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ORIGINAL ARTICLE

Does hyperbaric oxygen therapy facilitate peripheral nerve recovery in upper extremity injuries? A prospective study of 74 patients

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Abstract

Purpose Several experimental studies have investigated the effects of hyperbaric oxygen therapy (HBOT) on peripheral nerve regeneration. However, to the best of our knowledge, clinical studies to evaluate the effects of HBOT on peripheral nerve recovery are seldom performed. The aim of our study was to investigate the efficacy of HBOT following primary nerve repair in patients with upper extremity nerve injuries.

Methods Patients admitted to our hospital between 2015 and 2019 with ulnar and median nerve injuries were included in the study. Patients were randomized based on their application dates and divided into two different groups. Patients who received HBOT following standard epineural nerve repair were included in group 1, while patients who only underwent epineural nerve repair were included in group 2. All patients were followed up at 3, 6, and 12 months post-treatment and evaluated through electroneuromyography analysis of the traumatized nerve, injured nerve-related muscle strength, and two-point discrimination test.

Results Impulse transmission of injured nerves to the end organ was faster in group 1. Further, ENMG parameters demonstrated that injured nerves of patients in group 1 recovered faster. Patients in group 1 also reached higher power score and had significantly more rapid motor recovery than patients in group 2.

Conclusion This prospective study of upper extremity injuries demonstrated the favorable effects of HBOT on nerve recovery both clinically and electrophysiologically following nerve repair. One HBOT session each day for 5 days after surgical treatment can decrease morbidity and facilitate recovery.

Keywords Hyperbaric oxygen therapy · Nerve injury · Nerve repair · Nerve recovery

Introduction

Various studies are now investigating the relationship between hyperbaric oxygen and nerve regeneration as a possible alternative. Hyperbaric oxygen therapy (HBOT) is a treatment method involving intermittent exposure to 100% oxygen through a mask or hood in enclosed chambers at pressures higher than the atmospheric pressure of 1 atm [1]. By enhancing tissue oxygenation and production of cellular nutrients such as phosphocreatine, ATP, and hydroxyproline, HBOT provides support to the fibroblast-collagen matrix for neovascularization and optimum conditions for wound healing by increasing the bactericidal activities of leukocytes. Additionally, in areas damaged by trauma, the renewed vascular bed may positively influence neurotrophic factors leading to enhanced axonal transport and sprouting of nerve terminals in the repaired zone [2].

In his review study, Sanchez reported that several experimental studies in the literature have investigated the effects of HBOT on peripheral nerve regeneration [3]. Besides being used in pathological conditions, hyperbaric oxygen (HBO) has proved beneficial in peripheral nerve regeneration in experimental studies [4]. It has been proposed that HBO may demonstrate its effects on peripheral nerve regeneration by enhancing and/or inhibiting production of certain

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growth factors. Accordingly, Yu et al. reported that HBO reduced gene expression of glial cell derived neurotrophic factor in rats with spinal cord injury [5]. Moreover, HBO increased the production of basic fibroblast growth factor, vascular endothelial growth factor, and transforming growth factor-beta 1.

The beneficial effects of HBO on peripheral nerve regeneration following primary nerve repair have also been reported [6, 7]. In addition, an experimental nerve graft study reported significantly better functional results in rats exposed to HBO [8]. However, to the best of our knowledge, clinical studies evaluating the effects of HBOT on peripheral nerve recovery are seldom performed.

The aim of our study was to investigate the efficacy of HBOT following primary nerve repair in patients with upper extremity nerve injuries.

Patients and methods

Patients admitted to our hospital between 2015 and 2019 years with ulnar and median nerve injuries between the wrist and elbow zones were included in this prospective study. The patients were min. 18 to max. 55 years old and primarily repaired nerve injuries were included in the study. Smokers, patients with purely sensory nerve injuries, combined nerve injuries, crush injuries, and with relative and absolute contraindications to HBOT, and those with chronic diseases and irregular follow-ups were excluded. Due to clinical difference between partial and total nerve injuries patients with partial nerve injuries were also excluded to get optimal results. Patients applied in 72 h following injuries and only primarily repaired nerve injuries were included to the study. Patients were randomized based on their application dates and divided into two different groups. Patients who received HBOT following standard epineural nerve repair were included in group 1, while patients who only underwent epineural nerve repair without HBOT were included in group 2. Before the patients exposed to HBOT, routine procedures including ophthalmologic tests; ear, nose and throat examinations regarding to inherent ET dysfunction and underlying upper respiratory infections; and a chest X-ray were carried out. The epineural repair technique was applied to all nerve injuries using 7/0–8/0 non-absorbable, monofilament polyamide (Daylon®, Doğsan, Turkey) sutures. Ethics committee approval was obtained, and both verbal and written informed consents were acquired from all the patients included.

The patients in group 1 received HBOT at 2 atm absolute pressure for 2 h per day for 5 days starting from the first day following nerve repair. All patients were followed up at 3, 6, and 12 months posttreatment and evaluated through ENMG (electroneuromyography) analysis of the traumatized nerve, injured nerve-related muscle strength, and two-point discrimination test for assessing sensory rehabilitation. Additionally, patients with nerve injuries located in elbow were followed up at 2nd and 3rd years and assessment methods were performed. The patients with the proximal level injuries of median and radial nerves were not included in the study as this type of injury was mostly encountered in conjunction with the other nerve injuries. Furthermore, because of the pure sensory content, distal level injuries of radial nerve were not counted either.

All ENMG examinations were performed by two neurologists blinded to groups. Standard median nerve conduction studies were performed with surface recording from the abductor pollicis brevis muscle, stimulating at the wrist and elbow; while ulnar nerve conduction studies were executed by recording from both of the abductor digiti minimi and first dorsal interosseus muscles, with stimulation at the wrist, below-elbow and above-elbow [9]. Muscle strength exercises, and two-point discrimination tests were evaluated by the second surgeon who was also blinded to groups. The muscle strength score of patients was graded based on the Medical Research Council scale at 3, 6, and 12 months. Patients who had nerve injuries located in elbow were also assessed at 2nd and 3rd years and muscle power progress was recorded.

Statistical analysis

The statistical significance of the differences between the mean values was analyzed using SPSS 18.0 (USA) statistical software. Differences between the pre- and post-operative averages were evaluated for eligibility for normal distribution analysis. Since the differences were not normally distributed, Wilcoxon *t* test was used for pre- and post-operative analysis. p values of <0.05 were considered statistically significant.

Results

A total of 74 patients were included in the study, with 38 patients in the first group, and 36 in the second group. The average age in group 1 was 35.3 ± 2.6 (min. 17 and max. 59) years and in group 2 was 34.8 ± 1.9 (min. 17 and max. 58) years. The average follow-up period was 18 (min. 12 to max. 36) months. 18 patients with elbow level injuries were evaluated at their 2nd and 3rd years as well.

There were 16 patients with median nerve injury, and 22 patients with ulnar nerve injury in group 1; while 21 patients with ulnar nerve injury, and 15 patients with median nerve injury were in group 2 (Table 1).

In group 1, the neurologists reported significant improvement in nerve conduction velocities and latency

Table 1 Patients and injury characteristics

Level of injury	Injured nerve	Group	Patients (n)	Mean age
1/3 distal forearm	Ulnar nerve	Group 1	12	38.0
		Group 2	13	33.3
1/3 distal forearm	Median nerve	Group 1	16	39.5
		Group 2	15	35.2
Elbow	Ulnar nerve	Group 1	10	28.4
		Group 2	8	35.9

Table 2 Nerve recovery description by the neurologist at 12th month control according to ENMG results

	Patients with significant improvement	Patients with continuing regeneration	Patients with severe degeneration
Group 1	$n=18$	$n=10$	$n=10$
Group 2	$n=12$	$n=11$	$n=13$

periods on ENMG results of 18 patients at 12-month follow-up compared with 3- and 6-month follow-ups. Furthermore, nerve recovery processes were evident in ENMG results of ten patients, whereas severe degeneration findings were obvious in ten other patients (Table 2).

The levels of injury were determined as 1/3 distal forearm level and elbow level. Ulnar nerve injuries were assessed at the both levels. Patients in the two groups were matched for the same nerve injuries at the same upper extremity level, and their 3-, 6-, and 12-month ENMG results were compared for nerve conduction velocities and latency periods as demonstrated in Table 3, respectively.

At 3rd month follow-up of distal forearm injuries, conduction velocity of both median and ulnar nerves was significantly faster ($p \approx 0.011$, $p \approx 0.030$), while significant difference between latency periods was only seen in median nerve. ($p \approx 0.041$) There was no statistical difference between conduction velocities at 6th month ENMG results, however the values of latency periods were found significantly shorter in group 1. ($p \approx 0.028$, $p \approx 0.022$) No potential was observed at 3rd and 6th month ENMG results of elbow level ulnar nerve injuries. While the first transmission was demonstrated in the first group at 12th month follow-up, only significant difference was revealed between 2nd year results of conduction velocities (Table 4).

Reaching high scores of muscle strength at the early period was observed in group 1 at 3rd and 6th month follow-ups of the patients with distal forearm median nerve injuries. Significant difference between muscle strength scores of the patients with elbow level injuries of ulnar nerve was observed since 12th follow-up period ($p < 0.05$) (Table 5).

The static two-point discrimination test was conducted in both groups using an esthesiometer. Patients' normal two-point discrimination values and mean values at 12 months posttreatment for fingertip, thenar and hypothenar surfaces of hand are described in Table 6. Although the two-point discrimination values of fingertip were lower in group 1 ($p < 0.05$), there was no significant difference in the thenar and hypothenar surfaces of hand between two groups ($p > 0.05$).

Discussion

The basic principles of peripheral nerve repair pertain to tension-free neurorrhaphy of undamaged fascicules and the epineurium. It is essential to obtain nerve repair as early as possible, so motor and sensory rehabilitation should be considered in cases of neuroregeneration [10].

Prolonged motor and sensory distal latency of the nerve, decreased motor and sensory velocities are defined as diagnostic criteria of nerve injury [11]. Although electrophysiology is one of the most objective methods for evaluating functional recovery of nerves during the posttraumatic and rehabilitation periods, it frequently depends on the experience and skill of the person [12, 13]. Biopsy, ranked as a gold standard method often employed in experimental studies, cannot be applied in clinical studies which is one of the main limiting factors. In this study, we have tried to optimize conditions for obtaining standardized results by having the blind neurologists perform all the ENMG studies. Furthermore, patients in the two groups were matched for the same nerve injury at the same upper extremity level following a laceration pattern of trauma. To obtain the similar wound environments for the nerve healing in both groups, patients with partial nerve injuries, pure sensory nerve injuries and aged under 18 were not included in the study. Moreover, as the crush injuries result in a various amount of non-vital tissue, this type of trauma pattern was not included in the study either. Besides, because of the fact that isolated and multiple nerve injuries might affect the recovery outcome in different ways we excluded the combined nerve injuries from the study to obtain objective circumstances [14].

In our study, the functional recovery of the patients was graded based on Medical Research Council scale in keeping with the other clinical studies investigating peripheral nerve regeneration and scores of M3 ≤ were taken into consideration [15, 16]. Favorable results were seen in some of the patients at 3rd month examination in despite of no or low conduction velocity in ENMG results. These results were not approved as significant findings because fasciculations and spontaneous contractions are quite likely possible at early stages. At 6th month power score of % 62.5 of the patients exposed to HBOT was

Table 3 Comparison of ENMG parameters at 3rd, 6th and 12th months

Level of injury	Injured nerve	Group	Conduction velocity (m/sn)	*p value	Latency period (msn)	**p value
3rd month ENMG results						
1/3 distal forearm	Ulnar nerve	Group 1	48.8	**0.011**	15.4	0.089
		Group 2	15.1		22.3	
1/3 distal forearm	Median nerve	Group 1	43.4	**0.030**	9.5	**0.041**
		Group 2	29.0		19.1	
Elbow	Ulnar nerve	Group 1	–	–	–	–
		Group 2	–		–	
6th month ENMG results						
1/3 distal forearm	Ulnar nerve	Group 1	54	0.261	3.58	**0.028**
		Group 2	50.1		5.7	
1/3 distal forearm	Median nerve	Group 1	56.9	0.065	3.20	**0.022**
		Group 2	45.6		5.20	
Elbow	Ulnar nerve	Group 1	–	–	–	–
		Group 2	–		–	
12th month ENMG results						
1/3 distal forearm	Ulnar nerve	Group 1	55.5	0.280	2.10	0.212
		Group 2	52.3		2.97	
1/3 distal forearm	Median nerve	Group 1	56.9	0.194	2.42	0.188
		Group 2	53		3.74	
Elbow	Ulnar nerve	Group 1	52.1	–	4.01	–
		Group 2	–		–	

'–' no potential was obtained

**p* value of conduction velocity comparison

***p* value of latency period comparison

Bold values indicate the statistically significant results (p< 0.05)

Table 4 Comparison of ENMG parameters at 2nd and 3rd years

Level of injury	Injured nerve	Group	Conduction velocity (m/sn)	*p value	Latency period (msn)	**p value
2nd year ENMG results						
Elbow	Ulnar nerve	Group 1	54.3	**0.042**	3.9	0.078
		Group 2	38.2		5.30	
3rd year ENMG results						
Elbow	Ulnar nerve	Group 1	53.8	0.062	3.91	0.08
		Group 2	45.7		4.9	

*p value of conduction velocity comparison

**p value of latency period comparison

Bold values indicate the statistically significant results (p< 0.05)

Table 5 Muscle strength scores of the patients according to timeline

Level of injury	Injured nerve	Group	3rd month muscle strength score	6th month muscle strength score	12th month muscle strength score	2nd year muscle strength score	3rd year muscle strength score
1/3 distal forearm	Ulnar nerve	Group 1	M2	M4	M5		
		Group 2	M2	M3	M4		
1/3 distal forearm	Median nerve	Group 1	M4	M5	M5		
		Group 2	M2	M3	M5		
Elbow	Ulnar nerve	Group 1	M1	M2	M4	M5	M5
		Group 2	M1	M1	M2	M3	M3

Table 6 Comparison of two- point discrimination mean values in 2 groups

	Normal values	Group 1	Group 2
Fingertip	4.4 ± 2.5	4.1 ± 2.9	5.4 ± 2.7
Thenar surface	9.0 ± 5.7	10.5 ± 3.7	11.1 ± 4.5
Hypothenar surface	9.0 ± 5.7	9.8 ± 3.0	10.3 ± 5.2

M3 ≤, while it was seen in % 43.3 of the patients in group 2. ($p \approx 0.041$) (Table 5) (See Video, Supplemental Digital Content 1, which demonstrates motor recovery of the patient with ulnar nerve injury). Comparing the patients with injury at the level of distal forearm there was no significant difference between power scores at 12th month. However, difference was obvious between the patients with ulnar nerve injury at the elbow level. It can be interpreted to accelerating effects of hyperbaric oxygen treatment on healing process as the patients in group 1 reached the same power scores earlier.

Accordingly, apparent differences of the ENMG parameters between two groups became less significant in the following months (Fig. 1). Though a rapid increase of conduction velocity was observed in group 1 at 3rd month follow-up, similar values were presented in both groups in the following months. There was significant difference between latency periods of groups at 6th month ENMG results, while the conduction velocity values were not different at the same proportion; this contradiction remains controversial in terms of functional recovery. However, as the values of latency period were close to the normal range in group 2, significant shortening in group 1 was likely derived from the hyperbaric oxygen therapy. It was demonstrated that HBOT makes several growth factors, especially NT-3, increase in the experimental studies [17, 18]. These factors are up-regulated following nerve injury in the distal segments and transported to the nerve cell body in retrograde motion [3]. The nerve recovery in group 1 seems to be associated with the regenerative effect of HBOT that facilitates the sprouting of axons across the injury site.

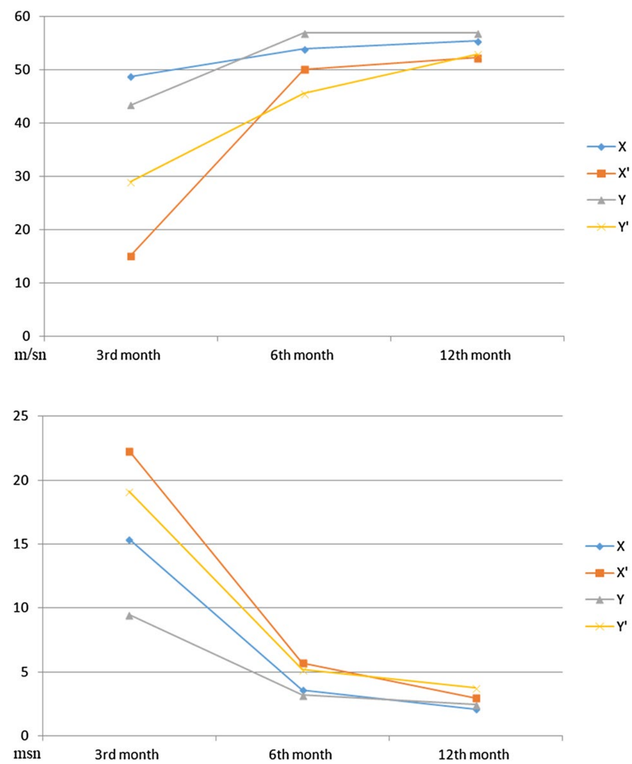

Fig. 1 Variance of conduction velocity (above) and latency period (below) values by months; X—distal forearm ulnar nerve injury in group 1; X'—distal forearm ulnar nerve injury in group 2; Y—distal forearm median nerve injury in group 1; Y'—distal forearm median nerve injury in group 2

Furthermore, comparing the ENMG and muscle strength score results, it can be inferred that clinical and electrophysiological progress are not observed together in the patients at any time of healing and these two assessment methods should be handled detachedly. It is clearly shown that improvement in nerve conduction velocity and latency period does not demonstrate itself in muscular healing at the same proportion. It can be explained with the different healing characteristics of nerve and muscle tissues. Moreover, conduction velocity became apparent at 12th month in the patients with elbow level injuries in group 1, and at 24th month in group 2. However, there was no significant difference between two point discrimination values at 12th month assessment. This inconsistency can be explained with the excellent adaptation mechanism of peripheral sensory neurons; collateral sprouting to the injured area is known to become apparent following trauma [19, 20].

Zhao et al. demonstrated that HBOT application following peripheral nerve repair had favorable results in patients with peripheral nerve injury [6]. However, details about the injured nerve, severity of nerve injury, follow-up periods, and HBOT duration were not reported in this study. In addition, evaluations of the specific nerves were not compared separately in the upper and lower extremities. Evidence in the literature suggests that nerve regeneration varies not just based on the specific nerve fiber but also between the upper and lower extremities [21]. Also, besides the scales grading motor and sensory recovery, no electrophysiological evaluations were applied in the aforementioned study. In our study, we presented the beneficial effects of HBOT on peripheral nerve recovery following nerve repair both clinically and electrophysiologically.

An experimental study investigating the relationship between nerve regeneration and HBOT duration has shown that HBO exposure started from the first day has the maximum effect on nerve regeneration. However, it has been reported that positive effect of HBO being eliminated if HBO was initiated after the 15th day post nerve repair [22]. There is no consensus about duration of hyperbaric oxygen treatment for peripheral nerve regeneration in literature; so several experimental studies demonstrated hyperbaric oxygen treatment periods for nerve regeneration varying from 3 to 7 days [23–26]. In clinical practice, there is no specific data about the dosage of HBOT in nerve recovery treatment; thus, further studies are needed to reveal the relationship between the HBOT sessions and nerve regeneration. Accordingly, considering feasibility of this treatment we designed our study such that HBOT was applied from the first day following nerve repair and therapy lasted 2 h per day for 5 days.

The main limitation of our study is the limited number of patients enrolled. Future investigations that include a large number of patients will contribute precious data to the literature on nerve healing. Furthermore, to get more significant data, the close relationship between age and nerve healing should be taken into consideration providing the patients at the same age range. In addition, accompanying muscle and tendon injuries in the groups might have an impact on the muscle strength; however, to match the patients according to the same tendon or muscle injuries also would significantly decrease the size of sample.

After all of this, several questions are remaining unanswered related to clinical nerve recovery: How much is ENMG adequate to demonstrate clinical nerve recovery? What are the optimum circumstances for investigation of clinical nerve recovery? In which proportion do latency period and conduction velocity reflect functional recovery? This is the preliminary study demonstrating favorable effects of HBOT on upper extremity peripheral nerve recovery both clinically and electrophysiologically following nerve repair. According to the results of our study, it can be emphasized that HBOT has some benefits for peripheral nerve recovery in upper extremity injuries, especially regarding to reaching targeted muscle power score and electrophysiological values at early stages. Here, we show that one HBOT session each day for 5 days after surgical treatment can decrease morbidity and facilitate nerve healing.

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Declarations

Conflict of interest None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Ethical statement This study conformed to the Helsinki Declaration. We (all of the authors) confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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