Hyperbaric oxygen therapy after spinal cord injury. A systematic literature review

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ABSTRACT

Hyperbaric oxygen therapy is the inhalation of 100% pure O_2 at increased pressure, i.e. at ambient pressure greater than 1 atm. The basic principles of hyperbaric oxygen therapy (HBOT) are based on the way in which the various gases – and especially O_2 - behave and act upon the tissues and fluids of the human body, under the influence of different conditions of volume and pressure. Spinal cord injury (SCI) is a very serious and complicated medical condition which greatly disrupts the patient's life. Historically, this condition has been associated with very high morbidity and mortality rates.

In the present study, the latest research data on the effectiveness of this method regarding spinal cord injuries was studied. In order to achieve this purpose, the research tool of systematic literature review was chosen.

Discussion: The systematic literature review resulted in the detection of 13 relevant published articles after 2015. There were 3 randomized controlled studies, 2 non-randomized clinical studies, 4 case series and 4 case reports. In total, 557 patients participated in the study. The main result of the study was that HBOT is a totally safe and without any clinically significant side effects adjuvant therapy for the treatment of SCIs, producing various degrees of improvement of the motor and sensory neurological condition of the patients suffering from various types of SCIs, along with their psychological condition.

Conclusion: Hyperbaric oxygen treatment is a totally safe adjuvant treatment method for patients suffering from spinal cord injuries, having the potential to improve both the neurological status (motor and sensory) and the psychological condition of the affected patients. Further research is needed to obtain specific guidelines in relation to the indications and the application protocols of the method.

Key words: Hyperbaric, Oxygen, Spinal, Cord, Injuries

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Introduction

The history of hyperbaric medicine begins in 1662, when Henshaw, a British doctor, used compressed air in order to treat various diseases of the respiratory system, developing the first hyperbaric chamber, which was named by him "the domicilium". Oxygen was discovered more than 100 years afterwards, in 1775 by another British scientist, John Priestley, but in was not until the first years of the 20th century, when Orval J. Cunningham, an American professor of Kansas University used, for the first time, oxygen in elevated partial pressures in order to treat various hypoxic conditions [1].

Nowadays, hyperbaric Medicine has became a separate medical sub-speciality and is applied with great efficiency in a large number of pathological conditions, such as treatment of burns, severe wounds and chronic ulcers, treating the side-effects of radiation therapy, migraines, hearing problems and even severe neuromuscular pathologies [2].

Spinal cord injury (SCI) is a very complex medical condition, which greatly disrupts the patients' life and is associated with high morbidity and mortality. Although there has been a disagreement regarding the pathology characterized as "spinal cord injury", most of the authors agree that all the lesions of the spinal cord and the cauda equina, either traumatic or atraumatic, should be viewed as spinal cord injuries [3]. It is estimated that 250.000 – 500.000 people every year worldwide suffer from this pathology, while two to three million patients live permanently with its consequences.

The purpose of the present study was to investigate the data of the recent literature regarding the effectiveness of the use of hyperbaric oxygen on the treatment and rehabilitation after spinal cord injuries.

The databases used for this review were: *PubMed / NCBI, Google Scholar, Cochrane Library and Scopus.* The applied key-words (mesh terms) included: *Hyperbaric oxygen therapy, HPOT, Spinal cord injury, SCI, Treatment, Rehabilitation,* in various combinations of the specific terms, and with the use of the separators *AND* and *OR*.

The inclusion criteria for the selection of the relevant published articles were: (i) original articles (randomized and non-randomized trials, case-series and case reports' presentations), involving humans, (ii) both traumatic and non – traumatic SCI, (iii) studies published after 2015, (iv) language of the publication in English and the availability of full-text studies.

On the other hand, systematic and narrative reviews were excluded, along with experimental trials and trials involving animals. The flowchart of this systematic literature review, according to the PRISMA principles [4], is presented in Figure 1.

Discussion

The systematic literature review, which was carried out according to the criteria mentioned in the previous chapter, resulted in the detection of 13 relevant published articles. There were 3 randomized controlled studies, 2 non-randomized clinical studies, 4 case series and 4 case reports. In total, 557 patients participated in the study. The findings of all those articles are summarized in Table 1.

All the recent published clinical studies concluded that HBOT is a totally safe, without any clinically significant side effects adjuvant therapy for the treatment of SCIs.

Almost all studies showed various degrees of improvement of patients' motor and sensory neurological condition suffering from various types of SCIs, along with their psychological condition.

Bunul et al., (2021) [16], in a small case series of 3 patients suffering from radiation-associated myelopathy did not find any improvement by this treatment. Marrosu et al., (2021) [14], reported that along with the dramatic improvement of a patient's neurological status, there were indications of reshaping of the cortico-cortical connectivity after the HBOT.

Another novel finding of the present literature review is that HBOT is an effective method for the prevention of spinal cord ischemia – reperfusion injury (SCIRI) in patients undergoing extensive posterior laminectomy and fusion for severe cervical and thoracic spinal stenosis [11].

The pathophysiological mechanisms of SCIs are complex, involving both primary and secondary lesions of the spinal cord. Primary lesions are due to the mechanical injury produced by the traumatic event, whereas the secondary injuries are more complex, may occur after a fairly long period of time and involve various physiological processes of the human organism,

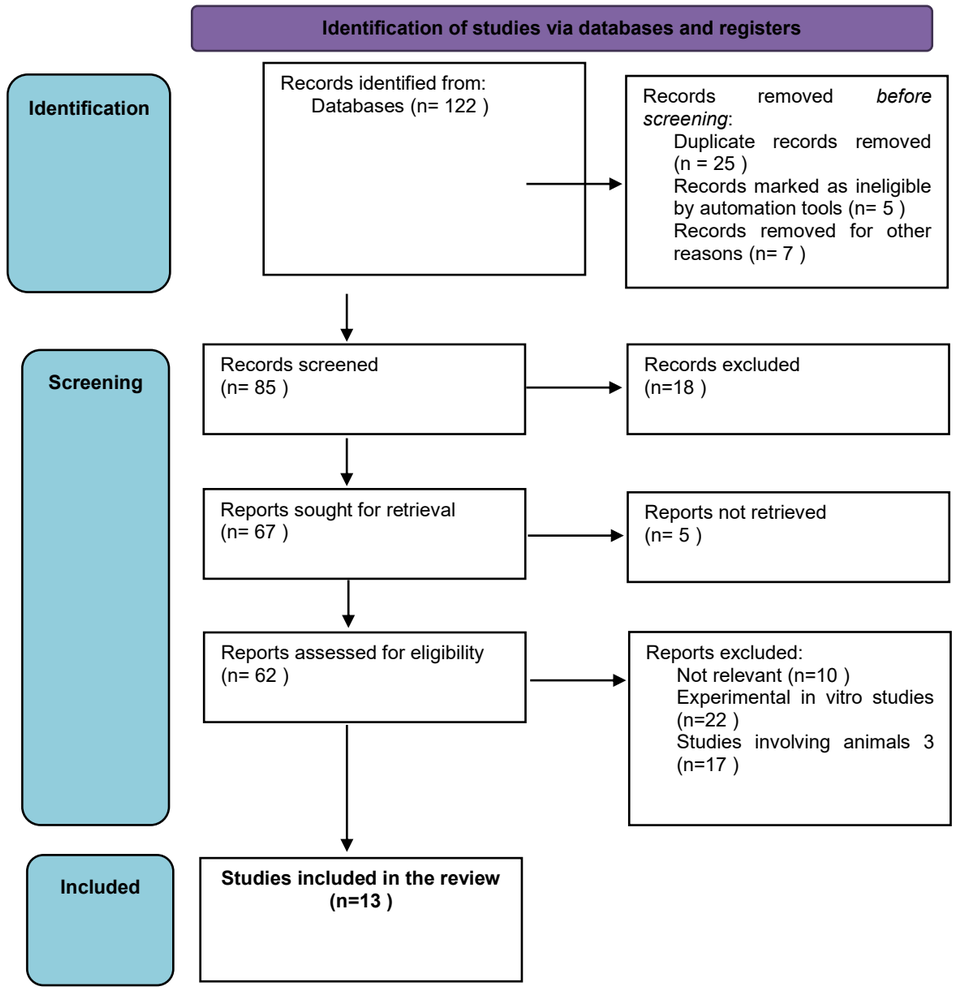

Figure 1: *The PRISMA flow diagram of the present systematic literature review*

including cellular death (apoptosis), injuries of the nervous system tissue due to oxidative stress, oedema and ischemia of the spinal cord, inflammation and toxicity produced by excitatory neurotransmitters like glutamate (excitotoxicity) [18].

Since in the majority of the serious SCIs, the primary spinal cord lesions are irreversible, recent scientific research focused on the successful treatment of the secondary spinal cord lesions. The medication used traditionally for these injuries is methylprednizole, in large therapeutic doses: the first dose is bolus, intravenous infusion of 30 mg/Kgr of patient's body weight, in the

Table 1: The results of the systematic literature review

Author, country	Type of study	Participants	Treatment	Results
Cheng et al., (2015) [5], Taiwan	Case report	Male, 30 years old, partial Brown-Sequard syndrome at the level of C4 – left side	HBOT 3 hours after the initiation of the symptoms	Significant improvement of the clinical and neurologic condition after two days of HBOT
Onen et al., (2015) [6] , Turkey	Case series	19 cases of iatrogenic SCI due to infections (mean age 54.6 years).	Average 20.1 HBOT sessions (10 - 40)	Safe and efficient adjuvant therapy
Xu et al., (2016) [7] , China	Case report	Male, 45 years old, acute paraplegia after needle biopsy – most probable due to air embolism	HBOT immediately after the incident	Partial improvement – paraparesis
Feng et al., (2017) [8], China	Randomized – controlled study	60 patients with incomplete spinal cord injury (20 patients in the HBOT group, 20 patients in the psychotherapy group, 20 patients in the control – conventional rehabilitation group)	HBOT at 2.0 ATA pressure, 6 days / week for 8 weeks	No side effects - Significant improvement of nerve function, psychological parameters and daily living activities. Further research needed, with larger sample and longer follow-up
Parotto et al., (2018) [9], Canada	Retrospective case series	7 patients with SCI after complex aortic repair	HBOT at 2.4 -2.8 ATA, once / twice daily until improvement or plateau of neurologic symptomatology	2 patients died (perioperative complications), 5 patients had varying degrees of neurological improvement – 1 patient had major complication (oxygen induced seizures). The method is beneficial for the neurologic recovery of patients with SCI.
Tan et al., (2018) [10] , China	Non – randomized controlled study	40 patients with acute SCI (29 in the BBOT group, 11 in the control group)	HBOT at 2ATA for 45 minutes, once/day for 30 days	HBOT group presented with significant improvement in the neurological parameters and the MRI findings ($p < 0.05$), in comparison to the control group. Is a very effective treatment at the early stages after an acute SCI
Chen et al., (2019) [11] , China	Randomized controlled study	186 patients with Spinal Cord Ischemia – Reperfusion injury	Group A: Combination of HBOT and methylprednisolone. Group B: Only dexamethasone	Statistical significant difference in the incidence rate of the SCI, in favour of the treatment group (Group A).
Wilson et al., (2020) [12], Canada	Case report	Male, 68 years old, acute SCI due to degenerative thoracic and lumbar canal stenosis	Five sessions of HBOT at 2.8 ATA for 90 minutes during the first 3 postoperative days	Immediate improvement from ASIA B to ASIA E after the first session which sustained through the following sessions.

VOLUME 74 | ISSUE 4 | OCTOBER - DECEMBER 2023

Ashton et al., (2020) [13], Australia	Retrospective case series	13 patients (median age 57 years), spinal cord infarction	Five of those patients received HBOT (average 15 sessions)	HBOT along with CSF drainage and pentoxifylline may reduce the disability caused by the disease
Marrosu et al., (2021) [14], Italy	Case report	Male, 45 years old, traumatic lesion of SCI at the level of C1 after a dive	Five cycles of HBOT, 18 session each cycle at 2.5 ATA	Dramatic improvement after the HBOT treatment. EEG recordings suggest reshaping cortico-cortical connectivity after the HBOT.
Li et al., (2021) [15], China	Randomized controlled study	80 patients with SCI after fractures of the thoracolumbar spine treated with posterior laminectomy and fusion	Group A: Control group (conventional treatment). Group B: HBOT combined with Riluzole and mannitol	Group B statistically significant superior to Group A for motor and sensory function scores.
Bunul et al., (2021) [16], Turkey	Case series	3 patients with radiation associated myelopathy	HBOT from the 12^{th} till the 30^{th} day after the occurrence of the symptoms	No significant improvement in the 2 patients – the third died because of his primary disease.
Zhang et al., (2022) [17], China	Retrospective non-randomized controlled study	78 patients with incomplete SCI, after spinal decompression and internal fixation	Group A: conventional treatment Group B: HBOT	HBOT is safe and effective method. Treatment group had superior results in comparison to the control group

first fifteen minutes, followed by continuous infusion of 5.5 mg/Kgr per hour, starting 45 minutes after the first, bolus infusion, and continuing for the next 23 hours [19]. The relatively limited effectiveness of this regimen, in combination to its limitations and side effects, made it necessary for further research in order to establish adjuvant therapeutic methods for the treatment of both acute and chronic SCIs.

One of the therapeutic methods, which has aroused the scientific interest during the last few years, is hyperbaric oxygen treatment therapy, in which 100% O_2 is administered to the patient at pressures between 1–3 ATA (atmospheric pressure). A number of experimental studies has shown that HBOT has the ability to offer strong protection to the patient's central nervous system (neuroprotection), with a broad variety of physiological mechanisms, including the following [18]: (i) decrease of the cellular death (apoptosis), (ii) reduction of the oxidative stress caused by the injury, (iii) reduction of the inflammation, (iv) reduction of the oedema of the spinal cord, (v) promotion of the creation of new vessels (angiogenesis) in the injured area and lastly, (vi) increasing the procedure of degrading and removing the injured and dysfunctioning neurones (autophagy).

After the beneficial effects of HBOT on the central nervous system were demonstrated in the experimental field, the first clinical, in vivo, studies on its effectiveness on humans gradually commenced.

Holbach et al., in 1977 [20], published one of the first case series regarding the effectiveness of HBOT in 13 patients suffering from compression SCIs, recording significant improvement in 6 out of the 13 patients, especially in their motor function. One year later, Jones et al.,(1978) [21], in another case series of 10 patients having sustained acute SCIs, recorded a more rapid and in a greater degree recovery of the motor function in 5 of them than the expected recovery through the traditional management.

Huang et al., in 2021[22], conducted a systematic review and meta-analysis of randomized controlled studies regarding the effectiveness of HBOT in patients who have sustained SCIs. In their study they covered the entire time period up to 2020 and finally included 11 clinical trials, involving 817 patients. The main results of this systematic review were the following: (i) HBOT improved statistically significantly the ASIA motor score, and the Modified Barthel Index (MBI), (ii) in 6 of the trials, HBOT improved statistically significantly the ASIA sensory score, (iii) in 4 of the trials, HBOT improved statistically significantly the needling score along with the light touch score and finally, (iv) HBOT decreased statistically significantly both the Hamilton Depression Scale (HAMD) and the Hamilton Anxiety Scale (HAMA).

The final conclusion of the authors was that the findings of the current literature indicate that HBOT most probably improves both sensory and motor function as well as the psychological parameters of patients suffering from SCIs, although more high-quality and with larger patients' sample was needed in order to definitely support the previous mentioned findings.

Limitations

The present study has a number of limitations: since the purpose of the dissertation was to study the most recent literature data, (after the year 2015), the high-quality randomized controlled studies published in that period were very few – only three, with another two non-randomized controlled studies and the rest of the articles being case reports or case series. Also, another limitation is the great heterogenity of the studies, which covered a variety of both acute and chronic, traumatic and non-traumatic spinal cord injuries. Definitely, further research with high quality of randomized – controlled studies, with larger numbers of participants in needed in order to prove the effectiveness of HBOT in the various context of SCIs

Conclusion

Hyperbaric oxygen treatment is a totally safe adjuvant treatment method for patients suffering from spinal cord injuries, which has the potential to improve both the neurological status (motor and sensory) and the psychological condition of the affected patients. Further research is needed in order to give specific guidelines in relation to the indications and the application protocols of the method.

VOLUME 74 | ISSUE 4 | OCTOBER - DECEMBER 2023

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VOLUME 74 | ISSUE 4 | OCTOBER - DECEMBER 2023

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