The Importance of Using the Glucocorticoid 9 – fluoro – 16 Methylprednisolone Therapy Before Splenectomy in Patients with Idiopathic Thrombocytopenic Purpura

OANA VIOLA BADULESCU[1] , ROXANA HULTOANA[2] *, MADALINA MOCANU[1] *, MARIA MAGDALENA LEON CONSTANTIN[3] *, STEFAN OCTAVIAN GEORGESCU[2]

[1]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Pathophysiology, 16 Universitatii Str.,700115, Iasi, Romania

[2] The second Clinic of General Surgery, University Hospital St. Spiridon, 1 Independentei Blvd., 70011, Iasi, Romania

[3]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine Iasi, Department of Internal Medicine and Departmentof Rheumathology, 16 Universitatii Str., 700115, Iasi, Romania

Idiopathic thrombocytopenic purpura is an autoimmune haematological condition that involves low platelet count in the peripheral blood of a lower amount of 100,000 items / mm^3. Thrombocytopenia is due to either a central cause, such as inhibition of platelets synthesis in the bone marrow or an accelerated hiperdistruction in the periphery. Intensified capture and destruction of platelets is most often induced by splenomegaly and hypersplenism. In patients with low platelets accompanied by splenomegaly refractory to drug, the only opimal therapy is the therapeutic splenectomy. Splenectomy is a surgical therapeutic manever indicated in multiple diseases, especially in the hematological field, practiced in order to increase the lifespan of platelets and decrease transfusion requirements. Although in idiopathic thrombocytopenic purpura, splenectomy is not curative, it leads to improvement of symptoms and an increase in platelets. Also, it is noted in patients with idiopathic thrombocytopenic purpura splenectomised no further need of immunosuppressive treatment and improved quality of life. Making splenectomy in the context of a low platelet count accurately involves establishing safety measures be put in place to avoid accidents with serious bleeding. The main measure is to balance patient by administering drug therapy leading to increased levels of platelets prior to surgery. The treatment methods are used corticosteroid therapy, and platelet concentrate. Product with potent glucocorticoid synthesis and conferring a remarkable increase in the number of platelets is dexamethasone (9-fluoro-16-methylprednisolone). This paper aims to highlight the importance of using therapy with 9-fluoro-16-methylprednisolone as a prophylactic measure against intraoperative bleeding incidents in patients with idiopathic thrombocytopenic purpura who will be practicing splenectomy.

Keywords: 9 – fluoro – 16 methylprednisolone, splenectomy, idiopathic thrombocytopenic purpura, hemorrhagic syndrome

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease that occurs more frequently in female patients, average age. The pathology is manifested by a hemorrhagic syndrome with skin or mucous membrane expression, clinical highlighted by the appearance of epistaxis, bruising, gums or petechiea (1). Hemorrhagic phenomena have varying intensity, from mild to server, such as intracranial or retinian bleeding.

According to studies conducted to date, idiopathic thrombocytopenic purpura has an incidence of between 10 – 40 up to 125 cases per million patients per year, the ratio between men and women is 1/2 – 6, and the age of peak incidence at adult is between 20 – 50 years. (2)

Idiopathic thrombocytopenic purpura (ITP) is the most common indications for splenectomy in hematological diseases. Hyperactivity of the spleen accompanied by increasing the size of the spleen promote the hiperdistruction of premature platelets at this level. Idiopathic thrombocytopenic purpura is characterized by the presence of antiplatelet antibodies that maintain continuous destruction of platelets. The main targets of antibodies are membrane proteins from the platelet surface that become antigenic sites. The spleen is the main center where the main complex platelets – platelet antibodies IgG is removed by the reticuloendothelial system. (3, 4)

There are two forms of ITP: acute and chronic. Meets with propensity acute ITP in children and occurs in the context of viral infection. It has a spontaneous resolution within two months. Chronic ITP persists for more than 6 months and etiopathogenic mechanisms underlying outbreak are not yet fully elucidated. Spontaneous remission of the disease in 80% of cases occur in children and rarely in adults. Establishing an accurate diagnosis is critical for addressing the ITP subsequent therapy. ITP can be primary, idiopathic or secondary, occurring in the context of associated diseases such as autoimmune diseases (SLE, collagen), lymphoproliferative syndrome, viral or bacterial infections. (5) It also includes the diagnostic algorithm of differential diagnosis of ITP and hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC).

Bleeding is the most serious complication of ITP, especially if the intracranial level. Bleeding mortality rate is about 1 to 5% of children and adults. In patients with severe thrombocytopenia and age over 60 years, the mortality rate at 5 years is significantly increased compared to patients younger than 40 years (47.8% vs. 2.2%). Thus, older age and history of bleeding increases the risk of severe bleeding in ITP in adults (6).

* email: *alicia_roxana@yahoo.com ; mocanu_madalina@ymail.com; leon_mariamagdalena@yahoo.com.*

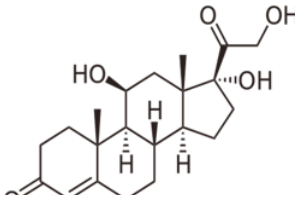

Fig 1. The general structure of glucocorticoids

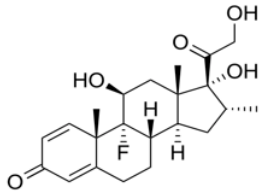

Fig 2. Chemical structure of dexamethasone (9-fluoro-16 methylprednisolone)

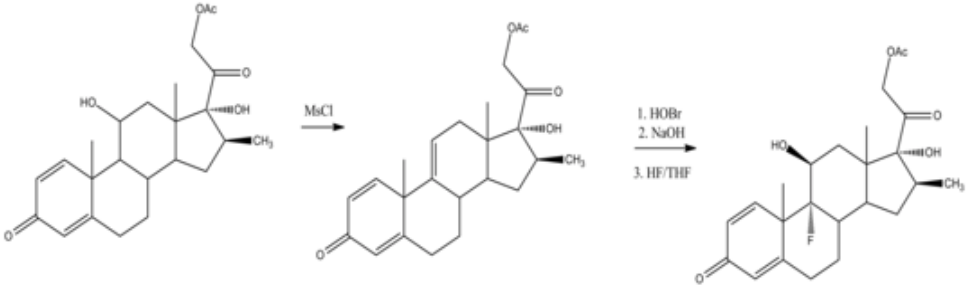

Fig 3. The synthesis reaction of dexamethasone

The goals of treatment in ITP aims at reducing the risk of bleeding and prolong disease remission. Pillars drug therapy used in this regard are corticosteroids and intravenous immunoglobulin (IVIg). Among the remarkable results observed glucocorticoid in patients receiving Dexamethasone was administered parenterally (9-fluoro-16-methylprednisolone).

Dexamethasone is a synthetic glucocorticoid plasma half-life of 3 h and the effect of long-term (36-54), which contraindicate its administration over extended periods of time. Dexamethasone sodium phosphate is a water – soluble derivative, is injected iv or i.m., is indicated in cases of emergency requiring treatment cortisone (7).

Dexamethasone has important anti-inflammatory action that interested all phases of the inflammatory process. It also has antiallergic action and immuno-suppressant dexamethasone marked, which is due preventing the synthesis of interleukin-2 (IL-2) and limfokininelor by T lymphocytes, due to lower their proliferation. At the same time are reduced inflammatory consequences of the antigen – antibody reaction.(8) This mechanism explains the role of the use of dexamethasone in patients with immune thrombocytopenic purpura.

In terms of chemical structure corticosteroids have steroid (C21) with a double bond in the 4 – 5 position, a function of oxygen (ketone or hydroxyl) in position 11 (they are called 11 oxisteroizi) a hydroxyl group in the 17α position and one in the 21 – position.

This structure corresponds to natural glucocorticoids: cortisone and hydrocortisone. By inducing a 1 – 2 double bond are obtained Δ1 derivatives: prednisone (Δ1 – cortisone) and prednisolone (Δ1 – hydrocortisone), 5 times more active as anti – inflammatory and glucoregulatory. Substitution of a methyl in the 6 – position (methyl prednisolone), or fluorine in position 9á (triamcinolone, dexamethasone, betamethasone) intensifies all the effects of glucocorticoids. Methylation in position 16á (dexamethasone, betamethasone) cancels the effects of type mineralocorticoid. (9 – 11)

Dexamethasone is synthesized from 16βb – methylprednisolone acetate that dehydration turns into derivative 9,11 – dehydro. It was treated with N – bromosuccinimide to form 9βa - bromo – 11β – hydrin derivative epoxy structure. The last stage of the synthesis reaction involves treatment of 9α – bromo – 11β – hydrin with tetrahydrofuran derivative that will lead to the formation of dexamethasone.

Clinical case

We present a patient aged 40 years, male, found in the Clinic of Hematology of Hospital Saint Spiridon in 2013 with idiopathic thrombocytopenic purpura without any significant pathological personal history. The patient is currently hospitalized in the revaluation clinical - biological. Biologically, the patient has: severe thrombocytopenia (6000 / mmc), analysis of peripheral blood smears reflects platelet very rare, anisocytosis, clotting profile lies within the normal range, and in terms of biochemical finds values slightly elevated LDH .

Clinical examination reveals a left upper quadrant tumor formation last, moderately painful on palpation, which seems to belong to the spleen. Evolution of platelets has been variable over the past two years with alarming declines and return close to normal steroid therapy in high doses. Severe thrombocytopenia (6000/mmc) imposed the current administration of platelet concentrate and high doses of steroids. The patient with favorable evolution post-treatment was discharged with a recommendation to the address for a reconsideration of surgical treatment.

The patient was hospitalized in the Second Clinic of Surgery with platelets below 10000/mmc, preoperative administering the units of concentrated platelets and high doses of steroids so that platelets have reached 130,000/mmc by the day of the intervention, which gave safety from the point of view of fluid – coagulation balance. Prophylactic therapy to increase platelet count was based on five vials of dexamethasone daily for 4 days. It was administered pneumococcal vaccine combined with vaccines containing seven of the most aggressive strains of S. pneumoniae and over 23 immunogenic poly-saccharide, prophylactic achievement splenectomy.

Initially, the surgical approach was laparoscopy, postoperative adhesions in the left abdomen, the left ascent angle of the colon and fixing the diaphragm made it impossible to identify spleen and requires conversion to the classic surgery.

Postoperative evolution was favorable, with normalization of platelet count three days after splenectomy (331000/mmc) without corticosteroid treatment. During hospitalization, the patient developed a postoperative wound infection that followed for specific

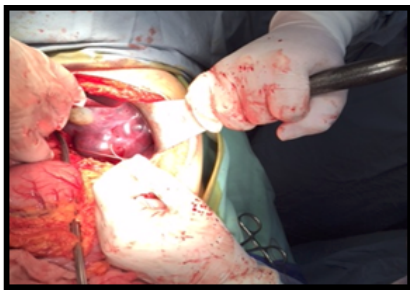

Fig. 4. Intraoperative appearance of the spleen

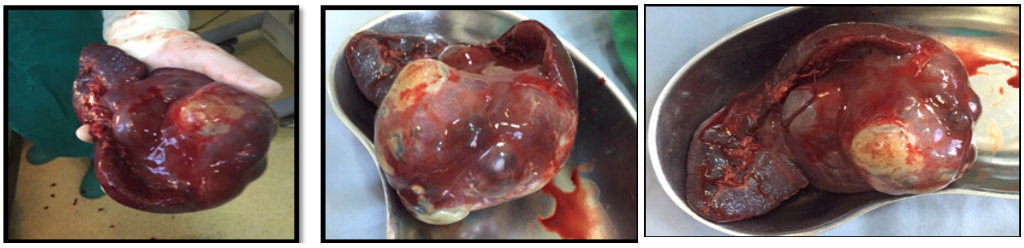

Fig. 5. The macroscopic aspect of the spleen

antibiotics. Discharge was performed 8 days after surgery, with good overall condition, the platelet count is in the normal range without any treatment which promotes platelet maintain normal.

Conclusions

ITP is a hematological pathology characterized by favorable development in most patients. The alternation of the periods of activity with the remission ones of the disease is common in most patients. Drug therapy targets aimed at increasing the duration of remission and preventing the onset of hemorrhagic syndromes manifest.

A special category of patients diagnosed with idiopathic thrombocytopenic purpura refractory cases represent multiple lines of therapy, splenomegaly associated with severe thrombocytopenia. At these patients, the only therapeutic solution is splenectomy. In the context of a low number of platelets, surgical intervention involves a major risk of bleeding. To perform safely splenectomy patients were administered dexamethasone, prepared potent corticosteroid, which led to increased platelet count and spleen excision possibility. Through this article, we stress the importance of using dexamethasone (9-fluoro-16-methylprednisolone) therapy prior splenectomy in patients with idiopathic thrombocytopenic purpura.

References

1.GAURAV K, KEITH R, MCCRAE. Immune Thrombocytopenia. Hematol Oncol Clin North Am. Jun. 2013; 27(3): 495–520.

2.PORTO APNA, LAMMERS AJJ, BENNINK RJ, BERGE IJM, SPEELMAN P. (2010) Assessment of splenic function. European Journal of Clinical Microbiology & Infectious Diseases 2010; 29(12): 1465-1473.

3.STASI R. Immune thrombocytopenia: pathophysiologic and clinical update. Semin Thromb Hemost 2012 Jul; 38(5): 454-462.

4.MCMILLAN R. Autoantibodies and Antigens in Chronic Immune Thrombocytopenic Purpura. Seminars in Hematology. 2000: 37(3): 239-248.

5.CINES DB, LIEBMAN H, STASI R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009; 46(1) :S2-S14.

6.BERCHTOLD, PETER, AND R. MCMILLAN., Therapy of chronic idiopathic thrombocytopenic purpura in adults, Blood 1989; 74(7): 2309-2317.

7.PELT AC. Glucocorticoids: effects, action mechanisms, and therapeutic uses. Nova Science 2011.

8.HARDY JR. A prospective survey of the use of dexamethasone on a palliative care unit. Journal of Palliative Medicine 2001; 15 (1): 3-8.

9.RHEN T, CIDLOWSKI JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. The New England Journal of Medicine 2005; 353(16): 1711–1723.

10.PAZIRANDEH A, XUE Y, PRESTEGAARD T, JONDAL M, OKRET S. Effects of altered glucocorticoid sensitivity in the T cell lineage on thymocyte and T cell homeostasis. FASEB Journal 2002; 16 (7): 727–729.

11.REKA G, BELA K, DANA CRISTINA B, MELINDA S, MONIKA K, SILVIA-IZABELLA P, ELOD N. Effect of Dental Prophylaxis on the Salivary Cortisol Levels and Alpha-Amylase Activity in Children. REV.CHIM. 2015; 66(12).

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