Hyperbaric oxygen in the treatment of acute retinal artery occlusion

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Key words
Vision disorders; Visual acuity; Outcome; Retrospective studies; Clinical audit

Abstract

Introduction: Acute retinal artery occlusion (ARAO) is a major cause of sudden, painless visual loss, often leaving no useful vision in the affected eye. Its incidence is cited at 0.85 per 100,000 persons per year but may be higher because of under-reporting. The natural history is difficult to study, but a spontaneous resolution rate of < 1–8% for acute, non-arteritic ARAO has been cited. Occurrence in an only eye is devastating for the patient. There is currently no consensus regarding management of ARAO and little evidence to support any treatment modality. Despite only limited case series, hyperbaric oxygen treatment (HBOT) is recommended for ARAO by the Undersea and Hyperbaric Medical Society (UHMS) and by the European Committee for Hyperbaric Medicine.

Methods: Between early 2003 and December 2012, all ARAO patients presenting to Christchurch Hospital were referred for consideration of HBOT. These 31 consecutive patients’ medical records were reviewed retrospectively. The time delay from onset of visual loss to commencing HBOT; the presenting visual acuity; various demographic data; the HBOT administered and the outcome visual acuity were documented.

Results: All 31 patients underwent at least one HBOT (median 4, range 1–7) at a pressure of 203–284 kPa for 1.5 to 2.0 h. One patient’s treatment was terminated after 60 min at their request; another declined further HBOT and one suffered middle ear barotrauma. Thirteen patients also received anticoagulants at the discretion of the referring ophthalmologist. Twenty-three patients had temporarily improved vision with the first HBOT. Seven patients had permanent, good visual recovery (6/18 or better; Snellen chart); and two only modest improvement (6/60). All nine patients who improved permanently were treated within 10 hours of symptom onset.

Conclusions: Where available, HBOT is indicated for ARAO. Our protocol may not have been aggressive enough and the UHMS protocol is recommended. A multi-centre, randomised controlled trial is feasible, but would be logistically difficult and expensive and may be ethically unsupportable given the lack of alternative, effective treatments.

Introduction

Acute retinal artery occlusion (ARAO), either central or branch occlusion, is a major cause of sudden, painless visual loss, often leaving no useful vision in the affected eye if a central occlusion. Its incidence has been estimated as 0.85 per 100,000 persons per year, but may in fact be significantly higher due to under-reporting.1 The natural history is difficult to study, but a spontaneous resolution rate of less than 1 to 8% for acute non-arteritic ARAO has been cited.1,2 Incidence in an only eye is catastrophic for the patient’s quality of life (QALY). There is debate regarding which, if any, treatment options are useful in the acute setting.

Dramatic improvement in visual acuity in a few ARAO patients undergoing hyperbaric oxygen treatment (HBOT) in our institution in the early 2000s3 gained the interest of ophthalmologists and hyperbaric specialists, and we have continued to use HBOT in ARAO. HBOT is available in most of the main centres in Australasia, and is utilised by some of these centres for treatment of ophthalmic vascular occlusive events. The only controlled trial showed HBOT improved visual acuity by three lines or more in 38% compared to 18% in a group without HBOT, but this difference was not statistically significant.2,4 ARAO first appeared as an indication for emergency HBOT in the 2009 committee report of the Undersea and Hyperbaric Medical Society (UHMS) in the USA.5 Recently this has been supported by the European Committee for Hyperbaric Medicine.6

We conducted a retrospective clinical audit of a consecutive series of patients with ARAO referred over a decade at our institution for consideration of HBOT.
Methods

Between early 2003 and December 2012, all ARAO patients presenting to Christchurch Hospital were referred for consideration of HBOT. Thirty-one consecutive patients’ medical records were reviewed retrospectively. This was an anonymous quality assurance review. The study was discussed formally with the Ethics Committee, Office of the Chief Medical Officer, Clinical Leadership, Protection and Regulation, Ministry of Health, New Zealand and they designated the study as an audit.

The diagnosis of ARAO was made by an ophthalmology specialist or registrar in training and was based on the history of sudden visual loss and the clinical signs of a cherry red spot, cessation of retinal artery flow and possible embolus. The time delay from onset of visual loss to commencing HBOT; the presenting visual acuity; various demographic data; the HBOT administered, other treatments used and the outcome visual acuity were documented. Time to presentation was not easy to elucidate with precision in some cases, particularly with those patients who stated that they noticed the problem on waking in the morning. In these cases, we have recorded the time to presentation as less than or equal to the approximate duration since they last were known to have unaffected vision (e.g., the previous evening). Visual acuity was measured as lines of vision on an ETDRS/Snellen-type visual chart. If letters could not be seen, then the categories of counting fingers, hand movements, perception of light or no perception of light were used.7

Hyperbaric treatments, with patients breathing 100% oxygen from a head hood, were given at a pressure of 203 kPa (2.0 ATA, equivalent to the pressure at 10 metres’ depth of seawater) or 243 kPa for 90 minutes (with a 10-minute air-breathing break after 45 min) or 284 kPa for 60 minutes, followed by a 30-minute decompression to ambient room pressure. Treatment plans were determined on a case-by-case basis at the discretion of the on-call hyperbaric physician.

Given the small population of patients, formal statistical analysis used a 2X2 contingency table, mid-P exact test P (2-tail) (http://www.openepi.com/TwobyTwo/TwobyTwo.htm).

Results

DEMOGRAPHIC AND CLINICAL DATA

Case records of 31 patients (21 male and 10 female; mean age 70 years, range 37 to 88 years) with a diagnosis of non-arteritic ARAO were identified in the ophthalmological department records between January 2003 and December 2012 (Table 1). Three patients were affected in an ‘only eye’, with the fellow eye having hand movements or worse vision. Time from symptom onset to presentation ranged from three to 25.5 hours (h). Nineteen patients had hypertension, on medication, and three had diabetes mellitus. The erythrocyte sedimentation rate, measured in 19 patients, was within the normal range. Other investigations, including intra-ocular pressures (IOP), which was performed in all patients, were unremarkable. Follow-up ranged from one to 79 months.

Carotid artery ultrasounds were performed in 18/31 and, of these, two cases proceeded to acute endarterectomy, one other had an 80% stenosis and the rest were regarded as within normal limits.

CO-THERAPY

The co-treatments used in conjunction with HBOT varied widely. Intraocular pressure was attempted to be reduced with oral acetazolamide in three cases, ocular massage was used in six cases and anterior ocular chamber paracentesis in nine. Ten patients were already on aspirin and one of those was also on dipryidamole. An additional nine patients were started on aspirin as therapy. Low dose heparin was started in four cases and full-dose heparin was used in another four cases. Four patients were on warfarin and another four were started on warfarin (these four were the patients that were initially put on full-dose heparin). One patient had an ARAO during a coronary angiogram and subsequently was put on clopidogrel. Two patients were started on steroids by their general practitioner before an accurate diagnosis was determined by the admitting ophthalmologist but both were stopped when the temporal artery biopsy was reported as negative for arteritis.

HYPERBARIC OXYGEN TREATMENT

All 31 patients underwent at least one HBOT (median 4, range 1–7). Three patients withdrew from further HBOT after the first treatment, one because of an acute upper respiratory tract infection, another because of claustrophobia and one suffered middle ear barotrauma (modified TEED grade 3). The initial HBOT was at a pressure of 203 kPa in eight patients, 243 kPa in 19 and 284 kPa in four. All subsequent HBOT was administered at a pressure of 243 kPa.

POST-HBOT VISUAL RECOVERY

Twenty-three of the 31 patients reported some temporary return of vision during or immediately following their first HBOT. In nine patients vision was restored permanently; to 6/18 or better in seven and to 6/60 in two (Table 1). The remaining 14 did not maintain the initial improvement. The other eight patients showed no improvement with the first HBOT. Two patients had further deterioration in vision despite treatment, whilst two patients who showed no improvement with the first HBOT had slight overall improvement in VA at discharge. Follow-up was a minimum of one month (range 1–79 months).

All nine patients who improved had a delay from onset of visual loss to HBOT of less than 10 h, out of a total of 22 patients presenting in that time frame; whereas one of the remaining nine patients with a longer delay improved.
## Table 1

Thirty-one consecutive patients with acute retinal artery occlusion treated with hyperbaric oxygen (HBOT); anticoag – anticoagulated; BRAO – branch RAO; HM – hand movement; LP – light perception; NPL – no light perception; VA – visual acuity

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Onset to pre-HBOT (h)</th>
<th>VA</th>
<th>Final VA</th>
<th>Follow up (months)</th>
<th>HBOT (n)</th>
<th>1st HBOT (kPa)</th>
<th>Improved 1st HBOT</th>
<th>Comments</th>
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<td>7</td>
<td>243</td>
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<td>No anticoag; carotids normal</td>
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<td>HM</td>
<td>HM</td>
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<td>2</td>
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<td>8</td>
<td>HM</td>
<td>HM</td>
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<td>4</td>
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<td>6.5</td>
<td>HM</td>
<td>HM</td>
<td>4</td>
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<td>F</td>
<td>3</td>
<td>6 over 36</td>
<td>6 over 9</td>
<td>11</td>
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<td>HM</td>
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<td>HM</td>
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<td>5</td>
<td>203</td>
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<td>No anticoag; carotids normal</td>
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the arbitrary delay time division of 9 h, eight of 22 patients treated within 9 h improved permanently, compared to only one of nine patients treated later than 9 h (2X2 contingency table, mid-P exact test (2-tail) = 0.13). Whilst the number of cases is too small to detect a statistical relationship between delay to treatment and outcome, our results are certainly suggestive that the sooner patients are treated with HBO, the better (Table 1).

Of the nine with a permanent recovery, five were fully anticoagulated but the other four had no anticoagulation at all (including aspirin). There appeared to be no other links between a permanent recovery and any other treatment modality. There was no evidence of a dose-dependent effect for oxygen in this small group of patients. No relation was evident between outcome and prior eye surgery, hypertension, diabetes mellitus or the presence or absence of a cherry-red spot. Whilst the average age of those improving permanently was less than those who did not improve, there was a wide range of ages in both groups (mean age 66, range 37–80 years and mean age 72, range 42–88 years respectively).
Discussion

HYPERBARIC OXYGEN THERAPY – MECHANISM OF ACTION

The inspired partial pressure of oxygen during a hyperbaric treatment at 203 kPa is almost ten times that when breathing air at normal atmospheric pressure. It is postulated that oxygen at higher pressures diffuses from the choroidal circulation or other patent retinal vessels to reach the ischaemic retina. This restarts cellular metabolism and keeps the retina alive, allowing time for emboli to break up or move on. This may explain the anecdotal phenomenon of visual return reported in the majority of this patient cohort during the first HBOT, with reduction of oedema in the retina allowing better acuity. It also suggests that HBOT would, at most, allow a few extra hours in which circulation may be restored to the retina. It will not help in situations where the retina is already infarcted and, therefore, is only of use in patients who present within a limited time of arterial occlusion. Since there appears to be an increased rate of improvement in vision in our patients treated within 10 h, it would seem sensible to provide HBOT to any patient with ARAO presenting within this time period.

The majority of non-arteritic central retinal artery occlusions are thought to be due to emboli. There are however, several different types of emboli. Cholesterol, platelet, or red cell emboli would each respond differently to any specific medical or mechanical attempts to dislodge or dissolve them. For example heparin may have little effect on a cholesterol thrombus. Successful treatment of an embolus would depend on the type of embolus involved. It seems sensible to combine HBOT with treatments designed to remove emboli in one way or another, such as anticoagulation, though there is no good evidence to substantiate this.

Whilst IOP was recorded as normal in all patients, IOP has no known relationship to CRAO. The perfusion pressure of the eye is mean ophthalmic arterial pressure (62 mmHg if BP is 120/80) minus IOP, i.e., a small increase in IOP does not alter perfusion pressure unless it reaches 50 mmHg or more. There is a relationship between IOP and central retinal vein occlusion, which makes sense as retinal venous pressure is about 20 mmHg and, when IOP approaches or is above this, the vein can be seen opening and collapsing at the disk. The relationship between IOP and HBOT has not been investigated.

COST

The average cost per HBOT for these patients in Christchurch Hospital was approximately NZ $500 (£325) during that period and, therefore, a series of five treatments totals approximately NZ $2,500. This compared to the cost of a cataract operation to the New Zealand Government at that time of approximately NZS4,000. It has been suggested that cataract surgery is one of the most cost effective medical interventions for QALY whereas treatment of ARAO before the advent of HBOT was one of the least cost-effective interventions. With HBOT, if our percentage recovery of useful vision (nine of 31 patients, 29%) is compared with the high-end Cochrane analysis (8%, thus a conservative estimate), then the number needed to treat with HBOT for useful visual recovery is approximately five patients, making HBOT a cost-effective intervention.

PUBLISHED EVIDENCE ABOUT HBOT FOR ARAO

There is only one controlled, non-randomised trial of HBOT in ARAO. This compared HBOT and haemodilution with haemodilution alone as the control. Fifty-one patients received HBOT and haemodilution and 29 patients haemodilution alone. In the HBOT group, mean VA improvement was three lines (P < 0.0001) versus one line in the haemodilution alone group (n.s.). However, there was no significant difference between the two groups at discharge or at follow-up. In an extensive review of the clinical evidence for HBOT in ARAO carried out for the UHMS, it was concluded that there was clear evidence of clinical benefit over and above other treatment modalities. In a literature review, 25 case series of HBOT for ARAO totalling 476 patients reported ‘improvement’ in 303 (64%). The quality of reported improvement and its relationship to delay to treatment were often poorly documented, and most reports showed obvious potential selection bias. Several of the better retrospective studies follow as illustrative of the generally weak quality of the existing literature.

Comparing eight patients undergoing HBOT for ARAO, to eight who refused HBOT or had contraindications, no significant difference in outcome was noted. In a comparison of 35 patients treated with HBOT no later than 8 hours after the beginning of their visual symptoms to 37 patients from a different centre not treated with HBOT, 29 patients in the HBOT group showed improvement compared to 10 in the non-HBOT group. This improvement in outcome, by three Snellen lines, for those patients treated with HBOT was statistically significant.

Finally, data from 11 patients with ARAO treated with HBOT, of whom eight achieved improved visual acuity, were combined with that from two other case series in which the clinical data had been recorded in a comparable manner to give a total of 51 eyes with 27 patients showing improvement of two or more lines with HBOT on a modified Snellen value. Analysis of the combined case series suggested that improvement in VA may be more likely if HBOT was given within less than 24 h, but the data are not particularly convincing.

A detailed management protocol was proposed by the UHMS. Reviewing this protocol, we believe that our management during that time was not sufficiently aggressive.
and that perhaps more of the patients who showed temporary improvement with the first HBOT could have benefitted from longer and/or more frequent hyperbaric exposures based on on-going close monitoring of vision and prompt re-treatment if deterioration was noted, as recommended in the UHMS protocol. The UHMS protocol has been slightly modified for use in our hospital in recent years (Table 2). In particular, it was not felt justified to automatically move to a US Navy Treatment Table 6 if improvement was not seen at 283 kPa, but that this would be at the discretion of the treating medical officer.

PUBLISHED EVIDENCE REGARDING ALL OTHER TREATMENTS FOR ARAO

We could find no published consensus on best practice or previous studies documenting current practice for ARAO management. The scientific evidence on this topic is weak. There do not appear to be any prospective, randomized controlled trials or cohort studies. A retrospective comparison of case series at Wills Eye Hospital from 1995 compares 40 patients treated with both carbogen and anterior compartment paracentesis, with 49 patients treated with neither.14 They found no significant difference in outcome. Case series of ARAO patients treated with local intra-arterial thrombolysis are relatively numerous; however, these are balanced by reports of stroke and intracerebral haemorrhage caused by both local and systemic thrombolysis, the conclusion being that the risks may outweigh any benefits.15,16

A survey of New Zealand ophthalmologists was conducted in 2003 with a 78% (76 from 97) response rate. A quarter of respondents indicated that they would not actively treat ARAO. Of those who would treat, only four followed a written protocol for management. A wide range of treatments was chosen, somewhat dependent on the time delay to presentation, including ocular massage, anterior compartment paracentesis, aspirin, oral acetazolamide and intra-ocular pressure lowering drops. Only five respondents chose HBOT, reflecting the fact that HBOT is not available to a large proportion of the New Zealand population. When asked if they would offer HBOT if it were available, a quarter indicated that they would refer for HBOT.

Conclusions

Hyperbaric oxygen treatment, where available, is a safe, relatively low-cost and moderately effective treatment option for patients with ARAO compared to the natural history of the condition. A multi-centre, randomized controlled trial of HBOT is feasible, but would be logistically difficult and expensive and may be ethically unsupportable given the lack of alternative, effective treatments.

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