The role of hyperbaric oxygen treatment in the management of spondylodiscitis

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Abstract
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Introduction: This study analysed treatment outcomes in a patient cohort diagnosed with spondylodiscitis, who received adjunct hyperbaric oxygen treatment (HBOT) in addition to antibiotic therapy at our clinic. Important considerations included the timing of HBOT initiation on treatment success, and recurrence rates.
Methods: We retrospectively reviewed the records of all patients diagnosed with spondylodiscitis who received HBOT at the Underwater and Hyperbaric Medicine Clinic in Gulhane Training and Research Hospital, between 1 November 2016 and 25 October 2022. The patients received HBOT at 243.2 kPa for a total of 120 minutes per session, once daily for five days a week for a total of 30 sessions.
Results: Twenty-five patients with spondylodiscitis were evaluated before and after combination HBOT and targeted antibiotic treatment. After treatment, patients had lower median (range) visual analogue pain scores (8 [4–10] vs 3 [0–7], $P < 0.001$) and C-reactive protein (22.3 [4.3–79.9] mg·L^{-1} vs 6.8 [0.1–96.0] mg·L^{-1}, $P = 0.002$) and lower mean (standard deviation) white blood cell counts (8.8 [3.5] x 10^{9}·L^{-1} vs 6.1 [1.6] x 10^{9}·L^{-1}, $P = 0.002$). When patients were examined (median) 48 months (2–156 months) after the completion of treatment, there were no persistent cases of spondylodiscitis.
Conclusions: Combination HBOT with targeted antibiotic therapy effectively managed our cohort of patients diagnosed with spondylodiscitis. Hyperbaric oxygen treatment was safe, with no complications experienced. Moreover, HBOT may have helped to eliminate persistence and recurrence of symptoms with long term follow-up. A randomised controlled study with a larger number of patients is needed for more definitive conclusions.

Introduction

Spondylodiscitis is a clinical condition resulting from the infection of the intervertebral disc and adjacent vertebral structures.[1] The terms 'vertebral osteomyelitis', 'spinal discitis', 'disc infection', and 'spondylodiscitis' are used interchangeably due to the frequent involvement of both the disc and vertebrae and the difficulty in distinguishing between them.[2] Risk factors for spondylodiscitis include intravenous drug use, infective endocarditis, degenerative spinal disease, prior spinal surgery, diabetes mellitus, corticosteroid use, and other immunosuppressive conditions.[3] Between 1998 and 2013, the annual incidence of hospital admissions for spondylodiscitis in the United States increased from 2.9 per 100,000 to 5.4 per 100,000.[3] This situation prolongs the hospitalisation period of patients and creates a serious burden on both the patient and the healthcare system.[3]

Hyperbaric oxygen treatment (HBOT) is an intervention in which patients breathe 100% oxygen in a hyperbaric chamber that is pressurised to higher than atmospheric pressure (101.3 kPa). This elevates tissue oxygen levels in partially ischaemic and hypoxic tissues which enhances oxygen-dependent leukocyte functions by promoting the production of hydrogen peroxide and superoxide.[4] Hyperoxia also supports osteogenesis and neovascularization to replace damaged tissue with healthy bone. Neovascularisation facilitates the entry of immune cells, antibodies, and antibiotics into the infected area, while HBOT also promotes the removal of bone debris by improving osteoclastic activity.[4] Several publications suggest the beneficial effects of HBOT in the treatment of spinal infections.[5–8] However, randomised controlled studies specifically examining the effectiveness of HBOT in managing these clinical conditions have not yet been conducted.

This study retrospectively assessed treatment outcomes in a patient cohort diagnosed with spondylodiscitis, who received adjunct HBOT in addition to antibiotic therapy at our clinic.

Methods

The study protocol was approved by the Gulhane Training and Research Hospital Clinical Research Ethics Committee with decision number 2023/73 on 12 April 2023.

We retrospectively reviewed the records of all patients diagnosed with spondylodiscitis who received HBOT at the Underwater and Hyperbaric Medicine Clinic in Gulhane Training and Research Hospital between 1 November 2016 and 5 October 2022.

The following factors were recorded from patient files and the hospital automation system: age, gender, elapsed time between diagnosis and HBOT, localisation, comorbidities, medications used, number of HBOT sessions received, 10-point visual analog scale (VAS) for pain before and after HBOT, white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), magnetic resonance imaging (MRI) results, and whether the disease recurred during patient follow-up. Additionally, any complications that occurred during therapy were noted.

The diagnosis of discitis was made when all three of the following criteria were present:

- Clinical symptoms and findings including recurrent low back pain, decreased spinal mobility, paravertebral muscle spasm, and positive bed-shaking test.
- Laboratory findings of elevated ESR and CRP values.
- MRI findings consistent with discitis being decreased signal intensity on T1-weighted images, increased signal intensity in both the disc space and adjacent vertebral bodies on T2-weighted images, and enhancement of the same areas with gadolinium.

In addition to analgesic therapy, an appropriate antimicrobial regimen was chosen for all patients based on the results of antimicrobial susceptibility tests and the recommendations of the infectious diseases specialist.

The patients received HBOT at 243.2 kPa for a total of 120 minutes per session, once daily for five days a week for 30 sessions. Once HBOT was completed, antibiotic treatment was stopped. Patients were mobilised with lumbo-sacral corsets when they felt comfortable.

STATISTICAL ANALYSIS

Data analysis was performed with the IBM® SPSS 25.0 program. Categorical variables are reported as numbers and percentages, while numerical variables are reported as mean (standard deviation [SD]) or median (range). The normality of numerical variables was checked using the Shapiro-Wilk test, histograms, and probability plots. The homogeneity of variances between groups was evaluated using Levene's test. For independent group comparisons of data exhibiting a normal distribution, the independent samples *t*-test was used. For independent group comparisons of non-normal data, the Mann-Whitney U test was used. For dependent group comparisons of data following a normal distribution, the paired samples *t*-test was used. For dependent group comparisons of non-normal data the Wilcoxon signed-rank test was used. In all analyses, a *P*-value of less than 0.05 was considered statistically significant. Because the time between diagnosis and HBOT did not follow a normal distribution, it was categorised based on a median value of 14 days as a cut-off point. The patients with a starting time of HBOT exceeding 14 days were grouped as 'long', while those with a starting time of 14 days or less were grouped as 'short'.

Table 1
Demographics, comorbidity and medication in the study cohort; BMI – body mass index; SD – standard deviation

Characteristic	***n* (%)**
Female	13 (52)
Male	12 (48)
Comorbidity absent	5 (20)
Comorbidity present	20 (80)
Two or fewer medications	9 (36)
More than two medications	16 (64)
Characteristic	**Mean (SD)**
Age (years)	52.9 (12.8)
BMI ($kg \cdot m^{-2}$)	28.3 (2.6)

Table 2
Disease and treatment characteristics in the study cohort; HBOT – hyperbaric oxygen treatment; MRI – magnetic resonance imaging

Etiology, *n* = 19, *n* (%)	
Vertebral tuberculosis	1 (5.27)
Previous vertebral surgery	18 (94.73)
Localisation, *n* = 24, *n* (%)	
Cervical	2 (8.3)
Lumbar 1-2/2-3/3-4	8 (33.3)
Lumbar 4-5/5-S1	10 (41.7)
Multiple disc involvement	4 (16.7)
Regression on MRI, *n* = 13, *n* (%)	
Absent	3 (23.1)
Present	10 (76.9)
Other parameters, Median (range)	
Time from diagnosis to initiation of HBOT (days)	14 (1–210)
Follow-up period (months)	48 (2–156)
Number of sessions	30 (10–40)

Table 3

Comparison of pain scores and laboratory parameters of patients before and after treatment; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; HBOT – hyperbaric oxygen treatment; SD – standard deviation; VAS – visual analog scale, WBC – white blood cells

Outcome measure	*n*	Before treatment Median (range)	After treatment Median (range)	*P*
Pain VAS (0–10)	25	8 (4–10)	3 (0–7)	< 0.001
CRP ($mg \cdot L^{-1}$)	24	22.3 (4.3–79.9)	6.8 (0.1–96.0)	0.002
ESR ($mm \cdot h^{-1}$)	16	32.0 (8.0–123.0)	35.0 (1.0–94.0)	0.171
Outcome measure	***n***	**Before treatment Mean (SD)**	**After treatment Mean (SD)**	***P***
WBC (cells x $10^9 \cdot L^{-1}$)	24	8.8 (3.5)	6.1 (1.6)	< 0.002

Results

Twenty-five patients with spondylodiscitis were evaluated before and after HBOT. Patients used antibiotics for an average of six weeks along with HBOT. Approximately half of the patients (n = 12) were over 50 years of age. Twenty patients (80%) had comorbid conditions. Diabetes mellitus was present in eight patients (32%), and ten patients (40%) were hypertensive. No patient experienced complications related to HBOT during the treatment sessions. The descriptive characteristics of the patients are reported in Tables 1 and 2.

At the end of the HBOT sessions, it was observed that patients had significantly lower pain VAS scores, WBC counts, and CRP levels compared to the measurements taken before treatment (Table 3).

The influence of the timing of initiation of HBOT on treatment outcomes was evaluated using VAS data collected pre- and post-treatment. No significant difference was found in the VAS change between the 'short' or 'long' groups, defined by the timing of initiation treatment.

Magnetic resonance imaging findings of 13 patients before and a median one month (range 0–24 months) after HBOT were compared revealing that 10/13 patients showed regression of the lesion. While no change was detected in the MRI findings of two patients one month after HBOT, no signs of spondylodiscitis were found in their MRIs taken 36 months later. The third patient had no other MRI scans.

When patients were examined 48 months (2–156 months) after the completion of HBOT, all 25 had resolution of their back pain and were clinically well.

Discussion

Pain is the most common symptom in patients with spondylodiscitis and is often disproportionate to clinical findings.[9,10] In our study, the mean VAS score of our patients was 8, which is not surprising. The VAS score of our patients decreased to 3 after 30 sessions of HBOT. Similarly In another study VAS scores in spondylodiscitis patients decreased from 8.8 to 2.2 after one month of combined HBOT and antibiotic therapy.[6] The combination of HBOT and antibiotic treatment may be beneficial in reducing the pain of spondylodiscitis patients.

Accurate diagnosis depends on a combination of clinical, laboratory, and imaging findings. High ESR and CRP values, as well as typical changes observed in MRI, are important parameters in establishing the diagnosis. They are used to follow the course of spondylodiscitis and to monitor the response to treatment.[11–14] A decrease in CRP values is significantly associated with clinical improvement. Other studies conclude HBOT reduces CRP in patients with spondylodiscitis.[6,15] In our study group, the average initial CRP level was high at 22.3 $mg \cdot L^{-1}$ but decreased to 6.8 $mg \cdot L^{-1}$ after treatment.

In recent years, MRI has become the preferred imaging modality for the diagnosis of spondylodiscitis due to its reported sensitivity and specificity of over 92%.[13,16] Others have shown that HBOT reduces inflammatory findings in MRI.[6,15] In our study, when comparing the pre-treatment and 3–4 months post-treatment MRI scans of 13 patients, a radiological reduction-healing in inflammatory appearance was observed. However, due to the limited number of patients with MRI scans both before and after HBOT, we were unable to perform statistical analysis in this regard. The improvement in MRI in 10 out of 13 patients suggested that our combination treatment might be beneficial. Studies with a larger number of patients are needed to reach definitive conclusions. No change was detected in the MRI findings of two patients one month after HBOT. However, no signs of spondylodiscitis were found in their MRIs taken 36 months later. We believe this may be related to the late reflection of clinical improvement on MRI, as reported elsewhere.[17]

The key principles for successful treatment of spinal infections include antibiotic therapy to eradicate the underlying infection, debridement of the spinal canal in the presence of neurological deficits or epidural abscess,

and fixation of the affected segment to maintain or restore spinal stability. Long-term parenteral antibiotic therapy and immobilisation adversely affect quality of life while significantly increasing the cost of care.[18,19] Additionally, major complications (e.g., colitis, kidney failure, allergic reactions) have been reported as side effects of long-term antibiotic therapy.[20] The duration of antibiotic therapy recommended in the literature for the treatment of spondylodiscitis varies. Repeated laboratory markers and the patient's clinical response are key parameters in determining the exact duration of antibiotic therapy.[11,21]

There are other studies where HBOT was used in addition to antibiotics in the treatment of spondylodiscitis.[6,15] In one of these,[15] at the end of HBOT or within the first month of follow-up, MRI revealed sufficient healing of the infection in 12 out of 13 patients. The author argued that HBOT may be beneficial in long hospitalisation stays, repeated surgeries, and morbidities.[15] In the other,[6] 22 spondylodiscitis patients were treated with antibiotics and HBOT, and they achieved infection control and recovery in all patients with a no recurrence. The authors concluded that HBOT is a beneficial adjunctive therapeutic measure in the management of spondylodiscitis.[6] In another relevant study, HBOT was administered in the treatment of neurosurgical infections after brain and spinal cord surgery.[7] Five out of seven patients with osteomyelitis and wound infections following spinal surgery showed improvement with combined treatment without the removal of foreign bodies.

Unfortunately, our study did not provide the opportunity to compare the group that received antibiotics and HBOT with a control group that received only antibiotics. However, a multicenter observational prospective study in which patients were treated only with antibiotics reported an average antibiotic duration of 14.7 weeks.[22] In another study involving 110 patients, the mean total duration of antibiotic therapy was 103.0 (standard deviation 40.4) days, with a range of 42 to 285 days.[23] Although our study recommended 40 sessions of HBOT, patients actually received 30 sessions. The results presented here represent the follow-up outcomes of our combination treatment, administered over an average period of six weeks. This combination therapy was associated with a statistically significant decrease in CRP levels, and the inflammatory changes on MRI decreased. This period was shorter than the periods cited above for antibiotic treatment alone. We believe that earlier improvement in WBC, CRP and MRI findings may be attributed to the adjunctive effects of HBOT, which is being used in addition to medical therapy in the treatment of various infections in bone and soft tissues.[4,7,23–25]

Upon examining our patients approximately 48 months after treatment, we observed no spondylodiscitis recurrence, and none of the patients reported experiencing back pain. In a study that reported long-term outcomes of vertebral osteomyelitis in 263 patients with 6.5 years of follow-up, relapse, persistent symptoms, and surgery rates were 14%, 31%, and 43%, respectively.[26] In another study involving 260 patients with vertebral osteomyelitis with long-term follow-up, neurological deficits and persistent back pain were seen in 16% and 32% of cases, respectively.[27] In our cohort, an absence of symptom persistence or recurrence was observed. Adjunctive HBOT may have contributed to these results.

Most infected tissues, including bones, are hypoxic due to ischaemia secondary to inflammation-induced tissue oedema.[25,28] Adequate oxygen delivery to ischaemic tissue is important for healing and mitigating infection.[21,29] In spondylodiscitis, oxygenation decreases due to inflammation. The bactericidal capacity of leukocytes is significantly impaired in a hypoxic environment.[4,30] Hyperbaric oxygen has been shown to increase oxygen tension in infected tissues, including bone.[29] Increased oxygen levels in ischaemic tissues stimulate the bactericidal effect of white blood cells. Hyperbaric oxygen also inhibits the growth of aerobic and facultative anaerobic bacteria by inducing various metabolic effects related to the synthesis of proteins, nucleic acids and essential cofactors of metabolic reactions.[24] Oxygen-based free radicals oxidise proteins and membrane lipids, cause DNA damage and inhibit metabolic functions essential for (bacterial) growth.[4] Lack of adequate vascular supply to the adult disc reduces the ability of the patient's immune system to fight infection.[21] Therefore, angiogenesis is of critical importance in wound healing. It has been shown that HBOT reduces ischaemia in tissues by inducing the formation of new capillaries.[31] Improved vascularity not only improves tissue oxygen tension and host defense but also facilitates the entry of leukocytes, antibodies, and antibiotics into the infected area.[25]

This study has several limitations. Firstly, our study is retrospective in nature, without a control group. We cannot confidently attribute the apparent benefit ascribed to adjunctive HBOT without a control group of similar patients to compare with. Our analysis was based on a limited number of patients. Additionally, our patients were a heterogeneous group in terms of age, infective organism, co-morbidities, and surgery. Despite the aforementioned limitations, this cohort of patients responded well to the combination therapy. Stronger conclusions would require more rigorous trials.

Conclusions

These results demonstrate that in our cohort of patients, the combination of HBOT and targeted antibiotic therapy was effective in the management of spondylodiscitis. Hyperbaric oxygen may have helped to eliminate the persistence and recurrence of symptoms over an average 48-month follow-up. Additionally, none of our patients experienced complications during treatment. Randomised controlled

studies with a larger number of patients are needed to reach more definitive conclusions.

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