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LEG ULCERS IN SICKLE CELL DISEASE: CURRENT PATTERNS AND PRACTICES

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Abstract

Leg ulcers are a debilitating complication of patients with sickle cell disease, and their frequency in North America was reported to be 2.5% by the Cooperative Study of Sickle Cell Disease more than 20 years ago. We sought to determine if the frequency of leg ulcers in sickle cell patients in the United States had declined and to assess which treatments providers use most commonly. We sent an e-mail survey to health professionals belonging to the national Sickle Cell Adult Provider Network. Responses were obtained from 31 of them (26.0%). Most of them (96.0%) reported having some patients with leg ulcers. Providers reported a total of 185 patients with active leg ulcers and 224 in the previous 5 years, for a total of 409 patients. Hb SS (homozygous sickle cell anemia) was the most common genotype of affected individuals, followed by Hb SC (double heterozygote for Hb S [$\beta 6(\text{A3})\text{Glu} \rightarrow \text{Val}$, GAG>GTG; HBB: c.20A>T] and Hb C [$\beta 6(\text{A3})\text{Glu} \rightarrow \text{Lys}$, GAG>AAG; HBB: c.19G>A]). Males showed a 2:1 predominance. Two-thirds of patients were treated with either hydroxyurea (HU) or transfusion therapy and most used compression stockings and topical therapies as directed by wound care services. We conclude that leg ulcers continue to be a debilitating complication of young adults with sickle cell disease, despite improved supportive care and the widespread use of disease modifying agents such HU and transfusion. While some providers offer office-based ulcer care, the majority prefer specialty consultation including podiatry, plastic surgery and dermatology. Despite their frequency, there is no clear consensus among providers as to the best treatment.

Keywords

Leg Ulcers; Sickle cell disease; Hydroxyurea (HU); Survey

INTRODUCTION

Sickle cell disease is an inherited disorder of hemoglobin (Hb) characterized by rigid, sickle-shaped red blood cells, vaso-occlusion, hemolytic anemia, and vasoendothelial dysfunction, which cause pain, end organ injury, and early mortality. Leg ulcers are the most

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common cutaneous manifestation of sickle cell disease resulting in significant morbidity, and were present in the first four reported patients with sickle cell disease (1,2). The worldwide prevalence of leg ulcers varies based on geographic location, with rates as high as 75.0% in Jamaica and 25.0% in the United States (3,4). Prevalence is low before 20 years of age and in genotypes other than homozygous sickle cell disease (Hb SS), but we have recently reported patients with Hb SC (double heterozygote for Hb S [$\beta 6(\text{A3})\text{Glu} \rightarrow \text{Val}$, $\text{GAG} \rightarrow \text{GTG}$; *HBB*: c.20A>T] and Hb C [$\beta 6(\text{A3})\text{Glu} \rightarrow \text{Lys}$, $\text{GAG} \rightarrow \text{AAG}$; *HBB*: c.19G>A]) disease and leg ulcers (5). Associations with increased hemolysis, pulmonary hypertension, priapism and lower Hb levels have been reported; therefore the history of cutaneous leg ulcers should be viewed as an indicator of severe disease (6–9). The presence of anemia and intravascular hemolysis have been implicated in the pathogenesis of chronic ulcers, as similar manifestations occur in other hemolytic anemias that do not have sickling, including hereditary spherocytosis, pyruvate kinase and thalassemia (10–12). Conversely, α -thalassemia trait has been found to be protective of ulcer formation, which has not been confirmed in later studies (13,14).

Many therapies have been used with some, albeit short term, success. Broadly speaking, therapies can be divided into two categories: those targeting the local wound environment and those addressing systemic factors. A recent Cochrane review listed all published trials and identified only three interventions that assessed changes in ulcer size as a measure of efficacy: arginine butyrate, RGD peptide and L-carnitine, with only the RGD peptide matrix showing a significant reduction in ulcer size when compared with a control group (15). The effect of hydroxyurea (HU) on leg ulcers in sickle cell patients is controversial, though it has been reported to cause leg ulcers in patients with myeloproliferative syndromes, it is known to increase total Hb and decrease hemolysis, thus mitigating the chronic anemia typical of sickle cell disease (16). The Multicenter Study of Hydroxyurea did not show an increased risk of leg ulcers in patients who were taking HU, but this aspect of sickle cell disease has not been studied prospectively in a randomized trial (17).

In this study, we surveyed the types of therapies that are currently being used by hematologists in the United States. We solicited information about systemic and/or topical treatments used, the total number of sickle cell patients cared for by the provider and how many had suffered from leg ulcers. Specific attention was paid to the perceived benefits of the two approved forms of sickle cell therapy, HU and chronic transfusions, on leg ulcers. Another aim was to investigate whether leg ulcers were still a common clinical complication of sickle cell disease in the United States.

METHODS

After approval from the Institutional Review Board of the National Heart, Lung, and Blood Institute, Bethesda, MD, USA, 120 health care professionals, primarily from the Sickle Cell Adult Provider Network, were sent an e-mail survey. The survey consisted of questions about the number of patients under their care with leg ulcers, both active and within the past 5 years. Providers noted the sickle genotype, age and gender of the patients. Treatments were divided into sections for systemic and topical therapies allowing the respondent to indicate their recommendations for each (*e.g.*, “have used and would recommend in select cases”). Separate questions addressed the use and perceived benefit of HU and transfusion therapy. Space was allotted for additional comments at the end of the survey. No patient identifying information was linked to the survey.

RESULTS

The overall participation rate was 26.0% (31/120). All questions were answered by 74.0% (23/31) of the respondents; the rest completed a majority of the survey questions. Respondents were divided geographically throughout the United States with 13.0% of respondents from the Western region, 10.0% in the Midwest, 32.0% in the South, and 45.0% from the Northeast. The vast majority of respondents, 96.0%, had patients with active leg ulcers. Overall, providers reported a total of 185 patients with active leg ulcers and patients in the previous 5 years, for a total of 409 patients treated with leg ulcers. Hb SS was the most common genotype of affected individuals, followed by Hb SC, reported by 23.0% of providers. Providers did not specify the number of patients of each genotype. There were no patients below the age of 20 years reported with leg ulcers. Males showed a 2:1 predominance (Table 1). The estimated total number of patients cared for by the surveyed providers was 3800, with an approximate prevalence of the ulcer phenotype of 1.0%.

About a third of the patients with leg ulcers were receiving HU, another third were on chronic transfusion therapy, and thus only 33.0% were not on any enhanced therapy for sickle cell disease. Of those that responded, HU was felt to be beneficial to ulcer healing by 25.0%. Chronic transfusion therapy was advocated by 33.0%; respondents equally used simple red cell transfusion and red cell exchange transfusion. Physical compression therapy, such as that provided by Unna boots or compression stockings, was universally used and recommended. Seventy percent of the respondents reported having used a skin graft and surgical debridement for select cases. One-third reported using oral/topical zinc sulfate supplementation. Treatment with maggot biotherapy ($n = 1$), hyperbaric oxygen ($n = 2$), and topical growth factors ($n = 3$) were limited. No provider reported using amputation as a form of treatment for sickle cell disease-related ulcers. Over half of the respondents (58.0%) referred patients outside their clinic for specialty wound care.

DISCUSSION

With this survey we focused on the demographics and common treatments used for sickle cell disease patients with leg ulcers in the United States in an attempt to offer a snapshot of current practices. We confirmed the male predominance of this phenotype, in agreement with previous studies (3). Interestingly Hb SC disease was noted as the second most common sickle cell genotype by our respondents, in contrast with older accounts of leg ulcerations being virtually unheard of in this group. More recent publications have indeed demonstrated that leg ulcers can occasionally be found in Hb SC patients, albeit with a lower incidence (14).

We identified predominant treatment strategies used for leg ulcers among United States providers. Only a third of providers prescribed oral or topical zinc sulfate, suggesting a decreased awareness that zinc deficiency has a high prevalence in the sickle cell population and is a component of wound healing (18). In addition, a controlled trial of oral zinc sulfate therapy in sickle cell patients showed improvement in leg ulcers (19). Physical compression, as with Unna boots or compression stockings, has not been prospectively tested in the sickle cell population, but is supported by research in other types of skin ulcers (20). This was the only therapy used and recommended by all respondents. The reported occasional use of skin grafts and surgical debridement demonstrates an adoption of treatment strategies from other populations, given studies that have shown efficacy in resistant ulcers in non sickle cell disease populations (21). Providers were not asked to comment on the failure rates of these therapies, which are reported to be high (3). Treatments historically used for other types of ulcers, such as maggot therapy and hyperbaric oxygen have not been studied in sickle cell patients and are in limited use by providers in our survey, probably because of the lack of

consensus on their effectiveness and difficult access. Recent randomized trials of maggot therapy in other types of leg ulcers have reported mixed results. Durnville *et al.* (22) observed reduced time to debridement, but increased ulcer pain and no improvement in rate of healing. In diabetic ulcers, maggot debridement provided outcomes equal to conventional surgical treatment (23). At the NIH Clinical Center, MedicalMaggots™ (disinfected *Phaenicia sericata* larvae; <http://www.monarchlabs.com>) have been utilized. In the last 5 years, four patients with sickle cell disease have received this therapy; the results have been mixed. We have observed a temporary improvement in ulcer appearance, quickly followed by relapse and unclear long-term benefit. Pain has been a limiting factor for the use of medicinal maggots in this population and at this point it is reserved only for poor candidates for surgical debridement (C.P. Minniti, personal observation). Hyperbaric oxygen facilitates healing in diabetic ulcers, though its use in chronic wounds associated with other pathologies still needs rigorous examination (24,25). Anecdotal reports of pain crisis exacerbation or initiation after its use in sickle cell disease and limited availability of appropriate facilities and economic factors may also restrict its use. Newer therapy modalities with reported efficacy including topical molgramostim, RGD peptide matrix, and IV or oral arginine butyrate were not used (26–28). This is probably due to the fact that these therapies are not commercially available, outside a clinical trial.

The role of HU for sickle cell ulcers remains controversial. Hydroxyurea, through its increase in mean Hb and fetal Hb, could be beneficial to ulcer healing, and indeed cutaneous ulcers are rare in Saudi Arabian patients with sickle cell disease, who usually have a high prevalence of hereditary persistence of Hb F (29). There are no prospective trials that specifically address the effects of HU use on leg ulcer healing or formation in the sickle cell population. On the other hand, there are reports of ulcer formation after HU use in other patient populations, and anecdotal evidence for worsening of leg ulcers in some patients with sickle cell disease (30,31). Only a quarter of providers in our survey felt that HU was helpful in healing leg ulcers. Transfusions have also not been subjected to a prospective controlled study in leg ulcers, but have been advocated for therapy, with the goal to increase the oxygen-carrying capacity of blood by raising the Hb concentration and diluting the Hb S (2,32). Complications associated with transfusion including iron overload, alloimmunization and patient preference.

The estimated prevalence of the leg ulcer phenotype from this survey is lower than what has been reported in sickle cell patients in North America over the past 50 years. This is a very imprecise estimation, due to the fact that this survey is, at best, a convenience sampling of the number of sickle cell patients with and without leg ulcers served by the responding practitioners. If we accept that the prevalence of the leg ulcer phenotype is decreasing, we can speculate that this may be due to an improvement in the overall care for this population and to the frequent use of disease modifying agents, such as HU or transfusion therapy. While many providers offered office-based ulcer care, the majority referred to specialty consultation services, including podiatry, plastic surgery and dermatology. A prospective comparative effectiveness study comparing management by wound specialists vs. sickle cell providers would help to validate this treatment approach, which could also be responsible for the decline in the number of patients with chronic leg ulcers. When interpreting the results of this survey, we acknowledge the limitations of convenience sampling and selection bias given the small number of respondents. It is known that surveys have a low rate of completion, more so when no incentive is offered, as in our study. However, the variety of responses support this as a valid representation of the numbers and therapies offered throughout the nation. The survey was sent to members of the Sickle Cell Adult Provider Network, many of whom primarily see adult patients, thus the number of pediatric patients is probably under represented.

While epidemiology and factors modifying risk have been explored, there continue to be significant gaps in the medical literature describing the natural progression of this serious complication, even in the HU era. The variety of treatment options used over the past 50 years have not been explored in definitive randomized clinical treatment trials aimed to help providers formulate “best practice” care plans. Therefore, much remains to be studied regarding leg ulcers in sickle cell disease.

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TABLE 1**Reported Patient Demographics**

		Number of Patients
Gender	Males	72
	Females	37
	Not reported	78
Active ulcers		187
Ulcers in the past 5 years		24
		Number of Respondents
Age	<10 years	0
	10–20 years	4
	20–40 years	22
	>40 years	13
Genotype	Hb SS	24
	Hb SC	7
	Hb S- β -thalassemia ^a	2
	Other	1

^aHb S- β -thalassemia: double heterozygote for Hb S and β -thalassemia.