre of blood is associated with a decreased mortality or morbidity (33, 34.)

Between the concentrations of 70 and 100 grams of haemoglobin per litre of blood, the decision to carry out a transfusion should be determined by the clinical condition of the patient.

One prospective randomised study showed that euvolaemic intensive care adult patients benefited from a restrictive approach that aimed at haemoglobin concentrations of around 80 grams per litre of blood, instead of transfusing red cells as soon as they fell below 90 grams. This study that excluded cardiac surgery patients and acute cardiac conditions was performed with non leukocyte-depleted blood (35). A recent comparable study performed in euvolaemic critically ill children demonstrated that a haemoglobin transfusion threshold of 70 grams per litre of blood decreased transfusion requirements without increasing adverse outcomes in comparison with a haemoglobin transfusion threshold of 95 grams per litre. In this study, leukocyte-depleted red cells were used (36).

End-of life conditions warrant a different approach, in which the emphasis is put on the comfort of the patient.

Patients suffering from chronic conditions may require repeated transfusions. For these patients, higher haemoglobin concentrations (than e.g. after a blood loss) should be reached after each transfusion in order to limit the number of transfusions, to ensure acceptable haemoglobin levels between these episodes and to avoid high-risk situations.

RECOMMENDATIONS

- Below 45 g/l haemoglobin, the life of the patient is in danger in the short term.
Below 70 g/l haemoglobin, the question to ask should be: "Why not transfuse?"
Above 70 g/l haemoglobin, the question to ask should be: "Why transfuse?"
Between 70 and 100 g/l, patients' clinical conditions (in particular cardiac and respiratory reserves) play a major role in deciding whether or not to carry out a transfusion.
Above 100 g/l haemoglobin, transfusion is rarely necessary.
- Symptomatic patients should receive a transfusion and their symptoms should be reassessed after the transfusion. Haemoglobin concentrations will be monitored to assess the efficacy of the transfusions.

E. Target haemoglobin concentrations

The haemoglobin concentrations observed in patients leaving hospital – which are sometimes referred to as '*target haemoglobin concentrations*' – provide interesting epidemiological information. They are not affected by the volume redistribution that takes place during and soon after blood loss, they make it possible to monitor global clinical trends and they help to provide insight into what clinicians feel comfortable with during their patients' convalescence. Extensive studies carried out in Belgium on commonly performed surgical procedures have shown that the '*target haematocrit*' has remained at a steady 33 %, despite the fact that there has been a significant drop in the number of red cell transfusions performed, with an increasingly higher number of older patients operated on, and with a gradual decline in the length of hospital stays (3, 4, 35). This has been observed regardless of the age, gender, or other individual characteristics of the patients. In the

literature, values above 30 % have been looked upon as reflecting rather liberal transfusion practices. However, target haemoglobin concentrations should only be interpreted as one of the broad variety of quality markers in medicine, which also include mortality and complication rates, the level of autonomy at discharge and the need for admission in specialised institutions for further convalescence. Target haemoglobin concentrations cannot be used to determine the appropriateness of earlier transfusions in a given patient. There are two reasons for this:

a - *post-hoc* analysis cannot determine whether a complication would or would not have occurred if the decision to/not to transfuse had been different, and,
b - (as is the case for 'trigger' haemoglobin concentrations) there is no way of predicting at which level a given patient will be safe.

RECOMMENDATION

- The 'target' haemoglobin concentration cannot be used to assess whether or not it is appropriate to provide care for individual patients.

F. Ordering blood

Only a physician is allowed to order blood products or blood components; he/she does so by filling in and signing a prescription; he/she is legally referred to as the 'prescribing physician' of a transfusion.

As regards medical patients, red cells are usually ordered after the decision has been made to carry out a transfusion: the quantities ordered are identical to the quantities transfused. For safety reasons, it is recommended to organise clinical practice in such a way that transfusions can be started during working hours.

As far as surgical and obstetrical patients are concerned, an effort should be made to ensure that preoperative transfusion orders match actual requirements. Excess ordering results in a reduced availability of blood for all patients and may lead to an increased proportion of units reaching their expiration date without having been transfused. Insufficient blood supply may affect patient safety. Reconciling patient safety, general availability of blood and optimal use of donations is no easy task.

The first requirement for a good organisation is the early identification of patients with difficult cross-matches, pre-existing anaemia or coagulation abnormalities.

Whenever possible, pre-existing anaemia and coagulation anomalies should be investigated and corrected.

It may be difficult to find compatible donors for patients with a history of transfusion or multiple pregnancies (including aborted pregnancies and miscarriages), patients from ethnic groups that form a minority amongst the donor population, and patients with rare blood groups or subgroups. Blood group determination and screening for irregular antibodies should be carried out on all patients that are likely to need a transfusion as soon as they are put on a surgical or in-vitro fertilisation waiting list, or as soon as their pregnancy is confirmed. The operating or obstetrical team will be alerted in case of a positive antibody screen, allowing them to take the necessary measures in coordination with the blood bank, thus ensuring the patient's safety.

Recent studies in obstetrics have documented an increase in the number of accidents that can be attributed to poorly assessed blood losses, delayed responses to bleeding and a general failure to correctly plan transfusions in time. This in turn means that it is justified to pay special attention to the way in which the supply of transfusions is organised in this field (24).

The use of Surgical Blood Ordering Schedules may constitute a useful means of determining which patients are most likely to need a transfusion. Female patients, who have a smaller red cell mass, require transfusions more frequently than male patients do. The Transfusion Committee reviews on a regular basis how preoperative blood orders match actual needs for the most frequent interventions and takes action to adapt preoperative transfusion requests.

RECOMMENDATION

- Blood should be ordered in time. Every hospital should have Surgical Blood Ordering Schedules. There should be appropriate planning for deliveries and scheduled operations.

G. Sampling for pre-transfusion testing

A major safety concern of the transfusion system is the persistence of errors that are committed in providing the right blood to the right patient. Most errors involve three specific stages in the process under discussion, i.e. determining which are the appropriate indications for transfusion, collecting blood samples for pre-transfusion testing and following bedside procedures before administering any blood.

In Belgium and several other countries, haemovigilance systems have reported that they estimate the frequency of "wrong blood" events to be 1:12-30,000 transfused units (37 - 41). These figures underestimate the truth, as many errors may not have been detected yet. In addition, prospective studies have yielded a much higher figure and report that mistakes occur in 1:400-1,200 transfused units (42, 43). In one of these studies, a blood lock system was used to identify and prevent errors (43).

As regards the collection and labelling of the pre-transfusion blood samples, a large, multicentre (62 hospitals), international (10 countries) survey designed specifically to determine the rate occurrence of this type of error yielded a median hospital performance of 1:165 mislabelled tubes (95 % CI: 1.2 – 17:1,000) and of 1:2,000 cases of wrong blood in the tube (95 % CI: 0.3 – 0.9:1,000) (44).

Patients must be identified before collecting a pre-transfusion blood sample.

Whenever possible the patient should be positively identified. This means that the patient should be asked his date of birth, name and surname. If this is not possible, for example when the patient is unconscious, the data on the wristband should be used. Patient identification must either be present on the sample label, or – if the sample carries only a sample identifier – on the request form accompanying the sample provided this bears both patient identification and sample identifier; such form must accompany the sample in the transfusion laboratory throughout the analytical process.

The most frequent errors involve neonates. This can be accounted for in a number of ways: Nobody is born with a wristband, newborns do not enter the hospital via the admissions desk, many newborns are only given a first name hours or even days after being born, newborns are sometimes registered under their mother's maiden name for clinical purposes until they have been officially registered by a civil servant, and the baby's surname may change as a result of the father's delayed recognition of paternity. Twins and multiple births request special attention to the identification of each baby. In addition, transfusing a neonate is more complex and requires even more precautions than transfusing an adult because the child may still carry antibodies of maternal origin.

RECOMMENDATIONS

- Patients must be identified on the basis of two identifiers: the first being their name and surname, and the second being their date of birth or unique patient number.
- The correct procedure to minimise pre-analytical errors is to label blood sample tubes at the bedside of the patient only.
- Each hospital must design a specific procedure to identify newborns in relation to their mother, effective from the very moment of birth.

H. Some practical issues concerning pre-transfusion testing

Many mistakes are made in the collection and labelling of pre-transfusion blood samples. In order to avoid incompatible blood transfusions, the results of two patient (ABO/D) blood group determinations, carried out on two different sample collections, should be compared and found to be identical before a crossmatch compatible blood unit is released.

Besides the Rh D antigen, the Kell antigen is the most immunogenic antigen; therefore, Kell negative blood is advised for women of childbearing age. As more than 90 % of the donors are Kell negative and a large proportion of the donors has been typed for the Kell antigen by the blood services, this advice is not difficult to comply with.

With 25 % of irregular antibodies dropping below the detection level over time, these antibodies must be taken into account and respected when selecting a red cell unit for a patient (45). It follows that there should be a (electronic) pass or a nationwide system that allows easy access to established irregular antibodies.

Automation and computerisation of blood grouping, crossmatching and searching for irregular antibodies are superior to manual techniques. Key requirements of the system are sample barcode identification, electronic reading of test results, clear warning if the blood group was typed only once, blocking if the required second sample yields a discrepant result and the ruling out of mismatched ABO combinations. They also include the setting up of a serological compatibility test, including an antiglobulin test and a product selection that must take into account patient factors (presence of irregular antibodies and preferably also information about factors such as irradiation, transfusion reactions

and information on passively administered "anti-D" antibodies), identification of outdated samples for serological compatibility tests and validation of the system.

Pre-transfusion type and screen testing can replace serological compatibility testing. Samples, that are less than 72 hours old if the patient was pregnant or received blood components in the preceding three months, must be tested against a validated panel of red cells for irregular antibodies and a negative result must be obtained. The red cell units must be shown to be ABO-compatible with the patient's red cells by means of an immediate spin method or an electronic crossmatch (46). Crossmatching is still required for preterm newborns (with maternal serum) or if there are any irregular antibodies.

The transfusion of leukocyte-depleted blood components from cytomegalovirus seropositive donors reduces the risk to levels that are similar to those when components from seronegative donors are used (47). Both approaches yield very low incidences of CMV-transmission. There is no consensus on the omission of CMV donor screening in addition to leukocyte depletion for some patient groups. A practical approach is to combine the two methods for intra-uterine transfusions.

RECOMMENDATIONS

- Before releasing a compatible blood unit, the results of two patient (ABO/D) blood group determinations should be compared and found to be the same. These tests must be performed on samples from two separate collections.
- For women under the age of 45, it is advisable to use Kell negative and Rh compatible blood.
- Immune irregular antibodies, once detected, should always be taken into account when selecting a red cell unit.
- Automation and computerisation of pre-transfusion testing are superior to manual techniques.
- Pre-transfusion type and screen can replace compatibility testing with the exception of preterm newborns and patients who have or have had irregular antibodies.
- Leukocyte-depleted red cell concentrates are an acceptable alternative to red cell concentrates from CMV-seronegative donors in reducing the risk of CMV transmission. A combination of the two methods is currently advised for intra-uterine transfusions.

I. The quantities that need to be transfused

The aim is to transfuse the quantity that is required to alleviate the patient's symptoms. It is as undesirable to transfuse too much as it is to transfuse too little. Similarly, care should be taken to avoid any delays in carrying out the transfusion.

Once the decision has been made to perform a transfusion, the amount that will need to be transfused will depend on the clinical situation.

The acute loss of 40 % of the total blood volume is lethal. In acute haemorrhage, any delays in correcting intravascular blood volume may speed up the appearance of coagulopathy. Red cell transfusions should be based on an estimate of the amounts of blood lost and guided by regular measurements of the haemoglobin concentration. Acute losses of over one circulating volume usually require the replacement of platelets and coagulation factors (in the form of fresh frozen plasma), even if intraoperative autologous blood retrieval has been used to restore the red cell mass; a blood sample should be drawn in order to carry out a platelet count and coagulation tests before administering these products, so that the prescribed therapy could be adapted according to the results. During the initial phase of acute haemorrhage, extravascular fluid has no time to dilute circulating blood and the haematocrit may remain misleadingly normal. With red cells also playing a role in haemostasis, blood viscosity and functional capillary volume restitution, it is advisable to aim at haemoglobin concentrations above 80 grams per litre of blood and every effort must be made to avoid or to treat factors known to contribute to the development of a coagulopathy, like hypothermia, acidosis, hypotension, shock and hypocalcemia (48).

As regards chronic outpatients who require regular red cell transfusions, it may be reasonable to administer two units per session in order to avoid unnecessary travelling. In contrast, a single unit should be administered at a time for hospitalised patients. These patients should be reassessed before the next unit is administered, in order to avoid giving two units when one is enough. This simple habit can reduce the total amounts transfused in a department without affecting quality of care.

J. Who is allowed to carry out a transfusion?

Only a physician can take responsibility for a transfusion; he/she does so by writing a medical order in the

medical file of the patient; this order must include the reason for the transfusion. He/she is legally referred to as the 'transfusing physician' and has the right to delegate the execution of this medical act to nursing personnel.

K. Getting a transfusion started

Bedside errors in the identification of either the patient or the red cell unit constitute the most frequent cause of accident in transfusion therapy. Many such errors result in alloimmunisation and some generate acute or delayed haemolysis, which is sometimes accompanied by shock, disseminated intravascular coagulation and/or renal failure. The act of transfusion must be preceded by means of strict verification procedures as well as their written documentation.

Full verification includes checking and recording (1) the identity of the patient and (2) the identification code of the red cell unit, (3) the blood group (ABO and Rh) of the patient and (4) the blood group of the unit, (5) a written document delivered by the blood bank ascertaining the compatibility between the patient and the red cell unit, (6) the expiration date and integrity of the unit and (7) the date of transfusion, (8) the type and the quantity of the product to be transfused and (9) the medical order to transfuse, (10) the reason for transfusion, (11) additional requirements (e.g. irradiation) and (12) the identity of the person actually carrying out the transfusion. Incomplete checking may be avoided by following and filling in a standard written form. Nevertheless, the procedure remains complex, if anything because it involves eleven steps: as is the case for any other human action carried out under optimal circumstances, each of these steps is associated with a 1/1,000 probability of error (49). This in turn yields an unacceptably high combined risk (of about one percent) of transfusing a wrong unit to a given patient. If two individuals perform the verification procedure independently, the chances of both of them committing the same error drops to a more reasonable 1/10,000. Electronic procedures using barcode technology may increase transfusion safety even more, provided they are carried out directly at the bedside of the patient with a unique patient identifier that can neither be duplicated nor removed from the latter. Moreover, the patient identifier codes must be different from the patient medical file identifiers. As regards the red cell unit, the existence of a unique barcode identifier standardised at the European level provides the necessary security.

The computerised procedure should consist in interrogating in real time the blood bank or blood transfusion centre data bank to know whether the unit being checked has been delivered for the intended patient.

L. Monitoring the transfused patient

Qualified personnel must monitor the patient as soon as the transfusion is started. Rapid and adequate diagnostic and therapeutic reactions to any symptoms that occur during the early phase of a transfusion are essential for the patient's safety.

M. Transfusion rate

The chain of cold must be maintained until transfusion is initiated. Red cells should be cold and transfused slowly. If the patient has cold agglutinins or if the transfusion needs to be carried out quickly, they may also be warmed up by means of a certified device. In addition to hypothermia and hypervolemia, the rapid transfusion of erythrocytes may induce hyperkalemia, which may put the patient in immediate danger of cardiac arrest in diastole, especially children and patients with renal insufficiency.

N. Follow-up

Clinicians under whose responsibility transfusions are performed must ensure that a clinical and biological follow-up is carried out in order to determine whether any additional transfusions are needed, whether any transfusions have been ineffective and whether delayed haemolysis may occur. Accidents and incidents should be reported to the blood bank and should be investigated and reviewed by the Transfusion Committee. When appropriate, they should be reported in due time to the national haemovigilance system.

The patient's family doctor should be informed of any blood component transfusion that has taken place as well as of any incidents that might have followed it.

Patients with alloimmunisations should be given appropriate warning and should receive a blood group card that mentions the presence of irregular antibodies as well as their immunological profile. All the clinicians of the hospital should have access to the information on this card, which should be clear and understandable. Sharing this information with other blood transfusion centres and blood banks could result in a nation-wide improvement of transfusion safety.

O. Organisational approach

The preceding paragraphs have highlighted the fact that in the present state of affairs, the quality of red cell transfusions depends more on organisational issues than on the individual decisions and skills of clinicians and medical personnel. The law has placed the responsibility for optimising the quality of transfusions in the hands of the hospital transfusion committee. This committee includes all those involved in the transfusion chain: the blood transfusion centre, the blood bank, the pharmacist and the blood users (physicians and nursing personnel), who are under the responsibility of the hospital director. It should attempt to draw up local Continuous Quality Improvement schemes that include all aspects of transfusion: education, procedures, supply, quality and quantity of supplies, blood orders, sampling, testing, distribution, bedside checking, transfusion, patient surveillance and follow-up.

Hospitals may differ in the practical solutions chosen to reach optimal safety. The "organisational distance" between the patient in need of a transfusion and the place where the blood is stored plays a major role in transfusion safety. It refers to a combination of factors that not only include actual distance, means of communication and transportation, but also the early detection of allo-immunized patients, well-designed administrative procedures, and round-the clock availability of personnel with adequate qualifications at all levels.

The need for allogeneic transfusion can be reduced or delayed by preventing any bleeding, optimising the patient's red cell mass or carrying out autotransfusions. These measures cannot replace a well-organised transfusion system, but should be integrated in the general scheme instead.

P. The most frequent errors

In the literature on safety, 'errors' are best defined as actions that lead to unintended consequences (50).

The French national haemovigilance system, the British SHOT program, the French enquiry about anaesthesia-related mortality, published case reports, medico-legal procedures and the Belgian haemovigilance program have all contributed to identifying some frequent errors that need to be avoided. Many are organisational flaws that are inherent to the system and that have disastrous consequences as a result of human

error. It was deemed appropriate to mention them in these guidelines.

- Lack of understanding amongst those involved in the transfusion chain of the constraints imposed on everyone else working in this area. This is usually rooted in a lack of knowledge that can be attributed to insufficient teaching and/or training.
- Unsafe procedures used in the identification of blood samples, blood units at the bedside, or patients, especially newborns.
- Failure to keep the cold chain unbroken until the erythrocytes are transfused.
- Excessive importance given to haematocrit values or haemoglobin concentration when facing acute haemorrhage.
- Delayed reaction to slow but prolonged bleeding, especially after an orthopaedic procedure or in obstetrics. Other frequent causes of error are the fragmentation of the observation period by multiple medical and nursing shifts as well as the organisational delays in obtaining blood.
- Failure to realise that merely transfusing red cells to treat a massive haemorrhage may result in coagulopathy caused by an insufficient number of platelets and/or coagulation factors.
- Delayed recognition and response to an early transfusion reaction, in particular the failure to call upon an intensive care specialist and/or for a transfusion specialist.
- Overconfident or casual attitudes towards actual blood availability: 'in our hands these things never bleed'.
- Low level of awareness of allo-immunisation in patients at high-risk of being immunised.
- Transfusing autologous predeposited red cells or plasma 'because it is there', i.e. without biological or clinical evidence in support of carrying out a transfusion.

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RÉSUMÉ

Un groupe de travail du Conseil Supérieur de la Santé a établi des recommandations visant à standardiser et à rationaliser les indications cliniques pour les transfusions des globules rouges en Belgique. A cette fin le Conseil Supérieur de la Santé a organisé conjointement avec la Belgian Hematological Society une conférence d'experts intitulée "Guidelines for the transfusion of red cells". Les experts ont débattu des indications transfusionnelles pour les globules rouges, du concentré érythrocytaire idéal, des aspects pratiques de la transfusion de globules rouges et de la transfusion de globules rouges chez les patients en état critique. Les recommandations élaborées par les experts ont été validées par le groupe de travail dans le but d'harmoniser la pratique transfusionnelle dans les hôpitaux belges.

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