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Amelioration of Sickle Cell Crises With Intensive Hyperbaric Oxygen

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Hart GB, Finklestein JZ, Groncy PK, Meyer GW, Strauss MB. Amelioration of sickle cell crises with intensive hyperbaric oxygen. J Hyperbaric Med 1991; 6(2):75–85.—Eight patients (5 males, 3 females, average age 19 ± 6 yr) were considered for hyperbaric oxygen (HBO) treatment when declared to be in crisis by the admitting physicians. The patients' admissions were divided into 2 groups: historic control admissions with symptoms existing more than 24 h (control group, no HBO given) and the HBO admissions with symptoms existing less than 24 h (treated group, received intensive HBO). The patients completed a comparable laboratory evaluation on 38 admissions during the period from 1 December 1987 to 1 December 1988. Severity was measured by the narcotics received (narcotic utilization index [NUI]). There was no difference in NUI between the 2 groups ($P = 0.9$). The HBO group received an average of 14.9 (SD 4.9) HBO treatments per admission, averaging 31 h total of HBO per admission. One patient received a maximum of 121 treatments (250 h of HBO) in eight separate hospitalizations during the year. No incident of acute CNS or pulmonary oxygen toxicity was observed in the patients treated. There were no significant differences between groups of red blood cell count, hematocrit, or hemoglobin, at admission or discharge. There was a significant reduction in the HBO group's white blood count (WBC) at discharge compared to the historic control WBC at discharge ($P = 0.01$), and the reticulocyte count was similarly reduced ($P = 0.002$). The historic controls averaged 7.6 (SD 3.3) days of hospitalization compared to the HBO group of 5.7 (SD 1.7) days ($P = 0.03$); a significant reduction in hospital stay of approximately 2 days.

sickle cell crises, hyperbaric oxygen therapy

Introduction

The vaso-occlusive crises of sickle cell anemia occurs during conditions that lower the oxygen tension of the patient's erythrocytes. Although erythrocytes of homozygous sickle cell patients are prone to deformation even in the fully oxygenated state, it is the desaturation of oxygen that allows hemoglobin S to polymerize, cause sickling, and the development of irreversibly sickled cells (ISC). The patient in crisis has ISC and cells that are desaturated but not yet irreversibly sickled. The sticking of the rigid erythrocytes within the microcirculation leads to tissue ischemia and infarction that is thought to be the underlying mechanism of a crisis. (1, 2)

The role of supplemental oxygen in the treatment of painful episodes of sickle cell disease has been discouraged in the past (3). However, it has been suggested when oxygen inhalation is used in the painful crisis, that it should be administered intermittently to avoid serious suppression of the erythropoietic system (4). Diggs (5) first suggested hyperbaric oxygen (HBO) may be useful in the treatment of painful sickle cell crises.

Hyperbaric oxygen is a treatment used to deliver oxygen to a patient at a pressure greater than 760 mmHg. To achieve this effect the patient is placed into a sealed pressure chamber and breathes oxygen at the prescribed pressure. The physiologic effects of hyperoxia are documented in animal and human studies (6–10). During the procedure there is a decreased heart rate, a generalized vasoconstriction, and tissue hyperoxygenation. Posttreatment there is a reflex vasodilation, more pronounced in the subcutaneous tissue than muscle, and a slow release of tissue oxygen physically dissolved in the tissue fluids to the metabolizing cells. HBO has received acceptance in treating certain diseases wherein there exists some degree of hypoxia (11).

There are two reports using hyperbaric oxygen in humans with vaso-occlusive crisis of sickle cell anemia. Lazlo et al. (12) treated 3 patients with sickle cell anemia (hemoglobin SS) disease, one with sickle cell trait (hemoglobin AS), and one with a sickle cell variant (hemoglobin DS) at 2 atm abs pressure for 20 min to 1 h. The percent of sickled cells in the peripheral blood was decreased both during and after the exposure (lasting 4 days in one instance). The treatment did not precipitate an aplastic crisis, nor did it affect the patients' perception of pain. A patient with sickle cell trait experiencing hematuria had an abrupt cessation of the hematuria after treatment. Reynolds (13) treated a woman with painful vaso-occlusive crisis at 2 atm abs oxygen for 90 min 3 times within a 24-h period, with temporary pain relief after the first two treatments, and pain resolution after the third exposure.

In 1987, we modified an intensive HBO treatment schedule to apply in the acute phase (first 24 h until asymptomatic) of all ischemic diseases having reports of a favorable response with HBO. The schedule of using Reynolds' treatment regimen of 2 atm abs, 90 min 3 times in each had unpredictable results in our experience. This type of intensive schedule had been reported as more successful in treating an ischemic state such as myocardial infarction (14). Patients were not accepted for treatment if the ischemic state, symptomatically, had been present for a period of time greater than 24 h because other ischemic diseases such as decompression illness are found to respond unpredictably after this time (15). A retrospective review of the patients in vaso-occlusive crisis was undertaken to evaluate HBO as an adjunct to the standard care with the following objectives:

1. To determine if the course of sickle cell crisis was altered by applying intensive HBO as measured by a) the use of narcotic analgesia and b) the length of hospitalization.

2. To document any toxicity of intensive hyperbaric oxygen on patients with sickle cell anemia.

Method

Patients, 12 yr or older, who were admitted to the hospital between 1 December 1987 and 1 December 1988 with the diagnosis of sickle cell crisis were reviewed. Each patient receiving HBO did so after having or their next of kin having agreed to an informed consent. Each patient had documented sickle cell anemia by electrophoresis and was diagnosed to be in vaso-occlusive crisis by the attending hematologist. In no case did the patient have a condition in which HBO could be used as an accepted adjunct to therapy. None demonstrated the following relative or absolute contraindications to hyperbaric oxygen:

- Claustrophobia
- First trimester of pregnancy
- Uncontrolled seizure disorder
- Existing malignancy
- Suspected viral infection (varicella, herpes, cytomegalovirus, influenza, AIDS, hepatitis, etc).

The medical management of the sickle cell crisis was directed by the pediatric hematologist, who decided whether the patient fell into the control or HBO group. Patients admitted within 24 h of the onset of crisis were treated with intensive HBO (Table 1), while the same patients admitted at other times during the review period with greater than 24 h from the onset of crisis to admission were used as controls. The treatment group was further divided into 2 subgroups; namely, those treated in less than 12 h from onset of crisis (group 1) and those more than 12 h from onset (group 2).

Temperature, pulse rate, and noninvasive blood pressure were taken at 4-h intervals. Height and weight were recorded for each admission. Fluid intake and output were observed and maintained at 3 liters $\cdot$ m^2 [body surface area (BSA)] $\cdot$ 24 h^{-1}.

A complete blood count, platelet count, and reticulocyte count were documented both at admission and before discharge. Urinalysis and other indicated blood chemistries were performed at the time of admission and repeated as indicated during the course of the hospital stay. Radiographs of the chest and other organs or regions were taken as indicated by the crisis presentation but were not a part of this review.

Cessation of Treatment

Treatment was stopped when the attending hematologist determined that the patient improved sufficiently to be discharged.

The total amount of narcotic used by each patient per admission was calculated in reference to their respective BSA in meters square and days of

Table 1: Intensive HBO Schedule

Exposure Number	Pressure, atm abs[a]	Gas Mix[b]	Exposure Time, h
First 24 h			
1	2	O_2	2
2	1	Air	1
3	1.5	O_2	3
4	1	Air	1
5	1.5	O_2	2
6	1	Air	2
7	1.5	O_2	2
8	1	Air	2
9	1.5	O_2	2
10	1	Air	2
11	1.5	O_2	2
12	1	Air	2
13A	1.5	O_2	1
Second 24 h			
13B	1.5	O_2	1
14	1	Air	4
15	1.5	O_2	2
16	1	Air	4
17	1.5	O_2	2
18	1	Air	4
19	1.5	O_2	2
20	1	Air	4
21	1.5	O_2	2
Third 24 h			

The HBO exposures are at 2-h intervals with 6 h of ambient air interspersed. This proceeds to twice daily treatments thereafter for the same duration if required. Pressures remain at 1.5 atm abs with 5-min air breaks following 30 min of oxygen during each of the HBO treatments.

[a]The exposures (even number exposures) at 1 atm abs air allows the patient to exit the chamber for such medical, surgical, and diagnostic interventions as required for continuation of care.

[b]After the first 2-h oxygen exposure all succeeding HBO treatments are given with 5-min air breaks following 30-min oxygen exposures.

hospitalization as a method to measure the degree of pain associated with each admission. The formula for this index is as follows:

$$\frac{\text{Narcotic Relative Value (NRV)}}{\text{BSA}} = \text{Narcotic Utilization Index (NUI)}$$

Where the NRV is ascertained by the following calculations:

$$\frac{\dfrac{\text{Total Amount of Narcotics}}{K}}{\text{Days of Hospitalization}} = \text{NRV}$$

Constant values *(K)* used for the following respective narcotics were:

$$\begin{aligned} K &= \text{Dilaudid} = 1 \\ &\quad\ \text{Morphine} = 10 \\ &\quad\ \text{Codeine} = 65 \\ &\quad\ \text{Demerol} = 100 \end{aligned}$$

Results

Eight patients, 5 males and 3 females, with an average age of 19 yr were reviewed. They were admitted on 43 occasions during the review period. Five admissions were excluded from the review as their laboratory data were incomplete, leaving 38 admissions for the comparative review. The patients arriving within 24 h from the onset of crisis were treated with HBO, hydration, antibiotics or antiseptics or both, and analgesia during 22 of the admissions. The same patients arriving for hospital admission after 24 h from the onset of crisis (control group) were treated with hydration, antibiotics or antiseptics or both, and analgesia during 16 admissions (Table 2).

The control admissions averaged 7.6 ± 3.3 days of hospitalization and the treated group 5.7 ± 1.7 days of hospitalization. A two-sample *t* test revealed the HBO group had significantly lower ($P = 0.03$) hospital days than the controls. There was no significant difference in hospital days between the 2 treatment subgroups (Table 3).

Analysis of the 38 admissions revealed no significant differences between any of the groups in the level of pain as reflected by the use of narcotics

Table 2: Review Subjects[a]

Patient	Sex	Age	BSA, m^2	Sickle Cell Type	Admissions to Study
CG	male	15	0.9	SS	9
MC	female	17	1.3	SS	3
FC	male	12	0.5	SS	2
AF	male	14	1.1	SS	9
BH	male	29	1.1	SS	2
KL	female	19	0.7	SS	2
MN	male	25	1.2	SS	9
BP	female	24	1.3	SS	2

[a]Average age = 19.3 yrs, SD = 6.02; [b]average BSA = 1.0, SD = 0.3

Table 3: Days of Hospitalization[a]

	Controls	HBO All	HBO Group 1	HBO Group 2
Admissions	16	22	12	10
Average days	7.6	5.7	6.1	5.2
SD	3.3	1.6	1.5	1.7

[a] *t* Test: analysis of controls vs. HBO all groups, $P = 0.026$; *t* test: analysis of Group 1 vs. Group 2, $P = 0.18$.

(Table 4). There were no significant differences between admitting and discharge (DC) hematocrits (Hct), hemoglobin (Hgb), or red blood cell (RBC) values comparing the various subsets. The hypothesis for difference was tested both against the pooled admitting values and separately for each group's admitting levels. There were significant changes, however, in the HBO-treated group both in the white blood counts (WBCs) and the reticulocyte counts between the admission and discharge values (Table 5).

The WBCs were significantly reduced ($P = 0.00001$) in the treatment group from admitting values and from the discharge values of the control group ($P = 0.01$). The admitting WBCs of the treatment group 1 cohort (average 13,300) were significantly less ($P = 0.01$) than the admitting WBCs of the treatment group 2 cohort (average 17,000), while there was no significant difference in the discharge WBCs. Although there was a reduction of discharge WBCs in the control group this did not reach significance with the numbers in this cohort comparing it with either the pooled or control admission data. There were significant decreases of the reticulocyte counts at discharge in the treatment group vs. both the pooled admitting group (*t* test, $P = 0.00001$) and the control group (*t* test, $P = 0.0002$) at discharge. The difference remained highly significant when the discharge treated group's reticulocyte count was compared against the admitting values. There were no significant differences in the vital capacities upon repetitive exposures to HBO in the 3

Table 4: Narcotic Utilization Index[a]

	Controls	HBO All	HBO Group 1	HBO Group 2
Admissions	16	22	12	10
Average NUI	4.36	4.40	4.9	3.8
SD	2.7	1.97	1.96	1.9

[a] *t* Test: analysis of controls vs. HBO group, $P = 0.96$; *t* test: analysis of HBO 1 vs. HBO group, $P = 0.2$.

Table 5: Laboratory Data

	Admission	Control*	HBO All*	HBO Group 1*	HBO Group 2*
Number:	38	16	22	12	10
RBC					
Average, ml	3.20	2.93	3.05	2.91	3.21
Std dev	0.87	0.7	0.8	0.81	0.79
Hct					
Average, %	24.7	24.03	22.86	22.57	23.20
SD	5.15	6.17	7.56	6.12	9.01
Hb					
Average, GM's	8.01	7.88	7.93	7.58	8.35
SD	1.55	1.87	1.92	1.91	1.95
WBC					
Average, K's	15.93	13.88	10.49	10.39	10.61
SD	4.68	3.69	2.18	1.46	2.91
Number:	24	8	16	8	8
Reticulocyte %					
Average	14.3	13.68	6.64	7.25	6.03
SD	4.72	3.44	2.85	3.09	2.64

Note: Asterisks indicate values at discharge from the hospital.

t Test analysis of laboratory data with the following significant differences:

All admission vs. all discharge WBCs:
$P = 0.00001$

Discharge WBCs, controls vs. HBO:
$P = 0.01$

Group 1 admission vs. group 2 admission WBCs:
$P = 0.01$

All admission vs. all discharge reticulocytes:
$P = 0.00002$

Discharge retic's, controls vs. all:
$P = 0.0002$

All other analysis showed no significant differences.

patients having more than one admission. The vital capacities averaged 70% of the predicted values and were unchanged from one discharge value to the following.

The HBO group averaged 14.9 ± 4.9 treatments per admission, whereas treatment group 1 was 16.5 ± 5.9 treatments, and treatment group 2 was 13 ± 3.2 treatments. No significant differences were noted between the cohorts in treatments received. One patient received 121 treatments during seven admissions. One patient (MN) elected to avoid admission on three

occasions and was treated successfully overnight intensively with HBO as an outpatient. These data are not included as treatment hours in the preceding computations nor were they included as admissions in days of hospitalization, but are regarded as a separate outpatient category. Most of the patients had some mild middle ear complaints during the treatments, which were relieved with nasal decongestants. One patient became resistive to receiving HBO after witnessing a medical emergency in the vicinity of the hyperbaric chamber. In general, all patients had symptomatic improvement while in the hyperbaric chamber. The symptoms did return, to a lesser degree, after returning to room air, with pain diminishing progressively as each treatment was provided.

Admission days during the specified period of review (1 December 1987 to 1 December 1988) were compared with the admission data of the following year (1 December 1988 to 1 December 1989). The first study period averaged 34.25 days per patient for the 8 patients receiving HBO. Two patients did not return for comparison in the latter study period; however, the 6 patients returning during this period averaged 41.5 days of admission.

Discussion

This review was undertaken to evaluate our experience with HBO as a modality of treatment in patients with sickle cell anemia and to acquire sufficient baseline data to determine whether a formal study of this therapeutic modality is warranted. Sophisticated biochemical evaluations were not performed. Others have pointed out that oxygenation and deoxygenation of red cells in circulation take place in a time frame that is of the same order and magnitude as the sickling and unsickling of hemoglobin S in vitro (16, 17). HBO at 2 atm abs would represent O_2 at 15 times that of air breathing and the Hb molecule remains at least in part oxygenated in the venous blood at rest at these pressures (18, 19).

Classical treatment programs for patients with sickle cell anemia have been confined to symptomatic care characterized by appropriate hydration utilizing high fluid intake, careful management of the painful crisis with analgesics, and transfusions for certain circumstances such as sequestration crisis, priapism, CNS infarction, pregnancy, aplastic crisis, preparation for surgery, and severe pneumonia. HBO may be an alternative method of care for patients with sickle cell crisis. It may also play an important role when there are questions as to the use of blood transfusions.

The major risks of the patient from HBO may be divided into those from changes in pressure and those due to increased partial pressure of oxygen (20). Barotrauma (the adverse effects of changes in pressure) may affect any gas-containing cavity of the body, i.e., lungs, sinuses, ears, teeth, and gastrointestinal tract causing pain or expansion injuries or both. Decompression illness or gas embolism may occur. These occurrences are rare with proper use of the chambers and instruction to the patients. The fire hazard of

high levels of oxygen is avoided by the exclusion of an ignition point from occurring within the chamber. Oxygen toxicity, especially to the lung and CNS, has been well described (21–23). The risk of CNS oxygen toxicity at an operating pressure of 1.5 atm abs is nonexistent in our experience. Utilizing an intensive therapy, wherein the patient is exposed to 100% oxygen at 1.5 atm abs at 30-min intervals with 5-min intervals of air breathing at pressure and with varying intervals of air at sea level equaling a sum of 14 h at pressure in the first 24-h period, is examined in this report. The use of air breaks is noted in both animal and human reports as raising the threshold of pulmonary oxygen toxicity (24–26). Although detailed pulmonary function tests were not performed, there were no clinical indications of impaired pulmonary function in the treated patients.

The experience noted here suggests that HBO may reduce hospital stay time when compared with standard medical care for vaso-occlusive crisis. Furthermore, it may act as an adjunct to the control of the infection process that stimulates the crisis phenomenon. Interestingly, a significant reduction in reticulocyte count was noted in the treated group. Yet there was no significant reduction in RBCs, Hct, or Hb. One could hypothesize a mechanism in which there was a protective effect on the red cells.

The treated group also demonstrated a lower WBC count at discharge. Whether this is related to oxygen improving polymorphonuclear leukocyte function, as reported in experiments performed in vitro (27–29), is not known.

This report is not of a randomized controlled study but rather a retrospective review of our experience with HBO treatment. The review was designed so that the same patients served both as the controls and as the HBO group. It is appropriate to note that this review was undertaken to identify any differential response attained if HBO is used early and intensively in the course of the crisis. A favorable result has been noted in decompression illness (30), carbon monoxide intoxication (31), and the treatment of ischemic flaps (32). Our review did not identify an advantage of administering HBO within the first 12 h of onset of symptoms.

We believe that HBO may be an alternative method of care for patients with sickle cell crises, particularly when there is an attempt to minimize the use of blood transfusions (33). Transfusions were not required in the patients reported here during the 1 December 1987 to 1 December 1988 period. The comparison of the treatment year of 1987–1988 to that of 1988–1989 revealed a longer hospital stay in the latter instance. However, this could be considered as reflecting the natural advancing disease process in these patients. Since HBO seems to be acceptable with relative safety and may affect the duration of a sickle cell crisis, we conclude that a randomized control study of the efficacy of HBO is now warranted.

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