Preoperative preparation of the patient with the abnormalities of red and white blood cells

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INTRODUCTION

The complete peripheral blood count analysis including laboratory screening tests of haemostasis and coagulation should be done in every patient before surgery, in order to detect specific abnormalities for primary or secondary haematologic disorder. These abnormalities might be very important cause of perioperative and postoperative complications. Therapy approach depends on the type and anaemia degree, and also on the type and time of surgery. If surgery is not urgent specific therapy according to the anaemia type (iron therapy, vitamin B12, folic acid, corticosteroids, recombinant erythropoietin) should be given in all anaemias with deficiency of iron, megaloblastic anaemias, acquired haemolytic anaemias and anaemias in end stage renal disease. Transfusion of red cells are most frequently given in patients with normovolemic anaemias with haemoglobin level of 10,0g/dl and hematocrit of 0,30, but lower levels in haemodynamic stable patients. Venesections should be done in patients with erythrocytosis in order to reduce total red cell volume, but taking into account the perioperative bleeding. Patients with leucocyte abnormalities suspected on primary haematologic disorder need urgent haematologic diagnostic procedures. In patients with leucocytosis the actual level of neutropenia is the bigger problem than the level of leucocytosis. In those patients treatment generally involves preventing infections, managing of febrile neutropenia with broad spectrum antibiotics and antifungal drugs, treatment with recombinant granulocyte hematopoietic factor, rarely transfusions of granulocyte concentrates and intravenous immunoglobulins.

Key words: preoperative preparation, anaemia, erythrocytosis, leucocytosis, leucopenia
1.1. ANAEMIA

Definition of anaemia

Anaemia is the most frequent hematologic abnormality seen during preoperative preparation of patients.

Anaemia is defined as a reduction in the haemoglobin concentration of the blood. Although normal values can vary between laboratories, typical values for anaemia would be less than 13.5g/dl in adult males and less than 11.5g/dl in adult females. From the age of 2 years to puberty, less than 11.0g/dl indicates anaemia. As newborn infants have a high haemoglobin level, 14.0g/dl is taken as the lower limit at birth. Alterations in total circulating plasma volume may significantly determine haemoglobin level. So, reduction in plasma volume (as in dehydration) may mask anaemia or even cause erythrocytosis; conversely, an increase in plasma volume (as in pregnancy, other diseases) may cause anaemia even with a normal total circulating red cell and haemoglobin mass. The special problem is acute major blood loss, in which anaemia is not immediately apparent because the total blood volume is reduced.

Classification of anaemia

There are a few different classifications of anaemia, but two most frequent used classifications are: those based on red cell indices (the mean corpuscular volume =MCV) and morphologic features and on pathophysiologic aspects.

Due to red cell indices (MCV) and morphologic features anaemia is divided into:

1. microcytic anaemia (MCV<80fl): iron deficiency, anaemia of chronic disorders, thalassemias, sideroblastic anaemia;
2. macrocytic anaemia (MCV>90/100fl): megaloblastic (vitamin B12 or folate deficiency) and non-megaloblastic anaemia (myelodysplastic syndrome, liver diseases, etc);
3. normocytic,normochromic anaemia (MCV 80-95fl): the most anaemias of chronic disorders, many haemolytic anaemias, after acute blood loss.

Due to pathophysiologic classification anaemia is divided into:

1. anaemia caused by decreased red cell production: at the level of haematopoietic stem cell (aplastic anaemia, pure red cell aplasia, anaemias due to bone marrow infiltration in haematologic and other solid metastatic malignancies), anaemias with disturbances of DNA synthesis (megaloblastic anaemias) or haemoglobin synthesis (haemoglobinopathias, thalassemias, iron deficiency);
2. anaemia caused by increased erythrocyte destruction: haemolytic anaemias (intrinsic abnormalities- membrane defect, enzyme deficiency and haemoglobin abnormalities; and extrinsic abnormalities -immune and non-immune);
3. anaemias caused by blood loss -acute and chronic.

In order to define the anaemia type the following laboratory analysis are needed: haemoglobin concentration, total red cell number, including morphologic features, MCV, reticulocyte number (normal 0.5-2.5%), iron stores (the best test is serum ferritin), signs for haemolysis (reticulocytosis, high serum total and unconjugated bilirubin, high serum LDH, low serum haptoglobin, positive urin urobilinogen, positive direct Coombs’ test). Also, it is very important to have the data about abnormalities of other peripheral blood cells (total number and differential count of white blood cells, number of platelets) because it may show the etiology of abnormalities and be helpful for further patient’s preoperative preparation.

Algorithm of analysis in anaemia

Concerning morphologic and pathophysiologic classification of anaemias, and laboratory results particularly about iron stores and haemolysis of erythrocytes, we use the following steps in algorithm for rapid definition of anaemia type:

1. In microcytic anaemia it is obvious to analyse iron stores, by serum ferritin as the best test. Anaemia of iron deficiency is defined with very low serum ferritin (as well as with low serum iron and high total iron-binding capacity, TIBC). Normal or high iron stores are seen in other types of anaemia, such as anaemia of chronic disease, myelodysplastic syndromes, haemoglobinopathias, etc.

2. In macrocytic anaemia it is obvious to analyse the reticulocyte number. If it is normal, the bone marrow analysis should be done in order to define megaloblastic or non-megaloblastic anaemia. If the reticulocyte number is risen, the analysis for haemolysis of erythrocyte should be done. Reticulocytes usually rise in haemolytic anaemias, but also slightly in chronic blood loss, as well as during the reticulocyte crisis 7-9 day after the beginning of vitamin B12 and folate therapy in megaloblastic anaemias of their deficiency.

Anaemia of acute blood loss

Acute blood loss is very important problem during preoperative preparation of patients. After a single episode of blood loss, there is initial vasoconstriction with a reduction in total blood volume. After that, the plasma volume rapidly expands and the haemoglobin and packed red cell volume fall, and there is a rise in neutrophils and platelets. The reticulocyte response begins on the 2nd or 3rd day and lasts 8-10 days. The haemoglobin begins to rise by about the 7th day, if iron stores are normal.

There is no need for red cell and blood transfusions in blood loss less than 500ml, but it becomes necessary if the loss is continuing and more than 1000ml, concerning all risks especially possible viral transmission. Massive blood loss (about 50% of total blood volume or volume which is similar to total circulating blood volume during 24 hours) is the cause of not only the loss of erythrocytes but also platelets and coagulation factors. Red cells transfusions contribute to further decreasing of platelets and coagulation factors. So, in this situation, patients are treated with transfusions of platelets (to reach platelets over 50, 50-100x10^9/l, especially in bleeding in polytrauma and cerebral haemorrhage), fresh frozen plasma 15ml/kg.
cryoprecipitate (PT and aPTT should be kept to less than 1.5 normal, and fibrinogen at least 1g/l), and recombinant VIIa factor$^{1,2,3}$.

**Therapy of anaemia in preoperative preparation of patients**

Therapy approach during preoperative preparation of patients with anaemia depends on type and degree of anaemia and urgency of surgery. If there is need for red cell transfusions, it should be kept on mind that every single red cell unit given to adult of average body mass increases haematocrit value for 0.03 (3%), haemoglobin concentration for 1g/dl, with the maximum of effects 24 hours after transfusion$^2$.

During perioperative period, the decision for transfusion is made according to the degree of blood loss, which is cause of hypovolemia and decrease of haemoglobin concentration at the same time. This kind of hypovolemia should be treated initially with crystalloid/colloid infusions. The most common threshold for red cell transfusions is haemoglobin level of 10,0g/dl and haematocrit of 0.30 in all normovolemic anaemias, with possible significantly lower limits in haemodynamically stable patients. Also, in patients with significant cardiovascular comorbidities (such as coronary artery disease) transfusions should be given even with haemoglobin level more than 10g/l.

Packed (plasma-depleted) and resuspended red cells are the most common used component of blood for correction of anaemia. Also, other haemoproducts such as filtered, washed, leucocyte-depleted and platelet-depleted red cells, or irradiated red cells might be used in some patients with anaemia in order to prevent biologic complications of transfusion (febrile nonhaemolytic reaction, acute lung injury, alloimmunisation, etc). These products are prepared using special filters for leucocytes, washing in saline fluids or treating by irradiation. These products are especially useful (with corticosteroid premedication) in autoimmune haemolytic anaemias, or in patients ongoing transplantation programme, due to the HLA alloimmunisation problems.

Transfusion of neocytes (young erythrocytes with lower iron level, more 2,3 DPG and longer lifespan of 90 days comparing to conventional red cells used in transfusion with lifespan of 50-60 days) should be given in rare anaemias such as thalassemias and aplastic anaemia, with often transfusions therapy. Neocytes are prepared from the whole blood unit using special technique.

Preoperative autotransfusion in order to collect autologous erythrocytes for further expected need for red cell transfusion is possible in all patients in good condition, with haemoglobin of 11g/dl, haematocrit over 0.34 and surgery planned within 2 to 5 weeks$^2$.

The specific anaemia treatment should be given immediately together with haematologist consultation, in all anaemias with iron, vitamin B12 and folate deficiency, acquired haemolytic anaemias and surgery planned within a month. Therapy is given according to the anaemia degree and initial haemoglobin concentration. In iron deficiency anaemia preparation of iron 100-200 mg daily are given up to one month after normalisation of haemoglobin level, to restore iron stores. In megaloblastic anaemia with vitamin B12 deficiency vitamin B12 is given 6x1000µg im 3-4 weeks, and after that every 3 months for life; in anaemia with folate deficiency folic acid 5 mg oral daily for 4 months is given. Acquired haemolytic anaemias are treated with corticosteroids 1-2 mg/kg body mass daily.

In anaemia of chronic renal failure, usually during dialysis, recombinant erythropoietin is given (3 times weekly, or once every 2 weeks, if glycosylated longer acting form is used). Also, the therapy of chronic disease is continuing$^{3,4,5}$.

**1.2. ERYTHROCYTOSIS**

**Definition of erythrocytosis**

The term erythrocytosis applies to patients who have increase of haemoglobin concentration due to normal values for gender and age. Also, it means limit levels for haematocrit over 0.51 for adult males and over 0.48 for women.

**Classification of erythrocytosis**

Due to pathophysiological classification erythrocytosis is divided into 2 big groups- absolute (primary and secondary) and relative erythrocytosis:

1. absolute erythrocytosis - with increased total red cell volume (>35 ml/kg in men and >32ml/kg in women) and normal total plasma volume (40-50 ml/kg)
2. relative erythrocytosis - with normal total red cell volume, but decreased total plasma volume.

Relative erythrocytosis are seen in patients with stress, cigarette smoking, in dehydration with plasma loss (vomiting, enteropathy, burns).

Absolute erythrocytosis is divided into primary and secondary. Secondary erythrocytosis are caused by compensatory erythropoietin increase in hypoxaemia (high altitudes, pulmonary disease, congenital cardiovascular disease with cyanosis), by inappropriate erythropoietin increase in renal diseases (hydronephrosis, cysts, stenosis a.renalis) or by erythropoietin-like cytokines in various tumours (uterine leiomyoma, hepatocellular carcinoma, cerebellar, adrenal and kidney tumours). Also, secondary erythrocytosis might be congenital in patients with abnormal haemoglobins such as haemoglobins with high affinity for O$_2$ and methaemoglobinopathy, and familial increase erythropoietin production. Primary erythrocytosis might be congenital (abnormalities of erythropoietin receptors in familial polycythemia) and acquired (polycythemia vera) in malignant myeloproliferative stem cell disorder$^{6,7}$.

**Algorithm of analysis in erythrocytosis**

Concerning basic characteristics and pathophysiologic classification of erythrocytosis, including anamnesis, clinical signs and laboratory results, the differential diagnosis between absolute and relative, and primary and secondary erythrocytosis should be done. It is obligatory to do following laboratory analysis (including peripheral blood counts analysis): arterial oxygen saturation, serum vitamin
B12, serum erythropoietin, total red cell volume and total plasma volume, neutrophil alkaline phosphatase score (NAP, staining on peripheral blood smears). If it is polycythemia vera (increased total red cell volume with normal total plasma volume, arterial oxygen saturation >95%, elevated NAP and serum B12, low serum erythropoietin) further haematologic investigations are needed. Therapy of erythrocytosis during preoperative preparation of patients

Clinical features of all erythrocytosis depends of the erythrocytosis degree, which causes blood hyperviscosity (headache, dispnea, visual disturbances, dizziness). So, the treatment is aimed at decreasing of circulating red cells and maintaining a normal hematocrit, using venesection (phlebotomy) usually 300-400ml (several time in one week). In patients with secondary erythrocytosis and clinical features of hyperviscosity venesections should be done if hematocrit is >0,56, but >0,52 in patients who are cigarette smoking and have arterial hypertension, ischemic cardiovascular disease, transient ischemic attacks or previous thrombotic events. Those patients should have hematocrit level of 0,45-0,47. The optimal level of hematocrit in polycythemia vera is 0,45, considering that those patients might have increasing number of platelets. If platelets are over 400x10⁹/l, patients should be treated, (after consultation with haematologist) with myelosuppressive drug hydroxurea and aspirin to prevent thrombotic events. However, these patients have also abnormalities of platelets’ function and therefore increased risk for haemorrhage as well. So, during preoperative preparation of patients, rhythm of venesections depends on degree and type of erythrocytosis, type of planned surgery, expected perioperative bleeding, with adding anticoagulant therapy in patients with thrombocytosis.2,8,9

2. WHITE BLOOD CELLS DISORDERS

The white blood cells (leucocytes) may be devided into 2 big groups: the phagocytes (polymorph neutrophils, eosinophils and basophils granulocytes, and monocytes) and immunocytes (lymphocytes and their precursors, and plasmocytes). In peripheral blood of healthy person there only mature phagocytes and lymphocytes. The function of these cells is in protecting the body against infection closely connected with two soluble protein systems, immunoglobulins and complement.

The granulocyte and monocyte series arises in bone marrow from the progenitor haematopoietic stem cell in the process of differentiation and proliferation controled by many growth factors, such as interleukins (IL-1, IL-3, IL-5, IL-6, IL-11), macrophage, granulocyte and monocyte stimulating factors (GM-CSF, G-CSF, M-CSF). These growth factors also affect the function of mature cells: phagocytosis, superoxide generation and cytotoxicity in the case of neutrophils; phagocytosis, cytotoxicity and production of other cytokines by monocytes. In the normal state, the bone marrow storage compartment contains 10-15 times the number of granulocytes found in the peripheral blood. Following their release from the bone marrow, granulocytes spend only 6-10 hours in the circulation, before moving into the tissues where they perform their phagocytic function, spending average 4-5 days before destruction. Monocytes spend more shorter in bone marrow than granulocytes, after circulating for 20-40 hours leave the blood and enter the tissues, where they mature and carry out their principal functions. After their transformation to macrophages they may have lifespan as long as several months, or even years.

Lymphocytes are the immunologically competent cells that assist the phagocytes in defence of the body against infection. In postnatal life, the bone marrow and thymus are the primary lymphoid organs in which lymphocytes develop. The secondary lymphoid organs in which specific immune responses are generated are the lymph nodes, spleen and lymphoid tissues of the alimentary and respiratory tracts. The immune response depends upon complex interactions between B and T lymphocytes, NK cells (cytotoxic CD8⁺ cells without T-cell receptor), plasmocytes (mature B cells producing immunoglobulins), antigen-presenting cells, complement and number of cytokines. Normal leucocyte blood counts are 4-11x10⁹/l (with neutrophils 2,5-7,5; eosinophils 0,04-0,4; basophils 0,01-0,1; monocytes 0,2-0,8; lymphocytes 1,5-3,5) for adults of white race. Disorders of leucocyte function are congenital (rare) and acquired, which are accompanied with leucocyte number abnormalities, the both leucocytosis and leucopenia.2,8,9

2.1. LEUCOCYTOSIS

An increase in total leucocyte number, as well as increase in every single group of phagocytes or immunocytes, might be observed in many disorders such as primary haematologic diseases (acute and chronic lymphoproliferative and myeloproliferative neoplasms, mostly in leukaemias, lymphomas, myelomas etc.), but also during acute and chronic infections, inflammation and tissue necrosis, metabolic disorders, neoplasms of all non-haematologic types, acute haemorrhage and haemolysis, using some drugs, allergic and autoimmune diseases, etc. Occasionally, there is excessive leucocytosis (>50x10⁹/l) characterized by the presence of immature cells (e.g. myeloblasts, promyelocytes and myelocytes, or activated lymphoid cells and lymphocytes). These leukaemoid reactions are associated with severe systemic infections, haemolysis or metastatic cancers. So, in all leucocytosis it is very important to analyse the leucocyte differential formula (in blood analyser and on blood smears), the absolute numbers of all cells, and after that if there are abnormalities in other peripheral blood cells or clinical signs, to consult haematologist for further diagnostic approach.8,9

2.2. LEUCOPENIA

Neutropenia is the most common observed leucopenia with clinical significance for preoperative preparation of patients. Neutropenia may be a part of a general pancytopenia (bone marrow failure in haematologic malignan-
Preoperative preparation of the patient with abnormal leucocyte count

Haematology diagnostic procedures should be done in every patient with suspected haematologic disorder. Leucocytosis in chronic lymphoproliferative and myeloproliferative diseases may be under control with 1-2 month of adequate haematologic therapy. So, it should be given in preoperative preparation of patients and not urgent surgery. The largest problem in patients with leucocytosis are neutropenia and acquired immunodeficiency, which are associated with postoperative complications.

So, concerning rules of asepsis and antisepsis, those patients need prophylaxis of infections, including oral antibacterial (co-trimoxasole, ciprofloxacin, colistin) and antifungal drugs (fluconasole, itraconasole, posaconasole). The granulocyte stimulating factor G-CSF is used as a neutrophil producing stimulating factor in patients after chemotherapy or in autoimmune drug-induced agranulocytosis. Concerning algorithms in patients with febrile neutropenia, after microbiology analysis, broad spectrum antibiotics should be given immediately (meropenem, tazocin, vancomycin/teicoplanin), with parentheral antifungal therapy in patients with probably and proven fungal infections.

Granulocyte concentrates have been used rarely, due to often posttransfusional reactions, e.g. HLA sensitisation. But, in some patients with agranulocytosis not responding to given antibiotic and antifungal therapy, granulocyte concentrates might be given with premedication (antihistaminics, analgo-antipyretics and corticosteroids). Literature data are confirming significant efficiency of granulocyte concentrates in therapy of sepsis in neonatal period, rare in adults with invasive fungal infections, and after various transplantations. Also, during preoperative preparation of patients with immunodeficiency and hypogammaglobulinemia, intravenous immunoglobulins (IVIG) are used up to 0,4mg/Kg daily. IVIG have protective functions increasing the activity of antimicrobial effector systems such as opsonins-mediated phagocytosis and antibody and complement dependent cell-mediated cytotoxicity. According to the literature data, there is also an immunomodulatory effect of IVIG to circulating immunoglobulins, B cells etc. After IVIG application it’s lifespan is 3 weeks at least2,8,9,10,11.

CONCLUSION

The complete peripheral blood count analysis including laboratory screening tests of haemostasis and coagulation should be done in every patient before surgery. If there are abnormalities in red and white blood cell counts, indicating possible haematologic disorder, haematologist should be included in further diagnostic procedures and therapy. Patients with anaemia and no urgent surgery are treated according to the data in the anaemia cause with iron, vitamin B12, folic acid, steroids or recombinant erythropoietin. Transfusion of red cells are given to the patients with severe anaemia and urgent surgery. Phlebotomy is used in patients with erythrocytosis in order to decrease the circulating red cell mass, but concerning the expected perioperative bleeding. Neutropenia and immunodeficiency are the most important abnormalities in patients with white blood cell disorders. So, those patients need prophylaxis of infections, therapy of febrile neutropenia with broad spectrum antibiotics and antifungal drugs, rarely recombinant granulocyte factor, transfusion of granulocyte concentrates and intravenous immunoglobulins.

SUMMARY

PREOPERATIVNA PRIPREMA BOLESNIKA SA POREMEĆAJEM BROJA ERITROCITA I LEUKOCITA

U bolesnika koji su predvidjeni za bilo koju hiruršku intervenciju neophodno je, u okviru preoperativnih nalaza, uraditi kompletну krvnu sliku uz rutinske testove hemo-staze i koagulacije, kako bi se, ako postoje, uočili poremećaji koji ukazuju na primarnu hematološku bolest ili hematološki poremećaji u okviru nekih drugih bolesti. Ovi poremećaji bi mogli da budu uzrok značajnih komplikacija tokom i posle operativnog zahvata. Anemije su najčešći hematološki poremećaji koji se vidje u toku preoperativne pripreme bolesnika. Terapijski pristup zavisi od...
tipa i stepena anemije, vrste hirurške intervencije, te vremena kada ona treba da se uradi. U svim oblicima anemije se treba početi specifičnu terapiju anemije. Pri tome, najčešći "prag" za transfuziju eritrocita je nivo hemoglobina od 10,0g/dl i hematokrit od 0,30, kada je rizik o euvolemijskoj anemiji, a kod hemodynamski stabilnih bolesnika ovaj prag može biti i znatno niži. U bolesnika koji imaju eritrocitozu terapija je usmerena ka smanjenju broja cirkulisanog eritrocita, što se postiže flebotomijama, vodeći računa o očekivanom perioperativnom krvenju. Kod bolesnika sa poremećajem broja leukocita i sumnjom na primarnu hematološku bolest treba odmah uključiti hematologa u dijagnostičku proceduru definisanja poremećaja. U bolesnika sa leukocitozom u lekemijama veći je problem stvarni stepen neutropenije koji ovi bolesnici imaju nego stepen leukocitoze. Stoga je u okviru terapije ovakvih bolesnika obavezna prevencija infekcija, primena granulocitnog hematopoetickog faktora rasta, a u slučaju febrilne neutropenije, primena antibiotika širokog spektra i obavezne anti-gljivine terapije, redove transfuzije granulocitnih koncentrata i imunoglobulina za intravensku primenu.

Ključne reči: preoperativna priprema, anemija, eritrocitoza, leukocitoza, leukopenija

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