

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of hyperbaric oxygen therapy on chronic neurocognitive function of deficits post traumatic brain injury patients – retrospective analysis
AUTHORS	Hadanny, Amir; Abbott, Stefanie; Suzin, Gil; Bechor, Yair; Efrati, Shai

VERSION 1 – REVIEW

REVIEWER	Xavier A. Figueroa University of Washington, Affiliate Assistant Professor, USA
REVIEW RETURNED	22-Apr-2018

GENERAL COMMENTS	<p>The paper is a clear and concise report of a retrospective analysis of a population of traumatic brain injury survivors that range from mild-to-severe in the GCS. The strength of this paper is the fact that it looks at a mixed population of TBI survivors that received HBOT and had metabolic imaging.</p> <p>The nature of the measures (objective neurocognitive and metabolic/perfusion) are ideal, as they remove subjective and variable responses of symptoms questionnaires from this study.</p> <p>This is an important paper that supports the observed outcomes that have been reported in mild-to-moderate TBI studies and add an important measure that has been missing from previous studies: neuroimaging and perfusion profiling.</p> <p>This important paper provides a concrete report of a population of clinical cases that correspond to various case reports in the literature. The authors present compelling evidence of real-world application of HBOT to treat the entire injury spectrum of TBI survivors.</p> <p>Some comment that I will make to the negative are the lack of reporting of PTSD assessments in this population described and the lack of a follow-up to assess the durability of the HBOT treatment in this population. Although there has been reporting of outcomes post-HBOT at 6 and 12 months, a follow-up on this population would have been ideal. Lastly, it would be helpful to the research and clinical population to highlight or categorize any patients that failed to improve due to the HBOT treatment. This may be helpful to clinicians in order to temper expectations on outcomes and demonstrate that this intervention acts like any other drug or therapy: there is a differential population response.</p> <p>Overall, this article is well written and consistent with the outcomes of previous reports and helps to fill in the gaps in the literature.</p>
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REVIEWER	Harshan Ravi National Institute of Health, USA
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	<p>First of all I would like to commend authors doing good job in showing the efficacy of HBOT in largest cohort study till date. There is always a speculation about HBOT role in improving in cognitive deficit. However, the authors did a poor job writing the paper and explaining the results. It is premature to publish this paper as it is. The paper could benefit further by following the suggestions discussed in the paper.</p> <p>The following modifications could be useful to further improve the paper.</p> <p><i>Major revisions.</i></p> <ol style="list-style-type: none"> 1) The authors on whole did not do proper job of proof reading the final draft before submitting the paper. The title itself has a major, it should be “deficits” instead of “delicts” (page1) 2) According to the objective in abstract, it seems that author is interested in learning more about the changes in the severity of deficits induced due to TBI rather than the rather than changes observed in the deficits induced by different severity of TBI. (page3) 3) The conclusion part of the abstract talks about “HBOT induced significant cognitive improvements in patients suffering from chronic deficits in TBI of all severity”, however there is conflicting results in literature that all atmospheric pressure doesnot leads to improved outcomes (1). So, generalizing that HBOT (1.5-2 ATA in this study) would lead to improved cognitive outcome is not appropriate. Further results are required suggesting the statement. (page3) 4) The rationality of the study should be emphasized and explained more: <ol style="list-style-type: none"> a. For the imaging modality authors introduce SPECT and MRI as 2 important modalities but donot further discuss why they select SPECT is advantageous over MRI. Rationally thinking MRI is easier to implement and non-invasive. (page7) b. The logic about sham control being not truly sham but low dosage needs explanation. Authors failed to consider the changes in flow due vasoconstrictive effect of oxygen. (page8) c. “Marked improvement defined as >10% increase compared to baseline cognitive index were found with different percentages in all study groups as summarized in Table 3.” (page12). “To correlate SPECT imaging and the cognitive changes, analysis was performed onthe top twenty patients who had the largest cognitive improvement” (page 15). why did the author select those criteria? 5) “Patients who suffered severe TBI were younger with higher proportion of males than in the mild and moderate
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TBI groups ($P < 0.0001$, $P = 0.002$ respectively, Table 1)”, this statement is too generalized and in general might not be true else where. (page13)

- 6) “The mild TBI subgroup had the largest improvement in attention (8.8 ± 2.1) followed by memory (7.9 ± 2.3). Patients following moderate had noticeable improvements in memory (11.1 ± 3.1) followed by information processing speed (6.6 ± 3.5) (Figure-4).” Authors did not the explain the results for severe TBI. What would they expect and which one between these 3 severities would have maximum benefit ? (page 14)
- 7) “There was a significantly larger magnitude of metabolism increase (5-8%), compared to the entire cohort average increase (2-4%) ($p < 0.05$). The most striking changes were found in the anterior cingulate (BA 24) and the post-324 central cortex (BA 5), the prefrontal areas (Ba 10,11, 46) and temporal areas (BA 20)” what does this result indicate ? (page15). In my opinion the author should incate the exact P value if it close to 0.05.
- 8) The authors should also include more discussion about what their results actually mean, what is the clinical significance of such results and what could be future implications. Overall, need to include more discussion.

Overall more effort is required by authors to make coherent. Need toAlso incorporating MRI techniques such CBF, susceptibility wiegthed imaging and diffusion imaging could further give more details about physiology of cognitive improvements and strengthen the paper.

Minor:

- 1) The aurhtors need to improve the writing style. Especially, to break long sentences into coheernt short sentences, proper sentence formation, typo and proper formatting of the paragraph. some of the sentences indicated above doesnot mean what author wants to convey in this paper. Some of the references are before periods and some of them are after periods. The authors should put more effort in proof reading the paper before sending ot out.
- 2) It is not clear from injury is classified as chronic. Time from injury is given but no further discussion natuire of injury.
- 3) The axis in the figure 4) seems to be of low font. Need to increase the font to make it more legible.

References:

1. Hu Q, Manaenko A, Xu T, Guo Z, Tang J, Zhang JH. Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside. *Medical gas research* 2016;**6**:102-110.

VERSION 1 – AUTHOR RESPONSE

Major revisions

Comment #1: “The authors on whole did not do proper job of proof reading the final draft before submitting the paper. The title itself has a major, it should be “deficits” instead of “delicts” (page1)

Reply: The manuscript was revised and proofed.

Comment #2: “According to the objective in abstract, it seems that author is interested in learning more about the changes in the severity of deficits induced due to TBI rather than the rather than changes observed in the deficits induced by different severity of TBI. (page3)”

Reply: Abstract objective was revised.

Comment #3: “The conclusion part of the abstract talks about “HBOT induced significant cognitive improvements in patients suffering from chronic deficits in TBI of all severity”, however there is conflicting results in literature that all atmospheric pressure does not leads to improved outcomes (1). So, generalizing that HBOT (1.5-2 ATA in this study) would lead to improved cognitive outcome is not appropriate. Further results are required suggesting the statement. (page3)”

Reply: This is the largest cohort presented in the literature with objective measures. Other studies had several other flaws in addition to using questionnaires rather than objective measures.

Abstract conclusion was revised to specify that in this large cohort, HBOT indeed induced these effects.

Comment #4a: The rationality of the study should be emphasized and explained more:
a. For the imaging modality authors introduce SPECT and MRI as 2 important modalities but do not further discuss why they select SPECT is advantageous over MRI. Rationally thinking MRI is easier to implement and non-invasive. (page7)

Reply: In order to evaluate the function of the different brain areas, there is a need for a functional imaging study. MRI is usually utilized to view the anatomical structure of the brain. Although recent developments in functional MRI and MRI DTI are being increasingly used, their stability is still discussed. In addition, there are no well accepted normal criteria for functional MRI and MRI-DTI. Nevertheless, this is a valid remark, and our center is working on the normal range of functional MRI and MRI DTI algorithms and we have started using it for evaluation of new patients.

Methods was evaluated accordingly.

Comment #4b: The logic about sham control being not truly sham but low dosage needs explanation. Authors failed to consider the changes in flow due vasoconstrictive effect of oxygen. (page8)

Reply: The paragraph was revised. The Sham control used in previous studies have been proven to be non-inert, thus not real sham therapies but rather low dosage of treatment.

In regards to vasoconstriction, the explanation has been added to the paragraph.

Comment #4c: "Marked improvement defined as >10% increase compared to baseline cognitive index were found with different percentages in all study groups as summarized in Table 3." (page12). "To correlate SPECT imaging and the cognitive changes, analysis was performed on the top twenty patients who had the largest cognitive improvement" (page 15). why did the author select those criteria?"

Reply:

Defining what should be considered as a clinical improvement in neurocognitive function is indeed a debatable issue, and no cutoffs have been set. Moreover, due to the wide variability of different cognitive tests available which making this issue harder.

We have used the mean relative change in order to eliminate the baseline score and measure the net effect of therapy. Different cut offs (5,10,15 %) were used and 10% was found best to correlate with patients' subjective experience of improvement.

We started with analyzing the SPECT changes for the entire cohort having SPECTs (N=100). However, it is clear that not all patients improve, and those who do improve have different magnitude of change. In order to focus on the most important areas in SPECT, we focused on the patients with the largest change in cognitive score. Thus, twenty patients were chosen as not too little and not too many for this analysis.

Comment #5: "Patients who suffered severe TBI were younger with higher proportion of males than in the mild and moderate TBI groups ($P<0.0001$, $P=0.002$ respectively, Table 1)", this statement is too generalized and in general might not be true elsewhere. (page13)

Reply: the statement was revised to clear it's found in this study alone.

Comment #6: "The mild TBI subgroup had the largest improvement in attention (8.8 ± 2.1) followed by memory (7.9 ± 2.3). Patients following moderate had noticeable improvements in memory (11.1 ± 3.1) followed by information processing speed (6.6 ± 3.5) (Figure-4)." Authors did not the explain the results for severe TBI. What would they expect and which one between these 3 severities would have maximum benefit? (page 14)

Reply: Severe TBI results were added to the paragraph. Repeated measures anova data was added to the paragraph.

Comment #7: "There was a significantly larger magnitude of metabolism increase (5-8%), compared to the entire cohort average increase (2-4%) ($p<0.05$). The most striking changes were found in the anterior cingulate (BA 24) and the post- 324 central cortex (BA 5), the prefrontal areas (Ba 10,11, 46) and temporal areas (BA 20)" what does this result indicate ? (page15). In my opinion the author should indicate the exact P value if it close to 0.05

Reply: The results suggest these areas are correlated with a higher cognitive improvement. These specific areas significance are discussed in the discussion extensively. P values ranged between 0.01 to 0.05. The p-values of the specific BA mentioned were added.

Comment #8: The authors should also include more discussion about what their results actually mean, what is the clinical significance of such results and what could be future implications. Overall, need to include more discussion

Reply: New discussion paragraph was added.

Comment #9: Need to Also incorporating MRI techniques such CBF, susceptibility weighted imaging and diffusion imaging could further give more details about physiology of cognitive improvements and strengthen the paper.

Reply: These patients were not evaluated using functional/perfusion MRI techniques, thus these data are not available for this study. However, our center is performing evaluations of new TBI patients using new functional imaging techniques including MRI (We have recently published a study on the first 11 patients that were evaluated using one of this techniques). Hopefully this data will be available in upcoming years.

Minor

Comment #1: The authors need to improve the writing style. Especially, to break long sentences into coherent short sentences, proper sentence formation, typo and proper formatting of the paragraph. Some of the sentences indicated above does not mean what author wants to convey in this paper. Some of the references are before periods and some of them are after periods. The authors should put more effort in proof reading the paper before sending it out.

Reply: manuscript was revised.

Comment #2: It is not clear from injury is classified as chronic. Time from injury is given but no further discussion nature of injury.

Reply: We have included all patients with time from injury to HBOT was at least 3 months. The mean time from injury to treatment was more than 4.5 years in all subgroups). Methods were revised.

Comment #3: The axis in the figure 4) seems to be of low font. Need to increase the font to make it more legible.

Reply: Graph was revised accordingly.

VERSION 2 – REVIEW

REVIEWER	Xavier A Figueroa University of Washington, Affiliate Assistant Professor Seattle, WA
REVIEW RETURNED	01-Jun-2018
GENERAL COMMENTS	Thank you for the changes in the manuscript. I look forward to seeing this paper published and adding to the growing body of knowledge to treat neurological injuries.