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PREOPERATIVNA PRIPREMA PACIJENATA SA PRIMARNOM IMUNSKOM TROMBOCITOPENIJOM ZA IZVOĐENJE ORALNOHIRURŠKIH ZAHVATA

PREPARATION OF PATIENTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA FOR ORAL SURGICAL INTERVENTIONS

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Sažetak

Uvod: *Primarna imunološka trombocitopenija (ITP) predstavlja stečeno autoimuno oboljenje koje se karakteriše izolovanim smanjenjem broja trombocita ispod 100×10⁹/L, bez prisustva drugih uzroka trombocitopenije. Smanjenje broja trombocita kod pacijenata sa ITP posledica je istovremenog ubrzanog razaranja trombocita i poremećene njihove produkcije. Dijagnoza se postavlja isključivanjem drugih mogućih uzroka trombocitopenije. Kod odraslih pacijenata najčešće se javlja hronični oblik bolesti, koji se karakteriše periodima remisije i relapsa.*
Cilj *ovog rada bio je da se istaknu principi oralno-hirurškog lečenja pacijenata obolelih od primarne imunološke trombocitopenije.*
Materijal i metode: *Analizirana je dostupna literatura kako bi se identifikovale osnovne karakteristike ITP-a, sa posebnim osvrtom na specifičnosti i principe stomatološkog i oralno-hirurškog tretmana ovih pacijenata.*
Zaključak: *Ne postoje jasno definisane smernice za pripremu pacijenata sa ITP-om za hirurške intervencije. Preporučuju se individualan terapijski protokoli koji uključuju primenu visokih doza kortikosteroida, imunoglobulina, kao i odgovarajuće postoperativne antikoagulantne mere. U poslednje vreme sve veću primenu nalaze i agonisti receptora za trombopoetin, sa ohrabrujućim terapijskim rezultatima. Primena svih sistemskih i lokalnih terapijskih mera pre, tokom i nakon oralno-hirurškog zahvata je od ključnog značaja. Takođe, bliska saradnja između oralnog hirurga i hematologa smatra se imperativom za uspešan ishod terapije.*

Ključne reči: *primarna imunološka trombocitopenija, lečenje, oralno-hirurške procedure*

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Abstract

Introduction: *Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterised by an isolated decrease in the platelet count below 100×10, in the absence of other identifiable causes of thrombocytopenia. The decrease in platelet numbers in patients with ITP results from both accelerated platelet destruction and impaired platelet production. The diagnosis is established by excluding other causes of thrombocytopenia. In adult patients, the chronic form is most often encountered, characterised by periods of remission and relapse of the disease.*
Aim: *This informative paperwork aims to highlight the principles of oral surgical treatment of patients with ITP.*
Material and Methods: *The available literature was analysed to identify the basic characteristics of ITP, with special reference to its specificity and principles of dental and oral surgical treatment of patients with ITP.*
Conclusion: *There are no guidelines for preparing patients for surgical interventions. Personalised therapeutic protocols with high doses of corticosteroids, immunoglobulins, along with postoperative anticoagulant protocols, are recommended. In recent years, thrombopoietin receptor agonists have also been increasingly used with success. The application of all therapeutic measures, both systemic and local, is necessary before, during, and after the oral surgical procedure. Numerous new medications enable the appropriate preparation of ITP patients for oral surgical interventions. In addition, close collaboration between oral surgeons and haematologists is considered imperative.*

Key words: *primary immune thrombocytopenia, treatment, oral surgical procedures*

Introduction

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterised by an isolated decrease in the platelet count below 100×10^9, in the absence of other identifiable causes of thrombocytopenia. The incidence is approximately 2–10 cases per 100,000 adults annually[1]. ITP is more common in women of reproductive age, although its peak incidence occurs in individuals over 60 years old, affecting both sexes equally.

While the exact aetiology remains unknown, as with all autoimmune diseases, recent advances have clarified aspects of the disease pathogenesis. The decrease in platelet numbers in patients with ITP results from both accelerated platelet destruction and impaired platelet production. The key event is the loss of immune tolerance to platelet autoantigens, which triggers the consequent activation of T and B cells[2].

The primary mechanism in the pathogenesis of ITP involves autoantibody-mediated platelet destruction. Platelets marked with anti-glycoprotein autoantigens are destroyed by tissue macrophages by Fc-gamma receptor activation[3]. Additionally, these autoantibodies contribute to platelet clearance through complement-dependent cytotoxicity and the induction of apoptosis[4,5]. Thrombopoiesis is reduced or normal in most patients with ITP, and the absolute count of immature platelets is often decreased[6].

Given that there are no reliable diagnostic tests to diagnose ITP with certainty, the diagnosis is made by excluding other causes of thrombocytopenia. After taking an anamnesis and an objective examination of the patient, a complete blood count and a peripheral blood smear are performed. Additional tests include the determination of the number of reticulocytes and the levels of immunoglobulin, as well as serological tests for hepatitis B and C, HIV, and Helicobacter pylori. Bone marrow examination, tests for antinuclear and antiphospholipid antibodies are often required to rule out secondary thrombocytopenia.

Regarding the duration of the disease, ITP can be:

- Newly diagnosed—lasting up to 3 months from the time of diagnosis,
- Persistent—lasting 3–12 months from the time of diagnosis,
- Chronic—lasting longer than 12 months.

In adult patients, the chronic form is mostly encountered, which is characterised by remissions and relapses of the disease.

The clinical picture typically begins gradually, with the appearance of spontaneous bleeding on the skin and mucous membrane in the form of petechiae, ecchymosis, hematoma, frequent episodes of epistaxis and menorrhagia. Bleeding into the central nervous system is the most severe complication, although it is rare, occurring only in 1.5–1.8% of adult patients with ITP[7]. Risk factors that increase the likelihood of bleeding include advanced age, reduced platelet count, comorbidities, and the use of anticoagulant or antiplatelet medications[8].

Therapeutic Possibilities in the Treatment of ITP

The main goal of treating patients with ITP is to prevent the occurrence of bleeding, as well as to maintain the platelet number at a safe level. The latest guidelines recommend that treatment be initiated when the platelet count is 30x10 or less, and/or when the haemorrhagic syndrome is present[9]. First-line therapy consists of corticosteroids (Methylprednisolone 1mg/kg of body weight divided into 2–3 daily doses for up to a month, after which the dose is reduced, or Dexamethasone 40 mg for 4 days up to 3 cycles). Initially, therapeutic response is achieved in about 60–80% of patients, and after discontinuing therapy, 20–40% of patients maintain a favourable therapeutic response[10]. The drawback of corticosteroids is their limited use at high doses and numerous side effects (psychological disorders, elevated blood glucose levels, infections). Intravenous immunoglobulins (IVIg) are also used in the initial therapy. They can significantly raise the platelet count in more than 80% of newly diagnosed ITP patients. Disadvantages include a relatively high price and a short-term effect of 2–3 weeks[11]. They are used in severe forms of the haemorrhagic syndrome, at doses of 1g/kg body weight for 1–2 days or 0.4g/kg body weight for 5 days with a similar effect[12].

In recent years, the combination of Rituximab and high doses of Dexasone has been tested, but with no improvement in therapeutic response[13]. Therefore, it is still not recommended in the initial therapy of newly diagnosed patients.

Although there is a high percentage of therapeutic response to initial therapy in newly diagnosed patients, the vast majority will experience a relapse, and 60–70% will progress to persistent or chronic ITP[14]. Therapy for these patients includes the use of thrombopoietin receptor agonists (TPO-RAs), Rituximab and Fostamatinib, and splenectomy.

Thrombopoietin receptor agonists have dramatically changed the modality of ITP therapy, given that they have shown that therapy is possible without the use of immuno-suppressants. These include Eltrombopag, Romiplostim and Avatrombopag, and the first two are approved in Serbia. The overall therapeutic response in previously treated patients with chronic ITP is 70% to 90%, and 50–60% of these patients can maintain the response with prolonged treatment[15]. It is important to note that there are no serious side effects.

Rituximab reduces the production of antiplatelet antibodies. The initial therapeutic response is achieved in 60–70% of patients, and long-term in about 21%[16,17]. However, long-term treatment with Rituximab can lead to severe side effects.

Fostamatinib achieved the initial response in 43% of patients, and maintenance therapy achieved a prolonged response in 44% of patients[18]. The most common side effects include diarrhoea, nausea, hypertension, and mild or moderate transaminase elevation in up to 30% of patients.

Even though splenectomy is less frequently used today, it gives the possibility of achieving long-term remissions in 60–70% of patients[19]. In patients who have not achieved remission, the disease has a milder course and therapy is more effective[20]. Extensive diagnostic and therapeutic preparation, complications both during and after the intervention, as well as the availability of new medications, are the main reasons why splenectomy is now less commonly performed.

Many immunosuppressive or immuno-modulatory medications are used in the treatment of ITP, such as Azathioprine, Ciclosporin A, Danazol, Mycophenolate mofetil, and Vinca alkaloids. However, due to the appearance of new medications, their use has become increasingly rare[21].

Preparation of ITP patients for oral surgical interventions

The therapeutic approach to preparing patients with ITP for surgical interventions must be individualized. Factors to consider include the patient's age, existing comorbidities, whether the ITP is chronic or not, previous treatments and the patient's response to them.

According to clinical guidelines, patients undergoing surgical procedures should have a platelet count of at least 50,000×10. For minor oral surgical interventions, a minimum of 75,000×10 is recommended, whereas for procedures with a high risk of bleeding, such as major oral surgeries, neurosurgical, or cardiac surgical interventions, a platelet count of at least 100,000×10 is required[22].

There are no guidelines for preparing patients for surgical interventions. Personalised therapeutic protocols with high doses of corticosteroids, immunoglobulins, along with postoperative anticoagulant protocols are recommended[23].

Corticosteroids (mainly Methyl-prednisolone) are administered at a dose of 1–2 mg/kg body weight and are generally efficient. However, a drawback is their tendency to increase blood glucose levels, which can delay wound healing.

Intravenous immunoglobulins are given at a dose of 0.4g/kg body weight for 5 days or 1g/kg body weight for 2 days. In general, they are effective, but platelet counts may begin to decline again just a few days after the treatment[24]. In addition, they are relatively expensive.

The administration of platelet transfusions can be complicated and unreliable, although it is sometimes used with good results[25].

Recently, thrombopoietin receptor agonists have been increasingly used with success. Eltrombopag, in particular, has shown greater effectiveness in achieving adequate platelet counts compared to IVIg (79% and 61%, respectively)[26]. Patients undergoing dental procedures while receiving Eltrombopag therapy did not experience significant bleeding complications[27].

Romiplostim has also proven to be highly effective in preparing these patients for surgical interventions[28]. Thrombopoietin receptor agonists have not shown a significantly increased risk of thrombotic events[29].

Platelet count should be assessed preoperatively, both before and after the administration of concentrated platelets. The use of local haemostatic measures—commonly applied in other bleeding disorders—is strongly recommended.

These include gelatine- or collagen-based products, oxidized regenerated cellulose, and, if necessary, their combination with antifibrinolytics. Depending on the type and complexity of the procedure, haemostatic sutures should be used. For patients with ITP who are currently on corticosteroid therapy or have been within the past two years, it is advisable to increase the corticosteroid dose prior to the surgical intervention

Conclusion

The need for oral surgical interventions in patients with ITP is common. To avoid serious complications in these patients, adequate preoperative preparation is essential. This involves the application of all necessary therapeutic measures, both systemic and local, before, during, and after the oral surgical procedure. Regular postoperative monitoring of the patient is also crucial.

A wide range of new medications now enables appropriate preparation of ITP patients for oral surgical interventions. Furthermore, close collaboration between oral surgeons and haematologists is imperative. Equally important is the implementation of preventive measures aimed at reducing the need for oral surgical procedures.

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