SEVERE ANEMIA

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Rationale

Patients who have marked loss of red blood cell mass by hemorrhage, hemolysis, or aplasia run the risk of lacking adequate oxygen carrying capacity by blood. The more quickly the severe anemia develops, the less tolerant the patient may be of the insult.

Hemoglobin (Hgb), a powerful carrier for oxygen, carries 1.38 ml of oxygen per gram. The amount of oxygen that will dissolve in one milliliter of plasma is 0.003 ml per mmHg of the partial pressure of oxygen (O_2) in inhaled gas. CaO_2 and CvO_2 respectively represent the arterial or venous content of oxygen in blood. The formula for determination of arterial oxygen content is given as follows:[1]

$$CaO_2 = (\text{grams Hgb} \times 1.38 \text{ ml } O_2 \times \% \ O_2 \text{ Hgb}) + (0.003 + O_2 \times \text{mm } pO_2)$$

Oxygen delivery (DO_2) is calculated by multiplying arterial O_2 content by cardiac index (CI) and is given by the following formula:[2]

$$CI = \text{cardiac output (CO)} \div m^2 \text{ body surface area (BSA)}$$
$$DO_2 = CI \times CaO_2$$

Oxygen consumption (VO_2) is calculated by the Fick equation given by the following formula:[3]

$$VO_2 = CO\,(CaO_2 - CvO_2)$$

On the average, the body extracts 5 to 6 ml of O_2 for every 100 ml of blood that sweeps through the microvasculature of most organ systems. Physiologic normal levels of Hgb readily supply tissue oxygen extraction rates of 5 to 6 volume percent. As Hgb drops to 6 g/dL, oxygen delivery, to offset these baseline oxygen extraction rates, becomes problematic and is clearly inadequate at Hgb levels below 3.6 g/dL.

Accumulative oxygen debt is defined as the time integral of the VO_2 measured during and after shock insult minus the baseline VO_2 required during the same time interval. Clinical research in evaluation of patients with severe hemorrhage, demonstrates no chance of survival if the accumulative oxygen debt exceeds 33 L/m^2. Multiorgan failure (MOF) occurs if the accumulative oxygen debt exceeds 22 L/m^2. All patients who have an accumulative oxygen debt of 9 L/m^2 survive without residual disability.[4]

Clinical Setting

Inability to transfuse red blood cells (RBCs) in severe anemia occurs when the patient refuses blood upon religious grounds or if the patient cannot be crossmatched to receive blood. Transfusion-transmitted infection (TTI), while statistically now less likely with nucleic acid testing (NAT) [approaches 1 per 2,000,000 units transfused for both human immunodeficiency (HIV) and hepatitis C (HCV)], still prompts patients to exercise their right to refuse transfusion.[5]

Untoward inflammatory and immunomodulatory effects of large RBC transfusions may also be a reason to seek alternatives.[6,7] Blood substitutes, by way of use of perfluorocarbons or cell wall free polymerized Hgb are still undergoing randomized clinical trials. While both approaches demonstrate advantages as well as disadvantages, neither have yet had final FDA approval for routine clinical uses.[8] Both approaches are still compatible with adjunctive hyperbaric oxygen (HBO_2) therapy. HBO_2 therapy for severe anemia has had a long-standing approval for use by the Centers for Medicare and Medicaid Services (CMS) and its predecessor, the Healthcare Financing Administration (HCFA).[9,10]

Pulsed HBO_2 therapy provides a way to clinically rectify accumulating oxygen debt in severe anemia when transfusion is not possible. The patient initially can be placed at treatment pressures of 2.0 to 3.0 ATA or 0.2 to 0.3 Mpa (million pascals) of oxygen with air breaks for up to three or four hours with surface interval titrated to avert symptoms associated with reoccurring oxygen debt. Occurrence of end organ dysfunction (altered mental status, ischemic EKG change, sprue-like diarrhea from ischemic bowel, hypotension, diminished urinary output, etc) also may be used as guidance, but are less desirable as their advent represents more progressed end points of illness or injury. By adjunctive use of hematinics, the surface intervals between HBO_2 treatments can be lengthened gradually until the patient's baseline Hgb builds to allow for proper O_2 delivery.[11]

Role of Hyperbaric Oxygen Therapy

The two most prodigious oxygen using, mammalian organ systems are the heart and the brain. Oxygen extraction rates of these systems based on patient activity are 6 ml of O_2 per 100 ml of circulated blood in the brain and 10-20 ml of O_2 per 100 ml of circulated blood in the heart.[12]

As early as 1959, Boerema demonstrated that swine which were exchanged transfused with 6% dextran/dextrose/Ringers' lactate solutions to produce Hgb levels of 0.4 to 0.6 g/dL could survive in the short-term if they underwent assisted O_2 ventilation in a hyperbaric chamber at 0.3 MPa.[13] HBO_2 therapy has repeatedly allowed survival in what would have otherwise clearly been unsurvivable clinical circumstance without blood transfusion.

HBO therapy provides a way in severe anemia to successfully correct accumulating oxygen debt in untransfusible patients.[14]

Evidence Based Evaluation of Hyperbaric Oxygen Therapy by the Undersea Hyperbaric Medical Society's Hyperbaric Oxygen Committee Standard Approval Criteria

In medical resuscitative intervention, the American Heart Association (AHA) evidence based criteria is wisely accepted to guide clinical therapeutic intervention.[15] Normobaric oxygen (NBO_2) is considered a class I indication while HBO_2 may be a class II.b. indication. Controlled animal studies support this assumption as referenced in the following table:

Evidence-Based Evaluation (29 studies found for review)			
AHA		NCI-PDQ *	BMJ **
Level	Class		
6a [16-37] (decisive control groups)	II.b. (acceptable and useful) [16-27] [29-30] [34-37] Indeterminate[28, 31, 32, 33]	NA	NA
6b[38-43] (not decisive control group)	II.b. (acceptable and useful)[38,39,40]		
	Indeterminate[41, 42, 43, 44]		

* National Cancer Institute Patient Data Query evidence-based criteria (NCI-PDQ)[45]

** British Medical Journal evidence-based criteria (BMJ)[46]

Rather consistently this body of literature confirms over and over again better survival in animal models of both hemorrhage to a predetermined mean arterial pressure (Wiggers model)[47] or fixed volume hemorrhage.[48] Both increased short-term and long-term survival for HBO_2 groups over normobaric air (NBA) or NBO_2 groups.

Published human case reports and case series allow similar evidence-based acceptance. Published case reports or case series are referenced below for tabulated uniform approval:

AHA		NCI-PDQ	BMJ
Level	Class		
5 (case series and case reports)	II.b. (acceptable and useful)[53] Indeterminate (11,49-52,55,56)	3.iii. (case series or presentation neither consecutive or population based)[11,49-53,55,56]	Most likely beneficial[11, 49-53, 55, 56]
6	II.b. (54)	NA	NA

(A more detailed repots of the above tabulated findings has been published in a focused journal review article on the use of HBO_2 in acute blood loss anemia)[57]

In summary, both by the support of animal work and human clinical experience evidence-based analysis firmly supports the use of HBO_2 as a treatment option in severe anemia using AHA, NCI-PDQ, and BMJ evidence-based criteria.

Utilization Review and Cost Impact

In review, HBO_2 should be considered in severe anemia when patients cannot receive blood products for medical, religious, or strong personal preferential reasons. Its use should be guided by the patient's calculated accumulating oxygen debt rather than by waiting for signs or symptoms of systemic or individual end organ failure.

HBO_2 therapy can be administered rapidly at pressures up to 0.2-0.3 MPa (2-3 ATA) for periods of three or four hours three times a day to four times a day if intra-treatment patient air breaks are used. Hematinics should be co-administered along with nutritional support to correct protein energy malnutrition. HBO_2 therapy should be continued with taper of both individual treatment to the time and frequency of treatment tables until RBC have been replaced adequately by patient regeneration or patient acceptance of transfusion if possible.

A single HBO_2 treatment table cost is comparable to the cost of one unit of packed RBCs.[11] Side effects of HBO_2 are few and infrequent[58,59,60,61] and safety of hospital-based HBO_2 therapy in the United States has been very good to date.

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