Peer Review File

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Reviewer A

This patient after spinal surgery showed an improvement of lower limb motor function after first HBO session. This case of patients is an interesting, but is only one responder to HBO.
I think HBO has effectiveness for surgical tissue edema rather than peripheral nerve injury, because only one HBO session dramatically improved motor paresis on 5 postoperative day. The authors had better describe HBO possibly reduces surgical wound edema in the discussion, not effectiveness for peripheral nerve injury.

Response: thank you for your suggestion that improvement of postoperative edema is among the plausible mechanisms for the neurologic improvement seen following HBOT in this case. In our revised manuscript, we have commented on this in the discussion section (supported by the introduction of new references which evidence the effectiveness of HBOT at reducing tissue edema).

Changes in text:

The paragraph on possible mechanisms by which HBOT improves recovery after neurologic injury, beginning on line 141, has been revised to:

There are few reports describing HBOT in the context of acute human neurologic injury, but there is a compelling mechanistic rationale for its use in the optimization of tissue healing: emerging work has identified functions of HBOT in reducing inflammation, reversing tissue hypoxia, activating stem cells, and inducing angiogenesis. While these mechanisms might explain a direct, restorative effect for injured nervous tissue, the efficacy of HBOT may also be mediated by its improvement of surgical wound edema arising after ischemia and potentially contributing to nerve compression.

In addition, line 125 now reads:

Neurologic injury during spine surgery can result from direct transection of exposed spinal nerves or compression by either surgical instruments or expanding hematomas in the postoperative period. Indirectly, it can stem from nerve ischemia in the context of vascular compression, thrombosis, edema, or sustained hypotension.

Reviewer B

Although anecdotal in terms of a case report, there was another anecdotal case that might be referenced of a NFFL athlete with a spinal cord injury similarly treated with HBOT.

Response: thank you for bringing this recent case to our attention. We have included it in our present manuscript's discussion of prior cases which report the use of HBOT as an adjunct therapy for spinal cord injury.

Changes in text:

The paragraph beginning on line 150 has been revised to include reference to this case study. It now reads:

Similarly, there is emerging evidence for HBOT in treating human nerve injury, comprising various levels of evidence. One case report describes rapid and sustained recovery from neurologic deficits following emergent thoracolumbar decompression and fusion with five sessions of HBOT at 2.4-2.8 ATA, while another reports significant improvement in a professional football player who underwent thoracic decompression and fusion for a complete spinal cord injury with adjunct treatments of HBOT (30 sessions at 2.4 ATA) and omega-3 fatty acids.

Reviewer C

The authors present a case of neurological injury following complex spine surgery. I think the case is worth presenting; however, I think the discussion needs a more thorough evaluation of the literature. Presently only cites broad reviews, but doesn't consider the clinical outcomes that are known in the literature as well. Please add a more thorough discussion of the following, and consider the following citations:
(1) Add information regarding the natural history of iatrogenic spinal injury (PMID: 35141645, 28451499).
(2) Aggregative clinical evidence on HBO for SCI (PMID: 33935063, 30391318).
(3) Limitations of the current state of clinical evidence.

Response: thank you for the time and effort you have dedicated to providing a critical review of our manuscript. We have restructured the discussion section of our revised submission to address each of these comments. In particular, as shown below, we have added detailed passages to the discussion section which overview: (1) the natural history of iatrogenic spinal cord injury; (2) the various levels of clinical evidence spanning from case reports to cohort studies, RCTs, systematic reviews, and meta-analyses, with our own evaluation and commentary of each, for HBOT used to treat spinal cord injury; and (3) the current limitations in available evidence which connects directly to our "future directions", where we identify critical research priorities for the academic community moving forward. All of the references you have suggested are now integrated into our submission, and each of these revised sections is provided in this order below.

Changes in text:

Beginning on line 125 of the revised manuscript, we draw on landmark studies to provide a concise overview of the incidence, natural history, and contemporary management of iatrogenic spinal

injury:

The incidence of iatrogenic spinal injury varies by type of surgery, with aortic and endovascular operations accounting for a majority of cases, and its natural history is heterogenous with some of the poorest outcomes observed in the context of ischemic injuries of the thoracic spinal cord. Strategies for the management of iatrogenic cord injury have not yet reached consensus, although early radiologic evaluation to rule out reversible cord compression or misplaced instrumentation, aggressive blood pressure management to avoid secondary injury caused by hypotension, and rehabilitation are the current mainstays of evaluation and treatment.

Our revised manuscript provides a detailed discussion of previous reports describing HBOT as an adjunct therapy for spinal cord injury, with various levels of evidence (presented in the order of case reports, case series, randomized controlled trials, systematic reviews, and meta-analyses). This section begins on line 150:

Similarly, there is emerging evidence for HBOT in treating human nerve injury, comprising various levels of evidence ranging from individual case reports to emerging meta-analyses. One case report describes rapid and sustained recovery from neurologic deficits following emergent thoracolumbar decompression and fusion with five sessions of HBOT at 2.4-2.8 ATA, while another reports significant improvement in a professional football player who underwent thoracic decompression and fusion for a complete spinal cord injury with adjunct treatments of HBOT (30 sessions at 2.4 ATA) and omega-3 fatty acids. A small cohort of seven patients who underwent HBOT for spinal cord injury following complex aortic repair demonstrates complete recovery in two patients and partial recovery in three, and a recent systematic review by Naik and colleagues describing complete or nearly-complete neurologic recovery in six of a further eight patients receiving HBOT as an adjunct treatment for iatrogenic spinal injury. A randomized controlled trial published by Sun and colleagues reports significant neurologic improvement of acute spinal cord injury managed with HBOT in addition to conventional therapy, accompanied by a reduction of plasma inflammatory biomarkers high mobility group box 1 and nuclear factor kappa-B. Finally, a recent meta-analysis of this randomized controlled trial along with ten others evaluating neurologic outcomes of spinal cord injury after HBOT, published by Huang and colleagues, ascribes a positive effect on both motor and sensory recovery to HBOT, although the included trials are small (the total number of patients receiving HBOT was 442) and all were vulnerable to some form of experimental bias.

Finally, we have supplemented the future directions identified in our manuscript (line 196) with a more thorough review of the core limitations inherent in the current state of clinical evidence. This new section begins on line 175 of the revised manuscript:

Several core limitations remain in the current state of clinical evidence for HBOT's application in the treatment of iatrogenic spinal injury, including a precise understanding of the therapeutic mechanisms accountable for its effectiveness. In addition, the optimal treatment protocols have yet to be elucidated, including the number of sessions, ambient treatment pressure, period of time after injury within which it should be initiated, and whether HBOT should be considered a first-line

therapy (where available) or reserved as salvage therapy when traditional management for this phenomenon has been unsuccessful.