

Effects of hyperbaric oxygen therapy after spinal cord injury: systematic review

Efeitos da oxigenioterapia hiperbárica no tratamento da lesão medular traumática: revisão sistemática

Efectos de la terapia hiperbárica en el traumatismo raquimedular: revisión sistemática

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ABSTRACT

Objective: to conduct a systematic review of experimental and clinical studies evaluating the effect of hyperbaric oxygen therapy on the spinal cord injury. **Methods:** ninety-three studies were identified in the database Pubmed. Among these, through a set of inclusion/exclusion criteria, 11 articles published between 1963 and 2009 were selected. In the nine experimental studies, different ways to apply the treatment were observed. The measured outcomes were: functional, histological, biochemical and electrophysiological. **Results:** in most of the studies, the results show recovery of locomotor function, histology and/or biochemical features. Regarding the two studies in clinical samples, the results are controversial. The samples are heterogeneous and the application of hyperbaric oxygen therapy is not the same for all patients in each study. **Conclusion:** considering the results of this review, further studies are necessary to define the role of hyperbaric oxygen therapy in acute spinal cord injury.

RESUMO

Objetivo: realizar uma revisão sistemática dos estudos experimentais e clínicos relacionados com a utilização da oxigenioterapia hiperbárica no traumatismo raquimedular. **Métodos:** noventa e três estudos foram identificados no Pubmed, sendo selecionados 11 artigos para análise, 9 experimentais e 2 clínicos, publicados entre 1963 e 2009. Os estudos experimentais apresentaram diferentes formas de tratamento, sendo o desfecho final mensurado pelas diferentes avaliações: funcional, histológica, bioquímica e eletrofisiológica. **Resultados:** na maioria dos estudos foi observada uma recuperação da função locomotora, histológica e/ou bioquímica. Entretanto, os resultados dos estudos clínicos se mostraram controversos, pelo fato de as amostras serem heterogêneas e a administração da oxigenioterapia hiperbárica ser diferente quanto à dose e o tempo de aplicação. **Conclusão:** considerando os resultados desta revisão, será necessária a realização de mais estudos para se ter uma definição sobre a eficácia da oxigenioterapia hiperbárica na lesão medular aguda.

RESUMEN

Objetivo: realizar una revisión sistemática de estudios experimentales y clínicos que evaluaban los efectos de la terapia hiperbárica en el traumatismo raquimedular. **Métodos:** se identificaron noventa y tres estudios en el Pubmed. De estos, por un conjunto de criterios de inclusión y exclusión, se seleccionaron 11 artículos publicados entre 1963 y 2009. Entre los nueve estudios experimentales, se observaron diferentes formas de aplicación del tratamiento. Los resultados mensurados fueron: funcional, histológico, bioquímico y electrofisiológico. **Resultados:** los resultados muestran, en la mayoría de los estudios, recuperación de la función locomotora, histología y/o características bioquímicas. Tratándose de los estudios clínicos, los resultados son controvertidos. Las muestras son heterogéneas y la aplicación de la terapia hiperbárica no es igual para todos los pacientes en cada estudio. **Conclusión:** considerando los resultados de esta revisión, se hacen necesarios más estudios para definir el papel de la terapia hiperbárica en la lesión medular aguda.

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Recebido: 29/7/2009

Aprovado: 20/8/2009

KEYWORDS: Spinal cord/injuries; Hyperbaric oxygenation; Experimental studies; Clinical studies; Review

DESCRITORES: Medula espinal/lesões; Oxigenação hiperbárica; Estudos experimentais; Estudos clínicos; Revisão

DESCRIPTORES: Médula espinal/ lesiones; Oxigenación hiperbárica; Estudios experimentales; Estudios clínicos; Revisión

INTRODUCTION

Spinal cord injury (SCI) is a disabling condition, with major effects on the patient's quality of life. This injury afflicts approximately 8,000 to 12,000 people in the United States every year¹. It is estimated that 40 new cases of SCI per million people occur every year worldwide². There are few data on SCI in Brazil. According to Masini³, an incidence of 10,000 new cases of SCI per year in Brazil is estimated, mainly due to trauma.

In relation to the SCI pathophysiology, after the primary mechanical injury, a cascade of events is triggered, which leads to degeneration and death of the potentially viable neuronal tissue⁴. Among the secondary injury components, hypoxia/ischemia is considered one of the most important factors implicated in the neuronal tissue injury⁵. Anatomical⁶, biochemical^{7,8}, and physiological⁹ studies have demonstrated that spinal cord microvascular potency and blood flow decrease just after severe contusion or compression injury. Available evidence suggests that oxygen radical formation and cell membrane lipid peroxidation have an important role in the progression of the secondary injury^{4,10,11}.

Many treatment modalities, which prevent the development of damaging effects after the SCI, were investigated¹²⁻²⁹. Among these interventions, hyperbaric oxygen therapy (HBOT) has been advocated to improve neurological recovery after brain injury and cerebral ischemia³⁰⁻³². The basic principle of HBOT is to increase the oxygen delivery to the damaged tissue. Wound healing is a complex process involving an inflammatory, proliferative and remodeling phase. Molecular oxygen is one of the critical nutrients of the wound, and it plays a central role in the reparative process^{33,34}. It results in increasing tissue oxygen tension and improves collagen synthesis, angiogenesis and epithelization^{23-26,29,35}.

The use of HBOT is well established for the treatment of decompression sickness, including the spinal cord decompression^{36,37}. To date, however, there are few studies exploring the utilization of HBOT in the treatment of SCI in humans, and few experimental studies with animal models. Also, the treatment mechanisms or the extent of hyperbaric oxygenation remains unclear. The aim of this paper is to review the literature on this subject and define the role of HBOT in SCI.

METHODS

Literature review

A search in the MEDLINE database was conducted in May 2009, covering the period from May 1963 to May

2009. The selected studies were clinical trials and experimental studies on the efficacy of HBOT in SCI. For the electronic search strategy, the following terms were used as keywords in these combinations: "hyperbaric oxygen and SCI" or "HBOT and SCI", without filters.

Inclusion and exclusion criteria

The selected articles were identified from titles and abstracts, by two independent reviewers, considering inclusion and exclusion criteria. The inclusion criteria included original studies in humans or animals, presenting abstracts in the PubMed database, in English, Portuguese or Spanish language, which tested the efficacy of HBOT after SCI and presented a Control Group in the study design. The exclusion criteria were: no abstracts in PubMed database, published in other languages, review articles, studies evaluating preconditioning with HBOT and which evaluated the role of the HBOT in decompression sickness or studies without a Control Group (case report or case series).

Full text reprints were obtained for relevant and potentially relevant studies, which seemed to meet the inclusion criteria and for those that had insufficient data in the abstract to make a clear decision.

RESULTS

The search retrieved 93 articles. After the abstract review, only 15 met the inclusion criteria, 6 were clinical trials and 9 experimental studies. The remaining 78 articles were excluded due to: reviews, case reports, or case series (n=26), without abstracts and/or were published in other languages (n=28), not concerning (or not involving spinal) SCI and/or other treatment modalities (n=13), regarding decompression sickness (n=7), and used as preconditioning therapy (n=4). Four of the 15 articles selected could not be found in full text and were excluded. Nine of the 11 articles were experimental studies, and the remaining articles were clinical trials.

In the experimental studies, five of them evaluated the efficacy of HBOT after SCI in rats^{21,23-25,29}, two in sheep^{27,28}, one in rabbits²⁶, and one in cats²². The most used SCI model was the weight-drop device technique^{22-24,27-29}. Other models used were the clip compression model²⁵, spinal cord transection²¹ and ischemia induced by occlusion of a balloon catheter placed into the abdominal aorta²⁶. The injury was mostly at the thoracic level, between the fifth and eleventh vertebra^{21-25,27-29}. In only one study, conducted in rabbits, the spinal cord lesion was produced at lumbar level (L2-L3)²⁶. The HBOT sessions lasted between 60 to 90 minutes in the majority of studies, except in one study, in which the session lasted three hours²². The

pressure used in all studies varied between 2.0 to 3.0 AtA. The measured outcomes used were: functional^[21,23,24,26-28,38], histological^[21,23,24,26,28,29,38], biochemical^[25,29] and electrophysiological^[22]. The results were heterogeneous, but most of the experimental studies demonstrated recovery of the locomotor function, histology and/or biochemical markers with HBOT (Table 1).

The results of the clinical trials^[20,39] are summarized in Table 2. Asamoto et al.^[20] evaluated the efficacy of HBOT in 34 patients with hyperextension SCI. These patients were allocated either to the HBOT Group (n=13) or to the Control Group (n=21). The clinical evaluation consisted of the Neurological Cervical Spine Scale (NCSS) and American Spinal Injury Association (ASIA) scale at admission and after treatment (the article did not specify when the functional evaluation occurred after treatment). There was a significant improvement in spinal function in the HBO Group. Yeo^[39] conducted a non-randomized comparative study, with 35 SCI patients treated using HBOT and 63 in the Control Group. All patients who underwent only one session were excluded from the final analysis. The primary outcome used was the observation of clinical improvement at least of two levels in the Frankel Grade, between the pre and posttreatment evaluation. There was no significant improvement between the two groups, and none of the patients in the HBOT Group with complete lesion before treatment has improved.

DISCUSSION

The main objective of this systematic review was to define what has already been established about the role of HBOT in SCI. Few studies about this therapy for SCI were identified in the literature. Most of the studies reviewed were experimental. In general, they have demonstrated good functional, histological and biochemical outcomes in the animals with SCI exposed to HBOT.

The first studies that evaluated the effect of HBOT were conducted in 1976 and 1977 by Yeo et al.^[27,28] in a sample composed by sheep, comparing HBOT with no treatment. The results suggested that HBOT applied two hours after SCI produces significant recovery of motor function in paraplegic sheep, compared with the untreated Control Group. The 1976 study^[27] did not provide histopathological analyses, this outcome was described in the following year. The 1977 study^[28] demonstrated better histological outcome in the HBOT Group, with less central cystic degeneration, compared with the Control Group.

Murakami et al.^[26] showed the influence of HBOT on delayed neuronal cell death in the spinal motor neurons. They demonstrated that if one session of HBOT is given 30 minutes after the SCI, this treatment has protective effects against ischemic spinal cord damage. The animals had less neurologic deficits and less degeneration of spinal motor neurons in ventral gray matter. These results were not found in the group that received HBOT six hours after SCI.

According to the Higgins et al. study^[22], in a period of six hours after surgery, the spinal cord evoked potentials were monitored for evidence of neuronal's recovery conduction through the site of injury and following histological evaluation. This study shows better results in cats with early therapy and less severe injuries. The histological evaluation showed no differences between Treatment and Control Groups. A noteworthy feature of this study is the recording of the spinal cord evoked potentials, an objective physiologic measure of the neuronal conduction during and after the SCI. These observations suggest that HBOT treatments can mediate preservation of marginally injured neuronal elements of long tracts of the spinal cord, during the early phases of traumatic SCI. Increasing magnitudes of impact force and delay in the onset of HBOT treatment markedly diminished the protective effects of HBOT on long-tract neuronal conduction following traumatic SCI.

Yu et al.^[29] investigated the effects of HBOT on the progress of secondary damage following SCI induced by a weight-drop device in rats. They compared three groups: a single HBOT administration, repeated applications of HBOT once daily in the following four days, and Control Group. The spinal cords were evaluated 6 hours, 12 hours, 1 day, 2 days, 3 days, and 4 days after the operation. Their results showed that the early onset of HBOT significantly diminished the number of apoptotic cells one day after the injury. The gene expression of glial cell line-derived neurotrophic factor (GDNF) and inducible nitric oxide synthase (iNOS) was significantly attenuated one day after the injury in the HBOT groups, compared with the Control Group. Also, in this study, it was observed that repeated hyperbaric oxygen treatment did not have greater effects than the single treatment on apoptosis and iNOS. According to some authors, overexposure to oxygen may induce neurotoxicity by increasing free oxygen radicals^[40,41].

The experiment of Huang et al.^[24] evinced a benefit of multiple sessions of HBOT. The authors evaluated whether serial HBOT, compared with a single session of it, extends the therapeutic windows after acute SCI with a rat model. The rats that received single HBOT intervention beginning at 30 minutes and 3 hours and those that received multiple HBOT treatment, starting at six hours following injury, had significantly greater neurological recoveries than those in the Untreated SCI Group. These rats also retained more sparing tissue than controls. The authors state that more frequent exposure to HBOT could help sustain its positive effects on the metabolism of the spinal cord and regeneration of the neuronal structure.

Gelderd et al.^[21] evaluated the combination of HBOT and dimethyl sulfoxide, a substance with various effects, such as reduction of tissue edema and inflammation, dispersion of microthrombi (due to the anticoagulant and hemodiluting properties), enhancing the penetration of several compounds across the blood brain barrier and the free radical scavenging property. The clinical outcome was

TABLE 1 - Characteristics of experimental studies

Author	Animals (number)	Treatment groups	TRM (level)	HBO treatment after SCI	Dosage, duration and HBO intervals	ATA	Histologic evaluation	Biochemical evaluations	Functional evaluation
Kahraman et al. ²⁵	Rats (28)	1) Methylprednisolone group 2) HBOT group 3) SCI without HBOT 4) Surgery without HBOT	Clip compression (T8-T10)	Immediately	8, 90 min, twice daily	2.8	No	Levels of TBARS, SOD and GSH-Px. Only HBOT administration diminished all parameters significantly	No
Hillard et al. ²³	Rats (90)	1) X-irradiated 2) Tempol - treated 3) HBOT treated 4) X-irradiated + tempol-treated 5) X-irradiated + HBOT-treated 6) Untreated control	Weight-drop (T9-T10)	20 min	One session, 60 min.	2	More spared tissue (less gliosis and cystic degeneration) with the X-ray therapy	No	BBB scale. Higher scores in the X-ray group.
Yu et al. ²⁹	Rats (60)	1) SCI without HBOT 2) SCI with HBOT once a day 3) SCI with HBOT one session	Weight-drop (T8-T10)	30 min	90 min. Group 2: more 1x/day until sacrifice	2.8	Less number of apoptotic cells related with early HBOT	The gene expression of GDNF and iNOS was attenuated in the HBOT group.	No
Huang et al. ²⁴	Rats (70)	1) Surgery without SCI 2) SCI without HBOT 3) HBOT 1 session 30 min post-SCI 4) HBOT 1 session 3 h post-SCI 5) HBOT 1 session 6 h post-SCI 6) HBOT 7 sessions 6 h post-SCI 7) HBOT 7 sessions 24 h post-SCI	Weight-drop (T9-11)	30 min, 3 h, 6 and 24 h	1x day, 60 min	2.82	Groups 3, 4 and 6: rats retained more sparing myelin tissue. Groups 2, 5 and 7: had necrosis, demyelization, cavitations	No	BBB scale. Higher scores in groups 3, 4 and 6
Murakami et al. ²⁶	Rabbits (23)	1) Surgery without SCI 2) SCI and HBOT 30 min 3) SCI and HBOT 6 h 4) SCI without HBOT	Ischemia (L2-3)	30 min, 6 h	One session, 60 min	3.0	Motor neurons in groups 3 and 4 decreased significantly compared with others groups	No	Johnson's criteria. Groups 1 and 2 could stand, whereas in 3 and 4 showed paraplegia
Higgins et al. ²²	Cats (25)	1) Without HBOT 2) HBOT immediately after SCI 3) HBOT 2 h after SCI	Weight-drop (T4)	Immediately and 2 h	One session, 3 h	2	No differences	No	Better evoked potentials with earliest therapy and less severe injuries.
Gelderd et al. ²¹	Rats (30)	1) SCI without HBOT 2) SCI with HBOT once a day 3) SCI with HBOT + dimethyl sulfoxide	Transection (T5)	15 min	Daily, for 47-54 days, 90 min	2.82	Reduction of collagen and increase in the number of nerve fibers in group 3.	No	Group 3 coordinated hindlimb movements; Group 2 bearing ability and sensory return.
Yeo et al. ²⁸	Sheep	1) SCI without HBOT 2) SCI with HBOT once a day	Weight-drop (T10)	2 h	One, 90 min.	3	Group 2: less central cystic change.	No	Improvement in hind limb function except at the fifth week.
Yeo et al. ²⁷	Sheep	1) SCI without HBOT 2) SCI with HBOT once a day	Weight-drop (T10)	2 h	One, 90 min.	3	No	No	Idem Yeo, et al, 1977

HBOT: hyperbaric oxygen therapy; SCI: spinal cord injury; BBB: Basso-Beattie-Bresnahan scale; TBARS: thiobarbituric acid reactive substances; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase; iNOS: inducible nitric oxide synthetase; GDNF: glial cell line-derived neurotrophic factor.

TABLE 2 - Characteristics of clinical studies

Author	Number	Treatment/ randomization	SCI / level	Number, duration and intervals of HBOT sessions	ATA	Functional evaluation
Asamoto et al. ²⁰	34	1) With HBOT 2) Without HBOT Not randomized	Hyperextension/ cervical region	One session/day 60 min 3-33 days of sessions	2.0	NCSS and ASIA scales. The improvement rate in the HBOT group was better than the Untreated Group ($p < 0.05$).
Yeo et al. ³⁹	45	1) With HBOT 2) Without HBOT Not randomized	Recent SCI/ not specified	1, 2 or 3 sessions in the first 20 h after the SCI, 90 min intervals	2.5	Frankel scales. Comparative analysis suggests no significant differences between the two groups.

HBOT: hyperbaric oxygen therapy; NCSS: Neurological Cervical Spine Scale; SCI: spinal cord injury.

assessed by reflexes, sensory and motor functions. The best results were provided by the combined therapy. The only difference between the Treatment and Control Group was a decrease in cavitation size and increased number of nerve fibers within the scar in animals showing coordinated hind limb movements.

Kahraman et al.²⁵ conducted a study to compare the effects of HBOT with methylprednisolone after experimental SCI in rats. In this study, HBOT was administered immediately after the SCI. Five days after the SCI, the spinal cord was evaluated in relation to oxidative status with thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). The authors observed that only the HBOT reduced the level of oxidative damage after SCI. The results of oxidative damage did not differ between the Untreated and the Methylprednisolone Group.

Only one study, designed to test the efficacy of HBOT, antioxidant nitroxide tempol and x-irradiation, associated or alone, in reducing histological damage and functional disability, demonstrated that a single hour session, 20 minutes after the SCI, does not promote histological or functional recovery²³. It was observed that only x-irradiation and tempol administered alone significantly improved function and reduced histological damage. There were no differences compared with the Untreated Group in the groups that received HBOT alone or associated with tempol or x-irradiation, or in the group that received x-irradiation associated with tempol.

Regarding the clinical studies, the samples were heterogeneous, the application of HBO was not equal for all patients in every study, and the results were controversial. In the study of Yeo³⁹, the randomization procedure is unclear as well as the criterion used to define the number of pressurizations. The primary outcome utilized was the observation of a clinical improvement of two levels on the Frankel scale, at least between the pre and posttreatment evaluation. The statistical analysis showed no significant improvement between the two groups and none of patients in the HBO-therapy group with a complete lesion before treatment has improved.

In the study of Asamoto et al.²⁰, the randomization process was unclear, the delay between admission and HBOT was within 24 hours and the duration of therapy ranged from 3 to 33 days (mean 12.1 days), because the protocol changed across the study observational time. The clinical evaluation consisted of the NCSS and ASIA impairment scale in the admission and after treatment. The mean improvement was 75.2 and 65.1% in the HBOT and Control Group, respectively ($p < 0.05$).

CONCLUSION

The majority of experimental studies with HBOT in the treatment of SCI had good results of this therapy. The quality of the two clinical trials reviewed was poor and cannot provide clear information about this treatment in humans with acute SCI. Further studies are needed to define the role of HBOT in SCI.

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