

ZNAČAJ ALFALIPOINSKE KISELINE ZA LEČENJE HRONIČNIH RANA NA NIVOU PRIMARNE ZDRAVSTVENE ZAŠTITE: PRIKAZI VIŠE POJEDINAČNIH SLUČAJEVA

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SAŽETAK

Iako se sam pojam „rane“ i njihovo lečenje u najvećoj meri vezuje za hirurške discipline i više nivoe zdravstvene zaštite, hronične rane su deo patoloških stanja sa kojima se lekari primarne zdravstvene zaštite u svojoj svakodnevnoj praksi susreću i koje zahvaljujući savremenim oblogama i sredstvima za lečenje hroničnih rana mogu biti uspešno lečene i na primarnom nivou zdravstvene zaštite ukoliko lokalizacija i stepen zahvaćenog tkiva to dozvoljavaju (najbolje je ako je zahvaćena površna tkiva). Uvođenje alfalipoiinske kiseline, pored primene savremenih sredstava i obloga za lečenje hroničnih rana, čak i kod osoba sa dijabetesom, podspešuje i ubrzava proces zarastanja. Alfalipoiinska kiselina ima jako antioksidativno i antiinflamatorno dejstvo.

Ključne reči: primarna zdravstvena zaštita, savremene obloge, alfalipoiinska kiselina, dijabetes, hronične rane

Uvod

Rana koja i uz primenjeno lečenje standardnim procedurama ne pokazuje tendenciju zarastanja, te ostaje otvorena duže od mesec dana, smatra se hroničnom (1,2). Kompleksno zarastanje hronične rane nameće i sveobuhvatni, holistički pristup pacijentu i lečenje osnovne bolesti, s obzirom da i jedan broj rana nastaje kao komplikacija osnovne bolesti, kao što su hronična venska insuficijencija sa varikoznim sindromom, venskim refluksom, trombozom i posledičnim venskim ulkusima. Osim toga, i kod šećerne bolesti progresivno oštećenje perifernih nerava predstavlja uvod za nastanak, najpre ulceracija na stopalu, a potom i gangrene, kao najteže komplikacije, koja neretko zahteva amputaciju obolelog ekstremiteta kao neophodnu terapijsku opciju.

Lečenje hroničnih rana za svaki zdravstveni sistem i samo društvo predstavlja značajno finansijsko opterećenje uzimajući u obzir troškove lečenja, te posledičnu invalidnost, pogotovu kod pacijenata sa dijabetesom. Epidemiološki podaci govore da 70-80% svih hroničnih ulkusa čini venski ulkus, te predstavlja najčešću hroničnu ulceraciju, čiji su recidivi jako česti i lečenje dugotrajno. Učestalost je veća kod ženskog pola, u 95% sluča-

jeva lokalizovani su na unutrašnjoj strani potkolenice, u neposrednoj blizini medijalnog maleolusa (1-5). Takođe se procenjuje da 15% dijabetičara ima hroničnu uleraciju (6). Savremene obloge za lečenje hroničnih rana, zahvaljujući svojoj strukturi, omogućavaju autolitički debridman rane. U kontaktu sa ranom ostvaruju održavanje relativno konstantne temperature i vlažnosti rane, odnosno koncept vlažnog zarastanja rane, čime se proces zarastanja značajno ubrzava. U odnosu na široko primenjivanu klasičnu pamučnu gazu, savremene obloge imaju niz prednosti, počevši od jednostavne upotrebe, do omogućavanja neophodne razmene gasova između rane i spoljašnje sredine, sprečavanja penetracije mikroorganizama u ranu, sve do one najbitnije, sprečavanja isušivanja rane, a samim tim i produženog inflamatornog odgovora, čime se omogućava adekvatna sinteza i migracija ćelija neophodnih za epitelizaciju i zarastanje rane (3,4,6). Alfalipoiinska kiselina predstavlja deo terapijske palete u lečenju pacijenata sa dijabetesom, ne samo u lečenju dijabetesne polineuropatije, već zbog svog izraženog antiinflamatornog dejstva pospešuje i ubrzava zarastanje hroničnih ulkusa (7,8).

CASE REPORT

THE IMPORTANCE OF ALPHA-LIPOIC ACID FOR THE TREATMENT OF CHRONIC WOUNDS AT THE LEVEL OF PRIMARY HEALTH CARE: A CASE REPORT**Dragan Marinkovic¹**¹ Healthcare service for adults, Health Care Center Negotin, Republic of Serbia**SUMMARY**

Although the term "wounds" and their treatment is mostly associated with surgical disciplines and higher levels of health care, chronic wounds are part of the pathological conditions that primary care physicians encounter in their daily practice and which, thanks to modern dressings and means for the treatment of chronic wounds, can be successfully treated at the primary level of health care if the localization and the degree of affected tissues allow (the best case is when only surface tissues are damaged). In addition to the use of modern means and dressings for the treatment of chronic wounds, the introduction of alpha-lipoic acid, in addition to the use of modern means and dressings for the treatment of chronic wounds, even in people with diabetes, accelerates and accelerates the healing process. Alpha-lipoic acid has a strong antioxidant and anti-inflammatory effect.

Key words: primary health care, modern wound dressings, alpha-lipoic acid, diabetes, chronic wounds

Introduction

Wounds that fail to heal, although the treatment with standard procedures was applied, and stay open longer than a month are deemed to be chronic (1,2). The complex healing of a chronic wound demands a comprehensive, holistic approach to patient care and the treatment of the primary disease, considering the fact that some wounds occur as complications of primary diseases, such as chronic venous insufficiency with varicose veins, venous reflux, thrombosis, and the consequent venous ulcers, as well as diabetes, whose progressive damage of peripheral nerves represents the introduction to the appearance of foot ulcers at first, and then gangrene as the most severe complication which often demands the amputation of affected limbs as a necessary treatment option.

The treatment of chronic wounds represents a significant financial burden for the healthcare system and society, as well, considering the costs of that treatment and the consequent disability, especially in patients with diabetes. Epidemiological data indicate that venous ulcer is the most frequent chronic ulceration accounting for 70-80%

of all chronic ulcers, with the frequent recurrence and long-lasting treatment. The incidence is higher in women, and in 95% of cases they are localized on the inner lower leg above the medial malleolus (1,2,4,5). Also, it has been estimated that 15 % of all people with diabetes have chronic ulcerations (6). Modern wound dressings used for the treatment of chronic wounds, thanks to their structure, enable autolytic wound debridement. In contact with the wound, they provide and maintain relatively constant temperatures and moist environment to the wound, that is, the concept of moist wound healing, thus accelerating the healing process. In comparison to the widely applied classic cotton gauze, modern wound dressings have several advantages. First, they are easy to apply, they allow gas exchange between the wound and environment, they prevent the penetration of microorganisms into the wound and most importantly, they prevent dehydration and therefore, prolonged inflammatory response, thus enabling the appropriate synthesis and migration of cells necessary for the epithelialization and wound healing (3,4,6). Alpha-lipoic acid is one part of

Cilj prikaza sva tri pacijenta je da se ukaže da se na primarnom nivou zdravstvene zaštite može koristiti, pored savremenih obloga i sredstava za lečenje hroničnih rana, kada su procesom zahvaćena površna tkiva, i alfalipoinjska kiselina.

Prikazi slučajeva

Prikaz 1

Pacijentkinja starosne dobi 67 godina, zbog dijabetesa je na peroralnoj terapiji od 2004. godine i ima sledeće dijagnoze: *insuff. vv. perforantes, sy. varicosum cruris billat, ulcus venosum cruris lat. sin.*, zatražila je pomoć od lekara primarne zdravstvene zaštite usled recidiva venskog ulkusa na medijalnoj strani leve potkolenice. Ulkus je lokalizovan perimaleolarno, nepravilnog je oblika i ivica, sa nekrotičnim tkivom na dnu ulkusa.

U decembru 2015. godine prvi put se pristupa lečenju hronične venske ulceracije primenom dvoslojne semiokluzivne poliuretanske obloge u cilju ostvarivanja autolitičkog debridmana rane sa već prethodno uvedenim preparatom alfalipoinjske kiseline u jutarnjoj dozi od 600 mg, pored svoje redovne terapije derivatima sulfonilureje i metforminom za lečenje šećerne bolesti, te antihipertenzivne terapije ACE inhibitorima, kao i acetilsalicilne kiseline. Takođe, u terapiju se uvode i antibiotici širokog spektra parenteralnim i peroralnim putem u trajanju od dve nedelje. Debridman hronične rane se od maja meseca 2016. godine, usled već oskudnije eksudacije, nastavlja upotrebom hidrokoloidne obloge, kao i aplikovanjem gela za epitelizaciju rana, deproteinizovanog hemodijalizata teleće krvi, sve do zarastanja ulkusa.



Slika 1. Venski ulkus leve potkolenice

05.01.2016. lečenje ulkusa dvoslojnom semiokluzivnom poliuretanskom oblogom se počinje još u decembru 2015. radi postizanja autolitičkog debridmana hronične rane;
24.05.2016. i 02.08.2016. debridman hronične rane usled već oskudnijeg eksudata se nastavlja hidrokoloidnom oblogom i aplikovanjem gela za epitelizaciju rana, deproteinizovanog hemodijalizata teleće krvi sve do zarastanja ulkusa;
28.07.2020, 01.09.2020. i 25.09.2020. recidiv hroničnog venskog ulkusa, lečenje se sprovodi hidrofилnom poliuretanskom oblogom i topikalnom primenom fusidinske kiseline.

the therapeutic palette used for the treatment of patients with diabetes. It is used not only for the treatment of diabetic polyneuropathy, but due to its pronounced anti-inflammatory effect, it improves and accelerates chronic ulcer healing (7,8).

The aim of case reports of three patients was to point to the fact that in addition to modern dressings and means for the treatment of chronic wounds, alpha-lipoic acid can be used at the level of primary healthcare when surface tissues are affected by the process.

Case reports

The first case report

A 67-year-old female patient has taken medications for diabetes orally and her diagnoses

are the following: *Insuff. vv. perforantes*, *Sy. varicosum cruris billat*, *Ulcus venosum cruris lat. sin.* The woman has sought help from the general practitioner due to the recurrence of venous ulcer on the medial side of the left inner lower leg. It was a perimalleolar ulcer with an irregular shape and edges, and with the necrotic tissue at the base of the ulcer. In December 2015, chronic venous ulceration was treated for the first time by the two-layered polyurethane semi-occlusive dressing, aimed at achieving autolytic wound debridement with the previously introduced preparation of alpha-lipoic acid of 600 mg in the morning, in addition to the regular therapy including sulfonylurea derivatives and metformin used for the treatment of diabetes, antihypertensive therapy with ACE inhibitors, and acetylsalicylic acid. Also, parenteral



Figure 1. Venous ulcerations on the left shin

January 5th, 2016 – the treatment of the ulcer with the two-layered polyurethane semi-occlusive dressing that started in December, 2015 in order to achieve the autolytic wound debridement.

May 24th, 2016 and August 2nd, 2016 – due to the decreased exudation, chronic wound debridement was continued with the hydrocolloid dressing and application of gel for wound epithelialization, deproteinized calf blood hemoderivative until the ulcer healed.

July 28th, September 1st, September 25th, 2020 – the relapse of chronic venous ulcer; it was treated with the hydrophilic polyurethane dressing and topical application of fusidic acid.

Primenjenom terapijom u trajanju od osam meseci, od decembra 2015. do početka avgusta 2016. godine, ostvaruje se zarastanje i epitelizacija hroničnog venskog ulkusa.

Već atrofirana koža leve potkolenice i konstantno izlaganje fizičkom naporu uslovljava pojavu novog recidiva nakon nepune četiri godine nakon zarastanja (slika 1). U 2020. debridman recidivantnog hroničnog venskog ulkusa se, takođe, sprovodi primenom savremene obloge za lečenje hroničnih rana uz topikalnu primenu fusidinske kiseline zbog znakova lokalne infekcije ulkusa. Aplikovanju hidrofilne poliuretanske obloge i fusidinske kiseline prethodi obavezno čišćenje rane. Zarastanje i epitelizacija recidivantnog hroničnog venskog ulkusa postiže se krajem 2020. godine.

Prikaz 2

Pacijentkinja starosne dobi 75 godina je na insulinskoj terapiji poslednjih dvadeset godina i ima varikozni sindromom. Lekaru primarne zdravstvene zaštite pacijentkinja se obraća mesec dana nakon povređivanja koje je inicijalno pokušala sama da leči. Motiv za obraćanje lekaru su bili lokalni znaci pogoršanja same povrede, edem stopala i početna gangrena distalnog dela petog prsta

levog stopala. U postelji zauzima pasivan stav, telesna težina pacijentkinje je 120 kg, a indeks telesne težine ukazuje na patološku gojaznost. Odaje utisak teškog bolesnika. U terapiju se uvodi klindamicin što dovodi do delimičnog poboljšanja i regresije edema levog stopala. Međutim, davanje klindamicina moralo je biti obustavljeno usled alergijske reakcije koja se manifestovala nakon trećeg dana od započete antibiotske terapije (slika 2). Intenzitet bola je posle trećeg dana od antibiotske terapije bio manji. Zbog alergijske reakcije na klindamicin u terapiju se uvodi ceftriakson, intramuskularno dva puta dnevno po 1 gr u trajanju od sedam dana, i alfalipoinjska kiselina 600 mg u infuzionim rastvorima, jedanput dnevno u toku sedam dana. Pacijentkinja je više godina unazad imala u terapiji 600 mg dnevno alfalipoinjske kiseline peroralnim putem, što može da objasni odsusustvo simptoma i znakova dijabetesne polineuropatije, kao i povlačenje edema i početne gangrene u relativno kratkom vremenskom periodu. Primenom navedene medikamentne terapije antibioticima i alfalipoinjskom kiselinom peroralnom i parenteralnom administracijom postiže se povlačenje edema i eritema, kao i početne gangrene lokalizovane na distalnom delu petog prsta levog stopala.



Slika 2. Početna gangrena petog prsta levog stopala

Slike 2.1, 2.2, i 2.3 prikazuju edematozno stopalo sa početnom gangrenom distalnog dela petog prsta levog stopala;

Slika 2.4 prikazuje povlačenje edema i početne gangrene na primenjenu antibiotsku terapiju i alfalipoinjsku kiselinu.

and peroral broad-spectrum antibiotics have been administered for two weeks. Since 2016, due to scarce exudation, chronic wound debridement had continued using the hydrocolloid dressing, as well as the gel for the wound epithelialization, that is, deproteinized calf blood hemoderivative until the ulcer healed.

The epithelialization and healing of the chronic venous ulcer was achieved by the applied therapy that lasted eight months, from December 2015 to August 2016.

The atrophic skin of the left inner lower leg and constant exposure to physical strain caused the appearance of the new relapse after less than four years after healing (Picture 1). In 2020, the debridement of the recurrent chronic venous ulcer was also done with the help of a modern chronic wound dressing with the topical application of fusidic acid due to the signs of local infection. The wound should necessarily be cleansed before the application of hydrophilic polyurethane dressing and fusidic acid. The epithelialization and healing of the recurrent chronic venous ulcer was achieved at the end of 2020.

The second case report

A 75-year-old female patient has been on insulin therapy for twenty years and she has had the varicose syndrome. The patient came to the doctor at the primary health care center one month after she had fallen and tried to treat the wound on her own. The motives for the visit to the doctor were local signs of the exacerbation of that injury, foot edema and the initial gangrene of the distal part of the fifth toe on the left foot. Her posture was passive in bed, her body weight was 120 kg, and the body mass index indicated pathological obesity. She gave the impression of a serious patient. Clindamycin was introduced into the therapy, which led to the partial improvement and regression of the edema of the left foot, but this therapy had to be stopped due to the allergic reaction that occurred three days after the beginning of antibiotic therapy (Picture 2). The intensity of pain decreased three days after the antibiotic therapy. Due to allergic reaction to Clindamycin, Ceftriaxone was introduced intramuscularly in a dose of 1 gr two times a day within 7 days and alpha-lipoic acid of 600 mg in infusion solutions once a day within seven days.



Figure 2. Initial gangrene on the distal part of the left fifth toe

The edematous foot with the initial gangrene on the distal part of the left fifth toe is shown in pictures 2.1, 2.2 and 2.3.

Picture 2.4 shows the regression of edema and the initial gangrene after the administration of antibiotic therapy and alpha-lipoic acid.

Prikaz 3

Pacijentkinja, stara 66 godina, je hronični srčani bolesnik i 2016. godine je imala infarkt miokarda. Od 2017. godine je na terapiji hidrosikarbamidom usled hroničnog mijeloproliferativnog oboljenja, kao i na antikoagulantnoj terapiji usled poremećaja srčanog ritma po tipu atrijalne fibrilacije. Javlja se izabranom lekaru dva meseca nakon nastale ubodne rane distalnog dela medijalne strane desne potkolenice i to zbog bolova, kao i zbog razvoja periulkusnog edema i eritema neposredno nakon povređivanja. Ordinira se klindamicin 600 mg peroralno, nakon čega se pacijentkinja subjektivno oseća bolje, uz povlačenje lokalnog eritema i edema na ivicama rane. Mikrobiološkim brisom ulkusa izolovan je *Proteus mirabilis* te se ulkus leči topikalnom primenom antibiotika po antibiogramu uz primenu hidrokolidne obloge, koja se oblikuje u odnosu na dimenzije rane. Pacijentkinja poreklom iz ruralne oblasti je bila edukovana da sama primenjuje oblogu u daljem toku lečenja. Nakon tromesečnog debridmana hronične rane hidrokolidnom oblogom uz toaletu rane i lokalnim aplikovanjem antibiotika po rezultatima antibiograma postiže se zarastanje hroničnog ulkusa.

Diskusija

Superficialni venski ulkus leve potkolenice u pacijentkinje sa dijabetesom na peroralnoj terapiji (prikaz 1), predstavlja hroničnu ranu koja najčešće recidivira i čije lečenje dugo traje, često više godina (6,9). Ujedno predstavlja i primer neophodnosti sveobuhvatnog lečenja pacijenata sa hroničnim ranama, a kod pacijenata sa dijabetesom adekvatna glikoregulacija je preduslov uspešnog lečenja. Početna gangrena distalnog dela petog prsta levog stopala (prikaz 2), kao i ubodna rana distalnog dela medijalne strane desne potkolenice (prikaz 3), nakon lečenja nisu pokazivale znake recidiva.

Svi prikazani pacijenti su poreklom iz ruralnih oblasti što često uslovljava potrebu za kućnim i lečenjem u terenskim ambulancama, ukoliko priroda i lokalizacija rane to dozvoljavaju. Jedan od kriterijuma za odabir adekvatne savremene obloge je i količina eksudata u rani. Tako su za lečenje hroničnog venskog ulkusa zbog umerene eksudacije korišćene poliuretanske i potom hidrokolidne obloge, dok su za ubodnu ranu zbog oskudnog eksudata upotrebene hidrokolidne obloge. Preparati alfalipoin-ske kiseline u dozi od 600 mg dnevno su zbog svog dokazanog protektivnog i antiinflamatornog dejstva pogotovu u pacijenata sa dijabetesom ordinirani peroralnim i parenteralnim putem, čija je upotreba



Slika 3. Ubodna rana desne potkolenice

22.08.2017, 05.09.2017 i 26.09.2017. ubodna rana desne potkolenice i hidrokolidna obloga; 28.11.2017. zarastanje ulkusa topikalnom primenom levofloksacina i hidrokolidnom oblogom nakon tromesečnog lečenja.

The patient had used 600 mg of alpha-lipoic acid perorally for years, which could explain the absence of symptoms and signs of diabetic polyneuropathy, as well as the regression of edema and initial gangrene in a relatively short period of time. The regression of edema and erythema, as well as the initial gangrene localized on the distal part of the left fifth toe was achieved by the peroral and parenteral administration of the above mentioned medical therapy.

The edematous foot with the initial gangrene on the distal part of the left fifth toe is shown in pictures 1, 2 and 3. Picture 4 shows the regression of edema and the initial gangrene after the administration of antibiotic therapy and alpha-lipoic acid.

The third case report

The 66 year old patient has a chronic heart disease and she had myocardial infarction in 2016. Since 2017, she has used hydroxycarbamide due to chronic myeloproliferative disease, as well as anticoagulant therapy due to cardiac arrhythmias by type of atrial fibrillation. She came to her doctor two months after she had had stab wounds to the distal part of the medial side of the right lower leg, due to pain as well as due to development periwound

edema and erythema immediately after injuries. Clindamycine was administered in a dose of 600 mg perorally, and after that she felt better with the regression of local erythema and edema on the edges of the wound. *Proteus mirabilis* was isolated from the ulcer with the microbiological swab, and the ulcer was treated with the topical application of antibiotics according to the antibiogram, as well as with the application of hydrocolloid dressing whose shape depends on the dimension of the wound. The patient was from a rural area and therefore, she was educated to apply the dressing on her own during the further course of treatment. After the wound debridement with the hydrocolloid dressing that lasted three months, as well as cleansing and local application of antibiotics according to antibiogram results, ulcer healing was achieved.

Discussion

Superficial venous ulcer of the left lower leg in the patient with diabetes who received the therapy perorally (Case report 1) represents a chronic wound that usually recurs and whose treatment lasts a long time, often several years. The presence of diabetes is an aggravating circumstance for the healing process (6,9). It also confirms the necessity for the comprehensive treatment of patients with



Figure 3. Stab wound on the distal part of the right shin medial side August 22th, September 5th, and September 26th, 2017 – a swab wound of the right lower leg and hydrocolloid dressing. November 28th, 2017 – healing of the ulcer with the help of topical levofloxacin and hydrocolloid dressing after the treatment that lasted three months.

zajedno sa savremenim oblogama uz antibiotsku terapiju značajno ubrzala lečenje.

Zaključak

Lečenje hroničnih rana je težak zadatak za zdravstveni sistem i samo društvo, uzimajući u obzir da može trajati više meseci, ponekad i godina. Primarna zdravstvena zaštita sa svim svojim segmentima predstavlja nezaobilazan deo zdravstvenog sistema u lečenju hroničnih rana. Masovnija upotreba savremenih sredstava za lečenje hroničnih rana, kao i uvođenje u terapiju alfalipoijske kiseline, za osobe sa dijabetesom bi u značajnoj meri olakšala i ubrzala lečenje.

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chronic wounds, while adequate glycoregulation is a precondition for the successful treatment in patients with diabetes. The initial gangrene of the distal part of the left fifth toe (Case report 2), as well as a swab wound of the distal part of the medial side of left lower leg (Case report 3) did not show signs of relapse after the treatment.

All presented patients were from rural areas, which often conditioned the need for the treatment at home or in field ambulances if the nature and localization of the wound allowed that. One of the criteria for the choice of appropriate modern dressing was the quantity of exudation in the wound. Therefore, polyurethane and hydrocolloid dressings were used for the treatment of chronic venous ulcers due to the moderate exudation, while hydrocolloid dressings were used for the swab wound due to the decreased exudation. The preparations of alpha-lipoic acid in a dose of 600 mg a day were administered perorally and parenterally in patients with diabetes due to their protective and anti-inflammatory effects, and their application together with modern dressings and antibiotic therapy accelerated healing significantly.

Conclusion

The treatment of chronic wounds is a difficult task for the healthcare system and society, as well, considering the fact that it can last several months, sometimes even years. The primary healthcare with all its segments presents an unavoidable part of the healthcare system in the treatment of chronic wounds. A wider usage of modern means for the treatment of chronic wounds, as well as alpha-lipoic acid, for people with diabetes would alleviate and accelerate the treatment significantly.

Literature

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