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REVIEW ARTICLE

# Perioperative strategies in patients who refuse blood product transfusion

**Authors' Contribution:**
**A**–Study Design
**B**–Data Collection
**C**–Statistical Analysis
**D**–Data Interpretation
**E**–Manuscript Preparation
**F**–Literature Search
**G**–Funds Collection

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Article history: Received: 13.03.2020 Accepted: 20.05.2020 Published: 21.05.2020

**ABSTRACT:** Treatment with blood and 'its substitutes is a common practice in surgical patients who bleed perioperatively; also, non-surgical patients with chronic disease receive blood/blood components. However, some patients refuse blood because of personal or religious beliefs, like in the case of Jehovah's Witnesses. Those patients may accept different artificial substitutes of blood components as well as some surgical techniques, that decrease the risk of bleeding or the volume of blood lost. It is extremely important to inform the patients about the risk of losing blood without its replacement and to get an informed consent, as well as to document which treatments and/or procedures the patient consents to and which they do not. Such patients must be correctly prepared for the operation with hematologic optimization. All drugs that influence hemostasis must be stopped preoperatively. There have been several interventions/methods of decreasing the need for transfusion developed. All surgeons and anesthesiologists must be familiar with indications and appropriate use of blood and blood components and their alternatives, but close liaison with hematology specialists and their local blood sciences laboratory is encouraged. Based on the latest guidelines, there are many options of preoperative preparations and treatment, very important for the surgical and anesthesiology team, described in the manuscript.

**KEYWORDS:** blood transfusion, Jehovah's Witnesses', perioperative care, refusal of blood transfusion

## ABBREVIATIONS

**aPCC** – activated PCC
**CRP** – C-reactive protein
**FDA** – Food and Drug Administration
**FEIBA** – Factor VIII Inhibitor Bypassing Activity
**PBM** – rules of conduct aimed at limiting the need for transfusion of blood and blood products
**PCC** – prothrombin complex concentrate
**PEEP** – Positive end-expiratory pressure
**POCT** – Point-of-care testing
**TACO** – transfusion-associated circulatory overload
**TRALI** – transfusion-related acute lung injury
**TSAT** – transferrin saturation ratio

## INTRODUCTION

Blood and blood products are an essential element of treatment in hospitalized patients, closely tied to the performance of surgical procedures. The demand for this life-giving medicine has existed for centuries, although in ancient times blood was a sacrificial element – it was drunk to heal, rejuvenate or secure victory, e.g. after drinking the enemy's blood. For ages there persisted the conviction conceived by Galen, that blood is formed in the liver from food previously digested in the stomach, followed by the formation of the lymph, which is absorbed in the intestine and reaches the liver through the portal vein, where it is transformed into blood, saturated with natural spirits [1, 2]. After improving knowledge of physiology, attempts were made to perform transfusions to patients, including with animal blood. The outturns varied and it was presumably the first time when a case of hemolytic transfusion reaction was documented. The discovery in 1901 of bloodgrouping by Karl Landsteiner signaled an era of improving the safety of blood treatment and became the nucleus of transfusiology. Forty years later, the rhesus factor was discovered, and subsequent years brought knowledge of antibodies: Kell, Diego, Lutheran, Duffy and Kidd [3]. Thanks to these findings, blood treatment became safer, although it is still not devoid of numerous threats – from weakly expressed complications in the form of merely rashes or fever, through infectious, to lethal consequences caused by severe hemolytic reaction. Poland currently has the Regulation of the Minister of Health of July 8, 2019 regarding blood treatment [4], and previously the 1997 Act on Public Blood Service [5]. Valuable in proper blood treatment are also the "Guidelines for the treatment of blood and its components and blood products in medicinal entities" [6] developed in 2014 by a team of experts. Unfortunately, we often don't succeed in avoiding the complications associated with blood treatment. Apart from those resulting from the administration of properly selected blood, there are also human errors [7, 8]. The most common, potentially fatal complications include: TRALI (transfusion related acute lung injury) and TACO (transfusion associated circulatory overload) [9–11]. Potential complications may be the reason why risk-aware patients refuse blood transfusions. Religious beliefs are another reason for the absence of consent, whereby the main group is made up of Jehovah's Witnesses.

Answering the question of the high risk of treating a patient who refuses a transfusion is difficult, and assuming that the vast majority of such patients are Jehovah's Witnesses, one can only approximate the scale of the problem. Information on the population of these believers are easily available and updated. In Poland in 2018 there were 116 299 followers registered, which with 38 433 558 citizens translates into an incidence of 1:330 people [12]. By comparison, in the UK, the chance of meeting a Jehovah's Witness is about 1: 440 [13, 14]. Such information, however, does not have a simple

transfer on the number of Jehovah's followers who are undergoing treatment and might in theory require a transfusion. It can be assumed that the overall scale of the problem is small, while in the case of a particular patient and refusal of transfusion in the event of a potential need, this issue assumes great relevance. It may prove difficult to manage such a patient in the case of the necessity for surgical treatment. Preoperative preparation should be started sufficiently in advance and belongs to the doctor who has contact with the patient at that time, i.e. to the surgeon or, if it is established by the surgeon, the GP. Nevertheless, a doctor who undertakes surgery on a patient who refuses transfusion must have expertise on relevant proceedings.

The aim of the paper is to show, based on the available literature and the current guidelines, the options and trends in conduct of doctors preparing for surgery on patients refusing a transfusion and managing them in the perioperative period.

## GENERAL CONSIDERATIONS

In literature we find the concept of Patient Blood Management (PBM), determining the rules of conduct to reduce the need for transfusions and blood products [15–17]. A large part of the PBM rules apply in the absence of consent to transfusion. There are various definitions of PBM elements – pillars. And so, according to Butcher et al. [18], the three main pillars of PBM in relation to patients undergoing elective surgery are the management of: (1) anemia, (2) perioperative bleeding, and (3) in postoperative anemia. Each of these three points is further divided into periods: pre-, intra- and postoperative.

In turn, based on the Western Australia Patient Blood Management Program, Leahy et al. [19] distinguish: pillar 1 – optimization of the red cell system; pillar 2 – minimizing bleeding and blood loss, pillar 3 – optimization of the physiological reserve for anemia. Here also, within each of these points, the procedure is described depending on the pre-, intra- and postoperative periods. The names of the pillars themselves show the lines of actions

Target-oriented management includes anemia management, bleeding prevention and transfusion restriction. The PBM principles apply to the entire patient population, without differentiating between those who consent to transfusion and those who object. It should also be borne in mind that the patient can change his mind at any time in the face of a threat to life and agree to transfusion [20]. The literature has long contained articles discussing the proceedings/suggestions for dealing with Jehovah's Witnesses in various fields of medicine, such as otolaryngology [21], hematology [22], obstetrics [23]. The general principles of PBM with regard to Jehovah's Witnesses are the same as in the rest of the population, except that higher emphasis is placed on: minimizing blood loss, using a cell-saver and adopting smaller values that constitute indications for transfusion. In 2016, the Royal College of Surgeons issued recommendations for patients refusing a transfusion [24]. The document contains general information intended to help operating doctors safely guide the patient through the perioperative period. In early 2019 there emerged amended British guidelines of the Association of Anaesthetists – "Anesthesia and peri-operative care for Jehovah's Witnesses and patients who refuse blood" [14], also confirmed by the Royal College of Surgeons. The primary component of therapy, apart from pharmacotherapy and surgical treatment, is taking into account: the patient's autonomy, his will and beliefs. The authors of the guidelines proceed on the basis that not every patient who refuses a transfusion is a Jehovah's Witness and not every Jehovah's Witness objects to a transfusion. Anyone who is at risk of bleeding must be informed of this and provided precise details on the consequences of not having a transfusion. It is the main task of the surgeon. If there are alternatives, they should be discussed. It is essential that the patient is allowed to discuss the problem with relatives, friends or members of a religious organization. It is immensely vital to document, clearly and unambiguously, the scope of the procedures that the patient agrees to and such to which he does not consent. A Jehovah's Witness closely following the teachings of the congregation will not accept blood or any blood product obtained from primary blood separation, i.e. a concentrate of red blood cells, plasma and platelets. However, he could agree to receive products from subsequent phases of blood preparation. Hence, experience shows that that many of them accept the supply of cryoprecipitate, fibrinogen concentrates, prothrombin complex concentrate, albumin; they also allow the use of fibrin glue or the so-called platelet gel. Jehovah's Witnesses accept the use of non-blood concentrates of recombinant coagulation factors, erythropoietin and iron. The supply of autologous blood obtained from previous donation of own blood is usually not acceptable. In turn, the method of acute normovolemic hemodilution, consisting of preoperative collection of a specific volume of patient's blood with its simultaneous supplementation with plasma substitutes, may be approved by some. Blood is taken into specially prepared containers which contain citrate and remains in a closed system with blood circulation. The use of a plasma replacement to supplement the volume of blood drawn from the patient leads to its dilution and, as a result, in the event of surgical bleeding, diluted blood is lost. On completing the procedure, the patient is given his own whole blood, received at the beginning of the procedure. Other blood circulation activities outside of the bloodstream that Jehovah's Witnesses may agree to include the use of a cell-saver during or after surgery, renal replacement therapy (hemodialysis or hemofiltration), extracorporeal circulation in cardiac surgery and extracorporeal oxygenation. In the case of the cell-saver some patients require that the system be a completely closed circuit.

## SUBSTANTIVE ISSUES

A major part of the guidelines is to discuss the immense importance of formal issues regarding consent to specific procedures and documenting this fact. The patient has the right to object to specific elements of treatment, such as blood transfusion, while agreeing to other medical procedures, such as surgery. The patient does not need to provide a reason for why he or she does not wish to continue with a certain procedure, but in the event of a potential risk of injury or death if the treatment is not followed, it must be clearly documented – both an informed refusal and the fact that the patient is aware of the potential consequences of such a decision. Doctors should always keep in mind that the patient may be influenced by other people, but at the same time they must not pressure him to change his mind. Under no circumstances should a conversation with a patient, operated on an elective basis, regarding consent to a transfusion be postponed to the operating theater.

## ACTIVITIES DEPENDING ON THE STAGE OF TREATMENT

### Preoperative conduct

The guidelines apply to people undergoing elective surgery; hence preparation of the patient should begin a few weeks before surgery. The recommendations involve cases where the predicted blood loss is over 500 ml, and to a large extent are elements contained in the PBM strategy.

#### *Type of operation and alternative procedure*

In patients requiring surgery and refusing transfusions, it should be determined whether there is another therapeutic alternative, e.g. instead of performing aortic aneurysm resection by laparotomy, it would be better to opt for percutaneous stent implantation; instead of classic transurethral resection of the prostate, we should consider transurethral laser therapy or abandon extracorporeal circulation for cardiac surgery without it. These alternative methods are associated with less blood loss, which is of the utmost importance in this case. If the clinic does not have the ability to perform the procedure in a less invasive way, the patient should be referred to the facility that has such treatment on offer.

#### *Preoperative consultations*

Surgery should be preceded by routine consultations with physicians experienced in the use of blood-saving techniques. The team should include hematologist, surgeon, anesthesiologist. They should also be available in emergency interventions. After qualifying the patient for surgery, there should be a discussion of the case in a team consisting of the above-mentioned specialists.

#### *Optimization of patient condition – the red cell system, the coagulation system*

The base for specific preoperative management is optimization of the red blood cell system, ensuring a pool of oxygen carriers, the loss of which in the event of bleeding or hemodilution caused by fluid therapy will not pose a risk. It is compulsory to postpone the scheduled surgery until this optimization is achieved. It is vital to evaluate the coagulation system to eliminate the risk of bleeding due to coagulopathy. A thorough interview about bleeding, ecchymosis or ecchymoses is mandatory. Information about the use of medications that affect hemostasis and planning strategies for their intake/withdrawal in the perioperative period are of primary importance. In the case of people who refuse transfusions, it is necessary to thoroughly examine whether they are taking dietary supplements, preparations that have not been ordered by the doctor, or even if they regularly use preparations containing ginseng or garlic. We know that many substances taken to support memory performance, cognition or as an element of so-called folk medicine, interfere with the coagulation system and patients can be, and generally are, entirely unaware of their adverse effects on the coagulation system [25]. Also, the doctor may not have such awareness, but while in most patients this problem is of minor importance and is likely to go unnoticed, in this group it may be the cause of major problems associated with bleeding in the perioperative period. In the immediate preoperative period, it is obligatory to obtain valid results in the coagulation system. Attention should be paid to avoiding unnecessary blood collection. We must check morphology, vitamin B12 and folic acid, iron economy (including transferrin saturation and serum ferritin) and coagulation along with fibrinogen. Hemoglobinopathy may be necessary in selected cases [26].

#### *Anemia correction – iron and erythropoietin supply*

At least 6 weeks before surgery for potential significant blood loss, hemoglobin levels should be checked and if they are less than 13 g dl-1 –optimization based on iron and/or erythropoietin should be considered. In the event of disturbances in iron management – absolute or functional iron deficiency, reduced iron stores or its sequestering, treatment with iron preparations must be initiated. In the case of supplementing deficiencies with oral preparations, it is necessary to verify the effectiveness after 4 weeks of treatment. When a period of 6 weeks is not attainable, surgery is not planned or the patient does not respond to enteral treatment and hemoglobin is still lower than 13 g dl-1, it is necessary to use parenteral form – more effective but also not devoid of risk. Intravenous iron administration should last 15–30 minutes and both during and 30 minutes after the infusion, basic vital functions should be monitored and secured with resuscitation equipment and an operating team. By way of illustration, in the UK, not every medical institution has conditions where it can be safely administered intravenously. Therefore, for example in Norfolk special mobile teams for intravenous iron administration have been established [27]. Iron supplementation can be combined with the supply of erythropoietin if the hemoglobin concentration is less than 13 g dl-1, and ferritin exceeds 100 µg l-1. The ranges of laboratory values of iron management exponents are established, which are necessary to take into account when planning optimization of the patient's condition before surgery. The normal condition is when the ferritin concentration is 100–300 µg l-1, TSAT, or transferrin saturation index – 20–50%, and CRP, or C-reactive protein is below 5 mg l-1.

Reduced iron stores are shown by ferritin levels below 100 µg l-1. Ferritin concentration less than 30 µg l-1 indicates absolute iron deficiency. Functional deficiency is observed in the case of ferritin concentration between 30 and 100 µg l-1, at TSAT less than 20% and/or CRP concentration greater than 5 mg l-1. Iron sequestration occurs when ferritin exceeds 100 µg l-1, at TSAT less than 20% and/or CRP concentration greater than 5 mg l-1 [28].

Preoperative preparation should be completed with the verification of a checklist containing points regarding the optimization of the patient's condition.

### Intraoperative conduct

Problems should be addressed in the team and during completion of the perioperative checklist. The authors of the guidelines suggest extending the checklist to include questions: "Is everyone aware of the answers given on the transfusion control card? Do they have knowledge of techniques for reducing blood loss that will be used in this case?" During the operation, it is appropriate to take measures to limit blood loss. Methods that spare whole blood loss include the previously discussed acute normovolemic hemodilution. It is advisable to use pediatric tubes during surgery; the use of closed systems allowing only the necessary volume of blood to be drawn from the vascular line. Devices that are part of a point-of-care-testing (POCT),

thromboelastogram or thromboelastometer should be available. Controlled hypotension may also apply. It is necessary to maintain normothermia. To minimize possible bleeding, tranexamic acid should be given. When there is a likelihood/risk that the anticipated blood loss may exceed 500 ml, consideration should be given to using a cell-saver from the beginning; in the case of oncological procedures – with a leukofilter. If significant bleeding occurs, it is advisable to use a thromboelastometer/thromboelastograph.

### *Transfusions of blood products and non-blood products*

Although transfusion of plasma or platelet concentrate is generally not accepted by Jehovah's Witnesses, they may, as previously mentioned, agree to administration of cryoprecipitate. Another option could be the use of prothrombin complex concentrates and fibrinogen concentrate. An increase in fibrinogen concentration by supplying its concentrate or cryoprecipitate may functionally compensate for platelet deficiency. Desmopressin at a dose of 0.3μg kg-1 improves the hemostatic effect by increasing large von Willebrand factor multimers, leading to increased procoagulant potential of platelets. An activated factor VII should be used as a last resort, as its use carries a very real risk of thrombotic episodes. Pulmonary ventilation during surgery should not be carried out with too high PEEP, which carries the risk of intensified bleeding due to increased venous stasis outside the chest. Reducing blood loss can be achieved by positioning the patient so that the bleeding site is as high as possible, however obtaining this position is not always possible and theoretically the risk of air embolism increases. It has been found that in some procedures, such as hip replacement, bleeding may be smaller when regional anesthesia is performed [26].

Of vital importance are surgical technique and highly accurate surgical hemostasis using hemostatic materials and tissue adhesives, using harmonic scalpels, diathermy, thermoablation techniques [24].

## Postoperative management

Surveillance and postoperative personnel must be aware of the patient's existing objections to the transfusion. It is also necessary to inform those involved about any complications/problems, if any such occurred during the procedure. Activities must be focused on: preventing bleeding, controlling and balancing hemostasis, optimizing oxygen delivery, and reducing the demand for it. It is advisable to use pediatric tubes, order selected blood tests for an individual patient, use POCT methods [14]. Where bleeding occurs after surgery with the use of the manchette, it is reasonable to use a cell saver. In the event of bleeding, 1 mg tranexamic acid should be administered. In patients with bleeding, drainage systems can be applied to allow simultaneous transfusion of lost blood [29].

### *General conduct in perioperative period*

Limiting the supply of allogenic blood by prior depositing of own blood is a long-standing method. However, these lines of action do not apply to this method. Some non-transfusion patients may agree to such conduct and subsequent blood transfusion if necessary. However, the mere question of donation of own blood is debatable: according to data from randomized trials, the number of patients receiving allogeneic blood and blood volume per patient is actually decreasing, but at the same time the risk of preoperative anemia increases, which paradoxically increases the number of intraoperative transfusions of auto- and allogenic blood, as well as costs. In the opinion of consultants and members of the American Society of Anesthesiologists, when own blood is preferred, the patient should be able to deposit it, but only if there is enough time left to normalize erythropoiesis [25].

### *Reversing the effects of drugs affecting hemostasis*

Pharmacological treatment to reduce blood loss, particularly applicable in, but not only, patients who refuse blood transfusions, includes: timely discontinuation of drugs that interfere with hemostasis, in urgent cases – the use of drugs that reverse anticoagulants, if such exist.

Currently, in the event of the need to immediately reverse the action of the so-called new anticoagulants, idarucizumab are available (Praxbind) for dabigatran (Pradaxa) and adnexanet alfa (Ondexxya) for apixaban (Eliquis) and rivaroxaban (Xarelto). Their function is to bind the anticoagulant, which leads to a reversal of its action within minutes. Idarucizumab is administered at a dose of 5 g (2 x 2.5 g). In the case of Ondexxya, dosage is more difficult and depends on the dose of the anticoagulant taken by the patient at the time of reversal of the anticoagulant effect, and on the time that has passed since taking the given anticoagulant. The total dose consists of bolus and infusion. The so-called low dose of adnexanet is 400 mg, while a high dose – 800 mg. Both are initially administered as a bolus at the target speed 30 mg min-1, followed by a two-hour infusion of 480 mg as an infusion of 4 mg min-1 for 120 minutes at low dose and 960 mg as an infusion 8 mg min-1 for 120 min in the case of high dose. And so, for apixaban, if the patient has taken it in an amount of ≤ 5 mg, regardless of the elapsed time, a low dose of adnexanet should be used, and if they have taken ≥ 5 mg or the dose is unknown, there are two options: if ≥ 8 hours have passed, a low dose should be given; if < 8 hours have elapsed or the time is unknown, a high dose should be used. In the case of rivaroxaban, the procedure is analogous to the fact that the initial dose of anticoagulant is 10 mg [30].

To reverse the effect of oral anticoagulants, a prothrombin complex concentrate, or PCC; at a dose of 10–15 U kg-1 can be used and – if necessary – again after 1-2 hours. Another alternative (also off-label) for direct antiXa inhibitors is activated PCC – aPCC (FEIBA; factor eight inhibitor bypassing agent) given in a dose 10–15 U kg-1 and – if needed – repeated after 1–2 hours or given immediately at 50 U kg-1 (maximal 100 U kg-1). In the case of vitamin K inhibitors, the treatment is based on the supplementation of missing coagulation factors by using PCC at a dose of 20–50 U kg–1 and vitamin K in the dose 5–10 mg intravenously as an additive to PCC. The effect of vitamin K requires several hours; PCC works immediately.

Fresh frozen plasma (10–15 ml kg-1), although impractical in the case of the need for an immediate effect, but having the potential to reverse the action of antivitamin K, is obviously impossible to apply in the discussed group of patients.

Furthermore, tranexamic acid is recommended regardless of the cause of the coagulopathy. The dose for bleeding in traumas, according to the recommendations from the CRASH-2 study [31], is 1 g administered for 10 minutes followed by another 1 g as an infusion lasting 8 hours.

Another dosage regimen, depending on the patient's clinical condition, is 1 g as a bolus, followed by 1 g every 6–8 hours [32]. Still other dosing schedules are available [33].

Reversal of the effect of heparin is obtained using protamine sulfate at a dose of 1 mg per 100 U of unfractionated heparin. For dalteparin, 1 mg of protamine per 100 U of anti-Xa should be administered, for enoxaparin – 1 mg of protamine per 1 mg of enoxaparin given in the last 8 hours, and if more than 8 hours have passed, a second dose of 0.5 may be given mg protamine per 1 mg enoxaparin.

As for patients taking antiplatelet medications, an improvement in platelet function can be obtained by using a 30-minute infusion of desmopressin at a dose of 0.3 μg kg–1. Increasing fibrinogen concentration by supplying fibrinogen concentrate (2 g) or cryoprecipitate may partially compensate for the effect of reduced platelet counts on coagulation – the clot structure improves and thereby strengthens. In the case of a Jehovah's Witness, such behavior depends on the individual decision of the patient. Transfusion of platelet concentrate is unacceptable in this group.

In selected cases of coagulation disorders, supplementation with factor VIII and IX, the supply of recombinant factor VIIa at a dose of 40–65 μg kg–1 may be considered. In view of the fact that mainly hematologists have experience in using these coagulation factors, it is recommended to consult the therapeutic decision with a doctor of this specialty [26, 34–36].

## OPTIMIZATION OF OXYGEN DEMAND

In order to improve oxygen supply to tissues in a situation of reduced amount of this gas carrier, the optimization of oxygen metabolism is a vital element in the perioperative period. It involves earlier treatment of any lung disease, depending on the patient's condition. However, in the perioperative period: passive oxygen therapy, prolonged respiratory therapy, sedation, striated muscle relaxation, hypothermia, treatment of possible shock and optimization of cardiac output, extracorporeal circulation, extracorporeal membrane oxygenation, treatment with hyperbaric oxygen [37].

## HEMOGLOBIN AS AN OXYGEN CARRIER

Awareness that hemoglobin is now much lower, representing the lower acceptable limit of refusal from transfusions in patients accepting transfusion of red blood cell concentrate, is important in the context of treating a patient opposed to transfusion. There are both Polish recommendations [6], according to which the absolute indication for transfusion of red blood cell concentrate is hemoglobin concentration less than or equal to 6 g dl-1, while the question of transfusion for hemoglobin levels between 6 and 10 gdl-1 depends on the body's compensatory possibilities and additional risk factors for complications due to anemia, as well as European guidelines [38], setting the target hemoglobin concentration during hemorrhage between 7 and 9 g dl-1 or an analysis of the Cochrane Database [39], showing that in most patients with a hemoglobin concentration between 7 and 8 g dl-1 transfusions can be avoided.

## ALTERNATIVES TO HEMOGLOBIN AS AN OXYGEN CARRIER

There are two types of artificial oxygen carriers: (1) using hemoglobin as carrier and (2) perfluorocarbons. The first transfer oxygen by way of diffusion is facilitated by the use of human or bovine hemoglobin; they are potentially acceptable to Jehovah's Witnesses. Unfortunately, their use is limited by serious adverse effects in the form of vasospasm (scavengers of nitric oxides) and the association found in clinical studies with myocardial infarction and death – many preparations did not meet safety requirements [40, 41]. A more recent direction of research concerns the effectiveness of hemoglobin obtained from stem cells [42]. Studies on various artificial oxygen-carrying substitutes have been conducted for years and have not yet been introduced into widespread use [43]. It is possible to administer SANGUINATE, Prolong Pharmaceuticals, South Plainfield, New Jersey, USA, after FDA approval, to a specific patient [44].

Perfluorocarbons are liquid solutions in which oxygen dissolves. This effect depends on the partial pressure of oxygen, so for maximum effect it is necessary to use oxygen at a higher pressure. For the first generation, its efficiency has not been proven. In the second case, clinical trials were suspended due to the difficulty in determining the correct dose and the risk of stroke [45, 46]. However, in Russia Perftoran (The Scientific-Productive Company "Perftoran", Pushchino, Russia) was produced from 1996 to 2011, and continues to be registered there. In Mexico, it was used under the name Perftec (KEM Laboratory, Tijuana, Mexico) and was given to over 30,000 patients. Work is in progress to place it on the market in the United States, Latin America and, again, Mexico under the name Vidaphor (Fluor$O_2$ Therapeutics, Inc., Wake Forest, NC) [47].

These data support the conclusion that it is not easy to create an ideal blood substitute, so the basis for safe patient conduct during the perioperative period remains proper preparation of the individual, followed by taking care of limiting blood loss. It is necessary for the doctor to be aware that blood transfusions can be avoided even in extensive procedures. It is a well-known fact that extensive preparation without blood transfusions is possible in prepared patients [48–50].

Treatment of a person who refuses blood transfusions and blood products is difficult, especially when bleeding occurs or is at risk. In order to present the problem with more detail and simplify the process, Jehovah's Witnesses formed a global network to address hospital treatment bypassing transfusions called the Jehovah's Witness Hospital Liaison Community which publishes materials available in every language to help doctors and institutions [12]. It is worth noting that – as stressed by the authors of these guidelines – there are dynamically functioning centers of Jehovah's followers in almost every country that can be contacted around the clock by phone.

Adherence to proper preoperative preparation, a rigorous approach to surgical techniques, smooth conduct of the procedure with care for preservation of hemostasis and homeostasis, followed by meticulous observation and treatment of bleeding in the postoperative period, blood recovery and, in selected cases, reduction of oxygen demand, allow for surgery without blood transfusion. The discussed treatments described in the cited literature should permit performance of safe procedures associated with the risk of blood loss.

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Liczba słów: 6200 Liczba stron: 7 Tabele: – Ryciny: – Piśmiennictwo: 50

DOI: 10.5604/01.3001.0014.1508 Table of content: https://ppch.pl/issue/13341



Competing interests: The authors declare that they have no competing interests.



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Cite this article as: Wujtewicz M.: Perioperative strategies in patients who refuse blood product transfusion; Pol Przegl Chir 2020: 92 (5): 43-49