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ORALNO HIRURŠKO ZBRINJAVANJE PACIJENATA OBOLELIH OD HEMOFILIJE

ORAL SURGICAL TREATMENT OF PATIENTS SUFFERING FROM HAEMOPHILIA

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Sažetak

Uvod: *Hemofilija je jedno od najčešćih hemoragijskih oboljenja iz grupe koagulopatija i nastaje kao posledica deficita faktora ogovornih za I fazu koagulacije.*
Cilj: *Cilj ovog informativnog rada bio je da se ukaže na principe oralnohirurškog tretmana pacijenata sa hemofilijom.*
Materijal i metode: *Analizirana je dostupna literatura kako bi se ukazalo na osnovne karakteristike hemofilije (na kliničku manifestaciju, mogućnosti lečenja i profilakse oboljenja), sa posebnim osvrtom na specifičnosti i principe stomatološkog oralnohirurškog tretmana obolelih od hemofilije.*
Zaključak: *Lečenje pacijenata sa hemofilijom se smatra jednim od najrizičnijih u svakodnevnoj stomatološkoj praksi. Uprkos tome, stomatološke intervencije se mogu uspešno i bezbedno obavljati. Međutim, stomatolog mora biti upoznat sa prirodom bolesti, njenim simptomima i težinom kliničke slike. Dalje, stomatolog treba da zna kakvu terapiju pacijent prima za lečenje hemofilije, da li je pacijentu dijagnostikovan inhibitor faktora koagulacije i da li pacijent ima prateće bolesti sa posebnim osvrtom na moguće zarazne bolesti. Uz to, ključ uspešne i bezbedne intervencije leži u dobro planiranom preoperativnom, perioperativnom i postoperativnom lečenju pacijenata sa hemofilijom.*

Ključne reči: *Hemofilija, Terapija, Oralnohirurški tretman*

Abstract

Introduction: *Haemophilia is one of the most common haemorrhagic diseases from the group of coagulopathies and results from a deficiency of factors responsible for the first phase of coagulation.*
Aim: *This informative paperwork aims to highlight the principles of oral surgical treatment of patients with haemophilia.*
Material and methods: *The available literature was analysed to indicate the basic characteristics of haemophilia (clinical manifestation, possibilities of treatment and prophylaxis of the disease) with special reference to specificity and principles of dental oral surgical treatment of patients with haemophilia.*
Conclusion: *The treatment of patients with haemophilia is considered one of the riskiest in everyday dental practice. Despite this, dental interventions can be successfully and safely performed. However, the dentist must be acquainted with the nature of the disease, its symptoms and the severity of the clinical picture. Furthermore, the dentist needs to know what kind of therapy the patient receives for the treatment of haemophilia, whether the patient has been diagnosed with inhibitors to the coagulation factor, and whether the patient has concomitant diseases with special reference to possible infectious diseases. Along with that, the key to a successful and safe intervention lies in a well-planned preoperative, perioperative and postoperative treatment of patients with haemophilia.*

Key words: *haemophilia, therapy, oral surgical treatment*

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Uvod

Hemofilija je jedno od najčešćih hemoragijskih oboljenja iz grupe koagulopatija i nastaje kao posledica deficita faktora ogovornih za I fazu koagulacije. U najvećem broju slučajeva, hemofilija je nasledno oboljenje. Ima podataka i o stečenoj hemofiliji, koja se javlja kao posledica stvaranja autoantitela na faktore koagulacije.

Za ovu bolest zna se već vekovima; prema nekim podacima, poznata je više od 2000 godina. Arapski hirurg Abulcasis je u X veku opisao slučaj porodice u kojoj su muški članovi umirali i nakon najmanje povrede. Svi kasniji zapisi ukazuju na to da su stručnjaci zapazili da postoje hemoragijska oboljenja prisutna samo kod muškaraca. Hemofilija je poznata i kao „kraljevska bolest“ – dovodila se u vezu sa kraljicom Viktorijom, koja je bila nosilac gena za hemofiliju, i njenim sinom Leopoldom, a prekoViktorijinih ćerki i sa mnogim nemačkim, španskim i ruskim kraljevskim porodicima, uključujući Romanove. U početku se hemofilija vezivala samo za deficit VIII faktora koagulacije, a onda je sredinom XX veka utvrđeno da hemofilija može nastati i kao deficit IX ili XI faktora koagulacije. Reč „hemofilija” prvi je upotrebio Johan Lukas Šenlajn u svojoj disertaciji odbranjenoj na Univerzitetu u Cirihu. Posredi je kovanica nastala od grčkih reči *hemo*, sa značenjem „krv”, i *philia*, sa značenjem „ljubav”. Genetski opis hemofilije prvi je dao dr Nase, koji je istakao da hemofiliju na svoje sinove prenose majke koje nisu bolovale od hemofilije[1-5].

Hemofilija je redak nasledni poremećaj koagulacije vezan za X hromozom, koji odlikuje nedostatak VIII faktora koagulacije (hemofilija A), odnosno IX faktora (hemofilija B). Opisana je i hemofilija C (nedostatak faktora XI), koja se prenosi autozomno-recesivno i uglavnom je prisutna u zajednici Jevreja Aškenaza. Ukupna učestalost hemofilija iznosi 1 : 10 000. Svetska zdravstvena organizacija (SZO) procenjuje da je broj muškaraca sa hemofilijom oko 1.125.000, s tim što kod većine bolest nije dijagnostikovana; među njima je i procenjenih 418.000 osoba sa teškim oblikom ove bolesti[1,6]. Hemofilija spada u grupu retkih bolesti i jedna je od četiri retke bolesti za koje u Republici Srbiji postoji nacionalni registar obolelih[7]. Najčešće se javlja hemofilija A (80% – 85%), koja se kod živorođene muške dece javlja u jednom od 5 000 slučajeva, a prati je hemofilija B, prisutna u jednom od 30.000 slučajeva.

Introduction

Haemophilia is one of the most common haemorrhagic diseases from the group of coagulopathies and results from a deficiency of factors responsible for the first phase of coagulation. In most cases, haemophilia is a hereditary disease. Acquired haemophilia, which occurs because of the formation of autoantibodies to coagulation factors, has also been described.

The disease has been known for many centuries, for even more than 2000 years according to some data. In the 10th century, the Arab surgeon Abulcasis described a case of a family in which male members died even after a minor injury. All subsequent records suggested that experts at the time noticed there were haemorrhagic diseases that affected men only. Haemophilia is also known as the "royal disease" given that it was associated with Queen Victoria, who was a carrier of the haemophilia gene, her son Leopold, and through her daughters with many German, Spanish and Russian royal families, including the Romanovs. In the beginning, haemophilia was associated only with coagulation factor VIII deficiency, but in the mid-20th century, it was established that the disease can also occur as a deficiency of coagulation factor IX or XI. The term "haemophilia" was first used by Johann Lucas Schönlein in his dissertation at the University of Zurich and is a coinage of the Greek words "hemo" meaning blood and "philia" meaning love. The genetic description of haemophilia was first given by Dr Nasse, who pointed out that haemophilia is completely transmitted by mothers who did not suffer from haemophilia to their sons[1-5].

Haemophilia is a rare inherited coagulation disorder linked to the X chromosome, characterized by a deficiency of coagulation factor VIII (haemophilia A) or factor IX (haemophilia B). Haemophilia C (factor XI deficiency), which is transmitted in an autosomal recessive manner and is mainly present among the Ashkenazi Jews, has also been described. The overall incidence of haemophilia is 1:10,000. The World Health Organization (WHO) estimates that the number of men with haemophilia is about 1,125,000, most of whom are undiagnosed, including an estimated 418,000 with a severe form of the disease[1,6]. It belongs to the group of rare diseases and is one of the four rare diseases for which there is a national register of patients in the Republic of Serbia[7].

Najređi oblik predstavlja hemofilija C, sa učestalošću 1 : 100 000 kod živorođene muške dece. Od hemofilije obolevaju uglavnom muškarci koji nasleđuju izmenjeni X hromozom od majke. Žene retko obolevaju od hemofilije; do toga može doći u slučajevima u kojima su oba X hromozoma izmenjena ili u slučajevima u kojima je jedan izmenjen, a drugi inaktivan. Žene sa jednim izmenjenim X hromozomom nazivaju se prenosiocima hemofilije[8].

Kliničke manifestacije hemofilije

Prvi znaci hemofilije uglavnom se otkrivaju u ranom detinjstvu. Primećuje se produženo vreme koagulacije koje nastaje kao rezultat potpunog nedostatka ili značajnog smanjenja određenog faktora koagulacije ili kvalitativno promenjenog faktora koagulacije, odnosno njegove koagulacione aktivnosti. Obično se javljaju neobjašnjive modrice kada dete puzi ili počinje da hoda ili nakon primanja medikamenata *per injectionem*.

Klinička manifestacija hemofilije zavisi od vrste hemofilije. Hemofiliju A karakterišu hemartroze, posebno u kolenima, skočnom zglobu, ramenu, laktovima i kuku, krvarenje u telesnim dupljama, potkožnom i mišićnom tkivu, kao i pojava krvi u mokraći. Mogu se javiti i sublingvalni i peritonzilarni hematomi kao urgentna stanja koja mogu ugroziti život. Hemofilija B uglavnom se manifestuje na isti način kao i hemofilija A. Hemofiliju C karakterišu krvarenje iz nosa, krvarenje posle povreda i hirurških intervencija, dok su spontana krvarenja izuzetno retka. Međutim, kliničke manifestacije hemofilije umnogome zavise od težine bolesti, koja se određuje na osnovu deficita faktora koagulacije. Za tešku hemofiliju (< 1 IU/dL (< 0,01 IU/mL) ili < 1% nivoa faktora koagulacije) tipična su spontana krvarenja u zglobovima, mišićima i unutrašnjim organima, za umerenu hemofiliju (1–5 IU/dL (0,01–0,05 IU/mL) ili 1% – 5% nivoa faktora koagulacije) povremena spontana krvarenja i produženo krvarenje posle manje traume ili hirurške intervencije, a za blagu formu hemofilije (5–40 IU/dL (0,05–0,40 IU/mL) ili od 5% do < 40% nivoa faktora koagulacija) teža krvarenja posle većih trauma ili hirurških intervencija; spontana krvarenja u ovom obliku retka su pojava[9].

Pacijenti sa hemofilijom imaju povećan rizik od smanjenja gustine kostiju[10]. Kod pacijenata sa umerenom i teškom formom hemofilije A hematomi pokazuju tendenciju

The most common is haemophilia A (80–85%) with a ratio of 1:5,000 of live-born male children, followed by haemophilia B with a frequency of 1:30,000, and haemophilia C with a frequency of 1:100,000 of live-born male children. Haemophilia mostly affects men who inherit an altered X chromosome from their mothers. Women rarely suffer from haemophilia, i.e., there are cases in which both X chromosomes are altered, or when one is altered and the other inactive. Women with one altered X chromosome are regarded as haemophilia carriers[8].

Clinical manifestations of haemophilia

The first signs of haemophilia are usually detected in early childhood in the form of prolonged coagulation time resulting from a complete lack or significant reduction of a certain coagulation factor or a qualitatively changed coagulation factor, i.e., its coagulation activity. Unexplained bruises usually occur when a child crawls or starts to walk or after receiving medication *per injectionem*.

The clinical manifestation of haemophilia depends on its type. Haemophilia A is characterized by hemarthroses, especially in the knees, ankles, shoulders, elbows and hips, bleeding in body cavities, subcutaneous and muscle tissue, and the appearance of blood in urine. Sublingual and peritonsillar haematomas can also occur and suggest urgent, life-threatening conditions. Haemophilia B generally manifests itself in the same way as haemophilia A, whereas haemophilia C is characterized by nosebleeds, bleeding after injuries and surgical interventions. Yet, spontaneous bleeding is extremely rare. However, clinical manifestations of haemophilia largely depend on the severity of the disease, which is determined by the deficiency of coagulation factors. Severe haemophilia (< 1 IU/dL (< 0.01 IU/mL) or < 1% of the coagulation factor level) is characterized by spontaneous bleeding in joints, muscles, and internal organs. Moderate haemophilia (1–5 IU/dL (0.01–0.05 IU/mL) or 1–5% of the coagulation factor level) is characterised by occasional spontaneous bleeding, prolonged bleeding after minor trauma or surgical intervention, whereas a mild form of haemophilia (5–40 IU/dL (0.05–0.40 IU/mL) or 5–< 40% of the coagulation factor level) is characterized by severe bleeding after major trauma or surgical interventions, and rare spontaneous bleeding[9].

Patients with haemophilia have an increased risk of decreased bone density[10].

progresivnog širenja u svim pravcima. Smatra se da u teške forme krvarenja spadaju hemartroze, krvarenja u mišićima i dubokim prostorima, kao i ona u sluzokoži usne duplje, nosa i genitourinarnog trakta, a u krvarenja opasna po život intrakaranijalna i gastrointestinalna krvarenja i krvarenja u predelu grla i vrata[11].

Poseban izazov i rizik predstavljaju pacijenti sa prisutnim inhibitorima faktora koagulacije. „Inhibitori" predstavljaju IgG aloantitela na egzogen FVIII ili FIX koja neutrališu funkciju unetih koncentrovanih faktora koagulacije. Najčešće se javljaju kod pacijenata sa teškim oblikom hemofilije, uglavnom hemofilije A. Rasa, nasleđe, forma bolesti, učestalost primanja i tip koncentrovanih faktora koagulacije predstavljaju potencijalno najvažnije faktore rizika za nastanak ovih inhibitora[12].

Terapijske mogućnosti u lečenju hemofilija

Osim zbrinjavanja akutnih krvarenja, kod pacijenata sa hemofilijom veoma je važna strategija profilakse, koja ima za cilj da smanji učestalost i intenzitet mogućih krvarenja i potrebu za hospitalizacijom pacijenta, a samim tim i da poboljša kvalitet života obolelih. Prema SZO, profilaksa može biti primarna i sekundarna, kontinuirana i privremena. Profilaktički tretman uglavnom počinje jednom ili dva puta nedeljno, a njegova učestalost povećava se dok se ne postigne puna primarna profilaktička doza, pre početka krvarenja u zglobovima ili drugih ozbiljnih krvarenja, u dobi od 12 do 18 meseci[1,13,14]. Na primer, u slučaju hemofilije A doza faktora VIII izračunava se telesnom težinom izraženom u kilogramima i množenjem sa željenim povećanjem faktora VIII i 0,5 jedinica/kg, a nivo faktora obično se meri od 15 do 30 minuta nakon primene da bi se proverila izračunata doza. Poluživot SHL FVIII iznosi oko 12 sati, dok za FIX iznosi od 18 sati do 24 sata. Koliko će profilaksa trajati i da li će biti prekinuta zavisi od samog pacijenta i njegovih simptoma[15,16].

Pedesetih godina prošlog veka u terapiji hemofilije koristila se sveže smrznuta plazma, a desetak godina kasnije počela je upotreba krioprecipitata. Liofilizovani faktori koagulacije iz plazme prvi put su upotrebljeni sedamdesetih godina prošlog veka. Premda se smatralo da oni predstavljaju revoluciju u terapiji hemofilije, mnogi pacijenti na ovoj

In patients with moderate and severe forms of haemophilia A, haematomas tend to progressively expand in all directions. It is generally considered that severe forms of bleeding include hemarthrosis, bleeding in muscles and deep spaces, mucous membranes of the oral cavity, nose and genitourinary tract, whereas life-threatening bleeding involves intracranial, gastrointestinal, and throat and neck bleeding[11].

Patients diagnosed with inhibitors of coagulation factors pose a special challenge and risk. "Inhibitors" represent IgG alloantibodies to exogenous FVIII or FIX that neutralize the function of concentrated coagulation factors. They most often occur in patients with severe haemophilia, mainly haemophilia A. Race, heredity, form of the disease, frequency of receiving and type of concentrated coagulation factors are potentially the most significant risk factors for the occurrence of these inhibitors[12].

Therapeutic possibilities in the treatment of haemophilia

In addition to treating acute bleeding in patients with haemophilia, a prophylaxis strategy, which aims to reduce the frequency and intensity of possible bleeding and the need for hospitalization, thus improving the quality of life of patients, is considered very important. According to the WHO, prophylaxis can be primary and secondary, continuous and temporary. In the beginning, the frequency of prophylactic treatment is usually once or twice a week, but it is increased until the full primary prophylactic dose is reached, before the onset of joint bleeding or other serious bleeding at 12–18 months of age[1,13,14]. For instance, in haemophilia A, the factor VIII dose is calculated by body weight in kilograms multiplied by the desired increase in factor VIII and 0.5 units/kg. The factor level is usually measured 15–30 minutes after administration to verify the calculated dose. The half-life of SHL FVIII is about 12 hours, whereas that of FIX amounts to 18–24 hours. How long the prophylaxis will last and whether it will be interrupted depends on the patients themselves and their symptoms[15,16].

Fresh frozen plasma was first used in haemophilia therapy in the 1950s, and ten years later the use of cryoprecipitates began. Freeze-dried coagulation factors from plasma were first used in the 1970s and were considered to have revolutionized haemophilia therapy.

terapiji bili su zaraženi HIV virusom ili hepatitisom C zbog kontaminacije, što je podstaklo dalja istraživanja i traganje za bezbednom i sigurnom terapijom hemofilije. Revoluciju u terapiji hemofilije unela je pojava rekombinantnog faktora VIII devedesetih godina prošlog veka, koja je terapiju hemofilije učinila znatno bezbednijom. Danas su dostupne četiri generacije rekombinantnog faktora sa produženim poluživotom ili bez njega; pritom, treća generacija rekombinantnog faktora danas se u mnogim zemljama smatra najprikladnijom[1]. Sem pomenutih, u terapiji hemofilije koriste se i antifibrinolitici (traneksamična kiselina – TXA, epsilon aminokapronska kiselina) i dezmopresin (DDAVP)[17-22].

Novi terapijski pristupi u lečenju hemofilije podrazumevaju gensku terapiju i terapiju preparatima koji ne sadrže faktore koagulacije, tj. terapiju monoklonskim antitelima. Preovladava stav da će genska terapija imati značajan doprinos u lečenju hemofilije. Odobrena je njena primena za hemofiliju A i B. Međutim, genska terapija u lečenju hemofilije za sada nije indikovana kod pacijenata sa sa oboljenjima jetre, deca, kao i pacijenti sa antitelima na faktor koagulacije[23]. Ograničavajući faktor nesumnjivo je i cena ovih preparata, koja je trenutno visoka. Ipak, treba pomenuti da se daje samo jedna doza. Međutim, danas se smatra da će preparati koji ne sadrže faktore koagulacije, odnosno monoklonska antitela, kakvi su npr. lekovi emicizumab, marstacimab, koncizumab, doneti pravu revoluciju u lečenju hemofilije. Naime, oni oponašaju funkciju aktiviranog molekula faktora koagulacije (ali ne liče strukturno ili imunološki na njih, pa inhibitori nemaju efekta) ili inhibiraju prirodne endogene antikoagulante (inhibitor aktivacije spoljašnjeg puta koagulacije – TFPI). Smatraju se bezbednim za upotrebu, imaju poluživot od četiri nedelje do pet nedelja i značajno smanjuju stopu krvarenja. Od svih navedenih monoklonskih antitela, emicizumab, koji se i najviše proučavao, za sada je pokazao najbolje rezultate[24,25]; trenutno je jedini odobren za kliničku upotrebu u najvećem broju zemalja. Njegova primena je u našoj zemlji odobrena kod pacijenata sa teškom formom hemofilije A i kod pacijenata sa inhibitorima. Marstacimab, koji je u završnoj fazi kliničkih ispitivanja, koristi se u profilaksi krvarenja kod pojedinaca sa teškom ili umerenom formom hemofilije A ili B, sa inhibitorima ili bez njih. Ovi preparati ne koriste se u tretmanu akutnih krvarenja.

However, due to contamination, many patients undergoing this therapy were infected with HIV or hepatitis C. This prompted further studies and a search for safe haemophilia therapy. The appearance of recombinant factor VIII in the 1990s brought about a revolution in the treatment of haemophilia and made it much safer. Nowadays, 4 generations of recombinant factor are available with or without extended half-life, with the third generation of recombinant factor now considered most suitable in many countries[1]. In addition, antifibrinolytics (tranexamic acid TXA, epsilon aminocaproic acid), and desmopressin (DDAVP) are also used in haemophilia therapy[17-22].

New therapeutic approaches in the treatment of haemophilia include gene therapy and therapy with preparations that do not contain coagulation factors—monoclonal antibodies. It is generally considered that gene therapy significantly contributes to the treatment of haemophilia, and its application has been approved for haemophilia A and B. The main limitations of gene therapy are currently patients with liver diseases, children, and patients with antibodies to factor[23]. The high price of these preparations is certainly a limiting factor, even though they are given in a single dose only. However, it is believed that preparations that do not contain coagulation factors, i.e., monoclonal antibodies, such as emicizumab, marstacimab, and concizumab, will revolutionize the treatment of haemophilia. They mimic the function of the activated coagulation factor molecule (but do not structurally or immunologically resemble them, therefore the inhibitors have no effect) or inhibit natural endogenous anticoagulants (inhibitors of activation of the extrinsic pathway of coagulation—TFPI). They are regarded as safe to use, have a half-life of up to 4 to 5 weeks, and significantly reduce bleeding rates. Of all these monoclonal antibodies, emicizumab has been studied most and so far has shown the best results[24,25]. Consequently, it is currently the only one approved for clinical use in the largest number of countries. In our country, its use is approved in patients with a severe form of haemophilia A and patients with inhibitors, whereas marstacimab, which is in the final phase of clinical trials, is used in the prophylaxis of bleeding in patients with a severe or moderate form of haemophilia A or B, with or without inhibitors. These preparations are not used in the treatment of acute bleeding, and in case of tooth extraction or oral surgical interventions, pre- and postoperative application of concentrated coagulation factors is required.

U slučaju ekstrakcije zuba ili oralnohirurških intervencija potrebna je preoperativna i postoperativna primena koncentrovanih faktora koagulacije. U fazi kliničkih ispitivanja je i preparat fitusiran (siRNA), koji deluje na antitrombin, a koristi se i u profilaksi krvarenja kod pojedinaca sa teškom ili umerenom formom hemofilije A ili B, sa inhibitorima ili bez njih.

Stomatološki tretman pacijenata sa hemofilijom

Tretman osoba sa hemofilijom smatra se jednim od najrizičnijih u svakodnevnoj stomatološkoj praksi. Stoga, veoma je važno da stomatolog dobro poznaje prirodu oboljenja, simptome i težinu kliničke slike hemofilije. Takođe, potrebno je znati koju terapiju pacijent uzima za lečenje hemofilije, kako i kada je uzima, da li je kod pacijenta dijagnostikovano prisustvo inhibitora faktora koagulacije, kao i da li pacijent ima pridružene bolesti; pritom, posebna pažnja obraća se na moguće infektivne bolesti (naročito na HIV i hepatitis C). Da bi se kod pacijenata sa hemofilijom postigla uspešna stomatološka sanacija, osim detaljne anamneze, koja stomatologu pruža sve potrebne informacije, neophodna je dobra i konstantna saradnja stomatologa i hematologa zaduženog za lečenje osnovnog oboljenja. Uvek su za izvođenje stomatološkog tretmana potrebni dogovor sa hematologom i njegova pisana saglasnost. Takođe, planirana intervencija mora se izvesti u tačno zakazano vreme, onda kada su vrednosti faktora unetih u organizam (krv) bolesnika najveće, odnosno jedan sat nakon primene faktora. Preporuka je da se, zbog odgovarajuće laboratorijske i hematološke podrške, intervencije izvode na početku radne nedelje, ali i ranije u toku dana.

Danas postoje vodiči za stomatološki tretman obolelih od hemofilije u kojima se pre svega ističe značaj prevencije oralnih oboljenja kao imperativa stomatološke struke, posebno kod teških oblika hemofilija i kod pacijenata sa inhibitorima anti-hemofiličnog faktora[26]. Sve to proizilazi iz činjenice da najčešća oralna oboljenja (karijes, gingivitis i parodontopatije) i njihova terapija mogu izazvati ozbiljna krvarenja, koja ponekad mogu ugroziti i život pacijenta.

Sa ciljem prevencije oralnih oboljenja ističe se značaj redovne i pravilne oralne higijene atraumatskim tehnikama. Preporuka je koristiti Basovu tehniku, za čije se izvođenje predlaže upotreba *ultrasoft* četkica za zube[26].

Fitusiran (siRNA), a preparation which has an effect on antithrombin, is also undergoing clinical trials, and is used in the prophylaxis of bleeding in patients with severe or moderate forms of haemophilia A or B, with or without inhibitors.

Dental treatment of patients with haemophilia

Treatment of patients with haemophilia is considered one of the riskiest in everyday dental practice. That is why it is essential that the dentist is acquainted with the nature of the disease, the symptoms, and the severity of the clinical picture. Furthermore, the dentist needs to know what kind of therapy the patient receives for the treatment of haemophilia, whether the patient has been diagnosed with inhibitors to the coagulation factor, and whether the patient has concomitant diseases with special reference to possible infectious diseases (especially HIV and hepatitis C). Apart from a thorough anamnesis that gives the dentist insight into all the mentioned information, success in the dental rehabilitation of patients with haemophilia unquestionably requires good and constant cooperation between the dentist and the haematologist in charge of treating the underlying disease. Prior agreement and written consent of the haematologist is always required for performing dental treatment. In addition, the planned intervention must be performed at the exact scheduled time, when the values of the factors introduced into the patient's body (blood) are highest, i.e., one hour after the administration of factors. Interventions are recommended to be performed at the beginning of the working week, as well as earlier in the day, due to appropriate laboratory and haematological support.

Nowadays, guidebooks for the dental treatment of haemophiliacs are available, primarily emphasizing the importance of preventing oral diseases as an imperative for dentists, especially in severe forms of haemophilia and in patients with antihemophilic factor inhibitors[26]. All this stems from the fact that leading oral diseases (caries, gingivitis, and periodontal disease) and their therapy can cause serious, sometimes life-threatening bleeding.

To prevent oral diseases, the importance of regular and proper oral hygiene using atraumatic techniques is highlighted. It is recommended to use the Bass technique, which implies the recommended use of ultrasoft toothbrushes[26].

U vodičima su navedene oralne intervencije koje ne zahtevaju pripremu pacijenta faktorima koagulacije; to se prvenstveno odnosi na uklanjanje mekih zubnih naslaga i kamenca (ali se ovo ne odnosi na ulanjanje kamenca upotrebom skalera). Pominju se još i ortodontski tretman mobilnim i fiksnim aparatima (uz obavezan oprez zbog mogućih mehaničkih povreda) i protetička rehabilitacija pacijenta mobilnim nadoknadama. U procedurama restauracije treba koristiti koferdam i biti pažljiv pri radu sa matricama, kočićima, sisaljkama i pri grubom uklanjanju vaterolni. Oprez je potreban i prilikom izrade intraoralnog rentgen snimka. Treba biti obazriv i tokom endodontskih tretmana. Pri obradi korenskog kanala poželjni su pažljiva instrumentacija i punjenje kanala do apeksa. Ako dođe do krvarenja, kanal treba ispirati natrijum-hipohloritom, a zatim ga napuniti preparatima na bazi kalcijum-hidroksida ($Ca(OH)_2$). Veruje se da su prilično bezbedne tehnike lokalne anestezije bukalna infiltracija, intraligamentna (intraperiodontalna) i intrapapilarna tehnika. Za sprovodne tehnike i lingvalnu infiltraciju neophodno je pak da hematolog pripremi pacijenta. Savetuje se da se prilikom izvođenja svih tehnika lokalne anestezije koriste što tanje, tj. atraumatske igle.

Oralnohirurški tretman pacijenata sa hemofilijom

Budući da su invazivne, hirurške procedure predstavljaju poseban rizik kod pacijenata sa hemofilijom. Rizičnim se smatraju sve oralnohirurške intrevencije. To važi i za parodontalnu hirurgiju, koja predstavlja visokorizičnu intervenciju. Naime, smatra se da u njoj postoji veći rizik i od ekstrakcije zuba i da je treba izbegavati što je više moguće. Indikovana je jedino ako konzervativne mere nisu imale uspeha i ako je oralna higijena pacijenta dobra.

Uprkos tome što sa sobom nose veliki rizik, oralnohirurške intervencije mogu se izvoditi prilično bezbedno. Međutim, za to su potrebni adekvatna laboratorijska podrška (krvna slika i skrining koagulacije), pažljivo preoperativno planiranje, odgovarajuća hemostaza sa dovoljnom količinom faktora koagulacije i drugih produkata, te adekvatan postoperativni tretman.

U preoperativnom periodu treba ukloniti meke i čvrste naslage sa zuba, i to sa dezinfekcijom usne duplje preparatima na bazi hloheksidina. Pre operacije obavezno treba odrediti nivo faktora i moguće prisustvo inhibitora.

Guidebooks highlight oral interventions that do not require the preparation of the patient with coagulation factors, primarily referring to the removal of soft dental deposits and calculus (excluding the use of scalers), orthodontic treatment with mobile and fixed appliances (with special caution to possible mechanical injuries), and prosthetic rehabilitation of the patient using removable restorations. During restorative procedures, the use of rubber dams is required, with great caution when working with matrices, dental posts, suction cups and rough removal of cotton rolls. Caution is also required when making an intraoral RO image. Endodontic treatment also requires great caution. During root canal treatment, careful instrumentation and filling of the canal up to the apex is desirable. In case of bleeding, the canal should be rinsed with Na-hypochlorite, and then filled with preparations based on $Ca(OH)_2$. Regarding local anaesthesia techniques, buccal infiltration, intraligamentary (intraperiodontal), and intrapapillary techniques are considered safe, whereas nerve-block techniques and lingual infiltration require mandatory preparation of the patient by a haematologist. It is recommended to use ultra-thin atraumatic needles for all local anaesthesia techniques.

Oral surgical treatment of patients with haemophilia

Surgical procedures are invasive and pose a particular risk to patients with haemophilia. All oral surgical interventions are considered risky, including periodontal surgery, which is a high-risk intervention. It is considered that it can pose a greater risk than tooth extraction and should be avoided as much as possible. It is only indicated when conservative measures have failed and in the presence of good oral hygiene.

Despite the high risk, oral surgical interventions can be performed quite safely, but this requires adequate laboratory support (blood count and coagulation screening), careful preoperative planning, appropriate haemostasis with enough coagulation factors and other products, as well as adequate postoperative care.

During the preoperative period, it is necessary to remove soft and hard deposits from the teeth and disinfect the oral cavity with chlorhexidine-based preparations. Prior to surgery, it is necessary to determine the level of factors and possible presence of inhibitors. Haematological preparation of the patient for the procedure is obligatory and is carried out together with a haematologist.

Hematološka priprema pacijenta za intervenciju obavezna je i sprovodi se u konsultaciji sa hematologom. Preporučena doza pre ekstrakcije zuba kod hemofilije A iznosi 50 IU/kg FVIII, a kod hemofilije B 100 IU/kg F IX. Preovladava stav da nivo faktora pre ekstrakcije zuba treba da bude najmanje 50%, odnosno od 75% do 100% pre ozbiljnijih hirurških zahvata. Posebno su rizične intervencije kod pacijenata sa razvijenim inhibitorima. Kod ovih pacijenata se i u hematološkoj pripremi i postoperativno uglavnom koriste aktivisani rekombinantni F VII ili FEIBA (engl. *Factor Eight Inhibitor Bypassing Activity*), kao i aktivisani koncentrovani protrombinski kompleks (eng. *activated prothrombin complex concentrate*-aPCC). Takođe, poželjno je da se pre većih hirurških intervencija razmotri sistemska preoperativna primena antifibrinolitika u danu pre hirurške intervencije (TXA 1 g/8 h ili EACA 50 mg/kg / 6 h), a zatim sa njom nastavi narednih dana (pacijent ovu terapiju prima ukupno sedam dana)[27].

Stomatološka hirurška intervencija trebalo bi da bude pažljivo i temeljno isplanirana i sprovedena tako da trauma tkiva bude što manja. Ako postoji indikacija da se izvadi veći broj zuba, preporučuje se da se izvede višestruka ekstrakcija zuba odjednom, zbog toga što češće davanje derivata krvi transfuzijom može usloviti pojavu inhibitora u krvi bolesnika. Posle pažljive obrade ekstrakcione rane, preporučuje se da se od lokalnih hemostatičkih sredstava upotrebe oksidisana celuloza (*Surgicel*®), hemofibrin, preparati na bazi kolagena, želatinski preparati, *TachoSil*® (humani fibrinogen i trombin na kolagenskom flasteru), kao i fibrinski lepak (*Beriplast*®, *Tissucol*®). Postoje i podaci o tome da se *Ethisorb*® koristi u oralnohirurškim intervencijama (apsorptivni poliglaktin, polidioksanon)[28]. Postavljanje sutura treba sprovesti pažljivo i sa minimalnom traumom tkiva, vodeći pritom računa o izboru šavnog materijala; preporučuje se primena silka ili resorptivnog šavnog materijala. U slučaju ekstrakcije većeg broja zuba treba razmotriti primenu mekog splinta u trajanju od najmanje 48 sati.

Postoperativnom oporavku treba posvetiti veliku pažnju zbog mogućih komplikacija, pa je potrebna svakodnevna kontrola pacijenata. Pacijentu treba dati precizna uputstva kako da se ponaša u postoperativnom periodu (ne treba da ispira usta naredna 24 sata, treba da jede meku hranu, ne treba da puši, ne treba da se napreže).

The recommended dose before tooth extraction in haemophilia A is 50 IU/kg FVIII, i.e., 100 IU/kg FIX in haemophilia B. It is generally considered that the factor level before tooth extraction should be at least 50%, i.e. 75–100% before major surgical procedures. Interventions in patients with developed inhibitors are particularly risky. In these patients, activated recombinant FVII, or FEIBA (Factor Eight Inhibitor Bypassing Activity), as well as activated concentrated prothrombin complex (aPCC), are mainly used both in the haematological preparation and postoperatively.

In addition, it is desirable to consider the systemic preoperative administration of antifibrinolytics one day before major surgical interventions (TXA 1 g/8 h or EACA 50 mg/kg/6 h) and then continue the therapy for the following 7 days[27].

Dental surgical interventions should be carefully and thoroughly planned and performed with as little tissue trauma as possible. If there is an indication for multiple tooth extraction, it is recommended to proceed with tooth extraction in one act, given that frequent administration of blood derivatives via transfusion may lead to the appearance of inhibitors in the patient's blood. After the wound has been carefully treated, it is recommended to use oxidized cellulose (Surgicel®), hemofibrin, collagen-based preparations, gelatine preparations, TachoSil® (human fibrinogen and thrombin on a collagen patch) and fibrin glue (Beriplast®, Tissucol®) as local haemostatic agents. The use of Ethisorb® in oral surgical interventions (absorbable polyglactin/polydioxanone) has also been described[28]. Suture placement should be carried out carefully with minimal tissue trauma, paying special attention to the choice of suture material—the use of silk or resorbable suture material is recommended. In the case of multiple tooth extraction, the application of a soft splint for at least 48 hours should be considered.

Postoperative recovery should be given great attention due to possible complications. Therefore, daily monitoring of patients is required. The patient should be given precise instructions on how to behave in the postoperative period (24 hours without rinsing the mouth, soft diet, no smoking, no stress). Bleeding can even be expected on the 4th day after the intervention due to the presence of fibrinolysis activators in saliva, which enable the conversion of plasminogen into active plasmin thus causing pathological fibrinolysis. Hence, it is necessary to use local fibrinolytics to prevent this reaction after oral surgical interventions.

Kod njih se i četiri dana nakon intervencije može očekivati krvarenje nastalo usled prisustva aktivatora fibrinolize u pljuvački; oni omogućavaju pretvaranje plazminogena u aktivni plazmin, što prouzrokuje patološku fibrinolizu. Upravo zato, nakon oralnohirurških intervencija treba koristiti lokalne fibrinolitike koji sprečavaju ovu reakciju. U te svrhe predlaže se da se koriste Capramol, Cyklokapron, Antagosan, PAMBA, u kombinaciji sa sorbacel gazom. Osim toga, utvrđeno je da lokalna primena TXA značajno smanjuje postoperativno krvarenje. TXA je desetak puta efikasnija od aminokapronske kiseline.

Predlaže se dvominutno ispiranje usta sa 10 ml 5% rastvora po četiri puta dnevno narednih sedam dana ili lokalna aplikacija tupfera natopljenih antifibrinolitikom na ekstrakcionu ranu; to se može kombinovati i sa terapijom tabletama u narednih pet dana. Kada je reč o primeni koncentrovanih faktora koagulacije u postoperativnom periodu, *World Federation of Hemophilia* (WFH) preporučuje da se supstituciona terapija primenjuje najmanje tri dana kod manjih i najmanje od sedam do deset dana kod većih hirurških intervencija.

Indikovana je i antibiotska i analgetska terapija, a po potrebi i terapija anksioliticima. Intramuskularnu aplikaciju medikamenata i primenu nesteroidnih antiinflamatornih lekova treba izbegavati. Kada su posredi analgetici, dozvoljava se upotreba paracetamola, paracetamola sa kodeinom, paracetamola sa tramadolom, kao i COX-2 inhibitora.

Zaključak

Iako se tretman osoba sa hemofilijom smatra jednim od najrizičnijih u svakodnevnoj stomatološkoj praksi, može biti uspešno i bezbedno realizovan. Međutim, veoma je važno da stomatolog dobro poznaje prirodu oboljenja, simptome i težinu kliničke slike hemofilije. Takođe, treba znati koju terapiju za lečenje hemofilije pacijent uzima, kako i kada je uzima, da li je kod pacijenta dijagnostikovano prisustvo inhibitora faktora koagulacije, te da li pacijent ima pridružene bolesti (posebna pažnja obraća se na moguće infektivne bolesti). Osim svega navedenog, za uspešnu i bezbednu intervenciju kod pacijenata sa hemofilijom potreban je dobro isplaniran preoperativni, perioperativni i postoperativni tretman.

For this purpose, the use of capramol, cyklokapron, Antagosan, and PAMBA in combination with SorbaCt gauze is recommended. Furthermore, topical application of TXA was found to significantly reduce postoperative bleeding. TXA is approximately 10 times more effective than aminocaproic acid.

It is recommended to rinse the mouth with 10 ml of 5% solution for 2 minutes 4 times a day for the next 7 days, or to apply swabs soaked in antifibrinolytic to the extraction wound, combined with tablet therapy for the next 5 days. Regarding the use of concentrated coagulation factors in the postoperative period, the World Federation of Haemophilia (WFH) recommends the use of substitution therapy for at least 3 days for minor and at least 7–10 days for major surgical interventions.

Antibiotic and analgesic therapies are indicated, as well as anxiolytic therapy if necessary. Intramuscular administration of medication should be avoided, as should the use of non-steroidal anti-inflammatory drugs. Analgesics such as paracetamol, paracetamol with codeine, paracetamol with tramadol, and COX-2 inhibitors are permitted.

Conclusion

The treatment of patients with haemophilia is considered one of the riskiest in everyday dental practice. Despite this, dental interventions can be successfully and safely performed. However, the dentist must be well-acquainted with the nature of the disease, its symptoms and the severity of the clinical picture. Furthermore, the dentist is obliged to know what kind of therapy the patient receives for the treatment of haemophilia, whether the patient has been diagnosed with inhibitors to the coagulation factor, and whether the patient has concomitant diseases with special reference to possible infectious diseases. In addition, the key to a successful and safe intervention lies in a well-planned pre operative, perioperative and postoperative treatment of patients with haemophilia.

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