

# Brief topical sodium nitrite and its impact on the quality of life in patients with sickle leg ulcers

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## Abstract

Cutaneous ulceration from sickle cell disease negatively impacts quality of life. Topical sodium nitrite has previously been shown to reduce the size of sickle leg ulcers. This study examined how topical sodium nitrite impacted the quality of life scores in patients with sickle leg ulcers.

We prospectively collected data in patients enrolled in a leg ulcer study (n = 17) or an allogeneic hematopoietic cell transplant study (nonulcer group, n = 15). Both groups completed a pretreatment Short Form-36 questionnaire; the ulcer group completed a second questionnaire after 4 weeks of topical sodium nitrite applications. Data were analyzed by age, sex, >50% area improvement postintervention, and sickle-related complications (vaso-occlusive crises, pulmonary hypertension, or avascular necrosis). Physical and mental component summary scores were analyzed with Student *t* test.

Physical summary scores were lower than mental summary scores in all groups, indicating leg ulcers among other sickle related complications negatively impacted physical quality of life measures. After sodium nitrite use, physical summary scores improved in the leg ulcer group (34.5 ± 9.4 to 39 ± 10.3, *P* = .03), and mental summary scores improved more in ulcerated patients ≤ 35 years old (40.7 ± 6.9 to 51.7 ± 9.7, *P* = .01).

Brief topical sodium nitrite has the potential to improve quality of life, especially in younger individuals. Longer treatment duration and randomized-controlled trials are needed to confirm the efficacy of this topical therapy.

**Abbreviations:** AVN = avascular necrosis, COPD = chronic obstructive pulmonary disease, MCS = mental component summary, NO = nitric oxide, PCS = physical component summary, PHTN = pulmonary hypertension, QOL = quality of life, SCD = sickle cell disease, SD = standard deviation, SF-36 = medical outcomes study short-form 36-item survey, VOC = vaso-occlusive crises.

**Keywords:** leg ulcer, quality of life, sickle cell, sodium nitrite, wound

## 1. Introduction

Improvements in managing acute and chronic complications of sickle cell disease (SCD) have led to an increase in overall life

expectancy for children living in high resource countries.<sup>[1]</sup> As a result, the prevalence of chronic end organ damage, such as stroke, pulmonary hypertension (PHTN), renal injury, avascular necrosis of bone and joints (AVN), and cutaneous ulceration, is likely to increase as most children with SCD are living into adulthood.<sup>[2]</sup>

Cutaneous ulcerations, or sickle cell ulcers, manifest mostly as distal leg ulcers around the malleoli, areas with thin skin and small amounts of subcutaneous fat.<sup>[3]</sup> Sickle leg ulcers have a complex and partially understood etiology with a prevalence of 8% to 10% in North America.<sup>[4–6]</sup> These ulcers heal as much as 16 times slower than venous stasis ulcers and have recurrence rates as high as 49% to 97%.<sup>[3,4,7,8]</sup>

Topical sodium nitrite, providing nitrite anions, is a vasodilator in vivo by generating nitric oxide (NO) in tissues with lower oxygen tension and pH.<sup>[9]</sup> This mechanism involves human hemoglobin and myoglobin as oxygen and pH dependent nitrite reductases, and sodium nitrite as the substrate for NO generation. When applied topically to the wound, sodium nitrite produces NO locally and promotes vasodilation. Additionally, NO may aid wound healing by stimulating extracellular matrix production, immune response modulation, and keratinocyte proliferation.<sup>[10]</sup> We applied topical sodium nitrite to sickle leg ulcers in a phase I safety trial, and previously reported the primary outcome of wound healing after sodium nitrite application.<sup>[10]</sup>

Sickle leg ulcers have a significant impact on patients' morbidity and quality of life (QOL).<sup>[11–13]</sup> These ulcers directly impact work capacity, mood, and sleep.<sup>[14,15]</sup> The time required for daily ulcer care and provider appointments can result in decreased participation in school, work, or family activities. The

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Clinical Trial Consortium for Comprehensive Sickle Cell Centers identified factors negatively associated with QOL.<sup>[16]</sup> Older age, specifically ages 30 to 50, vaso-occlusive crises (VOC), asthma, AVN, and concurrent use of opioid and antidepressants, all reduced QOL scores. In other studies, sickle leg ulcers have had significant individual effects on the scores of the SF-36 survey, a generic measure of QOL.<sup>[16,17]</sup> However, studies reporting the role of sickle leg ulcers on health-related QOL are limited.

Using these patient-reported outcomes allows surveillance of therapeutic modalities over time, and identify treatments that would most benefit patients, or document the magnitude of such benefit.<sup>[18]</sup> We now report a secondary outcome on the impact of sickle leg ulcers on QOL summary scores before and after 4 weeks of topical sodium nitrite.

## 2. Methods

All patients provided written informed consent in accordance with the Declaration of Helsinki to clinical research protocols approved by the institutional review board of the National Heart, Lung, and Blood Institute. We prospectively collected QOL data in two groups of adults with SCD. The leg ulcer group was comprised of those with at least one cutaneous ulcer of at least 4 weeks duration, and an ulcer surface area between 2.5 and 100 cm<sup>2</sup>, enrolling in a phase I trial using topical sodium nitrite (clinicaltrials.gov, NCT01316796).<sup>[10]</sup> The accrual to a higher dose of sodium nitrite, from 0.5% to 2%, was based on the tolerability (lack of blood pressure changes, pain or edema after application, or methemoglobinemia <7%). The leg ulcer group received standard wound care and experimental topical sodium nitrite twice weekly for 4 weeks while continuing their sickle specific therapy (hydroxyurea or chronic transfusions). Those with small ulcers (<2.5 cm<sup>2</sup>), ulcers with infection, or ulcers suspected to be due to comorbid diabetes, venous stasis, or peripheral vascular disease were excluded.

The control, nonulcer group consisted of patients with SCD enrolled to receive allogeneic hematopoietic stem cell transplantation (clinicaltrials.gov, NCT00061568).<sup>[19,20]</sup>

Both groups completed a baseline Medical Outcomes Study 36-item Short-Form Survey (SF-36). A follow-up SF-36 was obtained in the leg ulcer group after sodium nitrite treatment. All surveys were scored using the algorithm set forth by the SF-36 Health Survey Manual.<sup>[21,22]</sup> The SF-36 embodies 8 scaled health dimensions including: physical function, physical role function-

ing, bodily pain, general health, vitality, social role functioning, emotional role functioning, and mental health. These 8 subscales were combined and reported here as physical and mental component summary (PCS and MCS) scores, as frequently reported in the literature. Subscale, PCS, and MCS scores are on a 100-point scale and have a normative mean of 50, with a standard deviation (SD) of 10, based on the 1998 National Survey of Functional Health Status.<sup>[23,24]</sup> The accrual of the study was based on the tolerability of sodium nitrite application, not on secondary QOL measures.

The data were analyzed by age, sex, >50% leg ulcer area healing over the 4 weeks of the intervention, occurrence of at least one VOC within 12 months preceding the treatment intervention, PHTN (confirmed by right heart catheterization), or AVN (documented by imaging). PCS and MCS scores were averaged for each subgroup. Statistical analyses of the mean summary scores were performed with paired or unpaired Student *t* tests with significance defined as *P* < .05. Statistical analyses were conducted using the statistical software StatPlus (version 6.0, AnalystSoft, Inc.).

## 3. Results

The entire cohort included a total of 32 participants, mean age of 35.9 ± 9.4 years (range 18–58). Seventeen participants were in the leg ulcer group (mean age 37 ± 10.2) and 15 in the control group (mean age 34.67 ± 8.6; *P* = .49). In the leg ulcer group, 9 patients were taking hydroxyurea and 3 patients were receiving chronic transfusions. In the control group, all were taking hydroxyurea for at least 2 months in preparation for planned hematopoietic cell transplant. Mean baseline PCS scores were lower than MCS scores (*P* = .03) and below the national normal mean of 50 (Tables 1 and 2).

Using the overall mean age, we further analyzed those >35 years and those ≤35 years at baseline. Individuals ≤35 years with leg ulcers had lower baseline MCS scores (40.7 ± 6.9, *n* = 8) than those in the same age group without a leg ulcer (51.1 ± 10.9, *n* = 9, *P* = .03) and those >35 years with a leg ulcer (50.8 ± 9.8, *n* = 9, *P* = .01). No other significant differences were noted in baseline summary scores between the corresponding leg ulcer subgroups.

We then focused our analyses on the leg ulcer group. The leg ulcers were present for >12 months in 7 of 17 individuals (41%). The mean leg ulcer area was 6.0 ± 3.4 cm<sup>2</sup> before topical sodium nitrite application and decreased to 3.3 ± 2.7 cm<sup>2</sup> after 4 weeks of

**Table 1**  
Physical and mental component scores in patients with sickle cell disease.\*

	Subgroups	n	Baseline PCS	Postintervention PCS	Change in PCS postintervention	Baseline MCS	Postintervention MCS	Change in MCS postintervention
Control group	All	15	33.3 ± 12.9	—	—	51 ± 10.5	—	—
	≤35 y	9	30.5 ± 12.9	—	—	51.1 ± 10.9	—	—
	>35 y	6	37.4 ± 13	—	—	50.9 ± 10.8	—	—
	Male	6	39.7 ± 11.7	—	—	48.8 ± 12.5	—	—
	Female	9	28.9 ± 12.4	—	—	52.5 ± 9.4	—	—
Leg ulcer group	All	17	34.5 ± 9.4	39 ± 10.3	<i>P</i> = .03	46 ± 9.8	50.5 ± 8.9	<i>P</i> = .13
	≤35 y	8	33.3 ± 9.4	38.7 ± 8.8	<i>P</i> = .09	40.7 ± 6.9	51.7 ± 9.7	<i>P</i> = .01
	>35 y	9	35.6 ± 9.9	39.2 ± 12.1	<i>P</i> = .23	50.8 ± 9.8	49.5 ± 8.7	<i>P</i> = .73
	Male	8	38.3 ± 11.4	41.2 ± 13.3	<i>P</i> = .11	47.8 ± 7.6	52.8 ± 8.6	<i>P</i> = .26
	Female	9	31.2 ± 6.1	37 ± 7.2	<i>P</i> = .12	44.5 ± 11.6	48.5 ± 9.3	<i>P</i> = .36

MCS = mental component summary, PCS = physical component summary.

\* A score of 50 reflects the national average, with higher scores reflecting better well-being or less symptomatic. Intervention was 4 weeks of topical sodium nitrite to sickle leg ulcer of at least 2.5 cm<sup>2</sup> or greater.

**Table 2**  
Quality of life scores before and after sodium nitrite application\*.

		Analysis of disease characteristics						
Subgroups	n	Baseline PCS	Postintervention PCS	Change in PCS after intervention	Baseline MCS	Postintervention MCS	Change in MCS after intervention	
Leg ulcer group	>50% healing of ulcer area after intervention	8	34.6±9.5	41.3±7	<i>P</i> =.08	46.3±7.2	54.3±8.4	<i>P</i> =.16
	<50% healing of ulcer area after intervention	9	34.4±9.9	36.9±12.7	<i>P</i> =.26	45.8±12.1	47.2±8.5	<i>P</i> =.64
	No VOC in the past 12 mo	8	36.5±7.7	38.9±9.2	<i>P</i> =.33	49.5±7.6	54.1±5.7	<i>P</i> =.14
	1 or more VOC in the past 12 mo	9	32.7±10.9	39±11.8	<i>P</i> =.07	43±10.9	47.4±10.4	<i>P</i> =.4
	No PHTN	14	34.9±9.8	40.3±10.7	<i>P</i> =.02	45±8.9	50.2±9.3	<i>P</i> =.14
	History of PHTN	3	32.6±8.8	32.5±5.8	<i>P</i> =.98	51.1±14.1	52.3±8.1	<i>P</i> =.8
	No AVN	13	33.7±9.3	40±10.3	<i>P</i> =.01	46.6±9.9	50.3±8.7	<i>P</i> =.31
	History of AVN	4	37.3±10.8	35.7±11.2	<i>P</i> =.54	44.2±10.4	51.2±10.9	<i>P</i> =.25

AVN=avascular necrosis, MCS=mental component summary, PCS=physical component summary, PHTN=pulmonary hypertension, VOC=vaso-occlusive crisis.  
\* A score of 50 reflects the national average, with higher scores reflecting better well-being or less symptomatic.

applications (*P* < .01) (Supplementary Materials, <http://links.lww.com/MD/C627>, <http://links.lww.com/MD/C628>). One patient achieved complete closure. No serious adverse events occurred. There were grade 1 adverse events that resolved spontaneously: asymptomatic decrease in diastolic blood pressure below 50 mm Hg, burning, pruritus, and oxygen desaturation to 91%. No patient discontinued the trial because of drug-related toxicities.<sup>[10]</sup>

The overall PCS scores were higher postintervention (*P* = .03). Significant PCS score improvements were seen in those without PHTN (34.9±9.8 to 40.3±10.7, *n* = 14, *P* = .02) and without AVN (33.7±9.3 to 40±10.3, *n* = 13, *P* = .01).

In contrast to PCS, the overall MCS scores after the intervention were higher, but only as a trend (*P* = .13). None of the MCS scores in subgroup analyses showed a significant postintervention increase, except in those ≤35 years of age (40.7±6.9 to 51.7±9.7, *n* = 8, *P* = .01).

Improvements occurred in SF-36 health dimensions bodily pain (33.6±6.8 to 44.5±8.9, *P* < .01), vitality (43.8±7.3 to 49.5±9, *P* < .01), and social role functioning (39±11.8 to 46.4±9.9, *P* = .02).

#### 4. Discussion

This study aimed to quantify perceived health-related QOL metrics in a small cohort of patients with SCD and chronic ulcers before and after topical sodium nitrite therapy. Overall, baseline SF-36 component summary scores showed that these lower extremity ulcers had the potential to negatively influence the individuals' physical QOL (PCS), more than mental QOL (MCS). Previous studies have described similar outcomes in sickle cell patients and have correlated subjective pain at the ulcer site to impaired QOL.<sup>[16,17,21,25-28]</sup> It was not surprising that PCS was lower than MCS scores in our leg ulcer cohort, since pain had a greater impact on PCS scores.<sup>[22,29]</sup> It was also noteworthy to point out that leg ulcer pain may have contributed to pain crises, since the mean PCS score was lower in those with at least one VOC in the preceding 12 months (32.7±10.9), compared to those without VOC (36.5±7.7, *P* = .42).

Sickle leg ulcers may negatively impact MCS scores as well. The presence of ulceration in the ≤35 years subgroup was associated with lower MCS scores (40.7±6.9), which were below an accepted threshold of clinical depression (MCS=42).

Similarly, a sickle cell referral center in France examined a small cohort of patients with sickle leg ulcers and observed depression or mood changes in 85% of subjects.<sup>[30,31]</sup> We hypothesized younger patients with ulcers may have felt more alienated from their peers, resulting in increased psychological stress, lower self-esteem, and/or depression, since they were still maturing psychosocially.

After serial applications of topical sodium nitrite, the leg ulcer group demonstrated improvements in PCS scores, possibly related to a reduction in pain, as previously reported.<sup>[10]</sup> This improvement was observed especially in those with >50% ulcer healing (Table 2, *P* = .08), suggesting a possible relationship between ulcer size and QOL. Additionally, bodily pain improved the most among the SF-36 dimensions (Table 3).

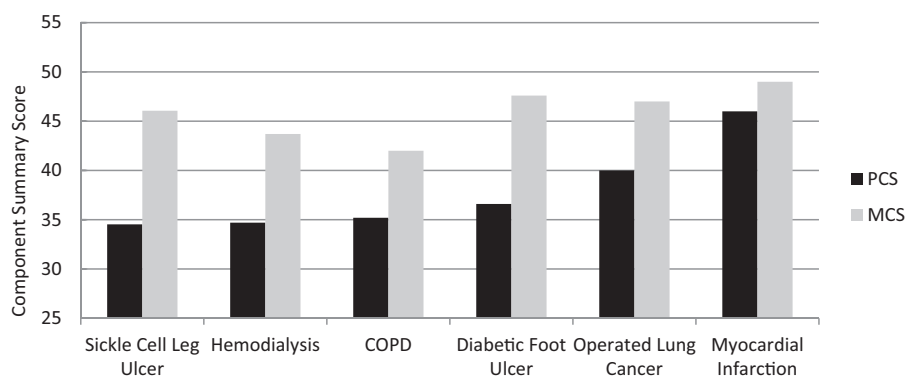
Postintervention MCS scores increased modestly overall and in subgroup analyses, mostly in the ≤35 years subgroup. This may signify that younger patients have a greater likelihood of QOL improvements with topical sodium nitrite use, though further studies are needed.

The SF-36 questionnaire had previously been validated and applied to other chronic conditions.<sup>[21,23,24,27,28,32,33]</sup> We compared our results to previously published PCS and MCS scores from patients with other diseases (Fig. 1). The PCS scores in patients with sickle leg ulcers were similar to patients with diabetic foot ulcers, receiving hemodialysis, or with chronic obstructive pulmonary disease, and lower than patients with operated lung

**Table 3**  
Mean pre-post intervention scores by SF-36 health dimension.

Health dimension	Baseline	Postintervention
Physical functioning	37	39.6
Physical role functioning	37.3	39.9
Bodily pain	33.6	44.5
General health	38.7	39.8
Vitality	43.8	49.5
Social role functioning	39	46.4
Emotional role functioning	40.1	43.7
Mental health	46.8	50.1

Note: The normative mean for the general population is 50±10.<sup>[24]</sup>



**Figure 1.** Comparative SF-36 summary scores. SF-36 component summary scores for groups with a sickle cell leg ulcer,<sup>[34]</sup> hemodialysis,<sup>[35]</sup> chronic obstructive pulmonary disease (COPD),<sup>[36]</sup> operated lung cancer,<sup>[37]</sup> or myocardial infarction.<sup>[38]</sup> Note: The normative mean for the general population is  $50 \pm 10$ .<sup>[24]</sup>

cancer or myocardial infarction. It was interesting to note that leg ulcers, which were perceived to be less medically urgent or require less medical attention, actually had a larger negative impact on QOL than some of the aforementioned diagnoses.

Our study was limited by small sample size, which likely reduced the generalizability to all patients with sickle leg ulcers. Additionally, longer than 4 weeks of treatment may be needed to confirm or observe greater improvement in QOL measurements, considering the recalcitrant nature of sickle leg ulcers.

## 5. Conclusion

Sickle leg ulcers contributed to the negative impact on health-related QOL scores, more than several medical illnesses that were perceived to require more care. Topical sodium nitrite has the potential to improve the broad physical component summary scores of QOL after 4 weeks of treatment. Longer treatment and randomized controlled trials would be needed to confirm the efficacy of sodium nitrite or other treatments.

## Author contributions

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