Blood substitution therapy – ethical and legal limits vs. medical risks and benefits

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Abstract: The patient refusing to receive blood or its derivates (due to religious reasons - Jehovah’s Witnesses, other reasons or simply for no reason) faces the physician with supplementary problems, especially in emergency situations. Independent from the religious issues, an opinion was formed in the medical community trying to minimize the blood and its derivates consumption due to transfusion risks, costs and limited availability. In this context, methods to substitute allogenic transfusions were developed, aiming to make the major surgical procedures available for the patients refusing transfusions, but also to reduce the transfusion needs for those patients accepting them. Although many of these methods have proven their efficiency, for some cases (acute or chronic) they might prove insufficient.

Key words: transfusion, blood substitution, bloodless surgery, erythropoietin, cell-saver, acute normovolaemic haemodilution

First attempts for transfusional therapy date back to the XVIIth century. Blood transfusion entered current medical practice during the First World War (1914-1918), the first blood bank being funded in London in 1921.[1]

Meanwhile, the development of major surgical procedures required a sustained transfusional therapy; heat and large vessels surgery, transplantation, oncologic surgery and arthroplasties became all possible.

Gradually, we noticed the development of the “bloodless surgery” concept. One of the reasons conducting to this idea was the need for those patients refusing allogenic transfusions to receive major surgical procedures. Another reason was the lack of donors and the impossibility to produce the majority of blood components in artificial environments.

The HIV/AIDS crisis in 1987 refocused the public attention on the infection risks related with blood transfusion, leading to the development of new protocols for donor selection and blood products testing. The transfusion risks and benefits were reassessed.[2]

New infectious agents are discovered every year. The more recent SARS (Severe Acute Respiratory Syndrome), West Nile virus and prions and the previous discovered HIV and B and C hepatitic viruses remind us the risks of infectious diseases transmission trough blood products.[3] Allogenic blood transfusion has been incriminated in multiple studies in
hospital stay length and costs increase by rising the postoperative infection risk, which is associated with transfusion immunosuppression.[4-8]

The “bloodless surgery” concept was developed to provide access for the patients refusing transfusions (because of religious reasons, other reasons or simply for no reason) to major surgical procedures classical known as “blood consuming”, like the large articulation replacement surgery (in orthopedics), cardiac and large vessels surgery, oncologic surgery. But this concept can also be extended in all patients, not only for those refusing transfusion.

This concept is based on a series of techniques; of those not all are widely available, requiring devices currently not found in all hospitals. Other techniques require just some “common sense” measures, that are simply forgotten or ignored in some hospitals (it’s easier to give some transfusion rather than perform a careful surgical haemostasis, for example). The purpose of this article is to list the most important of these techniques, discussing the risks and the benefits for them.

New studies appeared, sustaining the idea of bloodless major surgery. In 1994, the European Commission published the SANGUIS study group report (Safe and Good Use of Blood in Surgery), which was attempting to determine the transfusion pattern for 158 teams in European surgical centers between 1990 and 1991. On a series of 649 patients from 20 hospitals, having undergone a first elective total hip arthroplasty, the report highlighted a wide variation of the number of transfused patients with the hospital (between 44 and 100%), and a noticeable exposure of each transfused patient to more donors (a mean of 3 donors each). The predisposition of some surgical teams to transfuse more patients coupled with the inclination of those teams to transfuse each of them with more blood units. For the same surgical procedure, the report pointed a wide variation in blood and derivates use between the enlisted centers.[9]

The study published in 1999 by Hebert et al. regarding the transfusion needs highlighted that a restrictive transfusion strategy proved at least the same, even better than a classical blood administration strategy in critical ill patients. The authors compared 2 series of patients in critical state, one receiving red-cell transfusion for hemoglobin levels below 7 g/dL and having the serum hemoglobin kept in 7-9 g/dL interval, the other receiving transfusions for hemoglobin levels under 10 g/dL and having the concentration maintained between 10-12 g/dL. The patients in the restrictive transfused group were less ill or younger (under 55 years). The authors do not recommend the restrictive transfusion strategy for patients with cardiac dysfunctions.[10]

Once large patients groups refusing blood transfusion were available (mainly due to spreading of some religious concepts), the anemia risks became obvious in studies. In 2007, Hajjar et al. reviewed data from two previous studies. One study, on a group of 1958 Jehovah’s Witnesses, noted 1.3% mortality in patients with hemoglobin levels over 12 g/dL, and 33.3% for the patients with hemoglobin lower than 6 g/dL. The second study, on 2083 patients refusing transfusion for religious reasons, pointed that patients with postoperative hemoglobin levels under 8 g/dL have a 2.5 times higher chance of death for each gram decrease, after adjusting for age, cardiovascular disease and Acute Physiology and Chronic Health Evaluation II score.[2]

### Ethical and Legal Considerations

Although the legal, religious and ethical considerations are not the main goal of this printing, some aspects have to be outlined. The medical practice in Romania is governed by laws (Law 95/April 14th 2006 Regarding the Reform in the Health System, Law 272/June 21st 2004 Regarding the Protection and the Encouragement of the Children’s Rights), regulations (The Medical Deontological Code of the Romanian College of Physicians - 2008) and guidelines (provided by the Romanian College of Physicians and the National Health Department).

First of all is the patient’s right to decide, informed by his physician, the acceptance or refusal for all therapeutic procedures.

Art. 376. – (1) Excepting the cases of force majeure (act of God), emergency or when the patient or its legally or designated representatives are in impossibility of expressing their will or consent, the physician acts respecting the patient’s will and his right to refuse or stop a medical procedure.[11]
There are multiple reasons for a patient to refuse blood transfusion, some are religious, some not. It is known that Jehovah’s Witnesses patients, as a religious group, refuse allogenic blood transfusion, and also blood derivates and some/all of the reinfusion methods. Their spiritual guidance, The Watchtower Society, provide printed and multimedia materials encouraging the transfusion substitute methods.[12,13] They provide specific documentations for patients and for physicians and even some drugs and medical devices to help their members.

Although all the Witnesses refuse the allogenic blood and primary blood components transfusions (red blood cells, white blood cells, platelets, plasma), every member decides in a personal manner regarding the use of blood derivates (albumin, coagulation factors, hemoglobin-based solutions, immunoglobulins, interleukins, interferon, platelets-derived growth factors) and the use of medical procedures (autotransfusion, cardiac by-pass, hemodialysis and hemodilution, if pumps are loaded with non-sanguine fluid, organ transplantation). The physician should carefully question the patient before the treatment to determine what he/she finds acceptable and what he/she refuses.

A controversy persists on the condition of the adult patient in emergency situation, unable to express his transfusion refusal. The Jehovah’s Witnesses may carry a signed card or paper expressing their refusal to receive blood. Some Witnesses have signed a document entitling a specific person to take medical decisions instead of them. These kinds of papers have a doubtful value, due to their impossibility sometimes to provide pertinent information regarding the signing date or time period covered or if there were any witnesses when the paper was signed.

Going further, there is an obligation that consent (and refusal) should be informed. Or, according to the existing documentation, the Watchtower Society, the Jehovah’s Witnesses spiritual guide, informs its members on the risks of blood transfusions, ignoring its benefits. A multitude of therapeutic procedures to avoid transfusion are presented, making few or even no mentions of their drawbacks and risks.[12-15]

The Romanian law states:

Art. 651. - (2) When the legal representative or the closest relative cannot be reached, the physician ... can ask the supervisory agency for the medical procedure authorization, or they can act without the authorization in emergency situation, when the time passing to accordance will irreversibly put in danger the health and the life of the patient.[11]

Supplementary law clarification might be needed to protect the physician performing a procedure aimed to save the patient’s health/life in emergency, in case of civil/penal legal actions.

The physician has the obligation to completely inform the patient on the benefits and risks for the procedure that will be performed, the advantages and risk of blood products and the ways to avoid transfusion, using a language the patient can understand, as stated by the law (Art. 649.).[11] The Romanian College of Physicians recommends that, excepting the emergency situations, if the physician cannot provide the medical services, he can send the patient to another physician, providing him all the patient medical data needed.[16]

One of the legal problems is the child’s rights. The young incompetent child can benefit in countries as the UK, USA and Australia from blood transfusion when his life is in danger even against his parents refusal, when the doctor considers it’s needed.[17] The Romanian law does not directly specify the refusal eventuality, it only says:

Art. 43. – (5) In the exceptional situation in which the child’s life is in imminent danger or there is the risk of producing severe consequences regarding his health or integrity, the physician has the right to perform those strictly needed medical procedures to save the child’s life even without the child’s parents or legal representatives consent.[18]

But the Romanian law continues:

Art. 25. – (1) The child has the right for freedom of thinking, conscience and religion.

(2) The parents guide the child according to their own believes, in choosing a religion, according to the law, in correlation with the child’s opinion, age and maturity degree, without forcing him to join a specific religion or religious cult.
(3) The child’s religions aged 14 years and over cannot be changed without his consent; the child aged 16 years and over has the right to choose his own religion.[18]

In the same law cited above are specified the legal mechanisms for interventions against the parent, when he acts against the child’s right to be “raised in conditions allowing his physical development...”.[18]

Another legal controversy remains the situation of the adolescent, legally minor, but capable of discernment. Some countries and some US states are including the adolescent in the young child category, allowing the physician to perform transfusion in extreme emergency situations, while other countries/states are considering the adolescent will.[17]

The Romanian law specifies:

Art. 24. – (1) The discernment capable child has the right to freely express his opinion regarding any problem regarding him.
(2) In any judiciary or administrative procedure regarding him, the child has the right to be listened. It is mandatory the listening of the child aged 10 years or older. Even if the child is younger than 10 years, he can be listened if the competent authority decides that his listening is needed for the case solving.
(3) The right to be listened gives the child the possibility to ask and receive any pertinent information, to be consulted, to express his opinion and to be informed on any consequences his opinion might have, if followed, an on the consequences of any decision regarding him.[18]

Art 650. – The legal age for a patient to express his informed consent is 18 years. Minors can express their consent in the absence of their parents or their legal representatives in following case:
   a) emergency situations, when the parents or the legal representative cannot be reached, and the minor has the required discernment to understand his medical condition;
   b) medical situations related with the diagnostic and/or treatment of sexual and reproduction problems, at the precise demand of the minor aged 16 years or older.[11]

Transfusion Substitution Principles
Pre-operative

Facing a patient refusing allogenic blood transfusion, the physician must carefully asses the case, identifying its particularities. As shown above, some of the patients can accept some blood-derived products, as the others can totally refuse the blood reentrance in organism (for example an extracorporeal pump/shunt/circulation, cell-saver, and dialysis). Personal detailed history and coexisting comorbidities of the patient must be well known, in order to correctly evaluate the anemia tolerance and to predict the response to some therapeutic agents intended to be used (erythropoietin). Patients with cardiac dysfunctions were identified as being more anemia intolerant, [2,10] for those with severe sepsis there is the recommendation to correct anemia for hemoglobin levels under 7 g/dL. [19]

A carefully assessment of coagulation is recommended and any anomaly must be corrected before surgery (anticoagulant drugs or coagulation factors deficit).

The haemopoiesis improvement is an efficient method. Multiple protocols are available for the erythropoietin administration, varying with the type of surgical procedure aimed. In orthopedics, one of the existing products (EPREX® – Janssen-Cilag)[20] is injected in doses of 600 IU/kg weekly, with 3, 2 and respectively one week before the scheduled surgery, or 300 IU/kg daily for 10 days prior to operation (when a shortening of the pre-operative interval is needed). The administration must be stopped when reaching a hemoglobin level of 15 g/dL even if not all planned erythropoietin doses was given. Simultaneous use of intravenous iron products (as Venofer®)[21] is recommended, also folic acid and B12 vitamin; if possible, iron administration should precede the erythropoietin.

The recombined erythropoietin administration is indicated in adult patients enlisted for elective surgery having a mild anemia, on which a moderate blood loss is expected. The aim is to reduce the transfusion needs and facilitate the erythropoietic recovering. Another indication is in
patients in autotransfusion program, storing blood for their operation, to prevent the hemoglobin concentration decrease.[20]

The erythropoietin is contraindicated in patients with uncontrolled arterial hypertension, with coronary, peripheral, cerebral or carotid vascular disease or in patients with recent acute myocardial infarct or stroke. It is contraindicated in patients not participating in an autologous blood pre-deposit program and having cardiac dysfunction and also in patients who for any reason cannot receive antithrombotic prophylaxis.[20]

Price et al. (2005) presented a case of erythropoietin use in extreme conditions. A 62 year old female patient was surgically treated, the replacement of two heart valves being performed. Pre-operatory, a treatment with 24000 IU of erythropoietin 3 times per week was made and the hemoglobin level reached 14.6 g/dL. Postoperative, due to some complications, the hemoglobin level dropped to 4.2 g/dL associated with renal failure that necessitated dialysis. The erythropoietin treatment was restarted with the same doses, then with 38000 IU daily and the hemoglobin level reached to 10.1 g/dL. The patient suffered a fall which resulted in a hip haematoma that needed surgical evacuation and the hemoglobin level dropped again to 3.6 g/dL. The patient was treated again using large doses of erythropoietin. She left the hospital after 3 months in good condition.[22] In this case, higher erythropoietin doses were used than in other studies. These high doses, ignoring their costs and the global costs of other associated drugs and hospitalization, are presenting a higher risk for the patient, exposing him/her to severe complication as arterial and venous thromboses, seizures (3-7% of patients), medullar aplasia and others.[20]

The erythropoietin resistance was described for up to 10% of the patients with renal impairment. The main involved factors in developing the resistance are the iron deficit, infection and insufficient dialysis. Some anti-cytokines medications seem to improve the response to erythropoietin.[23]

In our practice, we used erythropoietin in two Jehovah’s Witnesses undergone major orthopedic surgery (total knee arthroplasty). Two weeks prior to surgery we administered erythropoietin 500 IU/kg, and 10 days before operation intravenous iron (Venofer®) 1f/day, also folic acid per os and B12 vitamin (1000 IU/day). The hematocrit increased with 30-35%, the hemoglobin levels reached over 14.5 g/dL. In these conditions, associated with a careful intra-operative haemostasis (with no major intra-operative bleeding), both the patients received only the reinfusion of the post-operative collected blood.

Autotransfusion (autologous blood transfusion) can be considered in patients refusing allogenic transfusion, but is generally rejected by Jehovah’s Witnesses. To prevent anemia, the blood harvesting can be coupled with recombined erythropoietin stimulations (in patients with mild anemia), with iron, folic acid and B12 vitamin supplements.[20] We are using this method for all suitable patients, reducing in this way the allogenic blood consumption.

A good teamwork between the surgeon and the anesthetist is important in order to evaluate and solve any problem that might occur during and after the operation. The surgical team must have all the available instruments and materials to face the eventuality of a massive bleeding: haemostatic agents, cell-saver and others.

**Intra-operative**

Acute normovolaemic haemodilution is a method accepted by some of these patients. It consists in removing a quantity of the circulating blood, which is replaced with cristaloid solutions. Intra-operative, a connection between the blood bag and the patient is maintained. It is considered that the blood lost intra-operative has not the original patient’s hematocrit, but a lower one. At the end of the operation, the previous removed blood is reinfused in the patient’s body, as needed. This method has relative contraindications in patients with severe anemia, cardiac ischemic disease or renal failure.

The positioning on the operating table is considered to be important by creating a lower venous pressure in the operated region of the body. It consists in a mild Trendelenburg position...
for the lower limb and a prone position without compressing the abdomen for the spine interventions.

The haemostatic band or the Tourniquet can be useful especially for the surgical interventions around the knee. It has the drawback of intra-operative “hiding” of the bleeding sources, thus interfering with the correct surgical hemostasis and the postoperative bleeding is often larger.

Arterial hypotension is indicated for reducing the bleeding, especially when the bleeding cannot be surgically controlled (bone bleeding). It can be achieved using systemic medication or regional anesthesia. If the hypotension is severe it might lead to renal, cerebral or cardiac failure. It also has the disadvantage of a larger postoperative bleeding, when the tension comes back to normal.

Haemostatic agents can be used systemic or local, in various forms (liquid, haemostatic powder, fibrin sponges, bone wax etc). They have limited efficiency, only for diffuse bleeding, not being able to stop the bleeding from large vessels.

Careful surgical haemostasis is extremely important. The use of electrocauthery for dissection and the ligation of larger vessels are recommended. Also, the harmonic scalpel is proving to be useful (where applicable).

Minimal invasive surgery can be considered, where available and applicable. Multiple stage interventions are another option, usually in bilateral disorders, choosing not to operate both lesions in the same intervention.

Reinfusing devices for the intra- and postoperative lost blood can be simple (they just filter the blood from the surgical wound) or with red blood cell “washing” (cell-saver type). Usually, a cell-saver device is used intra-operative and a simple filtering and reinfusion system (manual or automatic) is used postoperative. They are contraindicated in septic surgical interventions (revision of infected total hip or knee arthroplasty) and in neoplastic disorders.

We successfully used the cell-saver in multiple orthopedic surgical procedures (hip/knee replacement procedures), currently reinfusing 1-2 blood units. We used the post-operative reinfusion systems in patients with orthopedic interventions when the post-operative bleeding was expected to be high (non-cemented arthroplasties, prosthesis revision surgery), usually reinfusing 1 blood unit (recent systems allow up to 2 blood units reinfusion).

**Postoperative**

Fast detection and reintervention for postoperative bleedings can save important blood quantities. The patient must be carefully assessed during the first days following surgical interventions.

The stimulation of haematopoiesis can be restarted postoperative with iron products (intravenous administration being recommended), in association with folic acid and B₁₂ vitamin. Erythropoietin might be administered when needed.

We used with good results in moderate postoperative anemia intravenous iron-sucrose (Venofer®, Vifor AG), calculating the dose according to the intra-operative lost blood as recommended by the manufacturer (for each 400 ml unit blood lost – 200 mg Venofer), rarely needing erythropoietin stimulation. The anemia was corrected at discharge, approximately 14 days after surgery.[21]

Increase of oxygen delivery is achieved by having a good pulmonary assessment and quick intervening in case of respiratory problems. Oxygen supplementation and aggressive kinetotherapy of the thorax are recommended in some patients. Adequate infusion of colloid and crystalloid solutions is mandatory in assuring a normal circulating blood volume and tissue perfusion.

Oxygen consumption reduction is made by having an efficient analgesia and by preventing sepsis (the pain and sepsis are increasing the metabolism and the oxygen consumption).

Micro-sampling recipients for blood tests are important, especially in a polytraumatised patient in ICU, who needs repetitive assessment of blood parameters. Pediatric-size sample tubes
can be successfully used, as modern analyzing devices can perform tests with a limited quantity of serum.

Cryotherapy in some surgical procedure (like the total knee arthroplasty) is currently under evaluation, a recent meta-analysis showing small benefits in post-operative blood loss and no benefits after patient’s discharge.[24]

In a systematic review in 2006, assessing 668 world-wide studies performed between 1994 and 2004, Davies et al. concluded that the cell-saver systems can be a cost effective alternative to blood transfusion. The filtering-reinfusion systems and the acute normovolaemic haemodilution in orthopedic surgery seem to be more cost effective than the cell-saver devices, but in both cases the efficiency was compared with that of the cell-saver and not with the allogenic blood transfusion itself, further studies being needed to clarify these results.[25]

Conclusions

Allogenic blood transfusion refusal is still a problem for the physician, both in emergency and in elective procedures. No matter the patient’s reasons (religious or other or simply no reason) the physician must carefully and fully inform him using a language that he understands. A careful assessment of the current health status of the patient is important to prevent further problems. The patient has to be inquired regarding what he finds acceptable from the various blood transfusion replacement techniques (like cell-saver, extracorporeal circulation).

The increasing number of these patients and their health needs must lead to the developing of new medical and surgical techniques to replace transfusion. The demand on the market for blood saving devices and drugs determined more producers to provide then, which is expected to lead to a decrease in prices. The limited blood supply requires a reevaluation of blood use in current practice in all patients, not only in those refusing transfusions.

References
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