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Autologous transfusions for elective surgery – from existing approaches to upcoming challenges

Autologne transfuzije za elektivnu hirurgiju – od postojećih pristupa do predstojećih izazova

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Introduction

A well-balanced and rationalized decision making in regard to the implementation and/or accomplishment of haemotherapy or blood component therapy (BCT) is typically based on the individual consideration of responsible medical practitioner, her/his experience with the policy or guidelines of BCT, and the critical values of crucial clinical and laboratory parameters – first of all, the hemoglobin (Hb) concentration. However, when it comes to BCT, there are still sizeable differences in the strategies and approaches in practice. Namely, the same or similar pathological conditions/disorders and specific surgical requirements/requests have not been yet standardized. In addition, recommendations and principles of BCT are not always respected and applied necessarily by all therapists [1–3]. The final and correct decision regarding the realization of BCT, the type and quantity of required blood product should be in compliance with the general clinical condition, estimated and predicted blood (component) loss, as well as with the capacity of compensatory mechanisms of the patient [3–7]. Typically, BCT for surgical procedures involves red blood cell (RBC) transfusions, wherein one should consider minimum hematocrit (Hct) and Hb values required to provide sufficient or high-quality oxygen transporting capacity (blood oxiform function). Transfusion supported by platelets, plasma, cryoprecipitate, and other blood products is justified under conditions accompanied just with isolated blood constituent deficiencies and following extensive blood loss, preceded by massive RBC transfusions [1, 8–10].

Considering the Hb levels, when assessing indications for RBC support ("transfusion trigger" or "threshold"), a revised recommendation aroused as a consensus at Conference of the National Institutes of Health of the USA that patients having Htc ≥ 0.21 and Hb ≥ 70.0 g/L should not be treated by RBCs [5–7]. For an optimized decision of the BCT – especially for allogeneic RBC transfusions – the most important parameters are the ones that inform on blood oxiform function. Therefore, in order to determine an authentic and valid "transfusion trigger" for RBC usage it is thought that additional parameters, such as cardiac minute volume, oxygen blood saturation and its consumption in tissues, patient's age etc, should be applied. It is clear that amongst patients – potential candidates for surgical procedures – there are those requiring higher Hct/Hb levels. Namely, for a sizeable number of patients the most appropriate Htc would be ≥ 0.24 and Hb ≥ 80.0 g/L. Regarding elderly patients, those values should be even higher, Htc ≥ 0.30 and Hb ≥ 100.0 g/L [3, 7].

Regardless of the implementation of different effective preventive approaches and procedures [donor selection, blood

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screening procedures, white blood cell (WBC) and virus inactivation technology, the use of revised or reduced "transfusion thresholds"] – the use of allogeneic BCT in a sizeable number of patients is associated with a potential risk of post-transfusion morbidity, and sometimes even mortality – which justified the search for new solutions. That is why autologous transfusion (AT) of blood or blood products, as well as the application of other medical options – the use of blood substitutes, hematopoietic growth factors (HGF), antifibrinolytics and other pharmacological agents – are of particular significance as an alternative to allogeneic BCT [1, 11–13].

In a few words, AT consists of the collection of patient's own blood and reinfusion of autologous blood or its components to the same patient during or immediately after the surgical procedure. The goal is to satisfy the patient's need for blood products, but without the use of allogeneic transfusion. With the use of AT, the patient helps himself and contributes to acquiring higher safety of overall BCT. Namely, application of AT eliminates the risk of alloimmunization to RBC, WBC, platelet or plasma protein antigens, reduces of immunosuppression, and eradicates the risk of transmission of viruses or other infectious agents. Besides, certain AT procedures stimulate autologous donor's hematopoietic system needed for endogenous erythrocytopoiesis and in doing so they support and justify the safety of this type of transfusion. Considering that, and unfavorable effects of allogeneic transfusion, AT is the "safest manner" of BCT [1, 11–13].

Concerning AT, patient's blood can be collected using different strategies among which the most frequently applied are the following ones: 1) preoperative autologous collection/donation (PAD); 2) acute normovolemic hemodilution (ANH); and 3) perioperative blood recovery/salvage (PBR). In addition, the scheme of PBR includes: a) intraoperative blood collection/salvage (IBC) from the surgical field, and b) postoperative blood collection/drainage (PBC) by aspiration [1, 14–22]. Independently or combined, these AT-strategies proved to reduce the needs for allogeneic blood in elective surgery. Application of blood substitutes, hematopoietic growth factors and pharmacological agents (for the prevention/treatment of hemostasis disorders) can further reduce those requirements [1–3].

Finally, the examination of potential transfusion side effects and events should be the same or similar for autologous and allogeneic transfusions [5–7, 22–24]. Namely, autologous transfusions have no risk of infectious (virus) and immune-mediated complications (reduced "biohazard"), but carry a similar risk of bacterial contamination following storage (PAD), circulation volume overload, and misadministration compared with normal allogeneic units. For these reasons, autologous blood should not be transfused without a clear indication for BCT [1, 5–7].

Preoperative blood collection/donation

Briefly, candidates for PAD are stable patients with adequate general condition planned for surgical procedures in which transfusion is expected. PAD is the most frequently used AT technique intended for the elective surgery. It is simple to use, and applicable to the majority of patients undergoing the elective surgical procedure. If a patient is in good general condition – having Hb ≥ 110 g/L, Hct ≥ 0.34 and without inflammation symptoms and signs and if surgery can be performed within 2 to 5 weeks, it is recommended to make a PAD for AT blood. Patients who will probably not be needing blood transfusion support are not to be included in this category of AT program [5–7].

The use of PAD in elective surgery increased in the past few years. Considering that autologous donors are not voluntary blood donors, selection to incorporate patients into AT program is not based on the criteria for selection of normal blood donors. According to the requirements, the patient can donate up to 450 mL of autologous blood every fourth day, although weekly donations are most common. Thus, PAD can be performed in 7 days intervals in adults (exfused blood volume = 10–12% of the total circulating volume) – stipulated that Hb content prior to each donation should not be below [4, 6]. Duration of autologous donations in weekly intervals can last (according to the blood requirements) as long as the patient does not develop anemia symptoms and has Htc ≥ 0.30. It should be stated that the practice throughout the world is based on the "leapfrog" principle which allows obtaining five blood units within 29 days [1–3, 6].

It is recommended that the last autologous collection should take place at least 72 hours before the surgical procedure. Children older than 12 can also be included in the AT program, with the previously obtained parents' approval. Smaller quantities of blood are collected from children, in accordance with their body mass. Finally, persons ≥ 65 years are also candidates for PAD, in case they meet previously stated criteria referring to autologous blood donors [4–6]. The quantity of collected autologous blood depends on the expected blood requirements, although it can be limited by the available time interval preceding the surgical intervention and the patient's initial Hb level and his/her ability to maintain adequate (≥ 110 g/L) Hb concentration. Autologous blood units can be processed into components if it is foreseen that those components will be used intraoperatively. However, considering protection of other patients' health, autologous blood might carry certain risks and therefore, it should not be ever used for allogeneic transfusion [1, 6].

Generally, for the majority of patients PAD is safe and it always will be if criteria required for autologous donors are respected. When performing PAD, precaution should be taken regarding hypertension, hypotension, in elderly persons, in children and pregnant. Namely, pregnancy is not a contraindication for AT in a case of planned caesarean section. In essence, just severe aortic stenosis and coronary diseases are medical conditions considered as contraindications for PAD. In those patients, additional circulating volume and Hb decrease could have unfavorable/unexpected consequences. However, there are data reporting safe PAD in patients with certain cardiac diseases, even in those prior to cardiopulmonary transplantation [3, 25–28].

In summary, PAD is a safe and helpful BCT manner that, commonly, prevents patients' exposure to the applicati-

on of allogeneic blood products, supported by an ever increasing number of reports. In order to achieve higher efficiency of the PAD program, additional research in the following areas are required: 1) determination of the optimal autologous blood quantity for specific surgical procedures (in order to reduce/eliminate the use of allogeneic blood) and to have minimum disposal of collected blood units; 2) investigation of the safety and potential risks of PAD (supported by the follow-up of a corresponding control groups); 3) evaluation the role of erythropoietin (EPO) and iron support to improve the PAD-effectiveness; and 4) improvement of the methods for autologous blood collection and storage.

Acute normovolemic hemodilution

Acute normovolemic hemodilution (ANH) is performed immediately before or after the introduction of anesthesia by exfusion of autologous blood, associated with the immediate and necessary replacement of circulating volume by the infusion of adequate fluid(s) – crystalloids, rarely colloids or both [1, 6]. All vital functions, arterial blood pressure, Hb and Hct value in patients' blood must be maintained within carefully determined ranges. The total volume of infused replacement fluid depends on its type and composition, stipulated that normovolemic dilution must be maintained during the whole surgical intervention [3–5]. If blood replacement is obtained by crystalloids, the ratio between the volumes of exfused *vs* infused volume should be 1: 3 (because crystalloids rapidly leave from intra- to extra-vascular space). When colloids are used for replacement (most frequently synthetic solutions such us dextrin or gelatin), the withdrawn *vs* infused volume ratio is equal, that is 1: 1. The combination of crystalloids and colloids can be also used to replace the exfused autologous blood [1].

The collected autologous blood (usually one to two units) is kept in a surgical room in the course of intervention at $20 \pm 2^{\circ}$C. Reinfusion of collected blood is performed once surgical (vascular) hemostasis is achieved, usually at the end of the surgical procedure. Blood can also be transfused during the surgery process, depending on the patient's condition [1–5].

The objective of ANH is to achieve temporary reduction of all of the patient's blood constituents (blood cells and plasma). Precisely, the moderate and monitored anemia associated with normal intravenous volume, induced in that manner, shows the following favorable effects: 1) reduction of the blood viscosity and of the total peripheral resistance in patient's circulation; 2) increased cardiac output; 3) reduced formation of cell aggregates; and 4) reduced quantity of RBCs in the same volume of lost blood. Precisely, a patient having Htc = 0.45 and a loss of one liter of whole blood loses 450 mL of RBCs; however, if his Htc = 0.25, only 250 mL of RBCs are contained in lost whole blood. As a result – thanks to the hemodiluted reduction of Hct from 0.45 to 0.25 and – 200 mL of RBCs are preserved or "saved". However, the lowest and for patients the safest Hct value in AHN is yet to be exactly determined [1, 5–7].

ANH can be of particular significance in patients suitable for PAD, not having the time needed to collect required autologous blood units. However, this AT-strategy should not be used in all patients. It is indicated in patients expected to have intraoperative blood loss of 1,000–2,000 mL, and with a value of Hb ≥ 120 g/L. Severe coronary disease, respiratory or renal insufficiency or coagulation factors deficiency are contraindications for performing ANH [4–6].

Perioperative blood recovery/salvage

Generally, the system of PBR implies a collection of patient's blood from the surgical field using cell-savers (followed by *ex vivo* blood processing) and postoperative aspiration of blood from drains (with its subsequent reinfusion). Consequently, that is an AT-strategy that implies salvage of autologous blood, that patient had lost during IBC or immediately upon PBC surgical procedure. The routine of PBR provides a surgical and reanimation team with considerable quantities of blood or RBCs needed for urgent BCT of patients. Previously used very seldom, almost exclusively in cardiothoracic surgery, PBR has nowadays become a standard procedure in other surgeries, as well. In addition, it is used for life saving of the wounded in war conflicts [1, 19–22]. Finally, a number of practitioners believe that preoperative donation or intraoperative collection of plasma and/or platelets in cardiopulmonary bypass surgery may significantly improve hemostasis [6].

As mentioned, the name IBC or autologous blood recovery describes the technique of collecting and reinfusing blood lost by a patient during surgery. The "saved" blood is a source of RBCs having the adequate quality required for transfusion support that is for the performance of the surgical procedure. Namely, the oxygen-transport properties of recovered cells are equivalent to (or comparable with) stored allogeneic RBCs. PBC denotes the recovery of blood from surgical drains followed by reinfusion, typically without processing. This blood-salvage procedure can be initiated immediately after the surgical intervention and it is usually performed within the first 4–12 hours following the surgery. It has been demonstrated that survival of perioperatively collected and reinfused RBCs is compatible with the survival of transfused allogeneic RBCs [1, 6].

However, the use of AT is not a "nonhazardous" BCT approach. Artificially induced anemia is the most common unfavorable effect of ANH, while bacterial contamination is a potential, although very rarely, the risk of PBR. Besides, PBR procedures can sometimes be associated with air embolism and/or hemostasis malfunction. Namely, the salvaged blood has decreased coagulation factors, increased contents of the fibrinogen/fibrin degradation products and a considerable quantity of anticoagulants. These hemostatic defects are primarily manifested as bleeding moistening of the surgical field or bleeding along the surgical sutures due to the removal of platelets and plasma constituents during the *ex vivo* processing of "saved" whole blood. Seldom, due to platelet and WBC activation (in the course blood processing), transfusion-related acute lung injury (TRALI) can occur – termed also as the "syndrome of salvaged blood". Finally, infection

and malignancy in the surgical field are contraindications for performing of the PBR manner [1, 3–6, 22–24].

Efficient IBC is enabled by the use of specific devices (cell-savers) for rapid processing of whole blood collected from the surgical field. Although there are reports on specific aspects of the clinical use of this type of AT-strategy, certain aspects require additional research including the following: 1) investigation of the risks of IBC when there is a probability that blood contains malignant cells or is contaminated with bacteria; 2) conducting controlled prospective studies on benefits and risks of the use of autologous plasma and platelets (or platelet rich plasma) in cardiac surgery [6, 26].

Efficacy and safety of PBC in cardio-surgery has been demonstrated indisputably [7, 26]. Opinions regarding efficiency of PBC in orthopedic surgery are not unanimous and the following should be taken into consideration: 1) prospect studies to illustrate the benefits of transfusion of "saved" blood; b) make analyses of risks of transfusion of unprocessed blood, taking into special consideration possible contamination of blood with bacteria or chemical agents (e.g. metylmetakrylat) and 3) analysis of cost *vs* benefit aspects [6, 14–22].

In summary, not all AT-strategies are applicable or necessary for all patients. The choice should be reasonably complied with the expected BCT-needs, based on patient's general condition, a surgical procedure to be performed and available preoperative time interval. In order to make the right and correct use of AT, it should be considered not only by treating physicians, but also by patients, and it should be done before a decision is made regarding surgical procedure. Program of AT procedures shall be more functional if considered on the integration of all strategies needed for its realization and if continuous cooperation with transfusion and therapeutic establishments is ensured.

Cytokine/HGF stimulated erythrocytopoiesis

According to its chemical structure, erythropoietin (EPO) belongs to glycoproteins, a group of hematopoietic cytokines. It is the main regulator of erythrocytopoiesis – which practically expresses its stimulating effects starting from the population "oligopotent" stem cell stage all the way to the mature cell formation. The largest portion of EPO is produced in kidneys and a smaller portion in the liver. Hypoxia being a stimulator and the increase of Hb blood level is acting as an inhibitor of EPO synthesis by "negative feedback". In a simplified manner, EPO is initially bound to its receptor, followed by internalization of EPO complex and that receptor, then by signal transduction from the membrane to the core and finally by the expression of the erythrocytopoiesis regulatory gene [3]. Although RBC support for kidney patients (with endogenous EPO deficiency) is still in use, these transfusions should be completely replaced with the application of recombinant EPO (rHuEPO) [25]. Clinical use of rHuEPO is indicated for some other conditions associated anemia (with no deficiency of endogenous EPO) – e.g. for pretreatment of patients in which PAD for elective surgery planned [12, 13, 29–32].

Within the PAD policy (according to the American Association of Blood Banks – AABB standards), a collection of 450 mL of autologous blood is recommended on the third, and if it is necessary at the 10th and the 17th days before elective surgery. However, if the patient's Hb ≤ 110 g/L or if the blood requirements are elevated – a short term erythrocytopoiesis stimulation by high-dose rHuEPO pretreatment (300–800 IJ/kg, three times weekly) along with the iron therapy are indicated (initiated two weeks proceeding the first blood collection) [6, 29–32].

It has been shown that in patients included in the PAD program with the use of rHuEPO, it is possible to achieve a significant reduction of the need for the perioperative allogeneic transfusion. In one such comparative study [32] comparison was made between autologous donors treated and untreated with rHuEPO. Namely, subjects of the first (investigated) group were pretreated with rHuEPO (500 IU/kgbm applied twice weekly, during three weeks). Blood was collected after the first week of rHuEPO administration. Autologous blood was also collected from the subjects of the control group (they were not treated by rHuEPO). Iron therapy was administered to all patients, starting one week before the first blood collection. In the group of investigated subjects, Hb values remained equal to the initial values (recorded before the first blood collection). Contrary to that, considerable decrease and slow Hb normalization were noted upon PAD in control group. Likewise, only 10% of the investigated subjects (treated by rHuEPO) were transfused with allogeneic RBCs. In contrast, 40% of the control group subjects were treated with allogeneic transfusion. This study shows that the use of rHuEPO is especially beneficial in patients having a total circulating volume of about 4,000 mL, with the collection of around 2,000 mL of autologous blood [32].

Finally, even with the use of high doses of rHuEPO, side effects of this therapy are relatively rare [6, 12, 13]. Commonly, application of rHuEPO can be associated with the occurrence of side effects – the most frequent ones being an increase of the blood pressure (despite the use of antihypertensive medication), muscle cramps, "flu-like syndrome", bleeding or thrombosis. In some patients thrombocytosis can develop after several weeks of the use of rHuEPO or biochemical changes may occur (e.g. increase of potassium concentration). The rate of side effects rarely exceeds 5–l0%. Thus, patients usually tolerate well the rHuEPO pretreatment, used either intravenously or subcutaneously [6, 30].

Conclusion

Literature data describe general concepts and specific AT protocols; however, there are just seldom clinical investigations related to the most effective AT-strategy for all patients/situations. In future, relevant guidelines are needed with additional investigations in this area, including the following tasks: a) to define benefits and risks of AT-treatments and b) determination of criteria for selection of patients and optimal surveillance methods to perform the most satisfactory type of AT-strategy.

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