Hyperbaric oxygen therapy for vaso-occlusive crises in nine patients with sickle-cell disease

Jérôme Stirnemann, Edouard Letellier, Nazmiye Aras, Marc Borne, Louis Brinquin and Olivier Fain

Abstract


Introduction: Vaso-occlusive crisis (VOC) is the most frequent complication of sickle-cell disease and is associated with significant acute bone pain.

Objective: To evaluate the feasibility and efficacy of hyperbaric oxygen therapy (HBOT) for severe VOC.

Methods: We report our retrospective experience with HBOT in VOC in nine patients and 15 HBOT sessions.

Results: All nine patients had received appropriate conventional treatment prior to HBOT. Pain scores using a Visual Analog Scale (0 to 10) determined whether HBOT was effective or not in improving symptoms. While no change in pain score occurred before the HBOT session, pain scores fell significantly from 3.3 prior to HBOT to 1.9 24 hours after HBOT ($P = 0.002$). While morphine dosage increased before HBOT (median morphine dose 23 mg per day and 35.95 mg per day respectively on Day -2 and Day -1, $P = 0.04$), the median morphine dose one day after HBOT (Day +1 23 mg per day) tended to be lower than Day -1 ($P = 0.08$), and decreased to zero 2 days after HBOT ($P = 0.004$). Two patients had ear pain during compression, requiring rapid interruption of the HBOT session, although neither patient had any sequelae.

Conclusion: HBOT is feasible in sickle cell disease and appears to be effective in reducing the pain of VOC rapidly.

Key words

Haematology, hyperbaric oxygen therapy, pain, medical conditions and problems

Introduction

Vaso-occlusive crisis (VOC) is the most frequent complication of sickle-cell disease (SCD) and is associated with severe bone, thoracic and/or abdominal pain. It is the leading cause of hospitalisation among patients with SCD, as well as the leading cause of acute chest syndrome and of death. It is linked to sickling disorders and to vaso-occlusion and can be triggered by environmental factors such as acidosis, cold, dehydration, hyperthermia, infection and hypoxia. Hyperbaric oxygen therapy (HBOT) has previously been used to manage vaso-occlusive crises associated with SCD, but while some authors found it to be effective others did not. Unfortunately these studies are very dated even though HBOT continues to be used in certain strongly endemic regions. In a recent study, Medahoui related his experience of HBOT in 15 patients with VOC, in which a decrease in the degree of pain was obtained in 12 cases after the first session of HBOT; patients had an average of four successive sessions.

We report our retrospective experience with HBOT for VOC in nine patients followed in a French internal medicine department.

Methods

Patients were eligible for HBOT if they had VOC that necessitated hospitalisation and their symptoms were refractory to other conventional therapy (hydration, normobaric oxygen therapy, analgesics). The research project was reviewed and approved by the local Institutional Review Board of Ile-de-France (Comité de Protection des Personnes IdF X) and informed consent of the patients was obtained prior to HBOT. The HBOT sessions were conducted at the Val de Grace Hospital, Paris. Patients were treated at a pressure of 253.3 kPa (2.5 atmosphere absolute), each session lasting a total of 90 minutes, including a 15-minute compression and decompression, and a 60-minute treatment phase. Each patient could have up to four successive HBOT sessions. Each session was analysed independently. When an adverse event occurred, the HBOT session was interrupted, but data were still analysed as if the patient had been treated (intention-to-treat). Visual Analog Scale (VAS) score (0–10), daily morphine dose, C-reactive protein (CRP), haemoglobin and lactic dehydrogenase (LDH) levels were compared two days (Day -2) and one day (Day -1) before HBOT and one and two days (Day +1 and Day +2) afterward. VAS scores, morphine doses, CRP and LDH were compared using a non-parametric test (Mann-Whitney-Wilcoxon test). Statistical analysis was performed using R software <http://www.R-project.org/>.

Results

Nine patients presenting between March 2006 and July 2007 and receiving a total of 15 HBOT sessions were analysed. No further patients have been referred for HBOT since that time. The characteristics of the patients and HBOT sessions are shown in Table 1. Patients were hospitalized with a median stay of 3 days (range 0–11).
The median VAS score fell significantly (Figure 1) from 3.3 at Day -1 to 1.9 at Day +1 \((P = 0.002)\) and 1.4 at Day +2 \((P = 0.002; \text{data not shown})\). Before HBOT, median VAS score did not change significantly between Day -2 and Day -1 (VAS of 3 and 3.3 respectively, \(P = 0.08\)).

Before HBOT, the median dose of morphine increased between Day -2 and Day -1 (23 mg per day and 35.95 mg per day respectively, \(P = 0.04\)). The median morphine dose received during the first 24 h after HBOT (Day +1, 23 mg per day) tended to be lower than the dose received during Day -1 \((P = 0.08)\), and decreased to a median of zero after 48 h (Day +2) \((P = 0.004, \text{Figure 2})\).

No significant changes were noted in CRP, haemoglobin or LDH levels.

Two patients had ear pain during compression, requiring rapid interruption of the HBOT session, with no sequelae in either patient. One patient had paraesthesiae at the end of a session, although these disappeared spontaneously. No adverse events occurred in the other six patients. No transfusions, including exchange transfusions, were necessary after HBOT, except for one patient whose session had been interrupted by ear pain.

**Discussion**

The present results suggest that HBOT appears effective against pain associated with VOC, as witnessed by the drop in median VAS score from 3.3 at baseline to 1.9 at 24 hours and 1.4 at 48 hrs post HBOT, whereas this score did not change prior to HBOT. The patients had serious

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Type</th>
<th>ACS</th>
<th>Hydroxyurea</th>
<th>Haemoglobin (g L(^{-1}))</th>
<th>HBOT sessions</th>
<th>Complications of HBOT</th>
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<td>M</td>
<td>SS</td>
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<td>No</td>
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<td>1</td>
<td>Barotraumatic otitis</td>
</tr>
<tr>
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<td>18</td>
<td>M</td>
<td>SS</td>
<td>No</td>
<td>No</td>
<td>80</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>M</td>
<td>SS</td>
<td>Yes</td>
<td>No</td>
<td>80</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>M</td>
<td>SS</td>
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<td>2</td>
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</tr>
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<td>1</td>
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<td>SS</td>
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<td>75</td>
<td>1</td>
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</table>

The median VAS score fell significantly (Figure 1) from 3.3 at Day -1 to 1.9 at Day +1 \((P = 0.002)\) and 1.4 at Day +2 \((P = 0.002; \text{data not shown})\). Before HBOT, median VAS score did not change significantly between Day -2 and Day -1 (VAS of 3 and 3.3 respectively, \(P = 0.08\)).

Before HBOT, the median dose of morphine increased between Day -2 and Day -1 (23 mg per day and 35.95 mg per day respectively, \(P = 0.04\)). The median morphine dose received during the first 24 h after HBOT (Day +1, 23 mg per day) tended to be lower than the dose received during Day -1 \((P = 0.08)\), and decreased to a median of zero after 48 h (Day +2) \((P = 0.004, \text{Figure 2})\).

No significant changes were noted in CRP, haemoglobin or LDH levels.
VOC episodes and, in most cases, had been hospitalised for several days, during which conventional treatments had proven inadequate. While morphine remains the predominant treatment for pain associated with VOC, it is sometimes difficult to increase the dose sufficiently without risking alveolar hypoventilation and chest syndrome. Initial treatment of the nine patients proved insufficiently effective, as shown by the lack of improvement (Figure 1) and increasing doses of morphine (Figure 2) before HBOT.

Few data have been published on the use of HBOT in this setting, although one series (only reported in a textbook) has shown some efficacy. In the present series, HBOT was well tolerated. Barotraumatic otitis was the main complication and was successfully managed by decompression. No serious adverse events occurred in these nine patients, although the safety of HBOT cannot be fully ascertained given the small size of the series. Serious adverse effects of HBOT in other indications include rare cases of seizures, pneumothorax, and asthma attacks. These adverse effects necessitate close monitoring during HBOT sessions, and resuscitation equipment must be on hand.

HBOT could be beneficial in several ways during VOC. Although haemoglobin S polymerisation and red cell sickling under deoxygenated conditions are central to the pathophysiology of this disease, emerging evidence indicates that initial events may involve sickle red cell–endothelial interaction as one of the major potential initiating mechanisms in vaso-occlusion with implication of adhesion proteins. HBOT would tend to limit hypoxaemia and, thus, sickling. Hyperbaric therapy also appears to reduce cell stickiness by down-regulating adhesion proteins. Finally, HBOT seems to increase the release of nitric oxide (NO) and NO synthetase, which in turn could compensate for the reduction in NO that promotes vaso-occlusive complications in SCD. HBOT also reduces neutrophil adhesion to bovine aortic endothelial cells.

While the present study does not formally establish the efficacy of HBOT in VOC associated with SCD, it does, nonetheless, show the feasibility of this treatment. These preliminary observations warrant a prospective, randomised trial. Indeed, HBOT may be indicated for patients with refractory VOC, especially when transfusion therapies are not possible, such as in cases of allo-immunisation.

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References


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