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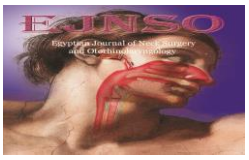

Value of Hyperbaric oxygen as an adjuvant treatment for necrotizing otitis externa

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Abstract:

Background: Necrotizing otitis externa (NOE) is an acute infective process of the external auditory canal that could progress leading to skull base osteomyelitis. Hyperbaric oxygen therapy (HBOT) is considered an adjunctive therapy for NOE. HBOT is the administration of 100% oxygen at increased atmospheric pressure delivering increased oxygen partial pressure to the cells.

Objectives: The purpose is to evaluate the effectiveness of HBOT as an adjuvant for NOE management.

Patients and methods: Twenty-two patients who had NOE were evaluated clinically and radiologically before treatment and the follow up duration was every three months. The antibiotic used was oral ciprofloxacin combined with ceftazidime. HBOT was administrated for period of 60 minutes once daily for 20 sessions and was repeated when needed. Factors as age, sex, otorrhea, complications, pain, laboratory changes, hospital stay and recurrence had been studied.

Results: 22 patients were classified into two groups: group A was treated with antibiotic therapy and HBOT and group B only received the antibiotic therapy. The pain severity showed quite improvement as it decreased from score 6.82±1.17 to 1.09±1.22 after 1 month in group A, while in patients who were treated only with the antibiotics the pain severity score decreased from 6.36±1.12 to 2.82±1.60 which shows a significant difference between both study groups in favor of hyperbaric oxygen. After HBOT the mean ESR was 20.09±7.58 which is significantly lower than antimicrobial therapy alone group 34.46±12.88.

Conclusion: Addition of HBOT to microbial therapy is effective with better results in NOE.

Key words: Hyperbaric oxygen therapy; Necrotizing otitis externa; adjuvant therapy.

Introduction

Necrotizing otitis externa (NOE) is an acute infective process of the external auditory canal (EAC), spreading via the fissures of Santorini at the osseous-cartilaginous junction to involve the infratemporal fossa. Without treatment, it may involve the skull base causing osteomyelitis with subsequent lower cranial nerve palsies. [1]

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The nomenclature for this disease has changed over time from malignant externa otitis to malignant otitis externa. However, the correct name should be necrotizing otitis externa, since the pathogenesis is degenerative and without neoplasm involved. [2-3] Mortality rate from NOE was assumed to reach 42% mainly in severe groups. [3]

Regarding cranial nerve palsies, it is believed to be a complication of NOE; on the other hand, it is a debatable prognostic factor. Pseudomonas aeruginosa is considered the most accused organism (>90%). [4] Other reports highlight the increasing frequency of non-Pseudomonas causative organisms of NOE as methicillin-resistant Staphylococcus aureus. Fungal infections are also present and commonly associated with immunosuppression, leading to diagnostic delays. [3]

The initial pathology occurs in the EAC and then progress to attack the skull base through the fissures of Santorini, stylomastoid and jugular foramina, and petrous apex. [4]

It has not been well established why NOE commonly affect diabetic patients; however, microangiopathy is a considerable predisposing factor. DM causes microangiopathy leading to poor tissue perfusion and weak cellular protection. [5]

NOE staging is significant for therapeutic purposes, so the disease has been staged to:

1. Stage one, confined to the EAC with or without facial nerve palsy
2. Stage two, skull base osteomyelitis and/or multiple cranial nerve palsies
3. Stage three, meninges or cerebral involvement.

Symptoms include deep-seated otalgia with history longer than four weeks, persistent otorrhea, headache, and cranial nerve palsies**.** [6]

Patients must complain at least three of five manifestations of NOE:

- Persistent otitis externa.
- Granulations in EAC.
- Radiographic confirmation of osteomyelitis of EAC or skull base.
- Intracranial involvement.
- Presence of Pseudomonas aeruginosa in the culture of ear drainage. [7]

Diagnosis needs more clinical intuition as pseudomonas is one of the normal commensals of the EAC. Therefore, clinicians should have high suspicion as the presence of granulations, otalgia, oedema, otorrhea and resistance to local management for more than 10 days. [8]

Disease outcome was significantly correlated with ESR and CRP levels. Once NOE is expected, ESR and CRP should be done and then followed up regularly until total disease resolution is obtained. [9]

Radiological investigation of NOE includes CT and MRI scans. High-resolution CT locates the disease and its extent in the form of demineralization of the cortical bone, soft tissue extension inferior to the EAC, and skull base involvement. [10]

MRI is useful if there is involvement of the central skull base and\or multiple cranial nerves, but both imaging modalities had low prognostic value, because regeneration is required before returning to normal imaging character. [10-11]

Radionuclide investigations used in NOE include: Technetium-99m, planar scan. Gallium imaging, single photon emission computed tomography (SPECT). [12-13] SPECT imaging accurately localizes the disease and can identify early bone inclusion that appeared negative in CT due to absence

of structural bone destruction. Gallium-67 citrate scan is a sound predictor of disease resolving, and it has also been assumed that normal results can be considered for the appropriate time to terminate medications. [14]

In large systematic review and metanalysis [15], the nuclear studies (Tc99m and Ga67) shown limited sensitivity and specificity to diagnose and monitor disease progression in NOE. The lack of anatomic resolution, high cost, hazards, and limited availability, made the use of these studies in the management of NOE unsupported. [10, 15]

The basic pharmacological treatment had been developed slowly by the aid of recently advanced antibiotics and the multidisciplinary approach. Strict glycemic control, improvement in immunity, proper systemic antibiotic for 3-6 weeks, and local debridement and topical antimicrobial has become essential in effective management of NOE. Antibiotics should start initially following clinical diagnosis, before culture and sensitivity results for bacterial and fungal smears appear. Initial choice of antibiotic is fluoroquinolones like Ciprofloxacin, and anti-pseudomonal Penicillins like Piperacillin with Tazobactam. [3]

Oral Fluoroquinolones like Ciprofloxacin (500 mg oral every 12 hours) have more predominant anti-pseudomonal action, replacing the need for intravenous antibiotics, along with better penetration into bones, leading them to be the drugs of choice for managing NOE especially in elderly diabetics. [16, 17]

Surgical options have been suggested for NOE patients' who are resistant to medical therapy and the inflammation cannot be completely controlled (e.g., inner ear fistula, petrous apex or facial nerve involvement). Biopsy and culture may be used to differentiate infection from malignancy. [18]

Hyperbaric oxygenation has been suggested to be an adjuvant therapy. [19] Hyperbaric oxygen therapy (HBOT) is crucial in managing decompression sickness, gas embolism, and CO poisoning. [20] It has also been regarded in the treatment of diverse infectious diseases including osteomyelitis [21] with special consideration in refractory osteomyelitis. [22]

Use of HBOT has been applied only as an adjuvant to the antimicrobial treatment. [23] It means breathing of pure 100% oxygen under increased atmospheric pressure. It is assumed that hyperbaric oxygenation could avert the small vessel disease**,** which give rise to aseptic necrosis, boosting the infection on the avascular cartilage of the external ear canal. [24] Moreover, multiple exposures to HBOT enhances tissue regeneration and bone remineralization by stimulating fibroblastic activity, collagen proliferation, and capillary neoangeogenesis. [25]

HBOT can lead to vasoconstriction and resolution of the edema in affected tissues, stimulation of fibroblasts, osteoblasts, neoangiogenesis, oxygen dependent antimicrobial action of leukocytes, and better antibacterial action of some antimicrobials**.** [23,26] Most oxygen carried in blood stream is engaged to hemoglobin, which is 97% saturated at standard pressure. However, some oxygen is carried in solution, and this portion is increased under hyperbaric conditions**.** [27]

The aim of our work is to assess the role of HBOT as an adjuvant therapy for NOE and its effect on the outcome at different stages of disease.

Patients and methods:

Study design and participators

Randomized controlled clinical trial was conducted on 22 NOE patients treated in Menoufia University Hospital and Egyptian Navy HBOT Center in Alexandria recruited from April 2021 to June 2023 after approval of the review board and a written informed approval was applied for all patients.

Patients were diagnosed as having NOE with pain, edema, exudate, granulations, and failure of local treatment for more than 1 week. Patients unfit for HBOT like those with cardiac co-morbidities, chest problems (as untreated pneumothorax or COPD), high fever, seizures, pacemakers, pregnancy and claustrophobic patients, all were excluded from the study. Some drugs are not compatible with HBOT therefore; it is absolutely contraindicated for such combinations. These drugs are Bleomycin, Sulfamylon, Doxorubicin and Disulfiram. On the other hand, the presence of complications as cranial nerve weaknesses or intracranial complications did not prohibit the patient from the study.

Grouping

Patients were divided equally and randomly into 2 groups using the software (StatSoft - random number generator) for randomization, each group included 11 patients according to sample size estimation. In group A, patients were treated with HBOT sessions added to the drug therapy, while in group B the patients were treated with only drug therapy.

Preliminary assessment and staging

Patients were evaluated preoperatively with history taking to detect the presence of any pre-existing medical co-morbidities such as (diabetes mellitus, malignancy and other causes of immunosuppression).

Clinical otorhinolaryngological examination was done as well as examination of cranial nerves: VII, IX, X, XII cranial nerves.

Audiological assessment including audiometry and tympanometry was done.

Lab investigations as ESR, CRP, HbA1C, liver function and renal profile were performed to all patients. Radiological assessment was performed by HRCT to set the diagnosis, exclude the malignancy as well as to define the extent and location of the disease process.

MRI scan (to define soft tissue involvement with better option for monitoring disease progression) was done only when indicated, as in case of staging or determining the progress and the response to treatment.

Clinical staging was done depending on the nerve involvement and the disease extent; stage I comprises disease affecting the EAC with or without facial nerve involvement, stage II comprises disease violating the skull base and/or involving multiple cranial nerves, whereas intracranial extension is considered stage III

Management plan

All patients underwent thorough aural suction twice weekly, culture smears for bacteria and fungi, and antibiotic sensitivity testing. All cases were subjected to tight glycemic control.

The medical therapy was according to the culture and sensitivity test. The antibiotic used was oral ciprofloxacin combined with injectable anti-pseudomonal cephalosporin ceftazidime.

The use of antifungal drug (e.g. Amphotericin B, Voriconazole) was according to culture and sensitivity test.

In group A we added HBOT session to the medical therapy as an adjuvant therapy. Treatment involved pressurization between 2 and 3 atmospheres absolute (ATA) for period of 60 minutes once daily. A basic course involved 20 treatments and was repeated when needed.

The contraindications to HBOT were seriously revised and considered. Absolute contraindications were untreated pneumothorax, congenital spherocytosis, and administration of chemotherapeutic. Relative Contraindications include asthma, claustrophobia, COPD, high fever, pacemakers, pregnancy, seizures, upper respiratory infection.

Outcome measures and follow up

Reduction of the nocturnal otalgia was used as a crucial indicator of disease resolving. The pain assessment was done by the aid of visual analogue score (VAS), which is a measurement of pain intensity, used to record patients' pain series, or compare pain severity between pains with similar circumstances. [28]

Inflammatory markers as total leukocyte count, ESR and C-reactive protein, in addition to periodic clinical examinations, was used to assess disease progression. On termination of the treatment course, follow-up was done every 3 months, until one year at maximum from beginning the course, including clinical follow up by endoscopic examination to check granulation tissue, otorrhea, patients' symptoms like nocturnal otalgia, and hearing loss. ESR and CRP of increasing pattern could be the first sign of disease recurrence.

Statistical analysis

Data were collected, tabulated and statistically analyzed using an IBM compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc. Released 2015. IBM SPSS statistics for windows, version 23.0, Armnok, NY: IBM Corp.). P value of < 0.05 was considered statistically significant.

Results

In the current study, the group A (antimicrobial therapy + HBOT group) included 5(45.5%) males and 6(54.5%) females with an age range from 54-80 years and a mean age of 67.36±8.95SD. The group B (Antimicrobial therapy alone) included 10(90.9%) males and 1(9.1%) female with an age range from 55 to 79 years and a mean age of 65.91±7.44SD. There were non-significant statistical differences between both groups regarding age and sex Table 1.

The presence of pseudomonas was 100% in group B and 81.1% in group A which shows insignificant difference between both groups Table 2. We reported two patients with complications (facial palsy) one in each group. All patients in both groups were diabetics.

There was no significant difference between both groups regarding pretreatment staging Table 3.Pretreatment pain severity score mean was 6.82±1.17 in group A and 6.36±1.12 in group B with no significant difference between both groups. Before treatment ESR levels in group A were 54.18±17.45 and in group B were 61.36±21.03 without significant difference Table 3.

Regarding post treatment staging, group A, had eight recovered patients and three patients in stage I while group B had four recovered patients, six in stage I and one in stage II. These results show a non-significant difference between both groups. Regarding the otalgia and ESR level, the mean pain

severity score was 1.09±1.22 in HBOT group compared to 2.82±1.60 in antimicrobial therapy alone. The mean ESR was 20.09±7.58 after HBOT compared to 34.46±12.88 in antimicrobial therapy alone group. These show a significant difference in favor of HBOT group regarding pain and ESR level, Table 4.

We noticed a significant difference in the length of hospital stay between the 2 groups, favoring HBOT group as the average hospital stay was 2.22±3.6 while in antimicrobial therapy alone group the mean hospital stay was 9.36±10.17 Table 5.

Table 1. Comparison between studied groups regarding socio-demographic data

	Group A Antimicrobial therapy + HBOT Group (N= 11)		**Group B Antimicrobial therapy alone Group (N= 11)**		**Test of significance**	**P-value**
Age Mean ± SD Range	67.36±8.95 54.0-80.0		65.91±7.44 55.0-79.0		t= 0.415	0.683
	No	**%**	**No**	**%**	**Test of significance**	**P-value**
Sex: Male Female	5 6	45.5 54.5	10 1	90.9 9.1	FE =5.238	0.063

SD: standard deviation, range (minimum- maximum), No: number
t: student t test, FE: fischer exact test, P >0.05: non-significant.

Table 2. Comparison between studied groups regarding NOE:

	Group A Antimicrobial therapy + HBOT Group (N= 11)		**Group B Antimicrobial therapy alone Group (N= 11)**		**Test of significance**	**P-value**
Age Mean ± SD Range	67.36±8.95 54.0-80.0		65.91±7.44 55.0-79.0		**t**= 0.415	0.683
	No	**%**	**No**	**%**	**Test of significance**	**P-value**
Sex: Male Female	5 6	45.5 54.5	10 1	90.9 9.1	**FE** =5.238	0.063
Bacteriology of ear discharge: Proteus pseudomonas	2 9	18.2 81.8	0 11	0.0 100.0	**FE**=2.200	0.476
Complications: Yes No	1 10	9.1 90.9	1 10	9.1 90.9	-	-
Presence of DM	11	100	11	100.0	-	-

SD: standard deviation, range (minimum- maximum), No: number
t: student t test, FE: fischer exact test, P >0.05: non-significant.

Table 3. Comparison between studied groups regarding Pre-treatment clinical and laboratory data

	Group A Antimicrobial therapy + HBOT Group (N= 11)		**Group B Antimicrobial therapy alone Group (N= 11)**		**Test of significance**	**P-value**
	No	**%**	**No**	**%**		
Stage of NOE: Stage 1 Stage 2	 7 4	 63.6 36.4	 6 5	 54.5 45.5	X^2= 0.188	0.665
Pain severity score: Mean ± SD Range	6.82±1.17 5.0-9.0		6.36±1.12 5.0-8.0		t= 0.932	0.363
ESR: Mean ± SD Range	54.18±17.45 37.0-95.0		61.36±21.03 33.0-94.0		U= 0.723	0.470

X^2: Chi square test, t: student t test, U: Man-whitney test, P >0.05: non-significant.

Table 4. Comparison between studied groups regarding post-treatment clinical and laboratory data:

	Group A Antimicrobial therapy + HBOT Group (N= 11)		**Group B Antimicrobial therapy alone Group (N= 11)**		**Test of significance**	**P-value**
	No	**%**	**No**	**%**		
Stage of NOE: Resolved Stage 1 Stage 2	 8 3 0	 72.7 27.3 0.0	 4 6 1	 36.4 54.5 9.1	X^2= 3.333	0.189
Pain severity score: Mean ± SD Range	1.09±1.22 0.0-3.0		2.82±1.60 0.0-5.0		U= 2.413	**0.016***
ESR: Mean ± SD Range	20.09±7.58 9.0-34.0		34.46±12.88 18.0-54.0		U= 2.470	**0.014***

Stages (1&2) are active stages of **NOE**

X^2: Chi square test, U: Man-whitney test, ***P <0.05: significant.**

Table 5. Comparison between studied groups regarding post-treatment outcome

	Group A Antimicrobial therapy +HBOT Group (N= 11)		**Group B Antimicrobial therapy alone Group (N= 11)**		**Test of significance**	**P-value**
	No	**%**	**No**	**%**		
Length of hospital stay days): Mean ± SD Range	2.22±3.6 0.0-15.0		9.36±10.17 0.0-30.0		**U**= 2.200	**0.040***
Follow-up: Non recurrent Recurrent	 10 1	 90.9 9.1	 6 5	 72.7 27.3	**FE=** 4.240	**0.022***

U: Mann-Whitney test, FE: Fischer exact test

Discussion:

NOE is an aggressive infection of the EAC invading adjacent tissues and typically into the skull base. [29] Diabetes has long been involved in this inflammatory process and its prevalence in NOE is almost 100% of cases. [29-30] All of patients in our study were diabetics and their mean age was 67 in group A and 65 in group B.

In agreement with related reports [31-33], we noticed a significant association between sex and incidence of NOE with a male predominance in our study.

It was previously proposed that the pseudomonas growth on ear cultures is amendatory criterion for diagnosis. [3] In our study, presence of pseudomonas was 100% in group B and 81.1% in group A without significant difference. Proteus was found in one patient in group A.

We reported two patients with cranial nerves palsies (facial palsy) in both groups. We did not find a significant association between cranial nerves affection and outcome. In addition, in previous studies [9,34] that analyze the prognostic factors in NOE, there was no significant difference in the prognosis of NOE considering any specific or multiple cranial nerves. On the contrary, others [35] found that patients with cranial nerve involvement, temporal bone erosion, and the presence of other comorbidities require more treatment period and have an adverse outcome.

HRCT scanning is a cost-effective and fast imaging modality in the early NOE patient's assessment. [10] Therefore, we depended on HRCT as an initial assessment not for follow up.

The results of our study revealed that NOE could be prognostically staged at the initial presentation. The clinical staging depended on the nerve inclusion, while the radiological staging depended on the extent of the disease. Stage I includes disease confined to the EAC with or without facial nerve palsy, stage II includes invasion of the temporal bone and/or inclusion of multiple cranial nerves, while cerebral inclusion is considered stage III. [9] This is the most recent staging system, which we used in our study and was done before HBOT. In group A seven patients were stage I and four patients were stage II, while in group B, six patients were stage I and five patients were stage II. There was not any significant difference between both groups regarding pretreatment staging. In post treatment staging, group A had eight recovered patients and three patients in stage I Figure 3. On the other hand, group B had four recovered patients, six in stage I and one in stage II Figure 4. These results show a significant difference between both groups regarding higher recovery rate and lower morbidity in HBOT group with no mortalities in both groups of patients.

Pain severity in both groups was assessed using VAS. Pretreatment mean score was 6.82±1.17 in group A and 6.36±1.12 in group B with no significant difference between both groups. After treatment we found a significant difference in HBOT group with mean pain severity score of 1.09±1.22 compared to 2.82±1.60 in antimicrobial therapy alone group Figure 2. These results delineate the effectiveness of HBOT in reducing patients' morbidity. We found that disappearance of nocturnal pain which is a sign for recovery is passed faster in HBOT group. This correlates with other report [36], as we found that 93.3% of HBOT patients had no pain after 2 months and only 28.6% in the antimicrobial only group.

In this study, we found that ESR levels were elevated in all patients, which appeared to function as a nonspecific inflammatory marker for diagnosis and resolution of the disease.

Others [2] supported our finding as the reduced ESR pattern with absence of leukocytosis was reflecting the disease resolution. We have also found that the patient's improvement of persisting nocturnal pain and lowering the ESR to near normal values were dependable indicators of disease fading. The normalization of the physical exam was also used as a confirmation. Before treatment ESR levels in group A were 54.18±17.45 and in group B were 61.36±21.03 with no significant difference between both groups. After HBOT the mean ESR decreased to 20.09±7.58 Figure 2 which is significantly lower than antimicrobial therapy alone group 34.46±12.88. These results confirm the role of HBOT in reducing inflammation and fastening recovery that goes with others results. [28]

These results are matching with many authors [7,36] who found a noticeable benefit from HBOT as an adjuvant treatment in increasing the rate of recovery with reduced hospital stay. According to **Amaro et al.** [10] **,** HBOT should be applied to each case of NOE and they found many advantages of HBOT in advanced stages (II and III) with lower incidence of recurrence and better response to antimicrobials therapy.

On the other hand, there are several other authors' opinion and experiences concerning HBOT role in NOE treatment. **Phillips and Jones,** [19] deny the efficacy of HBOT, considering high costs, time consuming and deficiency of credible clinical trials.

We noticed a difference, although not statistically significant, in the length of hospital stay between the two groups that in turn will affect the total cost. In HBOT group, the average hospital stay was 3.82±5.60. In the other group, the mean hospital stay was 9.36±10.17. This difference in hospital stay duration could be attributed to the effect of HBOT on the inflammation, the synergistic effect with the antibiotics and the better tissue oxygenation.

Follow-up was done every three months after end of treatment until one full year, which showed a difference between both groups although statistically insignificant. In HBOT group only one patient had a recurrence of infection, while in the other group, three patients had a recurrence.

Conclusion:

HBOT is a valuable adjuvant treatment when added to microbial therapy and is highly effective with marked improvement in controlling this serious infection.

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Conflicts of interest: No

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