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Recommendations for the management of leg ulcers in people with sickle cell disease

Recomendações para o manejo da úlcera da perna em pessoas com doença falciforme

Recomendaciones para el manejo de las úlceras de las piernas en personas con anemia de células falciformes

Eline Lima Borges; Josimare Aparecida Otoni Spira, Taysa de Fátima Garcia

ABSTRACT

Objective: to propose scientific evidence-based recommendations for the prevention and treatment of leg ulcers in people with sickle cell disease. **Method:** this integrative review was performed by searching through the Scopus, Science Direct, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library and Virtual Health Library databases in March 2020. **Results:** the ten studies found were published from 2010 to 2017. The 20 recommendations extracted offered evidence at levels rated very low, low and moderate, which was organized into five themes: evaluation of the patient and leg ulcer; management of the ulcer and edema; use of dressings in treating ulcers; recommendations for management of recalcitrant ulcers; and self-care for ulcer prevention. **Conclusion:** the study identified recommendations for prevention and treatment of leg ulcers in people with sickle cell disease, which can complement the conduct described in the Brazilian Ministry of Health handbook on the subject.
Descriptors: Anemia, Sickle Cell; Leg Ulcer; Clinical Protocols; Practice Guideline.

RESUMO

Objetivo: propor recomendações baseadas em evidências científicas para a prevenção e tratamento da úlcera da perna em pessoas com doença falciforme. **Método:** estudo de revisão integrativa, realizado a partir de busca nas bases de dados *Scopus*, *Science Direct*, *Cummulative Index to Nursing and Allied Health Literature*, *Cochrane Library* e Biblioteca Virtual em Saúde, em março de 2020. **Resultados:** foram publicados dez estudos entre 2010 e 2017. Extraíram-se 20 recomendações com nível de evidência classificado em muito baixo, baixo e moderado, organizadas em cinco temas: avaliação do paciente e da úlcera da perna; manejo da úlcera e do edema; utilização de coberturas no tratamento da úlcera; recomendações para manejo de úlcera recalcitrante; e autocuidado para prevenção de úlcera. **Conclusão:** o estudo permitiu identificar recomendações para prevenção e tratamento da úlcera da perna em pessoas com doença falciforme, que podem complementar as condutas apresentadas no manual do Ministério da Saúde a respeito do tema.
Descritores: Anemia Falciforme; Úlcera da Perna; Protocolos Clínicos; Guia de Prática Clínica.

RESUMEN

Objetivo: proponer recomendaciones basadas en evidencias científicas para la prevención y el tratamiento de las úlceras de pierna en personas con anemia falciforme. **Método:** esta revisión integradora se realizó mediante la búsqueda a través de las bases de datos Scopus, Science Direct, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library y Virtual Health Library en marzo de 2020. **Resultados:** los diez estudios encontrados se publicaron de 2010 a 2017. 20 recomendaciones extraídas ofrecieron evidencia en niveles calificados como muy bajo, bajo y moderado, que se organizó en cinco temas: evaluación del paciente y úlcera de pierna; manejo de la úlcera y el edema; uso de apósitos para el tratamiento de úlceras; recomendaciones para el manejo de úlceras recalcitrantes; y autocuidado para la prevención de úlceras. **Conclusión:** el estudio identificó recomendaciones para la prevención y el tratamiento de las úlceras de pierna en personas con anemia falciforme, que pueden complementar la conducta descrita en el manual del Ministerio de Salud de Brasil sobre el tema.
Descriptores: Anemia de Células Falciformes; Úlcera de la Pierna; Protocolos Clínicos; Guía de Práctica Clínica.

INTRODUÇÃO

Sickle cell disease (SCD) is a hereditary and autosomal recessive hemoglobinopathy with its geographic distribution mainly being driven by population movements, including the slave trade. Its incidence in Brazil varies between states, reflecting the ethnic heterogeneity of the population[1]. This disease is caused by a mutation in the gene which produces hemoglobin A (HbA), with a structural change in the β-globin chain on chromosome 11, where glutamic acid is replaced by valine, resulting in defective hemoglobin S (HbS)[2], which together with some other mutant hemoglobin characterizes SDC. Inherited mutations can be found in a homozygous state such as sickle cell anemia (Hb SS), or heterozygous caused by HbS inheritance in combination with another mutated hemoglobin, the most common being HbS/β-thalassemia, HbS/α-thalassemia, HbSC, HbSD and HbSE[3].

HbS polymerization is responsible for the main pathophysiological aspects of SDC. When deoxygenated, HbS polymerizes into long, rod-shaped fibers and damages red blood cells, leaving them in the classic “sickle or half-moon”

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shape. These damaged cells undergo early hemolysis, and therefore people with SCD have anemia, increased blood viscosity, an expression of adhesion molecules which cause obstruction of small blood vessels due to the shape and rigidity of the erythrocyte. Vessel occlusion usually triggers acute and chronic complications. Ischemia causes tissue damage resulting in severe pain or organ failure, and/or leg ulcer(s)[4].

Leg ulcers are more common in Hb SS disease. Its first occurrence is in the age group between 10 and 25 years, becoming rarer after 30 years[5]. A decrease in the bioavailability of nitric oxide leads to impaired endothelial function, and has been considered as a contributing factor to forming ulcers[6]. The ulcer is resistant to topical therapy, thus causing prolonged physical, psychological and social deficiency. It significantly affects quality of life, mainly due to pain which is one of the most striking differences in relation to ulcers of other etiologies[7]. In addition, these ulcers can relapse and many become recalcitrant. These two situations are associated with persistent severe pain and depression, leading to high health costs[8].

Preventing its onset or recurrence and successful treatment require coherent and systematized strategies to maximize patient compliance[9]. The Ministry of Health in Brazil published the document "Sickle cell disease - ulcers: prevention and treatment" (2012)[10] resulting from a narrative review, therefore it does not present studies which support the conducts established for preventing and treating ulcers. It is also noted that this document is out of date due to technological advances in inputs related to wound management.

In view of the above, this study aimed to propose recommendations for preventing and treating leg ulcers in people with SCD based on scientific evidence. These recommendations can complement the Ministry of Health document and assist nurses in clinical practice to identify the peculiarities of the ulcer and its management to direct care, since inadequate evaluation and a wrong choice of treatment can prolong the existence of the ulcer.

METHOD

This is an integrative review study consisting of a systematic analysis and synthesis of the findings from studies developed with different methodologies on a given subject, making it possible to include several questions or hypotheses in the same review[11]. A literature review was performed to prepare the recommendations by searching the Scopus, Science Direct, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library and Virtual Health Library (VHL) databases in which the Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), Nursing Database (BDENF) were accessed in March 2020.

Controlled descriptors were used to identify the publications according to the nomenclature of Health Sciences Descriptors (DeCS) of the Virtual Health Library (VHL) and Medical Subject Headings (MeSH) of the United States National Library of Medicine (USNLM), including: Leg Ulcer; Sickle Cell Anemia; Edema; Compression Bandages; Blood Transfusion; Recurrence. Furthermore, the following qualifiers and uncontrolled descriptors were used to broaden the search: drug treatment, Sickle Cell Anemia, Compression Therapy, prevention of recurrence. Crosses between the descriptors and qualifiers were performed with the Boolean operator "AND", using the same equation in all databases in order to refine the search for the studies (Figure 1). The reverse search feature was also used to optimize obtaining specific studies.

The following inclusion criteria were defined: studies available in full; primary study articles; and systematic or meta-analysis reviews published in Portuguese, English and Spanish in the last ten years on the study subject. This period definition is justified by the lack of original studies and guidelines on treatment, prevention and care for leg ulcers in people with SCD in recent years. Therefore, the extended time frame aimed to optimize recovering specific studies. Ongoing studies, studies on animals and narrative reviews were excluded.

The selected publications initially went through a reading and analysis by two reviewers. The disagreements were discussed with a third reviewer. An exploratory reading of the title and summary was performed to delimit the studies included in this review and supported by the inclusion and exclusion criteria. The articles selected in this phase were subjected to critical reading in full and evaluated according to the publication year, study type, evaluation of the patient with SCD and leg ulcer and topical treatment. The identification and selection process enabled selecting 10 articles, with five primary studies and five review studies (Figure 1).

The recommendations extracted from the primary studies were classified at the evidence level according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and ranked as: high (well-designed clinical trials with a representative sample, in some cases well-designed observational studies with consistent findings); moderate (clinical trials with mild limitations, well-designed observational studies with consistent findings);

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low (clinical trials with moderate limitations, comparative observational studies: cohort and case control); and very low (clinical trials with severe limitations, comparative observational studies with limitations, non-comparative observational studies, expert opinions)[21]. The review studies had their quality assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes checklist (PRISMA)[22].

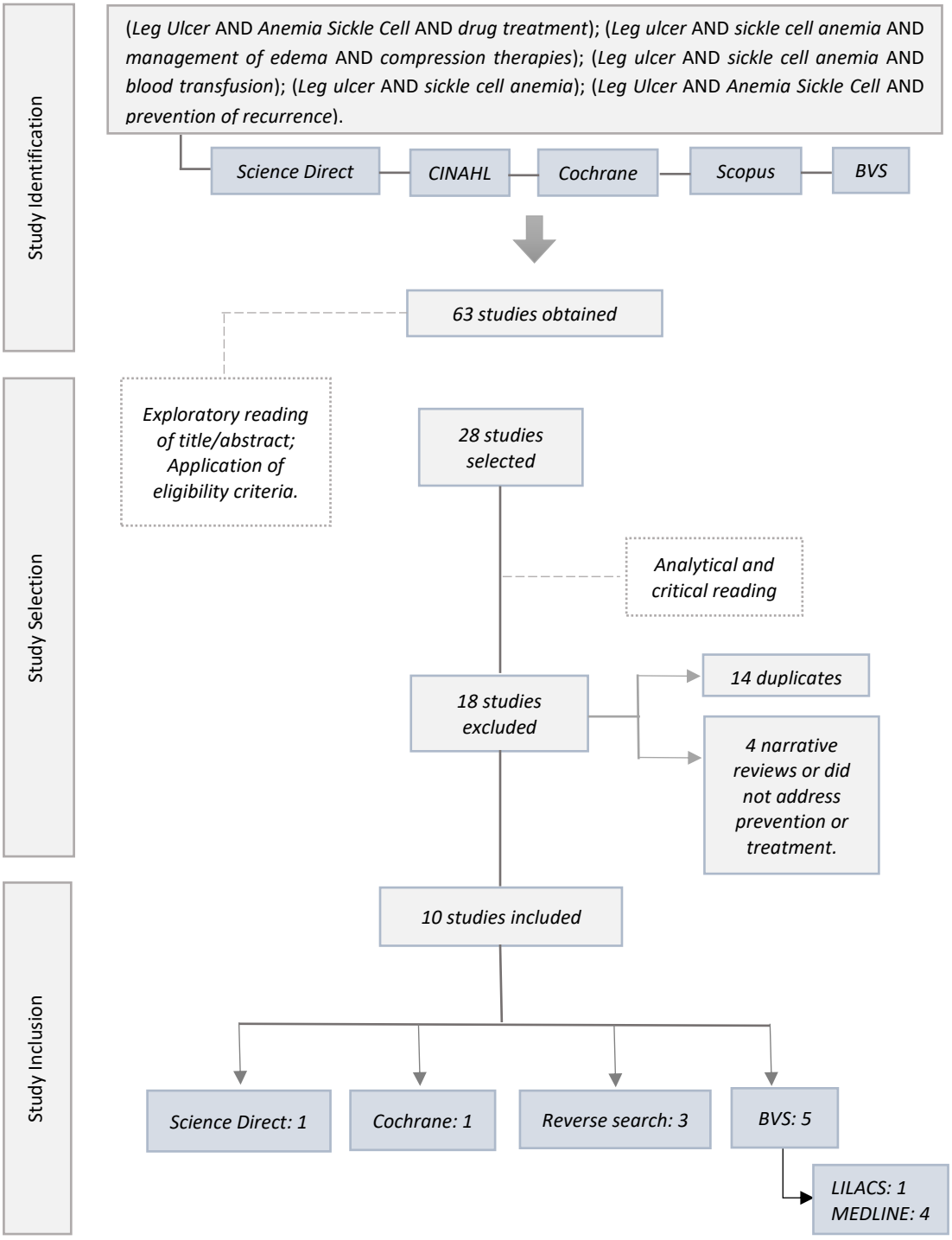

FIGURE 1: Review studies selection diagram flow. Belo Horizonte, Minas Gerais, Brazil, 2020

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RESULTS AND DISCUSSION

Five of the ten articles which comprised the sample (shown in Figure 2) were primary studies (clinical and observational), while the other five were reviews, four being systematic reviews and one classified as a critical review. The reviews were included and analyzed under PRISMA. One fully addressed the topics of title, summary, introduction, method, results and discussion, and four did not show relevance to the title, but partially met the method and summary and discussion topics. The weaknesses identified did not compromise the review quality, so they were considered eligible and maintained in the sample. However, due to the mentioned weaknesses these reviews were treated as expert opinions, and the recommendation was classified with a very low evidence level supported by GRADE.

Reference	Journal/Year	Location of the study	Study type	Database
Minniti CP, Kato GJ. [7]	Am. J. Hematol. 2016	USA	Critical review	Science Direct
Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH et al.[12]	JAMA, 2014	USA	Systematic review	BVS MEDLINE
Senet P, Blas-Chatelain C, Levy P, Manea EM, Peschanski M, Mirault T et al.[13]	Br J Dermatol, 2017	France	Prospective cohort	BVS MEDLINE
National Institutes of Health (NIH).[14]	National Institutes of Health, 2014.	USA	Systematic review	Reverse search
Martins A, Moreira DG, Nascimento EM, Soares E.[15]	Esc Anna Nery, 2013	Brazil	Single group clinician	BVS LILACS
National Health Service (NHS).[16]	National Health Service (NHS), 2010	United Kingdom	Systematic review	Reverse search
Minniti CP, Delaney KM, Gorbach AM, Xu D, Lee CC, Malik N et al.[17]	Am J Hematol, 2014	USA	Descriptive analytical	BVS MEDLINE
Delaney K-M H, Axelrod KC, Delaney K-M H, Axelrod KC, Buscetta A, Hassell KL, Adams-Graves PE, Seamon C et al.[18]	Hemoglobin, 2013	USA	Descriptive	BVS MEDLINE
Martí-Carvajal AJ, Knight-Madden JM, Martinez-Zapata MJ.[19]	Cochrane Database Syst Rev, 2014	Ecuador	Systematic review	Cochrane
Ogunkeyede AO, Babalola OA, Ilesanmi OS, Odetunde AB, Aderibigbe R, AdebayoW et al.[20]	Nigerian J Plast Surg, 2017	Nigeria	Comparative controlled	Reverse search

FIGURE 2: Characteristics of the sample articles (n=10). Belo Horizonte, Minas Gerais, Brazil, 2020.

The highest level of evidence was presented in a study when the same recommendation was present in two or more studies (primary or review).

The sample articles were published in 2010 (1/10%), 2013 (2/20%), 2014 (4/40%), 2016 (1/10%) and 2017 (2/20%). The study designs were systematic, epidemiological and comparative reviews with and without randomization. An analysis of these allowed to propose 20 recommendations with an evidence level classified as very low, low and moderate, being organized into five themes: a) evaluation of the patient and leg ulcer; b) management of ulcers and edema; c) use of dressings to treat ulcers; d) recommendations for managing recalcitrant ulcers; e) self-care for ulcer prevention.

The recommendations of this study will qualify the care provided to patients with leg ulcers resulting from SCD when adopted in clinical practice by the nursing team.

Recommendations for patient and leg ulcer evaluation

1. Investigate other causes of ulcers such as diabetes mellitus, collagen disease and chronic venous insufficiency[12] (very low evidence level).

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2. Inspect the lower extremities during the physical examination to detect active and/or healed ulcers, recording their number[14] (very low evidence level).
3. Assess the lesion and area for signs of infection[7] (very low evidence level).
4. Investigate the possibility of osteomyelitis in people with deep and recalcitrant ulcers[12, 14] (very low evidence level).
5. Measure and record the area (cm^2) and depth (cm) of each ulcer[7] (very low evidence level). The ulcer must be measured in two perpendicular directions for length and width.
6. Analyze findings related to the area and time of existence of the ulcer. An ulcer with an area < 8 cm^2 and an existence time < 9 weeks indicates healing in the next 6 months[13] (moderate evidence level).
7. Perform digital photography of the ulcer with a ruler to serve as a parameter to monitor the wound evolution and size[7] (very low evidence level).

The ulcer may appear spontaneously or due to trauma, however many arise as a result of mechanical trauma[5]. Ulcers are classified as chronic when they take more than a month to heal after emergence[3], and can develop into large ulcers which have a recalcitrant character over many years[9]. Six months seems to define recalcitrant ulcers[7].

The ulcers are mainly located in the malleoli, are shallow, exudative, with well-defined margins, slightly raised edges, and a bed with granulation tissue, which is often covered by slough[5]. The skin around the ulcer looks healthy at an early stage, but over the course of healing this skin becomes hyperpigmented, eczematous and swollen[23]. Drainage of serous exudate and thickened fibrous material are common, but erythema on the skin around the wound, purulent exudate, increased pain and ulcer size may indicate acute infection[7].

The Ministry of Health manual[10] presents a generic form which guides professionals in caring for patients with ulcers; however, information such as SCD subtype, blood transfusions and basal hemoglobin value are not present in this document, which are relevant to support professionals' clinical reasoning regarding the ulcer evolution.

Recommendations for managing ulcers and edema

1. First, implement care on the ulcer bed before progressing to treatment aimed at re-epithelialization of the edge. Local care includes debridement of devitalized tissue, controlling bacterial load or infection (distinguishing persistent inflammation from non-bacterial origin) and maintaining a moist environment in the wound bed[12,14] (very low evidence level).
2. Perform ulcer culture if infection is suspected[12,14] (very low evidence level).
3. Exclusively use systemic antibiotics when there are clinical signs of infection on the skin around the ulcer[7] (very low evidence level).
4. Manage the patient's pain, paying attention to determined facts[7,16-18] (very low evidence level).
   - Use opioid and non-opioid analgesics using skin adhesive patches, parenteral and oral routes.
   - Apply anesthetic ointments before cleaning the ulcer to reduce pain during the dressing.
   - Recommend the use of comfortable shoes and range of motion exercises.
5. Apply compression therapy, preferably multicomponent, to patients with edema or to those who spend a good time standing or sitting without alternating positions. The Unna boot should not be the first choice[7,16, 18,20] (low evidence level).

The pathogenesis of leg ulcers is complex and its exact cause remains uncertain, but there is consensus that it is multifactorial and there are several theories to explain them such as vaso-occlusion, hemolysis, hypercoagulability and thrombosis, autonomic dysfunction, genetic factors and venous incompetence, with the latter being amenable to intervention through compression therapies[9].

The Unna boot is used in managing edema, and is recommended by the Ministry of Health manual[10]; however, elastic compression therapy is not contemplated. The description of the Unna boot in that document is in the item of primary dressings, and not in a specific section for edema management. This can induce the professional to use it as primary dressing in an erroneous way.

It is known that SCD ulcers are extremely painful, being one of the most striking differences in relation to wounds of other etiologies[7]. However, the Ministry of Health manual[10] does not present recommendations for pain management in either dressing or in daily life.

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Recommendations for the use of dressings to treat ulcers

1. Select the appropriate dressing to keep the environment moist in the ulcer bed. Occlusive dressings are effective for treating ulcers[7] (very low evidence level).
2. Do not use topical antibiotics as blood circulation in the ulcer region is deficient, which facilitates the growth of resistant strains[7] (very low evidence level).
3. Use active therapies in the ulcer such as the Arginine-Glycine-Aspartic Acid peptide matrix[19] (very low evidence level), and pharmacological therapies[16,20] (low evidence level) when other factors have already been corrected and the ulcer remains stagnant[25].

The first step in treating an ulcer should be the use of a dressing which enables debridement of devitalized tissue, controlling infection and prolonged inflammation, in addition to maintaining the moisture balance[2,26] as follows:

• Curable wound: calcium alginate, plate hydrogel, hydrocolloid and acrylic.

• Critical colonization: dressings with silver or polyhexamethylene biguanide (PHMB).

• Persistent inflammation: covered with silver or PHMB.

• Hydration balance: foam, hydrofiber, calcium alginate, hydrocolloid, acrylic and film.

The Ministry of Health manual[10] presents a series of topical treatments, including adjuvant products (hydrogel), oils (essential fatty acids), enzymes (papain and collagenase) and antibiotic ointments, which are contraindicated according to the findings of this study. It also suggests the use of hyperbaric oxygen and vacuum therapy. It is noteworthy that a recent meta-analysis did not reveal the benefit of hyperbaric oxygen therapy in chronic wounds[27], but there are only reports of cases of its use in ulcers resulting from SCD7,[28]. Regarding vacuum therapy, no literature has been identified on its use in ulcers due to SCD[28].

Ulcers resulting from SCD are categorized according to the cure potential into curable, stagnant and non-curable. The approach to non-curable or stagnant wounds is more complex because the inability to heal may be related to inadequate blood supply or low hemoglobin levels (<8.0 g/dL). A stagnant wound is influenced by the patient's behavior, including treatment refusal and when the healthcare system does not provide appropriate blood to reach the appropriate hemoglobin level for wound healing[2].

Recommendations for managing recalcitrant ulcers

1. Refer the specialist to assess osteomyelitis. In this case, the doctor must order bone scintigraphy or magnetic resonance imaging and bone biopsy. Osteomyelitis is one of the complications of leg ulcers, especially the deepest ones[14] (very low evidence level).
2. Request advice and support from multidisciplinary teams, including wound care specialists for managing recurrent and recalcitrant leg ulcers[7,14] (very low evidence level).
3. Refer the patient to a general or plastic surgeon in case of large slow healing wounds. This professional can offer surgical debridement, removing chronic fibrotic borders which have low mitotic activity to stimulate healing[7] (very low evidence level).

Evaluation of the wound edge can indicate the epithelialization progress and confirm the effectiveness of the proposed treatment. A 20 to 40% reduction in the wound area after four weeks of treatment is a predictive factor for healing[23]. Non-curable wounds, as predicted, should be reevaluated and the care plan reviewed. The Ministry of Health manual[10] recommends that a patient with an ulcer should be referred to a specialized unit if the lesions do not regress after two months of treatment.

Attention should be paid to the hemoglobin level as values below 5.0 g/dL or above 20.0 g/dL are considered critical limits for both men and women, while values above 10 g/dL should be maintained (ideal) or a minimum of 8.0 g/dL[2] for healing. Grafts generally have a high failure rate and red blood cell transfusion should be considered before and after surgery, although this is an uncertain benefit[7].

Self-care recommendations for ulcer prevention

1. Guide the patient and caregiver about preventive measures, aids in curing, and minimizing the risk of recurrence[7,15] (low evidence level).
   - Avoid injuries, especially on the feet, ankles and legs, do not allow needle pricks in the lower limbs.
   - Keep the leg skin hydrated.

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- Wear socks and shoes with appropriate adjustments.
- Use insect repellents.
- Avoid prolonged periods of standing.
- Rest with lower limbs elevated as much as possible.
- Wear compression stockings when standing for extended periods.
- Avoid trauma if prompt treatment occurs.
- Seek early treatment of the ulcer.
- Maintain healthy habits: do not smoke and maintain a well-balanced nutritional diet.

2. Reinforce the fact that adherence to treatment is essential for successful cure[15] (low evidence level).

Compression stockings are recommended[9] to prevent ulcers and the risk of recurrence, however the Ministry of Health document[10] does not address this therapy.

CONCLUSION

This study identified 20 recommendations involving measures to prevent and treat leg ulcers in people with SCD, as well as complementing some of the guidelines presented in the Ministry of Health's "Sickle cell disease - ulcers: prevention and treatment" manual, thus adding new recommendations to patient management.

This study has some limitations such as the fact that the sample was exclusively composed of international articles, which may influence the definition and implementation of some recommendations by health professionals due to the precariousness of inputs in certain health services in Brazil; expanding the ten-year time frame due to the scarcity of current specific publications; in addition to including review studies as a source of evidence. These weaknesses occurred due to the insufficiency of primary studies with robust designs such as randomized controlled clinical trials comparing interventions for preventing and treating leg ulcers due to SCD.

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