

Efficacy of Hyperbaric Oxygen Therapy in the Treatment of Pyoderma Gangrenous

ABSTRACT

Pyoderma gangrenosum (PG) is a rare and severe neutrophilic dermatosis characterized by the formation of painful and frequently debilitating skin ulcers. Although the definite causes of PG remains uncertain, current evidence has suggested that the condition development might be associated with dysfunctions of the immune system along with multiple systematic conditions. Over the past years, hyperbaric oxygen therapy (HBOT) has been used as an adjuvant treatment in various chronic conditions, including PG.

The retrospective, observational, and descriptive study presented here aims to evaluate the effectiveness of HBOT in treating patients with PG, treated at the *Centro Mineiro de Medicina Hiperbárica*. Additionally, the investigation seeks to identify treatment response patterns, considering factors such as patient age, the number of HBOT sessions required, and the total duration of treatment.

The study sample comprised ten patients diagnosed with PG who underwent HBOT from January 2000 to December 2022. Most patients were female, with ages ranging from 43 and 72 years. A significant reduction in the area of skin lesions was observed in several patients, indicating a positive response to the treatment. Specifically, 70% of the patients experienced a decrease in the size of their lesions, in which some cases exhibited significant enhancement in areas originally affected by necrosis. Wounds were located in multiple topographies (i.e., perimalleolar, surral, and patellar regions) besides the abdominal and gluteal areas. The duration of treatment varied significantly, spanning from months to years, according to the primary wound features.

Despite the positive findings observed in our study, the definitive effectiveness of HBOT in managing PG necessitates further experimental evaluation, based on larger patient cohorts and more robust methodological designs. This highlights the inherent limitations attributed to our study and emphasizes the need for future research in the field of wound healing.

Keywords: Pyoderma Gangrenosum; Hyperbaric Oxygen Therapy; Neutrophilic Dermatitis; Adjuvant Treatment; Therapeutic Efficacy.

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by the presence of painful, rapidly progressing skin ulcers. Although the exact etiology of pyoderma gangrenosum is still not fully understood, it is believed to involve an immune dysfunction, often associated with inflammatory bowel diseases, rheumatoid arthritis and other autoimmune conditions.(1,2,3).The therapeutic approach aims to halt the progression of ulcers, promoting re-epithelialization, pain reduction, prevention of infection and minimization of scar formation. Local care, topical medication, systemic corticosteroids, immunosuppressant and immunobiological medications are used (4). In cases of PG associated with malignant diseases, the use of both immunosuppressant and immunobiological medications can present additional risks to the patient. Healthcare professionals are often unable to prescribe a “gold standard” intervention for this type of dermatological condition and end up prescribing only traditional treatments that lack on results of effectiveness and safety. The aim of this study was to evaluate the use of hyperbaric oxygen therapy (HBOT) as a complementary alternative in the treatment of PG.

Hyperbaric oxygen therapy is a therapeutic tool that involves pure high-pressure oxygen systemically in the patient, usually two to three times higher than normal atmospheric pressure. This therapy has been widely used in the treatment of various pathologies, including chronic wounds.(4,5) In the context of pyoderma gangrenosum, HBOT has been considered an adjuvant therapeutic option, especially in cases refractory to conventional therapies, for example the diabetic foot.(4)

Recent studies suggest that HBOT can promote ulcer healing by improving tissue oxygenation, reducing edema and modulating the inflammatory response.(4,5) Vieira et al.(4) reported a case of successful use of HBOT as an adjuvant treatment for pyoderma gangrenosum, highlighting the effectiveness of this therapy in accelerating the healing process. In addition, a review by Maronese et al. (5) highlighted the emerging evidence on the benefits of HBOT in the management of pyoderma gangrenosum, underlining the need for further clinical studies to validate these findings.

The incidence of pyoderma gangrenosum varies globally, and the condition presents significant challenges in both diagnosis and treatment. Monari et al. (6) conducted a prospective study, emphasizing the need for innovative and personalized therapeutic approaches to manage this complex condition.(6)

METHOD

This study was characterized as a retrospective, observational and descriptive study, conducted at the *Centro Mineiro de Medicina Hiperbárica*, located in Belo Horizonte, Minas Gerais, Brazil. Covering the period from January 2000 to December 2022, the study focused on patients diagnosed with PG who had undergone treatment with HBOT. The sample consisted of data from all patients with PG seen at the clinic and who underwent HBOT treatment during the research period, making it a convenience sample.

The inclusion criteria included patients of any age or gender with PG referred to the *Centro Mineiro de Medicina Hiperbárica* for HBOT treatment. Exclusion criteria included pregnant women, presence of an untreated pneumothorax or hemothorax, recent pulmonary thromboembolism, use of specific chemotherapy drugs (i.e., doxorubicin and bleomycin), use of the drug Sulfamylon, and patients who had undergone ophthalmic surgery less than 30 days before the procedure.

In the methodology applied at the clinic, patients signed an informed consent form after being referred to the Minas Gerais Hyperbaric Oxygen Therapy Center.

Treatment took place from Monday to Saturday, in monoplace or multiplace chambers, allowing up to seven patients to be treated simultaneously, with sessions lasting from 90 to 120 minutes. Every week, a nurse counted and measured the size of the lesions, while a doctor reexamined patients twice a month.

The data collection procedures involved the analysis of medical records by the researcher and two medical students. The information collected was recorded in a Microsoft Excel Spreadsheets and included the extraction of variables such as age, gender, time since diagnosis, size and number of lesions, underlying diseases, routine taken medications, number of relapses, and the number HBOT sessions.

RESULTS

From January 2000 to December 2022, ten patients with PG were treated with HBOT, as shown in Table 1, which reports the main outcomes evaluated. Patient's age ranged from 43 to 72 years, with female being registered (70%). The number of HBOT sessions varied significantly in between patients, with a minimum of 20 sessions and a maximum of 702 sessions. The diversity in the number of sessions reflects the need for individualized treatment, based on each patient's specific response and the severity of their lesions.

The presence of necrosis was observed in 70% of the patients, while serous exudate was present in 90% of cases. To note, we observed relevant reduction of necrotic tissue damaged among those individuals who presented a necrotic formation at the onset of the treatment. These indicators are critical for assessing the severity of the lesions and the inflammatory response associated with PG. The total area of the lesions varied widely, with some initial lesions as small as 3.6 cm² and others reaching 240 cm². After treatment, the areas of the lesions also varied significantly, with some lesions reducing substantially in size. A recent study shows that most patients benefit from the use of hyperbaric medicine. One hundred and seventy-five studies were retrieved using the search strategies. Thirty-four articles were included, covering 48 patients. The use of HBOT in the treatment of PG promoted complete healing of the lesions in 58.4% of patients and improvement of the lesions compared to the start of treatment in another 20.8% of cases. This type of study corroborates ours, demonstrating the benefits of hyperbaric medicine (7).

Table 1: Hyperbaric Oxygen Therapy Treatment Data for Pyoderma Gangrenosum

Gender	Age	Number of sessions	Presence Of necrosis	Initial total area	Final total area	Presence of serous exudate	Did the lesions close?	Treatment time
Female	43	69	No	240cm	91cm	Yes	No	4 months
Male	63	287	Yes	30cm	20,25cm	No	No	9 years

Female	55	702	No	3,6cm	3cm	Yes	Yes	2years
Male	58	20	Yes	10cm	24cm	Yes	Not reported	1 month
Female	62	82	Yes	35cm	1cm	Yes	Not reported	3 month
Male	64	460	Yes	48cm	28cm	Yes	Not reported	3 months
Female	72	160	Yes	45cm	60cm	Yes	Not reported	18 years
Female	69	30	Yes	12,5cm	42cm	Yes	Not reported	Not reported
Female	68	67	Yes	48cm	42cm	Yes	Not reported	3 months
Female	44	150	Yes	165cm	130cm	Yes	Not reported	1 year

DISCUSSION

A retrospective analysis of data from patients treated with HBOT at the *Centro Mineiro de Medicina Hiperbárica* demonstrates that HBOT can be a valuable therapeutic option for the management of PG. Although the response to treatment varied significantly between patients, many showed a reduction in the total area of the lesions and improvement in the clinical signs of inflammation, such as the presence of serous exudate. According to Xavier et al (7), the use of HBOT in the treatment of PG promoted complete healing of the lesions in 64.3% of patients and improvement of the lesions in another 19.6% of cases. Likewise, there are case reports in the literature demonstrating the benefits of adjuvant treatment of PG with HBOT, which consists of the patient inhaling 100% oxygen at a higher pressure than atmospheric inside a hyperbaric chamber (4). This oxygen-rich environment increases the amount of oxygen dissolved in the plasma, accelerating the healing process, increasing angiogenesis, reducing the pain associated with pyoderma lesions and the risk of infection (4,8,9).

The variability in the number of sessions and treatment time required to achieve improvement suggests that PG necessitates highly individualized treatment approaches. Factors such as the presence of necrosis, the initial area of the lesions, and the

inflammatory response already taken in place should be considered when planning treatment with HBOT. The wide range of treatment times, which varied from one month to 18 years, emphasizes the chronic and complex nature of PG and the need for continuous monitoring and therapeutic adjustments. Currently, no gold standard of treatment for PG is well-defined (10,11,12). Nevertheless, the different pharmacological and non-pharmacological interventions must target wound closure, reduce inflammation, adequately reduce pain, and minimize the development of infectious processes (13).

Despite the limitations of this study, such as the small sample size and the retrospective nature of the data collection, the results are promising and indicate that HBOT can be an effective addition to the arsenal of treatments for PG. Future studies, with larger samples and a prospective design, are needed to reinforce the observed findings and to develop a more standardized treatment protocols. The clinical variants of PG are: classic ulcerative, bullous, vegetative, pustular, periostomal, and post-operative (14,15). Thus, the difference in clinical types can affect wound closure.

Although only one patient reported complete closure of the lesions, most patients showed some form of improvement, indicating that HBOT can be effective in reducing the area and severity of PG lesions. Treatment times ranged from one month to 18 years, suggesting the need for prolonged treatments to achieve significant results in some cases. Hyperbaric medicine provides plasma and tissue oxygen, accelerating the healing process, increasing angiogenesis, reducing pain, and infection rates (16,17).

These results highlight the importance of a personalized approach to treating PG with HBOT. The variability in treatment responses and treatment times reinforces the need for further research to optimize therapeutic protocols and improve clinical outcomes for patients.

CONCLUSION

Hyperbaric oxygen therapy has shown to be an effective intervention in several cases of PG, providing a viable treatment option for patients who do not respond adequately to conventional therapies. Personalization of treatment and continuous follow-up are fundamental to maximizing the benefits of HBOT and improving the quality of life of patients with PG.

Ethical Approval

Data collection began only after approval by the CEP/Conep system. CAAE approval: 72841823.2.0000.5134.

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

- 1.
- 2.
- 3.

REFERENCES

1. Marzano AV, Borghi A, Wallach D, Cugno M. A comprehensive review of neutrophilic diseases. *Clin Rev Allergy Immunol*. 2018;54(1):114–30.
2. Alavi A, French LE, Davis MD, Brassard A, Kirsner RS. Pyoderma gangrenosum: An update on pathophysiology, diagnosis and treatment. *Am J Clin Dermatol*. 2017;18(3):355-372.
3. Marzano AV, Tournalaki A, Alessi E, Caputo R. Widespread idiopathic pyoderma gangrenosum evolved from ulcerative to vegetative type: a 10-year history with a recent response to infliximab. *Clin Exp Dermatol*. 2007;33:156-159.
4. Vieira WA, Barbosa LR, Martin LMM. Hyperbaric oxygen therapy as an adjuvant treatment for pyoderma gangrenosum. *An Bras Dermatol*. 2011; 86(6):1193-6
5. Maronese CA, Pimentel MA, Li MM, Genovese G, Ortega-Loayza AG, Marzano AV. Pyoderma Gangrenosum: An Updated Literature Review on Established and Emerging Pharmacological Treatments. *Am J Clin Dermatol*. 2022;23:615–634.
6. Monari P, Moro R, Motolese A, Misciali C, Baraldi C, Fanti PA, et al. Epidemiology of piodermagangrenosum: results from an Italian prospective multicenter study. *Int Wound J*. 2018;15(6):875-879.
7. Xavier, LF ; Guimarães, NS ; Santos, ALSC, Diniz, RC ; Canabrava, PP ; De Souza, AH ; De Oliveira, GV . Hyperbaric Oxygen Therapy as an Adjuvant

Treatment in Pyoderma Gangrenosum : A scoping review. Journal of the European Academy of Dermatology and Venereology JCR, v. 2024.

8. Seo HI, Lee HJ, Han KH. Hyperbaric oxygen therapy for pyoderma gangrenosum associated with ulcerative colitis. *Intest Res* 2018;16(1):155-157.
9. Magalhães RS, Moreira MJ, Rosa B, Cotter J. Hyperbaric oxygen therapy for refractory pyoderma gangrenosum: a salvage treatment. *BMJ Case Rep* 2021;14:e238638.
10. Monari P, Moro R, Motolese A, Misciali C, Baraldi C, Fanti PA, Caccavale S, Puviani M, Olezzi D, Zampieri P, Trevisan G, Nan K, Fiorentini C, Pellacani G, Gualdi G. Epidemiology of pyoderma gangrenosum: results from an Italian prospective multicenter study. *Int Wound J*. 2018;15(6):875-879.
11. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol*. 2011; 165(6):1244-50.
12. Gameiro A, Pereira N, Cardoso JC, Gonçalo M. Pyoderma gangrenosum: challenges and solutions. *Clin Cosmet Investig Dermatol*. 2015; 8:285-93.
13. Vieira WA, Barbosa LR, Martin LMM. Hyperbaric oxygen therapy as an adjuvant treatment for pyoderma gangrenosum. *An Bras Dermatol*. 2011; 86(6):1193-6.
14. Marzano AV, Borghi A, Wallach D, Cugno M. A comprehensive review of neutrophilic diseases. *Clin Rev Allergy Immunol*. 2018; 54(1):114–30.
15. Vieira LFDF, Almeida CLA, Souza AW, Rego J, Vale ES, Pegas JRP. Pyoderma gangrenosum: update and guidance. *Rev Bras Cir Plast*. 2022; 37(4):423-430.
16. Marzano AV, Ishak RS, Saibeni S, Crosti C, Meroni PL, Cugno M. Autoinflammatory skin disorders in inflammatory bowel diseases, pyoderma gangrenosum and Sweet's syndrome: a comprehensive review and disease classification criteria. *Clin Rev Allergy Immunol*. 2013;45(2):202-10.

17. Maverakis E, Marzano AV, Le ST, Callen JP, Brügger MC, Guenova E, Dissemond J, Shinkai K, Langan S. Pyoderma gangrenosum. *Nat Rev Dis Primers*. 2020; 6(1):81.

UNDER PEER REVIEW