THERAPEUTIC HYPERBARIC OXYGENATION AS AN ADJUNCT TO MULTIDRUG THERAPY IN HANSEN'S DISEASE

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ABSTRACT

Hansen's disease is a chronic infection caused by *Mycobacterium leprae*. Current therapy for this disease is with the WHO recommended Multi Drug Therapy (MDT) with DDS, rifampicin and clofazimine. Hyper Baric Oxygen Therapy (HBOT) has been used to treat many medical conditions including infections with a great deal of success. It's efficacy on various species of mycobacteria and other bacteria have been studied in vitro and in vivo and it is found to be an effective antimicrobial agent under specified conditions. HBOT has been used to treat Hansen's disease, including drug resistant lepromatous leprosy cases with good results. However there is a paucity of literature on this form of therapy. We have treated twenty cases of Hansen's disease with HBOT prior to exhibiting MDT as per the WHO schedule. There has been a marked regression in skin signs especially decrease in erythema and flattening of raised lesions. This correlated well with the histopathological picture which showed a reduction in the inflammatory exudate.

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KEY WORDS: Hansen's Disease; HBOT; Hyperbaric Oxygen; Leprosy; Therapy.

Introduction

Hansen's disease is a chronic infection caused by *Mycobacterium leprae*. Chaulmoogra oil was the first substance used to treat leprosy [1]. Later promine, diasone, promacotin and many other sulphones were tried, however in the 1940's dapsone came to be the mainstay of drug treatment for Hansen's disease [1].

WHO recommended multi drug therapy (MDT) with DDS, rifampicin and clofazimine for six months in paucibacillary leprosy and for two years or more in multibacillary cases, to combat resistance to DDS monotherapy and decrease the duration of treatment [2-4]. However after encouraging results initially, there have been resistant cases reported even after these schedules [5,6]. Furthermore it was observed that disease activity still persisted in a large number of cases, especially in the paucibacillary type of disease, after completion of the advocated duration of therapy [7,8]. "Leprea reaction" was also seen to occur in five to twenty one percent of patients who had completed

chemotherapy [8,9].

HBOT has been used in the treatment of many diseases including infections. This form of treatment involves placing an individual in a therapeutic recompression chamber at pressures between 1.2 -2.8 Absolute Atmospheres (ATA). HBOT is effective against mycobacterial diseases and has been used to treat Hansen's disease [10-12]. It has been used to treat drug resistant lepromatous leprosy cases, without concomitant anti leprosy drug therapy, with reportedly very good results [10,13]. It has also been observed that HBOT synergises with PABA antagonising drugs, enhancing their effect, causing them to be bactericidal [10,14].

This study has been carried out to examine the efficacy of HBOT as a therapeutic agent when used along with anti leprosy drugs, as the pilot study results were extremely encouraging.

Material and Methods

Twenty cases of Hansen's disease were included in this study. The study group consisted of cases attending the skin OPD and

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Fig. 1: Hansen's disease BT with well defined erythematous plaque prior to exhibition of HBOT.

Fig. 3: Flattened lesion with minimal erythema 6 months after exhibition of MDT (Same lesion in Fig. 1)

Fig. 2: Marked flattening and decrease in erythema immediately after HBOT (Same lesions in Fig. 1)

those admitted to our hospital. All cases were freshly diagnosed cases of Hansen's disease on the basis of history, clinical, bacterio-

Fig. 4: Hansen's disease BT with partially well defined erythematous plaque prior to exhibition of HBOT.

logical and histopathological examination.

The cases found fit to undergo HBOT, after being evaluated to

Fig. 5 : Marked flattening and decrease in erythema after HBOT. (Same lesion as in Fig. 4)

Fig. 6 : Well defined granuloma with epithelioid cells, mononuclear cells and Langhans' giant cells in Hansen's disease BT prior to exhibition of HBOT (Hematoxylin and Eosin stain 100 x)

Fig. 7 : Marked decrease in cellular infiltrate after HBOT (Same lesion as in Fig. 6) (Hematoxylin and Eosin stain 100 x)

exclude pulmonary, cardiovascular and central nervous system disease, otitis media and sinusitis, were given HBOT at 2.2 ATA (12 meters of sea water column of diving depth), for 60 minutes daily, for 12 days, in a multiplace hyperbaric chamber at the Department of Hyperbaric Medicine under the supervision of a Hyperbaric Medicine Specialist. After each treatment with HBOT, the

Fig. 8 : Epithelioid cell granuloma of Hansen's disease BT prior to exhibition of HBOT (Hematoxylin and Eosin stain 400 x)

Fig. 9 : Marked decrease in cellular infiltrate after HBOT (Same lesion as in Fig. 8) (Hematoxylin and Eosin stain 400 x)

chamber was flushed through with air and treated with ultra violet radiation for 15 minutes. The masks and tubing were flushed through with air, washed with savlon solution and treated with ultra violet radiation and with 80% alcohol.

The subjects were re-evaluated clinically, bacteriologically and histopathologically on completion of the above course of HBOT and subsequently MDT was exhibited as per the WHO schedule (DDS, rifampicin and clofazimine). They were similarly evaluated at the end of 3 months and 6 months respectively. Special attention was paid to number, size, distribution and morphology of skin lesions especially erythema and infiltration, impairment of superficial sensations, peripheral nerve thickening and tenderness and other stigmata of Hansen's disease. Raised lesions, erythema and areas of sensory impairment were marked on each individual's chart which were compared. Decrease in erythema, flattening and return of superficial sensations was regarded as evidence of improvement. Histologically the size and type of the granuloma and infiltrate was compared as was the bacteriological index (BI).

Observations and Results

All twenty cases were adults between the ages of 22 to 60 years. The sex distribution and types of leprosy in the study group is placed at Table 1. There were fourteen males and six females included in this study. Fifteen of these cases were paucibacillary and five were multibacillary cases of Hansen's disease.

TABLE 1
Sex Distribution and types of leprosy treated with HBOT

Type of leprosy	No. of cases		
	Male	Female	Total
Paucibacillary cases	11	04	15
Multibacillary cases	03	02	05
Total no. of cases	14	06	20

In the paucibacillary group there was moderate to marked decrease in erythema in all ten cases immediately after HBOT i.e. prior to exhibiting DMT (Table 2). Similar results were seen in the multibacillary group (Table 3). In the paucibacillary group seven of the ten cases (70%) had no erythema after six months and in the multibacillary cases there was no erythema seen in three of five cases (60%) after six months.

TABLE 2
Erythema in skin lesions in paucibacillary cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Present	10	—	—	—
Moderate decrease	—	04	02	01
Marked decrease	—	06	04	02
Absent	05	05	09	12
Total	15	15	15	15

TABLE 3
Erythema in skin lesions in multibacillary cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Present	05	—	—	—
Moderate decrease	—	03	02	01
Marked decrease	—	01	02	01
Absent	—	01	01	03
Total	05	05	05	05

The effect of HBOT on morphology of skin lesions is placed at Table 4 and 5. Moderate to marked flattening occurred in seven of the twelve cases (58.33%) immediately after HBOT. Nine (75%) of these cases had complete flattening after six months, in four out of twelve cases (33.3%) the well defined lesions became indistinct after HBOT whereas eight of fifteen cases (53.33%) had barely perceptible or no skin lesions at the end of six months. (Figures 1-5).

The effect of HBOT on superficial sensory loss is placed at Table 6. Only two of nineteen cases (10.53%) had complete recovery of superficial sensory loss after three months whereas three of thirteen cases (23.08%) showed partial recovery of superficial sensations after six months.

Nerve thickening decreased marginally in only two of nine cases (22.22%). The results are placed at Table 7.

Results of HBOT on BI are placed at Table 8. BI decreased rapidly after HBOT and became nil after three months.

All twenty cases showed a mild to moderate decrease in cellu-

TABLE 4
Morphology of skin lesions treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Raised/infiltrated	12	05	02	—
Moderate flattening	—	04	03	01
Marked flattening	—	03	02	02
Flat	08	08	13	17
Total	20	20	20	20

TABLE 5
Definition of borders in paucibacillary cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Well defined	12	08	05	04
Ill defined	03	07	06	03
No skin lesion/ barely perceptible	—	—	04	08
Total	15	15	15	15

TABLE 6
Superficial sensations in lesions in cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Absent	13	13	09	08
Decreased	06	06	08	09
Present	01	01	03	03
Total	20	20	20	20

TABLE 7
Nerve thickening in cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Gross	02	02	02	01
Moderate	07	07	07	06
Mild	—	—	—	02
Total	09	09	09	09

TABLE 8
BI in multibacillary cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
> 3 +	01	—	—	—
3 +	02	—	—	—
2 +	02	—	—	—
1 +	—	05	—	—
0	—	—	05	05
Total	05	05	05	05

lar infiltrate after HBOT. Five (25%) of these cases showing complete histological clearance. The results are placed at Table 9. (Fig-

ures 6-9). Nasal congestion in one multi bacillary case subsided after HBOT.

TABLE 9

Histopathological findings in cases treated with HBOT

	Before HBOT	After HBOT	After 3 mths	After 6 mths
Typical granuloma/infiltrate	12	—	—	—
Mild decrease in no. of cells	—	14	10	04
Moderate decrease in no. of cells	—	06	10	11
Non specific/sparse infiltrate	—	—	—	05
Total	20	20	20	20

There were no side effects seen in any of the patients treated with HBOT.

Discussion

HBOT has been used to treat many diseases including infections. HBOT is a broad spectrum anti-bacterial agent. It has been found to be effective in Hansen's disease but this has not been well documented [10-13].

Bacteria are protected from self destruction by their own oxygen free radicals and those from the host by superoxide dismutase (SOD) and peroxidase, and from hydrogen peroxide by catalase [10]. Mycobacterium leprae have no catalase and variable but low levels of peroxidase as compared to other mycobacteria [15]. Niwa et al found that in lepromatous patients of more than four years duration, there was significantly increased SOD activity and decreased oxygen moiety production. Clofazimine significantly increases the generation of hydroxyl radicals ($\text{OH}^\cdot$) in a dose dependent manner with subsequent decrease in hydrogen peroxide, but has no effect on SOD activity of polymorphs and monocytes. The $\text{OH}^\cdot$ radical is a potent oxidant and is capable of attacking any organic compound found in living tissue [16]. Hence HBOT will have synergistic action with clofazimine as it has with PABA-folate antagonising drugs [14].

In this study we have observed a fall in BI from 2+ and above to 1+ after HBOT therapy in all five multibacillary cases prior to exhibiting MDT due to the enhanced leukocyte killing effect under hyperoxic conditions [10]. This effect could probably be potentiated by the simultaneous use of anti leprosy drugs.

HBOT reduces oedema in inflamed nerves thus relieving pressure with consequent recovery of nerve function [10]. In this study there was decrease in nerve

thickening in only two of nine cases (22.2%) and only 10.53% had complete recovery of sensations whereas 23.08% had partial recovery of superficial sensations.

There has been a remarkable decrease in erythema immediately after HBOT in all cases. No erythema was seen in 70% of paucibacillary and 60% of multibacillary cases on completion of therapy. This is probably due to the vasoconstriction effect of HBOT [10].

It was observed that 58.33% of raised lesions showed moderate to marked flattening after HBOT. Complete flattening was observed in 75% of cases after six months. At the end of therapy, there were barely perceptible or no skin lesions in 53.33%. All cases had a mild to moderate decrease in the cellular infiltrate after HBOT and 25% had complete histological clearing at the end of therapy. The effect of HBOT on cell mediated immunity (CMI) in Hansen's disease is not documented. From the above observation it appears that HBOT modifies the CMI beneficially in Hansen's disease.

HBOT was found to be effective in reducing erythema and resulted in flattening and clearing of skin lesions in Hansen's disease. The BI showed a remarkable decrease after HBOT. Clinical signs correlated well with histopathological findings which showed regression in the cellular infiltrate and decrease in granuloma size. Long term follow up of these cases is required. Simultaneous exhibition of MDT with HBOT could probably have yielded better results.

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