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Patient Blood Management – Team Working Between Clinical Transfusiology And Clinical Pharmacology

LJubinka I. Nikolić[1], Emina S. Čolak[1], Slobodan M. Janković[2,3], Srdjan Z. Marković[1,4], Dragana A. Kastratović[1]

[1] University Clinical Center Serbia, Belgrade, Serbia
[2] University Clinical Center Kragujevac, Kragujevac, Serbia
[3] Faculty of medical Sciences, University of Kragujevac, Kragujevac, Serbia
[4] Center for Physical Chemistry of Biological Systems, Faculty of Physical Chemistry, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction: Blood transfusion is the process of donating blood or blood components from a donor to a recipient of blood or blood components. Clinical pharmacology is a medical discipline created in the 20th century, that implies the most effective application of drugs, and it could be considered the culmination of all therapeutic procedures in medicine, or simply in the preservation of human health.
Methods: Online search of pharmacology and transfusion literature was conducted using PubMed, Cochrane, Embase, and Scopus databases.
Topic: Patient blood management (PBM) is a multidisciplinary multimodal patient-centered approach designed to minimize the use of allogeneic blood components in order to improve the clinical outcome of patient treatment. PBM consists of 3 main pillars with specific clinical goals. 1) First pillar: increasing red cell mass including clinical-pharmacological correction such as erythropoiesis stimulating agents (ESA) - iron and another drugs and optimizing the time for surgical intervention in relation to achieving the required hemoglobin value; 2) Second pillar: minimize blood loss through an adequate selection of surgical and anesthetic techniques, treatment with tranexamic acid (TXA) and autologous blood salvage, and the use of blood substitutes, 3) Third pillar: increasing the patient's tolerance to anemia through maximum improvement of pulmonary and cardiac function, optimizing ventilation, oxygenation and restrictive application of blood components. Clinically it is clear that clinical transfusiology and clinical pharmacology are part of each other originating from the fact that the use of classical medicine as well as the therapeutic use of blood achieves a therapeutic effect in order to improve the clinical status of the patient.
Conclusion: Patient blood management implies health teams composed of clinical pharmacologist and clinical transfusiologist with other health care specialists making successful healthcare institutions. The most important thing is to monitor the development of new drugs, new transfusion solutions, and in this area, be especially careful when applying new drugs because of serious side effects that may occur. The agility of PBM is reflected in three pillars that must be harmonized and require continuous team education.

Keywords: Patient Blood Management, Clinical Transfusiology, Clinical Pharmacology, Tree Pillars

Corresponding author:
Primarius Dragana A. Kastratović, MD, PhD
Specialist in Clinical Pharmacology
University Clinical Centre Serbia, Pasterova 2, 11000 Belgrade, Serbia
E-mail: prim.drmaca.kastratovic@gmail.com

INTRODUCTION

Clinical transfusion includes the activity of storing and issuing blood and blood components for therapeutic use, pretransfusion tests, care for the optimal use of blood and blood components, autologous transfusion, therapeutic apheresis procedures, tests for hemostasis disorders, perinatal tests related to the incompatibility of blood cells antigens between mother and fetus, monitoring the effects of treatment with blood components and is performed in hospital blood banks (hereinafter: clinical transfusion) [1]. Blood transfusion is the process of donating blood or blood components from a donor to a recipient of blood or blood components [2]. In other European countries, the legal use of blood and blood products is regulated by applicable Directives [3,4].

Clinical pharmacology is a medical discipline created in the 20th century, that implies the most effective application of drugs, and it could be considered the culmination of all therapeutic approaches in medicine, or simply in the preservation of human health. It is a field that spontaneously appeared within the medical science and from the very beginning its unique perspective is in the unity of practice and science [5].

A drug is a product containing a substance or a combination of substances produced and intended for the treatment or prevention of disease in humans or animals, diagnostic, improvement or alteration of physiological functions, as well as for the achievement of other medically justified goals [6].

METHODS

Online search of pharmacology and transfusion literature was conducted using PubMed, Cochrane, Embase, and Scopus databases. The search was done on the following keywords: clinical transfusiology, clinical pharmacology, patient blood management, blood clinical effects, erythropoiesis stimulating agents, Hemostatic agents, side effects. The literature was searched only in English and Serbian equally, which can be a limiting factor in the search results.

TOPIC

Is blood a drug? The cooperation between clinical pharmacology and clinical transfusiology or the practical acceptance that they are part of each other originates from the fact that the use of classical medicine as well as the therapeutic use of blood achieves a therapeutic effect in order to improve the clinical status of the patient. However, blood and drugs often do not cure the patient's illness, but offer relief from the symptoms of the disease or medical condition.

Transfusion can be considered a liquid tissue transplant, and blood derivatives (not the blood components) could be considered as a human drugs of human originated. Different academic approaches to this issue can be found in the literature. An example of this is the new therapeutic approach of transfusion - patient blood management (PBM) in which the focus of treatment is shifted from the blood to the patient [1,3,4,7,8].

PBM is a multidisciplinary multimodal patient-centered approach designed to minimize the use of allogeneic blood components in order to improve the clinical outcome of patient treatment. PBM consists of 3 main pillars (Table 1) with clinical goals:1) First pillar: increasing red cell mass including clinical-

Table 1. Patient blood management - 3 pillars

PBM - 3 Pillars		
First Pillar	**Second Pillar**	**Third pillar**
Increasing red cell mass including: • erythropoiesis stimulating agents (ESA) • iron and vitamin • optimizing the time for surgical intervention in relation to achieving the required hemoglobin • Avoid drug / drug interaction that could prolong bleeding	Minimize blood loss: • dequate selection of surgical • adequate selection anesthetic techniques, • treatment with antifibrinilitics systemically and locally • autologous blood salvage • and the use of autologous tissue adhesives Artificial oxygen carriers: • perfluorocarbons • hemoglobin-based oxygen carriers	Improving anemia tolerance: • optimization of pulmonary and cardiac function • optimization of ventilation • optimization oxygenation • restrictive application of blood components.

pharmacological correction such as erythropoiesis stimulating agents (ESA) - iron and another drugs and optimizing the time for surgical intervention in relation to achieving the required hemoglobin value; 2) Second pillar: minimize blood loss through an adequate selection of surgical and anesthetic techniques, treatment with tranexamic acid (TXA) and autologous blood salvage, and the use of blood substitutes, i.e. perfluorocarbons as oxygen transporters, 3) Third pillar: increasing the patient's tolerance to anemia through maximum improvement of pulmonary and cardiac function, optimizing ventilation, oxygenation and restrictive application of blood components. Clinical pharmacology applied in hospitals-hospital pharmacology is a supportive branch of medicine that improves the outcomes of treatment and can sometimes anterograde indicate a change in the diagnosis of the disease [2,9,10].

First pillar

First pillar implies increasing red cell mass including clinical-pharmacological correction such as erythropoiesis stimulating agents (ESA), iron and vitamin supplements and optimizing the time for surgical intervention in relation to achieving the required hemoglobin. Based on the Cancer and Leukemia Group-B (CALGB) re-analysis using the 2000 IWG guidelines, transfusion-dependent patients are considered to be those who have been transfused for a period of less than 56 days, meaning that a red blood cell (RBC) transfusion-independence was defined as no RBC-transfusions for ≥56 days [11,12]. Usually transfusion dependent are renal patients on dialysis, Myelodisplastic syndrome (MDS), Sickle cell disease, congenital disorders of the red blood cell such as hemoglobinopathies, Myeloproliferative neoplasm, Aplastic anemia, Paroxysmal nocturnal hemoglobinuria, Blackfan-Diamond syndrome and beta-thalassemia. Another criteria definition RBC-transfusion-dependence is defined as ≥8 U RBC per year. Based on the laboratory values of ferritin, which is tested after administration of 8-10 units of RBC in transfusion-dependent patients, iron chelators (deferasirox) are administered to prevent unwanted toxic effects of iron [13].

In transfusion-independent patients, transfusion is often used in anemia (pregnant women, GIT diseases, inadequate nutrition, malignant diseases, autoimmune diseases). In these cases, transfusion can be avoided by using pharmacological ESA products [14].

The group of antianemics includes:
- Iron preparations: divalent iron (oral preparations), trivalent iron (oral preparations), trivalent iron (parenteral preparations), iron in combination with folic acid, iron in other combinations. In clinical practice, the most commonly used are: a) Ferrofumarate, iron II sulfate, iron III hydroxide polymaltose complex, iron protein succinylate, iron II glycine sulfate, dextroferon, iron in combination with folic acid, folic acid (vitamin B11), cyanocobalamin, hydroxocobalamin, epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa, methoxypolyethyleneglycol-epoetin beta; b) Oral hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) such as roxadustat, daprodustat, etc. Due to serious side effects: Increased Risk of Death, Myocardial infarction, Stroke, Venous Thromboembolism, and Thrombosis multi-year follow-up of this group of drugs and cost/benefit analysis will be necessary [15].
- Vitamins – ascorbic acid, vitamin B, vitamin D.
- Oligoelements: Magnesium, Potassium, Zinc, Cobalt.

Second pillar

Second pillar implies minimize blood loss. This can be achieved through an adequate selection of surgical and anesthetic techniques, treatment with tranexamic acid (TXA), and Epsilon amino caproic acid (EACA) systemically and locally, autologous blood salvage, and the use of autologous tissue adhesives (fibrin glue and platelet-fibrin gel), carriers O2 [16].

Application of antifibrinolytic therapy can be systemic and topical. Blood loss, transfusion rates, and number of patients needing transfusion was lower with the application EACA and TXA [16].

Autologous tissue adhesives are the most frequently used in open surgical procedures (neurosurgery, ophthalmology, liver surgery, thoracic surgery, plastic surgery, etc), endoscopic surgery, and all regions where the bleeding comes from small blood vessels. Authors of this paper support autologous human adhesives because of diminishing of serious side effects and positive cost/benefit affects.

Artificial oxygen carriers (AOCs)

are synthetic solutions with the ability to bind transport and unload oxygen in the body [17,18]. Some authors prefer the term oxygen therapeutics, which includes AOCs, for those agents designed to deliver oxygen to hypoxic tissue and organs [19, 20]. Types of artificial oxygen carriers are two viable categories of AOCs currently exist: hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbons (PFCs). Hemoglobin taken directly from RBCs cannot be used as an intravascular oxygen carrier. To avoid spontaneous breakdown of hemoglobin and the toxicity of hemoglobin extracted from RBCs, HBOCs use purified human, animal (bovine), or recombinant hemoglobin as raw materials. The purified hemoglobin is then either altered chemically or microencapsulated [17,18,19, 21]. For satisfied clinical effects the best clinical usage are perfluorocarbons. Perfluorocarbons require emulsification because they do not readily mix in aqueous systems such as blood, and after they can be used as intravascular drug [17,18,19], till now not registered in Serbia.

Third pillar

The effectiveness of improving anemia tolerance through pulmonary and cardiac function, optimization of ventilation, oxygenation and restrictive application of blood components depends on the compensatory capacities of the individual patient in the specific medical situation. The third pillar is managed by an anesthesiologist [22].

Taking into account the importance and side effects of blood therapy, the current guidelines emphasize a restrictive approach to blood transfusion [23].

PBM is an approach with the primary purpose of avoiding the morbid side effects of transfusion, such as the transmission of infectious agents (HIV, HBV, HCV, CMV), hypocalcaemia, and the immunomodulatory effect (sensitization to erythrocyte and platelet antigens and a decrease in the general immune status) of the use of allogeneic blood. The use of new drugs has brought with it even more serious side effects for patients. Therefore, a good cost/benefit approach is needed with an emphasis on clinical outcomes and medical staff who are continuously educated [16, 24, 25].

Additionally, it is necessary to take care of safety of blood donation from individuals with drug treated hypertension, meaning introducing a standard Liquid chromatography-mass spectrometry (LCMS) screening procedure as a tool for testing the blood of donors taking drugs [26].

CONCLUSION

Patient blood management implies health teams composed of clinical pharmacologist and clinical transfusiologist with other health care specialists making successful healthcare institutions.

The most important thing is to monitor the development of new drugs, new transfusion solutions, and in this area, be especially careful when applying new drugs because of serious side effects that may occur. The agility of PBM is reflected in three pillars that must be harmonized and require continuous team education. Old drugs keep their place, PBM has reduced the number of transfusions and the number of adverse transfusion reactions, and new drugs have a very risky safety profile, so successful application is possible only with great caution.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Mendžment transfuzijom – timski rad kliničke transfuziologije i kliničke farmakologije

LJubinka I. Nikolić[1], Emina S. Čolak[1], Slobodan M. Janković[2,3], Srdjan Z. Marković[1,4], Dragana A. Kastratović[1]

[1] Univerzitetski Klinički centar Srbije, Beograd, Srbija
[2] Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija
[3] Univerzitetski Klinički centar Kragujevac, Kragujevac, Srbija
[4] Centar za fizičku hemiju bioloških sistema, Fakultet fizičke hemije Univerziteta Beograd, Beograd, Srbija

KRATAK SADRŽAJ

Uvod: Transfuzija krvi je proces davanja krvi ili komponenata krvi od davaoca primaocu krvi ili komponenata krvi. Klinička farmakologija je medicinska disciplina nastala u 20. veku, koja podrazumeva najefikasniju primenu lekova, i može se smatrati završnicom svih terapijskih postupaka u medicini, ili jednostavno u očuvanju zdravlja ljudi.
Metode: Online pretraga farmakološke i transfuzijske literature sprovedena je korišćenjem baza podataka PubMed, Cochrane, Embase i Scopus.
Tema: Menadžment primene transfuzije krvi pacijentu (PBM) je multidisciplinarni multimodalni pristup koji postavlja pacijenta u centar, dizajniran da svede na minimum upotrebu alogenih komponenata krvi kako bi se poboljšao klinički ishod lečenja pacijenata. PBM se sastoji od 3 glavna postulata sa specifičnim kliničkim ciljevima. 1) Prvi postulat: povećanje mase eritrocita, uključujući kliničko-farmakološku korekciju sredstvima za stimulaciju eritropoeze (ESA) - gvožđe i drugi lekovi i optimizacija vremena za hiruršku intervenciju u odnosu na postizanje potrebne vrednosti hemoglobina; 2) Drugi postulat: minimizirati gubitak krvi adekvatnim izborom hirurških i anesteziooloških tehnika, primenom traneksamične kiseline (TKSA) i intraoperativnim spašaanjem krvi i upotrebom krvnih zamena, 3) Treći postulat: povećanje tolerancije pacijenta na anemiju kroz maksimalnu poboljšanje plućne i srčane funkcije, optimizacija ventilacije, oksigenacije i restriktivne primene komponenata krvi. Klinički je jasno da su klinička transfuziologija i klinička farmakologija jedna celina, proistekla iz činjenice da se primena krvi u kombinaciji sa lekovima može posmatrati kao farmakoterapijski pristup.
Zaključak: Menadžment primene transfuzije krvi pacijentu (PBM) sprovode zdravstveni timovi sastavljeni od kliničkog farmakologa i kliničkog transfuziologa, sa drugim zdravstvenim specijalistima koji čineći celu zdravstvenu ustanovu uspešnijom. Najvažnije je pratiti razvoj novih lekova i novih transfuzioloških rešenja, pri tom u ovoj oblasti treba biti posebno oprezan u primeni novih lekova zbog ozbiljnih neželjenih efekata koji se mogu javiti. Agilnost PBM-a se ogleda u tri postulata koji se moraju poštovati i biti usklađeni. Da bi ovo postigli neophodna je kontunuirana edukacija timova.

Ključne reči: menadžment primene krvi pacijenta, PBM, klinička transfuziologija, klinička farmakologija, postulati

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