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Effects of hyperbaric oxygen therapy on postoperative recovery after incomplete cervical spinal cord injury

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STUDY DESIGN: A retrospective study of incomplete cervical spinal cord injury (SCI) treated with and without hyperbaric oxygen (HBO) therapy after operation.

OBJECTIVE: To investigate the effects of hyperbaric oxygen therapy on patients' postoperative recovery after incomplete cervical spinal cord injury.

SETTING: Shulan Hangzhou Hospital, Hangzhou, China.

METHODS: We analyzed the clinical data of 78 patients admitted in the Orthopedic Department of our hospital from June 2014 to June 2016, due to trauma-induced incomplete cervical spinal cord injury. All study subjects underwent nerve decompression and internal fixation procedures within 2 weeks of injury. The patients were divided into hyperbaric oxygen therapy (HBO) group ($n = 40$) and non-hyperbaric oxygen therapy (NHBO) group ($n = 38$) according to the chosen treatment option. The NHBO group only receive the conventional treatment regimen while the HBO group received a combination of conventional treatment and hyperbaric oxygen therapy. The subsequent changes in spinal functions and activities of daily living (ADL) were assessed by The American Spinal Injury Association (ASIA) scale and the Barthel Index at different time points (pretreatment, 1 month and 3 months of treatment, as well as 6 months, 1 year, 2 years, and 3 years after the surgical procedure).

RESULTS: There were no significant differences in age, gender, injury site, and disease condition between patients ($p > 0.05$). The results showed a significant difference in treatment total effectiveness rate between the HBO and NHBO groups ($p < 0.05$) (90% and 78.9%, respectively). Analyses of the ASIA scores and Barthel indices between the two groups indicated significant differences at 1 month and 3 months treatment time points, as well as 6 months and 1 year after the initial operation ($p < 0.05$). It showed that subjects in the HBO group had a better recovery than their NHBO counterparts, with the 1-month treatment time point being the most significant. In addition, the results indicated significant improvements in Barthel Index scores as well as ASIA sensory and motor function scores in both groups after a 1-month treatment, with the HBO group faring significantly better than the NHBO group ($p < 0.01$).

CONCLUSIONS: Our results not only showed that hyperbaric oxygen therapy is safe and effective for the treatment of incomplete cervical spinal cord injury but also indicated that the longer the treatment lasts (therapy initiation within 3 months after the surgical operation), the better the effects. In addition, a correct hyperbaric oxygen therapy leads to a peak in recovery within the first postoperative 3 months and can effectively promote spinal cord functions, reduce the disabilities, and improve patients' quality of life.

Spinal Cord (2022) 60:129–134; https://doi.org/10.1038/s41393-021-00674-w

INTRODUCTION

Spinal cord injury (SCI) is a severe lesion of the central nervous system generally resulting in high disability and mortality rates, with significant implications for patients and their families. It is a tremendous social burden and loss since most of SCI patients are young adults. Because of the complexity of its pathophysiological mechanisms, it is often difficult to treat with hardly an ideal outcome and little to none hope of recovery, especially when it is a complete SCI. However, recently, hyperbaric oxygen (HBO) therapy has been shown to regulate body functions and promote recovery in cases of incomplete cervical SCI. Indeed, experimental and clinical studies have shown that HBO can not only prevent or reverse SCI-induced pathological changes through various mechanisms but also promote the repair and regeneration of neurons, as well as contribute to the recovery of spinal cord functions [1]. Due to the severity of cervical SCIs and the aim of providing further evidence for the clinical application of HBO in the treatment of incomplete cervical SCI patients, this study utilized, on top of the conventional therapeutic option, HBO therapy on patients with the above condition. The subsequent recovery was assessed, analyzed, and compared at different periods.

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Received: 14 November 2020 Revised: 10 July 2021 Accepted: 13 July 2021
Published online: 29 July 2021

Table 1. Comparison of general information and condition of patients of two groups.

Group	Number	Gender (*n*)		Age	Time window of operation (*n*)				Damaged segment (*n*)			ASIA grade (*n*)			
		M	F		<8 h	8 h to 1d	1d to 1w	>1w	C1–2	C3–5	C6–7	A	B	C	D
HBO	40	22	18	37.5 ± 11.2	8	10	12	10	2	25	13	0	8	12	20
NHBO	38	21	17	36.9 ± 12.17	7	11	11	9	3	23	12	0	9	11	18

Time window of operation = the time from patients'cervical cord be injured to received operation treatment, damaged segment = the segment of injured cervical vertebra. There were no significant differences in age, gender, injury site, and disease condition between patients ($p > 0.05$).
N number, *H* hour, *D* day, *W* week, *ASIA* The American Spinal Injury Association.

METHODS

Data collection and grouping

The study included 78 patients with traumatic cervical SCI from our hospital's orthopedics department from June 2014 to June 2016. The inclusion criteria were as follows: (1) confirmed traumatic cervical SCI; (2) motor and sensory dysfunctions below the injury plane; (3) a diagnosis confirmed by either imaging examinations (X-ray/CT/MRI) or surgery; (4) a cervical SCI needing decompression and stabilization. The exclusion criteria were as follows: (1) a cervical SCI caused by degeneration; (2) chronic diseases such as hypertension, heart disease, or diabetes mellitus; (3) craniocerebral injuries; (4) other neurological disorders. Patients meeting the inclusion criteria were divided into two groups according to whether they had HBO treatment with their baseline characteristics shown in Table 1. The preliminary analysis did not indicate significant differences in age, sex, time from onset to treatment, injured segment, and The American Spinal Injury Association (ASIA) scores between the two groups ($p > 0.05$) (Table 1) (https://figshare.com/articles/dataset/Table_1_docx/13259522).

Treatment

All patients in both groups received immediate treatment after their admission. Those admitted within 8 h post-injury were first given bolus methylprednisolone (30 mg/kg in the first hour, 5.4 mg/kg/h in the next 23 h) coupled with mucosal protective agents, all patients followed by diuretic agents and neurotrophic drugs (mecobalamine, 0.5 mg every time, IV, every other day at a time). All subjects underwent anterior, posterior, or combined anteroposterior surgeries within 2 weeks of admission and after stabilization of their condition. Decompression and internal fixation procedures were successfully performed, and physiotherapy was immediately initiated after the surgery. In addition to the conventional regimen, patients in the HBO group also underwent HBO therapy as soon as possible in a multi-person HBO chamber (model: YC2885/0.3-14IV; manufacturer: Yantai Ice Wheel Hyperbaric Oxygen Chamber Co., Ltd.). Patients undergoing HBO treatment were accompanied by a physiatrist for monitoring purposes. The pressure was set at 0.2 MPa (2.0 ATA). All HBO subjects wore masks and were given pure oxygen for 30 min twice with a 5 min break (cabin air was given during the break). One course of treatment is comprised of 30 cycles, with a frequency of once a day and a duration of 95 min per cycle.

Efficacy assessment

Each patient's spinal cord functions (ASIA score) and activities of daily living (ADL) (Barthel Index) were assessed by multiple physicians before surgery treatment, as well as 1 month, 3 months, 6 months, 1 year, 2 years, and 3 years after surgery [2, 3]. Subsequent average values were obtained for each assessment method. The ASIA score is comprised of: (1) a sensory function score for the assessment of both sides 28 dermatomes (skin area dominated by the posterior root of the spinal cord) including their ability to sense a sharp object (using a disposable safety needle) and light touch (using cotton wisp). The test results were classified into three different grades with 0 indicating an absence of sensory functions or the inability to distinguish between blunt and sharp stimuli, 1 indicating partial dysfunctions including hypersensitivity, and 2 indicating normal sensory functions. The total maximum score is 224. (2) A motor function score for the evaluation of each patient's key muscle groups using the Manual Muscle Test (MMT) method. The muscle strength scoring, similar to the MMT rating, ranges from 0 to 5 points. The higher obtainable score on each side of the body is 50 points (maximum of 100 points for one patient). The ASIA injury grading is comprised of: (1) grade A (complete injury), no motor or sensory functions below the injury level (including the sacral S4–S5 region); (2) grade B (incomplete injury), presence of sensory functions below the injury level including the sacral region with no motor functions; (3) grade C (incomplete injury), presence of motor functions below the injury level with a muscle strength <3 in key muscles; (4) grade D (incomplete injury), presence of motor functions below the injury level with a muscle strength ≥3 in key muscle groups; (5) grade E (normal), normal sensory and motor functions. The Barthel Index is comprised of several items such as being able to eat, bathe, groom (face washing, hair combing, teeth brushing, and shaving), dress, bladder control, go to the toilet, transfer from the bed to a chair, walk, and go up and down the stairs. The maximum obtainable score is 100 points, and the higher the score, the lighter the degree of dysfunction. Recoveries in sensory and motor functions were monitored and blindly assessed by two professionals. The treatment was considered as clearly successful with an improvement of 2 grades in the ASIA impairment scale. Meanwhile, it was considered as efficacious when a 1-grade improvement was observed and ineffective when no improvements in signs or symptoms were seen.

Statistical analysis

All analyses were performed on SPSS 22.0 software package. Data are expressed as the mean ± standard deviation. The within-group and between-groups comparisons were conducted using Paired *t*-tests. $P < 0.05$ indicated a statistically significant difference.

RESULTS

Comparison of spinal cord functions

The pre- and post-treatment spinal cord function scores of the two groups are detailed in Table 2 (https://figshare.com/articles/dataset/Untitled_Item/13259570). The data showed that there were no significant differences in ASIA sensory and motor scores between the two groups before the treatment ($p > 0.05$). The 1 month after treatment assessment indicated improvements in ASIA sensory and motor function scores in both groups ($p < 0.01$), with the HBO group exhibiting significantly better scores than the NHBO group ($p < 0.01$). These findings suggested that both treatment options can significantly improve recovery within the first postoperative month, with the addition of HBO significantly improving recovery odds. The 3 months data indicated that subjects in both groups had improved ASIA sensory and motor function scores compared to their 1-month scores ($p < 0.05$). However, subjects in the HBO group had better scores than their NHBO counterparts ($p < 0.05$). It showed whether conventional + HBO or conventional treatment, both options, can gradually improve functions in patients with cervical SCI. However, the addition of HBO significantly improved patients' recovery ($p < 0.05$). In addition, the 6th postoperative month assessment indicated continuous improvements in function (ASIA sensory and motor functions) in both groups ($p < 0.05$, compared to the 3 months' values), with the HBO group exhibiting significantly better results ($p < 0.05$). The 1 year, 2 years, and 3 years follow-ups did not yield significant improvements in ASIA sensory and motor function scores in both groups ($p > 0.05$, compared to the 6 months data). Nevertheless, the between-group comparison indicated that the HBO group fared better than the NHBO group

($p < 0.05$). These results show that HBO can promote and improve the recovery of cervical SCI patients during the early postoperative stages.

Comparison of Barthel Index scores

The pre- and postoperative Barthel Index scores of both groups are shown in Table 2 (https://figshare.com/articles/dataset/Untitled_Item/13259570). The preliminary analysis did not show any significant difference in the Barthel Index score between the two groups ($p > 0.05$). Consistent with the changes observed on the ASIA sensory and motor function scores, both groups showed significant improvements in the 1-month treatment scores compared to their pretreatment values ($p < 0.01$). However, the between-group comparison indicated that subjects in the HBO group fared significantly better than their NHBO counterparts ($p < 0.01$). The postoperative 3 and 6 months' assessments also yielded similar results ($p < 0.05$, compared to the 1-month data and the 3 months data, respectively), with the HBO group showing significant improvements in ADL scores compared to the NHBO group ($p < 0.05$). In addition, the 1 year, 2 years, and 3 years follow-ups also showed similar trends to the 1-month assessment with significant improvements in Barthel Index scores of both HBO and NHBO groups ($p < 0.05$, compared to the 6 months data), and significantly higher scores in the HBO group ($p < 0.05$). These findings suggested that regardless of the choice of treatment (conventional or the conventional + HBO), patients with cervical SCI are still able to gradually recover some of their ADL abilities within the postoperative 6 months to 3 year. However, HBO therapy can significantly promote and improve patients' ADL abilities if implemented during the early stages of the treatment.

DISCUSSION

SCI mechanisms are comprised of two key components: the primary mechanical and secondary pathological injuries. Due to the nature of the pathogenesis involved in SCI, three therapeutic methods are usually implemented in a clinical setting: (1) relieve of the continuous compression of the spinal cord due to external factors and avoidance of further expansion of the injured area (methods such as surgical decompression and diuretic agents); (2) avoidance of further worsening of patient's condition through the protection of remaining axons and neurons from secondary injury (blockage or limitation of secondary pathological reactions by utilizing treatment options such as methylprednisolone and pulse therapy); (3) promotion of nerve tissue regeneration and repair during the chronic stages of the condition through therapies such as neurotrophic drugs, cell transplantation, gene therapy, or HBO treatment [1, 4–16]. However, unlike subjects with partial SCIs who still have a chance of nerve recovery due to the presence of living tissues in their injured segments, those with complete spinal injuries have slim to none chances of nerve regeneration and nerve tissue repair due to cell death. Therefore, this study selected patients with cervical SCI as the research subjects due to the proven effectiveness of surgery in such subgroups. The conclusions of this study confirmed that HBO could promote and improve the recovery of spinal cord functions and ADL abilities of patients with partial SCI.

With the increasing use of HBO in clinical settings, a large number of experimental studies have shown that HBO can prevent or reverse the pathological changes after SCI and promote functional recovery in injured experimental subjects [9–24]. Asamoto et al. [17], through their clinical study, found that HBO can quickly correct the hypoxic state of damaged spinal areas, reduce pressure in the spinal canal, and relieve tissue edema. The possible reasons behind the HBO-induced improvements in spinal cord functions and ADL ability after 3 months of treatment are: (1) HBO can cause the dilatation of arteries, accelerate blood flow, and increase spinal cord blood supply, thus, correcting the

Table 2. The pre- and post-treatment spinal cord function scores of the two groups.

Group	ASIA sensory of HBO	ASIA sensory of NHBO	ASIA motor of HBO	ASIA motor of NHBO	Barthel Index of HBO	Barthel Index of NHBO
Before treatment	89.1 ± 6.9	88.9 ± 7.6	34.3 ± 3.7	34.9 ± 3.6	33.1 ± 3.2	32.9 ± 2.6
1 month after surgery	131.6 ± 6.9	116.5 ± 6.5	44.2 ± 4.9	42 ± 4.8	59.2 ± 3.4	43.6 ± 4.7
3 months after surgery	159.9 ± 8.3	138.5 ± 8.8	55.9 ± 5.8	47.9 ± 5.8	70.6 ± 3.3	53.9 ± 5.7
6 months after surgery	189.4 ± 7.2	160.5 ± 8.7	66.1 ± 5.6	53.4 ± 6.3	81.7 ± 4.6	60 ± 5.6
1 year after surgery	192.3 ± 7.8	161.2 ± 8.3	66.3 ± 5.8	53.9 ± 6.2	88.2 ± 3.1	68.5 ± 5.5
2 years after surgery	192.5 ± 8	162.2 ± 7.7	66.8 ± 5.9	53.6 ± 5.9	90.2 ± 2.1	72.5 ± 5.4
3 years after surgery	192.6 ± 7.9	162.8 ± 7.8	66.4 ± 6.4	53.2 ± 6.2	91 ± 2.5	73.9 ± 6.2

	ASIA sensory of HBO	ASIA sensory of NHBO
before treatment	89.1	88.9
one month after surgery	131.6	116.5
three months after surgery	159.9	138.5
six months after surgery	189.4	160.5
one year after surgery	192.3	161.2
two years after surgery	192.5	162.2
three years after surgery	192.6	162.8

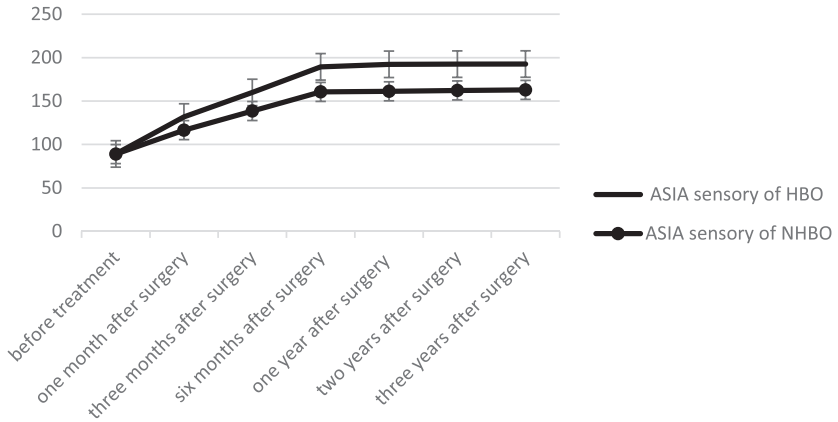

Fig. 1 ASIA Sensory Function. Comparison of ASIA sensory function of patients of two groups pre- and post treatment.

	ASIA motor of HBO	ASIA motor of NHBO
before treatment	34.3	34.9
one month after surgery	44.2	42
three months after surgery	55.9	47.9
six months after surgery	66.1	53.4
one year after surgery	66.3	53.9
two years after surgery	66.8	53.6
three years after surgery	66.4	53.2

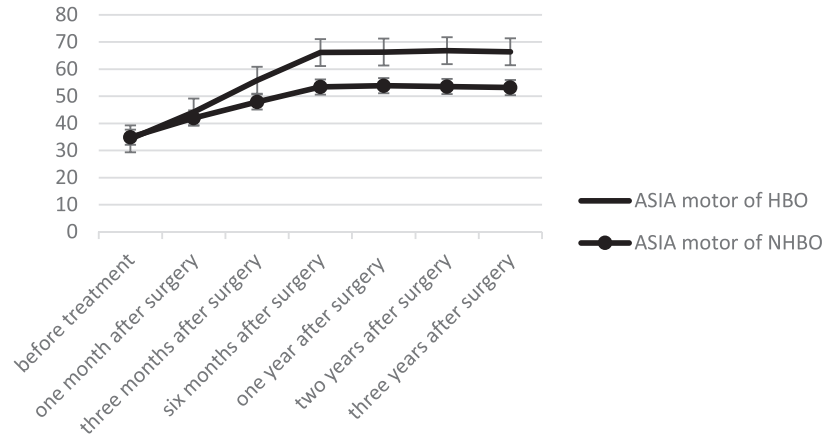

Fig. 2 ASIA Motor Function. Comparison of ASIA motor function of patients of two groups pre- and post treatment.

underlying ischemia and hypoxia of injured areas; (2) HBO can inhibit the production of free radicals, accelerate their clearance, and reduce ischemia-reperfusion-related injuries; (3) HBO can inhibit lymphocyte-mediated immune response, reduce the formation of scar tissues, and provide favorable conditions for nerve/axon regeneration and nerve function recovery. In addition, HBO has been proven to protect the surviving nerve cells within the injured segment as well as muscle tissues and promote the establishment of collateral circulation in cervical SCIs. Thus, providing the necessary conditions for the formation of conduction pathways and neuronal regeneration [4–8].

A case performed by Wilson et al. [11] reported that the application of HBO contributed to the immediate and sustained improvement in motor recovery after postoperative SCI. HBO may represent a new avenue of therapy for SCI. In addition, Huang et al. [24] also indicated that both treatments between 8 h and 1 week following SCI could also improve the neurol functions and ADL of SCI patients, but the curative effects of HBO therapy

	Barthel index of HBO	Barthel index of NHBO
before treatment	33.1	32.9
one month after surgery	59.2	43.6
three months after surgery	70.6	53.9
six months after surgery	81.7	60
one year after surgery	88.2	68.5
two years after surgery	90.2	72.5
three years after surgery	91	73.9

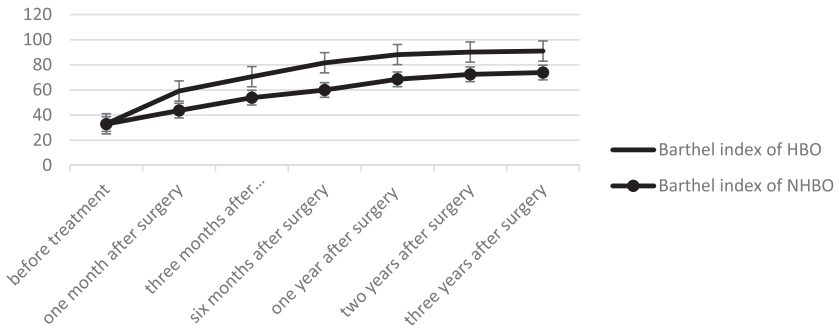

Fig. 3 Barthel Index Function. Comparison of Barthel Index function of patients of two groups pre- and post treatment.

were better than conventional treatment. More studies have also reported a positive correlation between early HBO treatment and better outcomes in cervical SCI cases [20, 21]. HBO generally requires the patient to be moved from the ward to other facilities for the treatment. However, cervical SCIs are often accompanied by multiple injuries involving several areas of the body, unstable vital signs, and an unstable cervical spine, further complicating the implementation of such recommendation in a clinical setting. Therefore, it can only be started as soon as the conditions allow it. Therefore, a complete and systemic assessment of each patient's condition upon admission is crucial for early decompression, stabilization, and initiation of HBO therapy.

This study results showed that subjects in the HBO group had far better results on the 3 months neurological functions recovery than their counterparts, stressing the need for a prolonged HBO treatment. However, there is also a positive correlation between the duration of the HBO treatment and the financial burden on the family (other rehabilitation treatments are also needed in addition to HBO treatment, further increasing the financial burden). In addition, the curve in Figs. 1–3 also showed a decline in the recovery of nerve function after 3 months of treatment, indicating that it loses its effectiveness after such an extended period (https://figshare.com/articles/figure/fig_1_xlsx/13259615) (https://figshare.com/articles/figure/Fig2/13259648). The results also found that the study subjects' ADL scores continued to improve regardless of their group even 6 months after the surgical procedure (https://figshare.com/articles/figure/Fig3/13259663). It shows that patients with a better initial nerve function recovery have a significantly greater chance at a fast and significant ADL ability improvement. Additional measures such as practice and training can also further improve patients' quality of life even after the plateau period (after 6 months).

HBO treatment should be started as soon as possible after surgical decompression and stabilization and maintained up to 3 months for optimal results in patients with incomplete cervical SCI. In addition, supportive treatments, such as exercises, should be continued indefinitely to promote better and faster recovery.

DATA AVAILABILITY

There were no data to deposit. Original data: (https://doi.org/10.6084/m9.figshare.13292498.v1), Table 1 (https://figshare.com/articles/dataset/Table_1_docx/13259522), Table 2 (https://figshare.com/articles/dataset/Untitled_Item/13259570), Fig. 1 (https://figshare.com/articles/figure/fig_1_xlsx/13259615), Fig. 2 (https://figshare.com/articles/figure/Fig2/13259648), Fig. 3 (https://figshare.com/articles/figure/Fig3/13259663).

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AUTHOR CONTRIBUTIONS

ZZ was responsible for designing the review protocol, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, creating "Summary of findings" tables, and writing the report. LQ and YX were responsible for designing the review protocol, writing the protocol and report, extracting and analyzing data, interpreting results. ZY, LB, and DP were responsible for updating reference lists and creating "Summary of findings" tables. HT and YJ contributed to data extraction and provided feedback on the report.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

Approved by the ethics review committee of Shulan (Hangzhou) Hospital: this study is basically in line with the ethical norms and agreed to be carried out. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41393-021-00674-w.

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