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PRIPREMA PACIJENATA SA HEMOFILIJOM A ZA ORALNOHIRURŠKE INTERVENCIJE

PREPARATION OF PATIENTS WITH HEMOPHILIA A FOR ORAL SURGERY

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Sažetak

Hemofilija A je nasledna bolest koja se karakteriše nedostatkom koagulacionog faktora VIII i sklonošću ka krvarenju. Prenosi se preko X hromozoma. Hemofilija A se karakteriše prekomernim krvarenjem u raznim tkivima organizma, uključujući mekotkivne hematome i hemartrozu. U dijagnozi hemofilije A, pored dobro uzete anamneze i pregleda, potrebno je uraditi i laboratorijske analize. Ekstrakcija zuba je najčešća hirurška procedura kod pacijenata sa hemofilijom. Hematološka priprema podrazumeva primenu koncentrovanog faktora VIII jedan do dva dana pre intervencije da bi se postigao željeni nivo faktora VIII za operaciju. Kod ekstrakcije zuba ovaj nivo iznosi 50% pre i pet dana posle ekstrakcije zuba, uz primenu antifibrinolitika. Kod oralnih hirurških intervencija željeni nivo faktora VIII preoperativno iznosi 50-80%, a posle operacije 30-80% pet dana i 30% do 14. dana, takođe, uz primenu antifibrinolitičke terapije. Pacijenti sa hemofilijom i inhibitorima se pripremaju za intervencije primenom rekombinovanog FVIIa u dozi od 120 mcg po kilogramu, sa ponavljanjem doze na svaka dva sata, u trajanju od 7 do 10 dana posle intervencije. Neophodna je primena antifibrinolitika i mere lokalne hemostaze. Mere lokalne hemostaze su nezaobilazne u slučaju oralnohirurških intervencija kod pacijenata sa hemofilijom A. Primena ovih procedura u oralnoj hirurgiji ima ulogu da minimizira mogućnost intra- i postoperativnih krvarenja kod pacijenata sa hemofilijom A. U tu svrhu se najviše koriste suture resorptivnim koncem, preparati kolagena oksiceluloze, želatina, fibrinskog lepka, uz lokalnu primenu traneksemične ili epsilon aminokapronske kiseline.
Zakljucak:*Uska saradnja hematologa i oralnih hirurga je neophodna u cilju minimiziranja neželjenih komplikacija kod pacijenata sa hemofilijom A.*

Ključne reči: *hemofilija A, oralnohirurške intervencije, krvarenje, lokalna hemostaza*

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Abstract

Hemophilia A is an inherited disease characterized by deficiency of coagulation factor VIII and bleeding tendency. It is transmitted through the X chromosome. Hemophilia A is characterized by excessive bleeding in various tissues of the body, including soft tissue hematomas and hemarthrosis. In formulating the diagnosis of hemophilia A, in addition to a well-taken medical history and physical examination, laboratory tests should also be carried out and analyzed. Tooth extraction is the most common surgical procedures in patients with hemophilia. Hematological preparation implies the application of a concentrated factor VIII for one to two days prior to the intervention to achieve a desired level of factor VIII needed for the operation. In tooth extraction, this level has to be 50% before and after the tooth extraction for 5 days, with the application of antifibrinolytic agents. In oral surgical interventions the desired level of factor VIII is 50-80% preoperatively, 30-80% for 5 days after surgery, and 30% up to 14 days, also with the use of antifibrinolytic therapy. Patients with hemophilia and inhibitors are prepared for intervention through the application of recombinant FVIIa at the dose of 120mcg/kg, repeated every 2 hours for the period of 7-10 days after the intervention. It is necessary to apply antifibrinolytic agents and local hemostatic measures. Measures of local hemostasis are unavoidable in the case of oral surgical interventions in patients with hemophilia A. Implementation of these procedures in oral surgery has the role of minimizing the possibility of intra- and postoperative bleeding in patients with hemophilia A. For this purpose, the following are mostly used: absorbable suture thread, preparations of collagen, oxycellulose, gelatin, fibrin glue, with topical application of tranexamic or epsilon aminocaproic acid.
Conclusion*: Close cooperation between hematologists and oral surgeons is essential in order to minimize unwanted complications in patients with hemophilia A*

Key words*: : hemophilia A, oral surgical interventions, bleeding, local hemostasis*

Hemofilija A

Hemofilija A je nasledna bolest koja se karakteriše nedostatkom koagulacionog faktora VIII i sklonošću ka krvarenju. Prenosi se preko X hromozoma. Češća je pojava hemofilije A (85%) u odnosu na hemofiliju B (15%). Procenjuje se da je učestalost hemofilije A 1:5000 novorođene muške dece. U Srbiji živi oko 500 osoba sa hemofilijom A, a u svetu više od 400 000 [1]. Javlja se u svim etničkim grupama i u svim delovima sveta.

Do pojave hemofilije A dolazi usled mutacije gena za VIII faktor, koji je lociran na dugom kraku X hromozoma. Bolest se javlja skoro isključivo kod osoba muškog pola. Žene su prenosioci bolesti. Njihove kćeri imaju 50% šansi da budu prenosioci, a sinovi 50% šansi da obole od hemofilije A. Sve kćeri obolelih od hemofilije će biti prenosioci, a svi sinovi će biti zdravi[1]. U mnogim slučajevima pojave hemofilije nema podataka o obolelim u porodičnoj anamnezi. Smatra se da je oko 30% slučajeva hemofilije A nastalo usled spontanih mutacija na genu za VIII faktor. Mutacije nastale u gametu muške osobe usloviće da njegove kćeri budu prenosioci, a unuci će oboleti od hemofilije A[2]. Hemofilija kod žena je ekstremno retka, zabeleženi su pojedinačni slučajevi kada je otac bio sa hemofilijom A, dok je majka bila prenosilac. Može se javiti i kod osoba ženskog pola sa poremećajima X hromozoma, kao što su Tarnerov sindrom, mozaicizam.

Na hemofiliju treba posumnjati ukoliko se dobiju anamnestički podaci o:

- hemofiliji u porodici,
- pojavi krvarenja u ranom detinstvu,
- pojavi spontanih krvarenja (pogotovu u zglobovima i mišićima),
- produženom krvarenju nakon povrede, ekstrakcije zuba ili hirurške intervencije.

Učestalost krvarenja zavisi od težine hemofilije A. Na osnovu nivoa faktora VIII smatra se da tešku hemofiliju imaju pacijenti sa vrednostima ispod 1%, umerenu sa vrednostima 1-5%, a blagu sa vrednostima 5-30%.

Kod dece sa teškom hemofilijom se simptomi krvarenja obično javljaju već u

Hemophilia A

Hemophilia A is an inherited disease characterized by deficiency of coagulation factor VIII and bleeding tendency. It is transmitted through the X chromosome. The occurrence of hemophilia A is much more frequent (85%) in comparison to hemophilia B (15%). It is estimated that the incidence of hemophilia A is 1:5000 male newborns. Accordingly, there are about 500 people with hemophilia A living in Serbia, and more than 400000 in the world [1]. It occurs in all ethnic groups in all parts of the world.

The appearance of hemophilia A is caused by the mutations in the factor VIII gene, which is located on the long arm of the X chromosome. The disease occurs almost exclusively in males. Women are the carriers of the disease. Their daughters have a 50% chance of being carriers, while their sons are 50% likely to suffer from hemophilia A. All daughters of hemophilic patients will be carriers, and all the sons will be healthy[1]. In many cases of hemophilia, there are no data of the family history of the disorder. It is believed that about 30% of hemophilia A cases occur due to spontaneous mutation in the factor VIII gene. Mutations occurring in a gamete of a male will condition that his daughters be carriers of, and his grandchildren will suffer from hemophilia A[2]. Hemophilia in women is extremely rare, and individual cases have been reported where the father was with hemophilia A, while the mother was a carrier. It can occur in females with X chromosome disorders, such as Turner syndrome, mosaicism.

Hemophilia may be suspected if the following anamnestic data are obtained:

- history of hemophilia in the family
- bleeding having occurred in early childhood
- spontaneous bleeding (especially in the joints and muscles)
- prolonged bleeding after injuries, tooth extraction or surgical intervention.

The incidence of bleeding depends on the severity of hemophilia A. Based on the

prvoj godini života, ili nešto kasnije, sa početkom veće fizičke aktivnosti deteta, a naročito sa prohodavanjem. U slučaju umerene i blage hemofilije, krvarenje se obično javlja kasnije, prilikom povreda ili hirurških intervencija. Hemofilija A se karakteriše prekomernim krvarenjem u raznim tkivima organizma, uključujući mekotkivne hematome i hemartrozu, koja vremenom dovodi do teške hemartropatije. Krvarenje u zglobnim strukturama čini 75% svih epizoda krvarenja kod pacijenata sa teškim oblikom hemofilije A[3]. Najčešće su zahvaćeni zglobovi kolena, lakta, gležnja, ramena, kuka i ručja. Hemartroze počinju osećajem nelagodnosti u predelu zahvaćenog zgloba, koja može trajati od par minuta do nekoliko sati. Zatim se javlja progresivni bol, otok, toplota i ograničena pokretljivost zgloba. Ponavljana krvarenja u zglobovima dovode do izražene destrukcije zglobne hrskavice i hiperplazije sinovije. Iako dolazi do resorpcije krvi, depoziti gvožđa iz zaostale krvi se smatraju glavnim činiocem u patogenezi hemofilične artropatije [4]. Glavna komplikacija ponavljanih krvarenja je deformacija zgloba praćena atrofijom mišića i mekotkivnim kontrakturama.

Hematomi mekih tkiva su takođe jedna od karakteristika hemofilije A. Hemoragija u potkožnom vezivnom tkivu i mišićima može se javiti spontano ili posle traume. Jednom formirani hematomi se mogu stabilizovati i postepeno resorbovati. Međutim, kod pacijenata sa umerenim, a pogotovu sa teškim oblikom hemofilije A, hematomi pokazuju tendenciju progresivnog uvećanja i širenja u svim pravcima. Usled toga, može doći do ozbiljnog ugrožavanja funkcije raznih organa i nastupanja životno ugrožavajućih situacija.

Kod pacijenata sa hemofilijom A se javljaju i krvarenja u mukozi, pseudotumori (hemoragične ciste), hematurija. Intrakranijalno krvarenje je jedan od najopasnijih hemoragijskih događaja kod pacijenata sa hemofilijom A[5]. Naime, krvarenja u mozgu su vodeći uzrok smrti kod pacijenata sa hemofilijom A. Iako se mogu spontano javiti, uglavnom su izazvane traumom, koja može biti i trivijalna. Simptomi mogu ponekad biti odloženi danima ili nedeljama.

factor VIII level, patients are considered to have severe hemophilia with values below 1%, moderate with values of 1 -5%, and mild hemophilia with values of 5 -30%.

In children with severe hemophilia, the symptoms of bleeding usually occur in the first year of life, or little later, with the beginning of increased physical activity of the child, in particular, with the first steps. In the cases of moderate and mild hemophilia, bleeding usually occurs later, on the occasion of injuries or surgical interventions. Hemophilia A is characterized by excessive bleeding in various tissues of the body, including soft tissue hematomas and hemarthrosis, which eventually leads to severe hemarthropathy. Bleeding in articular structures comprises 75% of all bleeding episodes in patients with severe hemophilia A[3]. The most commonly affected joints are the knee, elbow, ankle, shoulder, hip and wrist. Hemarthroses begin with a sense of discomfort in the affected joint, which can last from a few minutes to several hours. It is followed by progressive pain, swelling, heat and resulting limited joint movement. Repeated bleeding in the joints leads to pronounced destruction of articular cartilage and synovial hyperplasia. Although there is resorption of blood, deposits of iron from residual blood are considered to be the major factor in the pathogenesis of hemophilic arthropathy[4]. The main complication of recurrent bleedings is the joint deformation accompanied by the atrophy of muscles and soft tissue contractures.

Soft tissue hematomas are also characteristic for hemophilia A. Hemorrhage in the subcutaneous connective tissue and muscles can occur spontaneously or after trauma. Once formed hematoma may become stabilized and gradually get reabsorbed. However, in patients with moderate and especially with severe hemophilia A, hematomas show a tendency towards progressive enlargement and expansion in all directions. As a result, a serious threat to the function of various organs and life-threatening situations may occur.

U slučajevima uporne glavobolje, uvek treba razmišljati o intrakranijalnim krvarenjima.

U dijagnozi hemofilije A, pored dobro uzete anamneze i pregleda, potrebno je uraditi i laboratorijske analize. Testovi koagulacije pokazuju produženo aktivirano parcijalno tromboplastinsko vreme (aPTT) kod teške i umerene forme hemofilije A, a kod blage može biti u granicama normale. Definitivnu dijagnozu zato treba bazirati na testovima određivanja nivoa faktora VIII.

U diferencijalnoj dijagnozi treba isključiti hemofiliju B, koja se teško može klinički razlikovati od hemofilije A, mada nedavni literaturni podaci ukazuju da hemofilija B ima blaže kliničko ispoljavanje [6]. Fon Vilebrandova bolest takođe može praviti konfuziju u dijagnozi hemofilije A. Zato je neophodno određivanje nivoa faktora VIII, IX i FonVilebrandovog faktora u plazmi.

Lečenje pacijenata sa hemofilijom A sprovodi se na temelju dva principa: po potrebi, tj. u slučaju krvarenja i profilaktički, davanjem intravenskih preparata FVIII. Doza se izračunava množenjem polovine telesne mase pacijenta u kilogramima sa željenim nivoom faktora VIII u procentima.

Priprema pacijenata sa hemofilijom A za oralnohirurške intervencije

Pacijenti sa blagom hemofilijom A, a ponekad i sa umerenom, mogu biti neprepoznati sve dok hirurška inervencija ne dovede do ozbiljnog krvarenja. Krvarenje može biti odloženo nekoliko sati, a ponekad i nekoliko dana. Zarastanje rane kod ovih pacijenata je usporeno zbog neadekvatnog formiranja ugruška. Ekstrakcija zuba je najčešća hirurška procedura kod pacijenata sa hemofilijom. I druge oralnohirurške intervencije se relativno često primenjuju. Da bi se sprečile ozbiljne komplikacije koje mogu ugroziti život ovih pacijenata, kao što su širenje faringealnog ili sublingvalnog hematoma,nastalih zbog same intervencije ili primene regionalne blok anestezije, neophodna je adekvatna priprema pacijenta.

Ona podrazumeva primenu adekvatne terapije pre, za vreme i posle intervencije.

Patients with hemophilia A may also develop bleeding in the mucosa, pseudotumors (hemorrhagic cysts), hematuria. Intracranial hemorrhage is one of the most dangerous hemorrhagic events in patients with hemophilia A[5]. Specifically, bleeding in the brain is the leading cause of death in patients with hemophilia A. Although they may occur spontaneously, they are usually caused by trauma, which can be trivial. Symptoms can sometimes be delayed for days or weeks. In cases of persistent headaches in patients with hemophilia A, intracranial bleeding should always be suspected.

In formulating the diagnosis of hemophilia A, in addition to a well-taken medical history and physical examination, laboratory tests should also be carried out and analyzed. Coagulation tests show prolonged activated partial thromboplastin time (aPTT) in severe and moderate forms of hemophilia A, while in the mild form it may be within normal limits. Therefore, a definitive diagnosis should be based on the tests for determining the level of factor VIII.

The differential diagnosis should exclude hemophilia B, which can hardly be clinically differentiated from hemophilia A, although recent literature data indicate that hemophilia B develops milder clinical symptoms[6]. Von Willebrand disease can also make confusion in the diagnosis of hemophilia A. Therefore, it is necessary to determine the levels of factors VIII, IX, and von Willebrand factor in plasma.

Treatment of patients with hemophilia A is conducted on the basis of two principles: on demand (i.e. in case of acute bleeding) and prophylactically, by administering intravenous preparations of FVIII. The dosage is calculated by multiplying half the patient's weight in kilograms with the desired level of factor VIII expressed as a percentage.

Preparation of patients with hemophilia A for oral surgery

Patients with mild, and sometimes with moderate hemophilia A as well may be unrecognized until surgical intervention leads to serious bleeding. Bleeding can b delayed for several hours, and sometimes even for several days. Wound healing in these patients is slowed down due to inadequate clot formation.

Zahteva usku saradnju hematologa i oralnih hirurga, sa multidisciplinarnim pristupom, uključujući pre-hiruršku hematološku pripremu i adekvatnu peri-operativnu lokalnuhemostazu[7,8].

Hematološka priprema podrazumeva primenu koncentrovanog faktora VIII jedan do dva dana pre intervencije da bi se postigao željeni nivo faktora VIII za operaciju. Kod ekstrakcije zuba ovaj nivo iznosi 50% pre i pet dana posle ekstrakcije zuba, uz primenu antifibrinolitika (traneksemična kiselina 1 g tri puta dnevno ili epsilon aminokapronska kiselina 50 mg/kg četiri puta dnevno) neposredno pre i do sedmog dana nakon ekstrakcije [9]. Kod oralniohirurških intervencija željeni nivo faktora VIII preoperativno iznosi 50-80%, a posle operacije 30-80% pet dana, pa 30% do 14. dana, takođe uz primenu antifibrinolitičke terapije[10].

Pacijenti sa hemofilijom i inhibitorima pripremaju se za intervencije primenom rekombinovanog FVIIa u dozi od 120 mcg po kilogramu, sa ponavljanjem doze na svaka dva sata, u trajanju 7-10 dana posle intervencije. Neophodna je primena antifibrinolitika i mera lokalne hemostaze. U lakšim slučajevima se mogu koristiti i lekovi kojima se može premostiti delovanje inhibitora (FEIBA) i visoke doze koncentrovanog FVIII. Mere lokalne hemostaze su nezaobilazne u slučaju oralnohirurških intervencija kod pacijenata sa hemofilijom A. Primena ovih procedura u oralnoj hirurgiji ima ulogu da minimizira mogućnost intra i postoperativnih krvarenja kod pacijenata sa hemofilijom A. U tu svrhu se najviše koriste suture resorptivnim koncem[11], preparati kolagena[12], oksiceluloze[13], želatina[14],fibrinskog lepka[15], uz lokalnu primenu traneksemične ili epsilon aminokapronske kiseline. Primenom ovih mera, 7 do 14 dana posle intervencije, prema literaturnim podacima, krvarenja se javljaju kod manje od 2% pacijenata sa hemofilijom[7,12].

Tooth extraction is the most common surgical procedures in patients with hemophilia. Other oral surgical interventions are relatively often applied, as well. In order to prevent serious complications that can endanger the life of these patients, such as the spread of pharyngeal or sublingual hematoma caused by the intervention itself or the application of regional block anesthesia, adequate preparation of the patient is required, involving the administration of appropriate therapy before, during and after the intervention. It requires close cooperation between hematologists and oral surgeons, with a multidisciplinary approach including presurgical hematological preparation and adequate perioperative local hemostasis[7,8].

Hematological preparation implies the application of a concentrated factor VIII for one to two days prior to the intervention to achieve a desired level of factor VIII needed for the operation. In tooth extraction, this level has to be 50% before and after the tooth extraction for 5 days, with the application of antifibrinolytic agents (tranexamic acid 1 g three times daily or epsilon-aminocaproic acid 50mg/kg four times a day) immediately before and up to seven days after the extraction[9]. In oral surgical interventions, the desired level of factor VIII is 50-80% preoperatively, 30-80% for 5 days after surgery, and 30% up to 14 days, also with the use of antifibrinolytic therapy [10].

Patients with hemophilia and inhibitors are prepared for intervention through the application of recombinant FVIIa at the dose of 120mcg/kg, repeated every 2 hours for the period of 7-10 days after the intervention. It is necessary to apply antifibrinolytic agents and local hemostatic measures. In less severe cases, medications which can bridge the effect of the inhibitor (FEIBA) and high doses of FVIII concentrates may also be used.

Postoje istraživanja i sa novim sredstvima lokalne hemostaze. Nova studija navodi dobre rezultate primene autologne plazme bogate faktorima rasta u poređenju sa fibrinskim lepkom [16]. Radi se o gelu visoko koncentrovanih autolognih trombocita. Objavljena je i prva studija sa novim hemostatičkim agensom koji sadrži ekstrakte biljaka (Ankaferd Blood Stopper), sa dobrim rezultatima kontrole krvarenja kod pacijenata sa hemofilijom A[16].

Za sada ne postoje randomizovane studije koje bi pokazale koja je najbolja kombinacija procedura lokalne hemostaze i omogućile izradu terapijskih vodiča.

Zaključak

Dentalne procedure su najčešće hirurške intervencije kod pacijenata sa hemofilijom A. Komplikacije mogu biti brojne i teške, pa čak mogu ugroziti i život pacijenata. Neophodna je primena svih terapijskih mera, sistemskih i lokalnih, pre, za vreme i posle oralnohirurške intervencije, kao i redovno postoperativno praćenje pacijenata.

Uska saradnja hematologa i oralnih hirurga je neophodna, u cilju minimiziranja neželjenih komplikacija kod pacijenata sa hemofilijom A. Ona podrazumeva i primenu svih preventivnih mera, kako bi se smanjila potreba za oralnohirurškim intervencijama.

Measures of local hemostasis are unavoidable in the case of oral surgical interventions in patients with hemophilia A. Implementation of these procedures in oral surgery has the role of minimizing the possibility of intra - and post-operative bleeding in patients with hemophilia A. For this purpose, the following are mostly used: absorbable suture thread[11], preparations of collagen[12], oxycellulose[13], gelatin[14], fibrin glue[15], with topical application of tranexamic or epsilon aminocaproic acid. With the application of these measures 7 to 14 days after the intervention, bleeding occurs in less than 2% of patients with hemophilia, according to the literature[7,12].

There are some researches with new local hemostatic agents, too. A recent study reports good results of the application of autologous plasma rich in growth factors, as compared to fibrin glue[16]. It is a gel of highly concentrated autologous platelets. The first study carried out with a new hemostatic agent that contains plant extracts (Ankaferd Blood Stopper), showing good results in the control of bleeding in patients with hemophilia A, was published as well[16].

So far, there have been no randomized studies that would point to the best combination of local hemostatic procedures and facilitate the design of treatment guides.

Conclusion

Dental procedures are the most common surgical interventions in patients with hemophilia A. Complications can be numerous and difficult, and may even endanger the patient's life. The application of all therapeutic measures, both systemic and local, before, during and after the oral surgical intervention and regular postoperative monitoring of the patient are necessary.

Close cooperation between hematologists and oral surgeons is essential in order to minimize unwanted complications in patients with hemophilia A. It also includes the application of all preventive measures aimed at reducing the need for oral surgery.

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