

Nonhealing Wounds Caused by Brown Spider Bites: Application of Hyperbaric Oxygen Therapy

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ABSTRACT

BACKGROUND: Bites by *Loxosceles* spiders (also known as recluse spiders or brown spiders) can cause necrotic ulcerations of various sizes and dimensions. The current standard of care for brown spider bites includes analgesics, ice, compression, elevation, antihistamines, and surgical debridement. Hyperbaric oxygen therapy (HBOT) in the treatment of brown spider bites has been administered in the early stage of ulceration, or 2 to 6 days after the bite. Unfortunately, the diagnosis of spider bite-related ulcers is often delayed and weeks or months may elapse before HBOT is considered.

OBJECTIVE: To evaluate the effect of HBOT on nonhealing wounds caused by brown spider bites in the late, chronic, nonhealing stage.

METHODS: Analysis of 3 patients with brown spider-bite healing wounds treated at The Sagol Center for Hyperbaric Medicine and Research in Israel. Patients presented 2 to 3 months after failure of other therapies including topical dressings, antibiotics, and corticosteroids. All patients were treated with daily 2 ATA (atmospheres absolute) with 100% oxygen HBOT sessions.

RESULTS: All 3 patients were previously healthy without any chronic disease. Their ages were 30, 42, and 73 years. They were treated once daily for 13, 17, and 31 sessions, respectively. The wounds of all 3 patients healed, and there was no need for additional surgical intervention. There were no significant adverse events in any of the patients.

CONCLUSIONS: Microvascular injury related to brown spider bites may culminate in ischemic nonhealing wounds even in a relatively young, healthy population. Hyperbaric oxygen therapy should be considered as a valuable therapeutic tool even months after the bite.

KEYWORDS: brown spider, hyperbaric oxygen therapy, nonhealing wounds, recluse spider

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INTRODUCTION

Loxoscelism results from bites by spiders from the *Loxosceles* genus, generally known as brown spiders or recluse spiders. There are more than 100 species distributed around the world. In the United States, most cases are caused by *Loxosceles reclusa* and *Loxosceles deserta*, found in the Southeast and Southwest, whereas *Loxosceles rufescens* causes most cases in Europe and Mediterranean countries.¹ These spiders are nocturnal and reclusive, hiding in closets, garages, and other enclosed spaces. The spider bites when it is provoked, as when trapped or crushed against the skin. The bite is usually painless, and the spider is often crushed or escapes, making positive identification difficult.²

In 10% of loxoscelism cases, significant necrotic ulceration may develop because of enzymes secreted in the spiders' venom, including hyaluronidase, esterase, alkaline phosphatase, and sphingomyelinase D. Moreover, the venom triggers a complex inflammatory response that causes an ischemic reperfusion injury and enhances dermonecrosis. The pathophysiology of the ischemic reperfusion injury includes adherence of neutrophils to microvascular endothelium and subsequent basement membrane and interstitial tissue penetration. These neutrophils produce reactive oxygen metabolites (hydroxyl, superoxide, peroxidase, and myeloperoxidase) that cause tissue cytotoxicity.³ In addition, arteriolar vasoconstriction, complement activation, release of proinflammatory cytokines, platelet aggregation, and activation of the clotting system enhance the hypoxia.⁴⁻⁶

Bites by *Loxosceles* can cause necrotic ulcerations of various sizes and dimensions. The bite starts as an erythematous macule surrounding a central papule, which is frequently mistaken for cellulitis. Should it advance to the necrotic phase, the lesion will mature into a central blister with a surrounding dusky macule and ring of blanched skin that has an asymmetrical erythematous border (known as the halo effect). Necrosis is evident after 72 hours, with large and deep necrosis occurring in 10% of the cases.⁷ From days 5 to 7, the cutaneous lesion

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delimits and forms a dry necrotic eschar with well-defined borders. The necrotic tissue detaches after 7 to 14 days, exposing fatty necrosis 1 to 3 cm deep and eventually leaving a stellate ulceration ranging from 1 to 30 cm in diameter. In non-healing ischemic ulcers, secondary skin grafting or plastic surgery may be required.⁸

Standard therapies for brown spider bites include ice, compression, elevation, analgesics, electric stimulation, antihistamines, and surgical debridement. However, there is little evidence to support any of these treatments.⁹ Corticosteroids are useful for systemic reactions that include hemolysis, but they do not augment wound healing in either systemic or intralesional application.^{10,11} Early wide excision is disabling and disfiguring, and the extent of venom distribution margins is difficult to define.¹¹ Prophylactic antibiotics may reduce secondary infection risk.⁹ Dapsone had some effect in necrotic ulcerations that is mediated by antineutrophil activity¹²; however, it usually misses the surge of neutrophils that occurs 1 hour after bite, and it may cause seizures and hemolytic anemia.¹³ The optimal management of necrotic bites is yet to be determined.

Previous studies have posited the efficacy of hyperbaric oxygen therapy (HBOT) for brown spider bites; however, data so far are relatively scarce. In animals, HBOT applied in the acute wound phase (0-3 days after the bite) showed mixed results with a relatively short follow-up time.¹³⁻¹⁵ In 2 randomized controlled trials using rabbits, the HBOT group had a significant decrease in wound size and decreased necrosis in histological examination by the 10th day postbite.^{13,14} However, HBOT applied to piglets during the first 3 days after a spider bite resulted in no beneficial effect.^{7,15}

In humans, there are only 2 case series describing the beneficial effect of HBOT initiated early in wound healing, or 2 to 6 days after the bite.^{16,17} The use of HBOT in the late, non-healing wound phase, weeks to months after the bite, has not been studied. Unfortunately, in clinical practice, diagnosing spider bite-related ulcers can be delayed because, in most cases, these ulcers affect a relatively healthy young population who wait to seek medical consult. Therefore, studying HBOT for late-stage nonhealing ulcers has the potential to better inform actual clinical practice.

METHODS

The cases presented include retrospective analysis of patients with nonhealing wounds caused by brown spider bites treated at The Sagol Center for Hyperbaric Medicine and Research, Assaf Harofeh Medical Center, Zerifin, Israel, between January 2010 and December 2013. Because of the low prevalence of spider-bite ulcers, the large heterogeneity of patients, delayed

time of diagnosis, and treatments received, a randomized controlled trial would have been difficult to perform.

Diagnosis of brown spider bite was obtained by patient history (brown spider observed during the bite) and documented evolution of the bite-related ulcer by the primary physician. Patients presented after more than 2 months of other therapies, including topical dressings, antibiotics, and corticosteroids. Patients were evaluated by a wound care specialist. Transcutaneous oxygen pressure ($tcpO_2$) was measured at the ulcer's margins while breathing air at sea level and while breathing 100% oxygen at 2 ATA (atmospheres absolute). The wounds were photographed at presentation, after 10 to 14 sessions, and 1 month afterward. All patients were treated with once-daily 90-minute HBOT sessions with exposure to 100% oxygen at 2 ATA, with 5-minute air breaks every 30 minutes.

RESULTS

All 3 patients were treated for nonhealing necrotic wounds induced by brown spider bites. All patients were previously healthy, without known chronic disease. Therapy was initiated 2 to 3 months after the bites. Patients were treated with a daily session of 2 ATA HBOT for a median of 17 sessions. The ulcers of all 3 patients healed without any need for additional intervention.

CASE 1

A 30-year-old man, without any significant medical history, presented 3 months after a brown spider bite. He suffered from a nonhealing wound on his left calf, which did not improve under antibiotics, abscess incision and drainage procedures, or topical dressings. At presentation, the ulcer size was 1.5 × 1.5 cm with 0.3-cm depth. Its margins had extensive cellulitis changes, a necrotic border, and lack of any granulation tissue.

The $tcpO_2$ measured in the ulcer margins was 37 mm Hg on room air and 635 mm Hg while breathing 100% oxygen at 2 ATA.

The patient was treated with 13 daily HBOT sessions. At the end of the 13 sessions, there was no necrotic tissue in the wound, and there was more than 90% healthy granulation tissue. Complete wound closure with white flat scarring occurred 3 weeks after cessation of HBOT (Figure 1).

CASE 2

A 42-year-old woman without prior history of chronic disease presented 2 months after a brown spider bite. She suffered from a nonhealing wound on her left hip, which did not respond to high-dose prednisone (80 mg) or topical dressings. At presentation, the ulcer surface was 5 × 4 cm with 0.5-cm depth, with purulent drainage, extensive slough/necrotic tissue, and edematous margins (Figure 2). The $tcpO_2$ measured at the ulcer margins was 29 mm Hg at room air and 316 mm Hg while breathing 100% oxygen at 2 ATA.

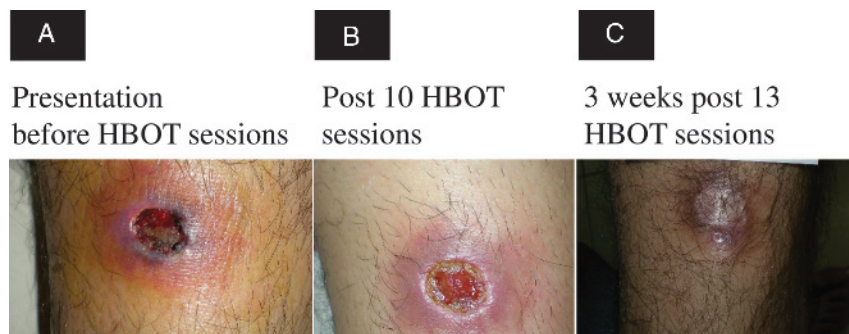
After 17 daily HBOT sessions, there was no drainage and no necrotic tissue, and the wound was covered with more than 70% healthy granulation tissue. Complete wound closure with brown flat scarring occurred 6 weeks after HBOT cessation (Figure 2).

CASE 3

A 72-year-old woman without prior history of chronic disease presented 2 months after a brown spider bite. She suffered from a nonhealing wound above the right medial malleolus, without any improvement using antibiotics, corticosteroids, or topical dressings. At presentation to The Sagol Center, the ulcer surface was 2.5 × 2.5 cm with 0.5-cm depth. It had edematous margins, purulent drainage, 10% fibrin tissue, and 30% unhealthy granulation tissue (Figure 3). The $tcpO_2$ measured

FIGURE 1.

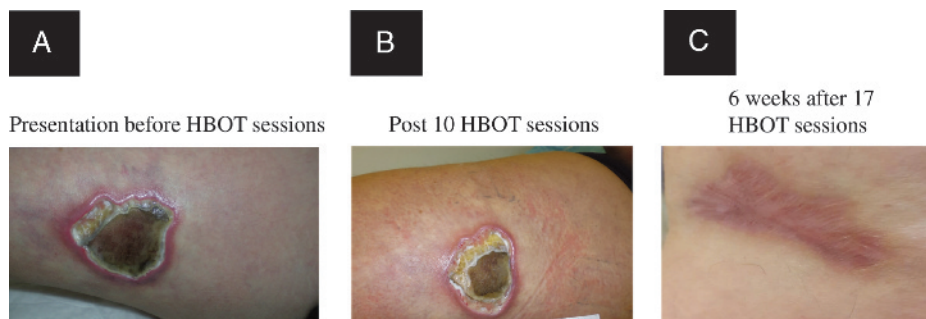
A 30-YEAR-OLD MAN PRESENTED WITH NONHEALING ULCER 3 MONTHS AFTER BROWN SPIDER BITE



Notice the necrotic borders with lack of granulation tissue before treatment (A). At the end of 13 hyperbaric oxygen therapy sessions, there was a dramatic improvement with disappearance of necrosis and formation of granulation tissue (B). Complete wound healing with scarring 3 weeks after therapy (C).

FIGURE 2.

A 42-YEAR-OLD WOMAN PRESENTED WITH NONHEALING NECROTIC WOUND ON HER LEFT HIP 4 WEEKS AFTER A SPIDER BITE



Notice the necrotic area before treatment (A). After 17 hyperbaric oxygen therapy sessions, there was a significant wound improvement with no drainage and necrosis and appearance of fibrotic tissue (B). Complete wound healing after 6 weeks (C).

in the ulcer margins showed 19 mm Hg on room air and 339 mm Hg while breathing 100% oxygen at 2 ATA.

After 31 daily HBOT sessions, there was no drainage, and the wound had more than 85% healthy granulation tissue. The wound completely resolved, and a white flat scar formed 1 month after HBOT cessation and 4 months after the initial spider bite (Figure 3).

DISCUSSION

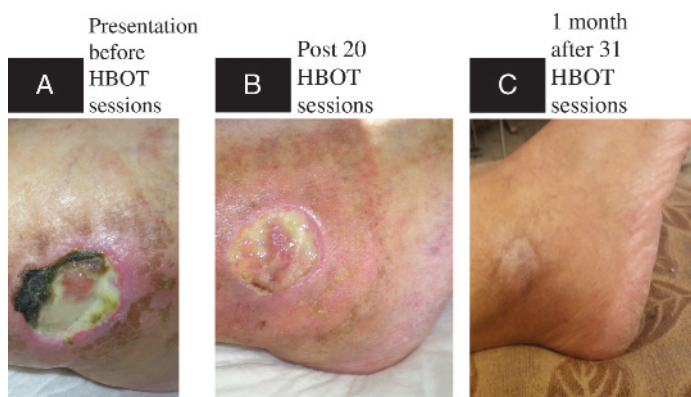
This is the first case series evaluating the effects of HBOT on spider bite–induced, chronic, nonhealing ulcers. The HBOT was initiated more than 2 months after each bite, and all patients had significant improvement in wound healing culminating in

complete resolution with satisfactory scarring. All wounds were hypoxic ($tcpO_2 < 40$ mm Hg on room air) with marked improvement during HBOT ($tcpO_2 > 200$ mm Hg).

Hyperbaric oxygen therapy has beneficial effects on nonhealing wounds when ischemia is the rate-limiting factor for tissue regeneration.^{18–34} This can be attributed to an increased amount of free oxygen molecules dissolved in the bloodstream and transferred to the wound tissues. The standard HBOT protocol for treating wounds includes administering 100% oxygen at 2 to 3 ATA, which elevates the oxygen partial pressure in the plasma greater than 1500 mm Hg. This enables improved tissue oxygenation even under ischemic and poorly perfused tissues.

FIGURE 3.

A 73-YEAR-OLD WOMAN PRESENTED WITH NONHEALING WOUND ON THE RIGHT MALLEOLUS 2 MONTHS AFTER SPIDER BITE



Notice the necrotic area and drainage before treatment (A). After 31 hyperbaric oxygen therapy sessions, there was a dramatic improvement (no drainage and appearance of fibrotic tissue) (B). A complete wound healing 2 months after hyperbaric oxygen therapy (C).

All regenerative and/or healing processes require energy, which is dependent on oxygen supply. Hyperbaric oxygen therapy increases oxygen levels for improved wound healing. Regardless of the primary etiology of the nonhealing wound, multiple regenerative processes are activated by increased oxygenation. Among them are as follows:

- **Angiogenesis.** To generate new blood vessels, omnipotent stem cells need to differentiate into endothelial cells and energy (oxygen). Hyperbaric oxygen therapy increases the generation and release of stem cells from the bone marrow to the bloodstream and then on to the damaged tissue.^{35–40} The induction of stem cells is mediated by increased production of nitric oxide.^{41–46} In addition, HBOT increases the release of vascular endothelial growth factor, an important factor for angiogenesis.⁴⁷ In other words, the improved oxygenation generated by HBOT in the damaged tissue creates the necessary environment needed for stem cell proliferation.
- Increased release of hypoxia-inducible factor 1 that, in turn, increases cellular proliferation⁴⁸
- Increased availability of wound growth factors, such as nitric oxide and platelet-derived growth factor⁴⁹
- Endothelial cells exposed to high oxygen pressure increase antioxidant production.⁵⁰
- Release of fibroblast growth factor and increased fibroblast proliferation⁵¹
- Increased epithelial migration^{39,40}
- Increased osteoblast activity and new bone generation^{52,53}
- Increased collagen synthesis⁵⁴
- Direct antibacterial effect and increased white blood cell activity^{55–61}
- Decreased edema in the periwound area⁶²

These regenerative effects of HBOT are beneficial for nonhealing hypoxic wounds, including diabetic ulcers,¹⁸ venous ulcers,^{19,20} arterial insufficiency ulcers,²¹ chronic wounds,²² vasculitis nonhealing wounds,³³ and pyoderma gangrenosum.⁶³ As seen in the highlighted cases, brown spider-bite ulcers are hypoxic as well (proved by pretreatment $tcpO_2$ measurements), which makes them suitable candidates for HBOT. Given the mechanism of action, spider bites may induce hypoxia because of the venom's effects on tissues and vascular bed around the wound.

In the acute phase of brown spider-bite ulcers (2–10 days from the bite), HBOT has additional specific beneficial mechanisms, including hyperoxia-induced inactivation of sphingomyelinase D (found in the spider's venom)¹⁴ and inhibition of the venom-induced ischemia-reperfusion injury mediated by neutrophils.³

This case series has obvious limitations because of the small sample size and the lack of control group. However, patients included in this case series may serve as their own control because they presented at the chronic, nonhealing stage. Although it is

possible that the ulcers healed spontaneously, such a dramatic improvement seems highly unlikely after 2 or 3 months of failed conventional treatment.

Further randomized controlled trials are needed to evaluate HBOT effects but may be difficult to conduct because of the low prevalence of spider bites. Multicenter cooperation is one way to overcome this barrier.

CONCLUSIONS

It is well known that nonhealing ischemic wounds should be treated with HBOT if there is no revascularization option. However, this is the first study that suggests nonhealing spider-bite ulcers have persistent hypoxia that can benefit from HBOT. It is reasonable to assume that, if applied earlier in the wound healing process, HBOT could save the patient a long period of debilitation.

Hyperbaric oxygen therapy may offer effective and safe treatment for nonhealing ulcers caused by brown spider bites even at the late, chronic phase. As there is scarce evidence for other effective treatments, HBOT should be considered a valuable therapeutic tool for these ulcers. ●

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