The role of hyperbaric oxygen therapy in the management of perioperative peripheral nerve injury: a scoping review of the literature

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ABSTRACT

Background/importance Peripheral nerve injury is an uncommon but potentially catastrophic complication of anesthesia and surgery, for which there are limited effective treatment options. Hyperbaric oxygen therapy is a unique medical intervention which improves tissue oxygen delivery and reduces ischemia via exposure to oxygen at supra-atmospheric partial pressures. While the application of hyperbaric oxygen therapy has been evidenced for other medical conditions involving relative tissue ischemia, its role in the management of peripheral nerve injury remains unclear.

Objective This scoping review seeks to characterize rehabilitative outcomes when hyperbaric oxygen therapy is applied as an adjunct therapy in the treatment of perioperative peripheral nerve injury.

Evidence review The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping reviews, using a systematic screening and extraction process. The search included articles published from database inception until June 11, 2022, which reported clinical outcomes (in both human and non-human models) of peripheral nerve injury treated with hyperbaric oxygen therapy.

Findings A total of 51 studies were included in the narrative synthesis. These consisted of animal (40) and human studies (11) treating peripheral nerve injury due to various physiological insults. Hyperbaric oxygen therapy protocols were highly heterogenous and applied at both early and late intervals relative to the time of peripheral nerve injury. Overall, hyperbaric oxygen therapy was reported as beneficial in 88% (45/51) of included studies (82% of human studies and 90% of animal studies), improving nerve regeneration and/or time to recovery with no reported major adverse events.

Conclusions Existing data suggest that hyperbaric oxygen therapy is a promising intervention in the management of perioperative peripheral nerve injury, in which tissue ischemia is the most common underlying mechanism of injury, neurological deficits are severe, and treatment options are sparse. This positive signal should be further investigated in prospective randomized clinical trials.

INTRODUCTION

Peripheral nerve injury (PNI) is a rare yet potentially devastating complication of anesthesia and surgery. Approximately 0.03%–0.1% of patients undergoing surgery with a general anesthetic will suffer perioperative PNI.[1–3] The American Society of Regional Anesthesia and Pain Medicine (ASRA) further defines the risk of perioperative PNI following peripheral nerve blockade, ranging from 15% for short-term paresthesiae to 0.024% for serious/permanent nerve damage.[4] Fortunately, the vast majority of perioperative PNI symptoms resolve spontaneously or with conservative management alone.[5] For those patients who do suffer persistent neurological symptoms for longer than 3 months postoperatively, or for whom electrophysiological studies report significant axonal loss, experts—along with ASRA—recommend surgical referral.[5–7] However, it is difficult to predict individual likelihood of benefit from surgical treatment, and only one quarter of patients who undergo surgical repair will derive significant improvements in pain or function.[8] Many patients who suffer PNI will never return to baseline functioning, especially if surgical intervention is attempted more than 6–9 months after injury,[9] and consensus statements seldom offer recommendations for the management of PNI among patients who do not improve with surgical repair or are not surgical candidates at the outset.[5]

While the cause of perioperative PNI is often multifactorial, nerve ischemia has been proposed as a central feature underpinning different types of injury.[10 11] Limiting ischemia and restoring tissue oxygen delivery are therefore important factors to mediate nerve repair.[12] As such, one emerging intervention for PNI is the use of hyperbaric oxygen therapy (HBOT).[13] HBOT involves the exposure of patients to >95% oxygen delivered at pressures above 1.3 ATA (atmosphere absolute), in a hyperbaric chamber. Its therapeutic effects are mediated by an increase in oxygen tension and oxygen solubility in plasma, increasing the blood oxygen carrying capacity and generating a heightened diffusion gradient to enhance oxygen delivery to cells,[14 15] in order to improve conditions of relative ischemia. Repeated exposure to a hyperoxic environment is thought to facilitate neurogenesis and angiogenesis and the proliferation and mobilization of stem cells, while also reducing inflammation and driving metabolic changes.[15–17] In addition to a putative role in the acute recovery phase from direct ischemia,[13] early reports suggest a potential for HBOT to feature in the treatment of other forms of ischemic nerve injury, such as chemotherapy-induced nerve injury or diabetic neuropathy.[18 19] Our own HBOT program has previously reported on the application of HBOT for two adult patients with complex regional pain syndrome, both of whom experienced remarkable improvement in symptoms.[20 21] However, the role

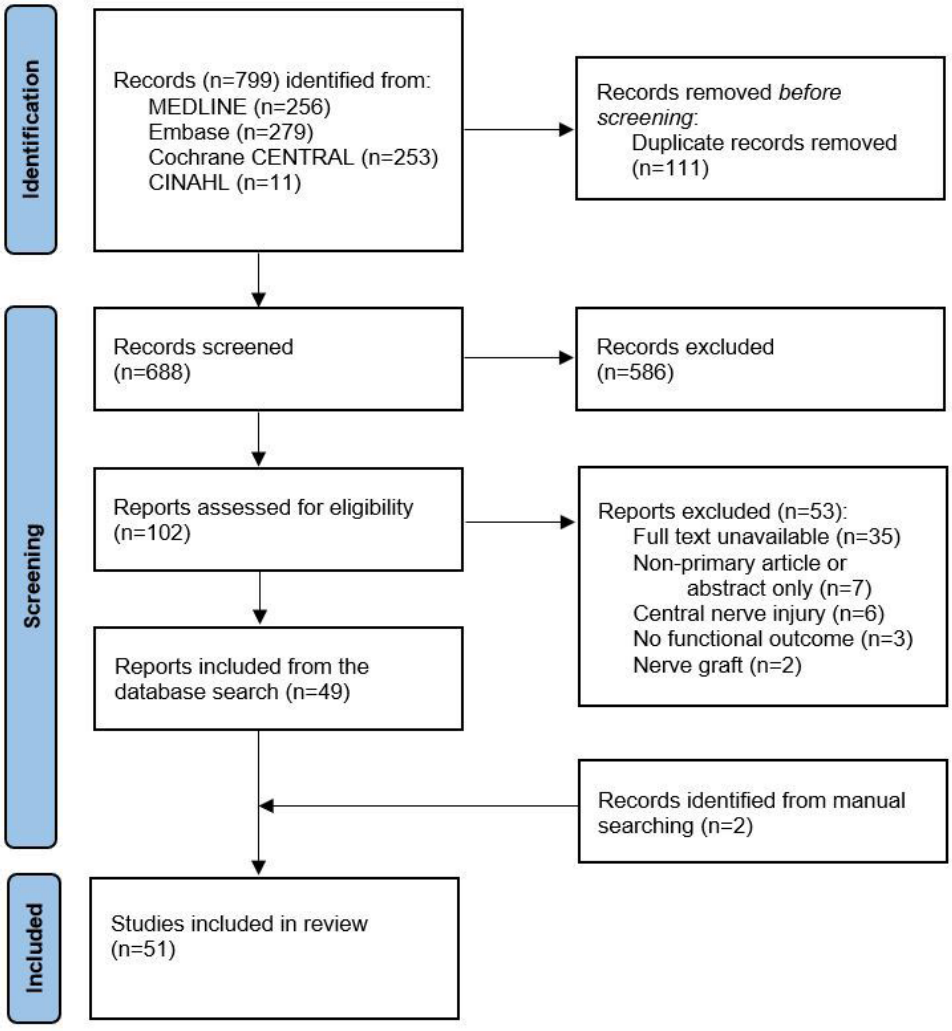

Figure 1 PRISMA flow diagram outlining article acquisition and screening. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

for HBOT in the management of perioperative PNI has not been clearly elucidated. Therefore, the present scoping review seeks to evaluate the evidence base for HBOT in the context of PNI, in both the acute and delayed setting, to characterize its potential role in the management of perioperative PNI.

METHODS

Protocol and reporting guidelines

The protocol for this scoping review was registered through the Open Science Framework (https://osf.io/z5amr/) on June 11, 2022. We had intended to explore the use of HBOT in the treatment of PNI in the setting of anesthesia and surgery, but because of a paucity of studies specific to PNI in the perioperative period we broadened the scope of our review to include HBOT for PNI regardless of setting. The review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Scoping Review guidelines, for which a transparency checklist is provided in online supplemental file 1.[22]

Information sources and literature search strategy

We systematically searched four databases on June 11, 2022, including (1) the Ovid versions of MEDLINE and MEDLINE Daily including e-publications, in progress, and non-indexed citations, (2) Embase Classic and Embase, (3) Cochrane CENTRAL, and (4) CINAHL. Preliminary searches were conducted to mine the literature for relevant keywords and controlled vocabulary terms. Search terms were built into three discrete concept blocks: HBOT, PNI, and chemotherapy or radiation injury. The complete search strategy is provided in online supplemental file 2.

Study selection

The search included all studies presenting original data, in any language, that described the use of HBOT in treating PNI. These included studies of both adult human participants or animal models, describing the effect of HBOT on clinical outcomes of nerve injury management such as nerve regeneration, pain, sensation, motor strength, or patient-reported satisfaction. We included studies examining both acute (eg, crush or transection injuries) and delayed (eg, neuropathy, complex regional pain syndrome) nerve injuries. Review, commentary, and 'expert opinion' articles, which did not present original data were excluded. Similarly, articles were excluded if they did not examine the role of HBOT as an intervention, if they used pediatric and/or cadaveric models and/or ex vivo models, if they examined central nerve injuries (ie, of the brain or spinal cord), and if they included only molecular or mechanistic but not clinical outcomes. Finally, studies were excluded if a full text could

not be accessed for review. No exclusions were applied on the basis of language or country of origin.

Study screening and data extraction process

After duplicate citations were removed, titles and abstract screening and full-text screening were performed independently and sequentially by two investigators (CB and SK). The reference lists of all included studies were also screened for relevant articles. Data extraction from included studies was similarly performed by two independent reviewers (CB and SK) and qualitatively analyzed. Extracted data included study design and model demographic, type of nerve injury, elapsed time before HBOT, HBOT protocol, measures of clinical outcomes, and concluded utility of HBOT. We designated 3 months elapsed from the time of injury to the initiation of HBOT as the threshold to differentiate between acute and delayed presentations of PNI, aligning with the International Association for the Study of Pain definition of chronic pain.[23]

RESULTS

Study screening

The search strategy yielded 256 results from MEDLINE, 279 from Embase, 253 from Cochrane CENTRAL, and 11 from CINAHL, totalling 799 articles. After removing duplicate articles (111), 688 records remained. A further 586 articles were excluded by title and abstract screening, leaving 102 records. The full texts of these papers were reviewed, and 49 articles met the inclusion criteria. An additional two studies were found through manual searching, as well as forwards and backwards searching by reviewing the reference lists of included studies through the Scopus database. Ultimately, 51 articles were included in this scoping review. The results of our systematic search are presented in a PRISMA flow chart in figure 1.

Study characteristics

We identified six trials describing HBOT as a treatment for PNI in human subjects, comprizing two prospective cohort studies and four randomized controlled trials (table 1).[24–29] These trials represent a variety of countries and patient demographics and, collectively, describe the use of HBOT in 148 adults. Only two reported the sex distribution of enrolled participants, with a male:female ratio of 2:1 in one[25] and 1:12 in the other.[27] An additional five case reports describe a total of two female and three male patients, aged 24–50, treated with HBOT for PNI (table 2).[20 21 30–32] The remaining 40 studies, which are illustrated in table 3, describe experiments performed in a rat model,[33–70] with the exception of two which used a rabbit model.[71 72] Collectively, they chronicle more than 800 animal models of HBOT for the treatment of PNI.

Nerve types

Four human trials describe PNI of the ulnar and median nerves,[24] sural and peroneal nerves,[25] pudendal nerve,[27] and brachial plexus,[28] while the remaining human studies describe patients with variable or widespread nerve injuries such as complex regional pain syndrome or distributed peripheral neuropathies (table 1 and table 2).[20 21 26 29–32] Among animal studies (table 3) the most common nerve of interest (in 28/40 studies) is the sciatic nerve,[33 37 41–44 46–56 58 60–64 66–68 70 72] while others examine the L5 spinal nerve,[38 45 57] peroneal nerve,[65 69] or cavernous nerve.[59] Several additional animal studies describe distributed peripheral neuropathies.[34–36 40 71]

Table 1 A descriptive overview of human trials included in the review, including patient populations and peripheral nerve injury details

Study	Country	Study design	Sample size	Average age (years)	Sex distribution	Nerve type	Mechanism of injury	Category
Ince, 2022[24]	Turkey	Randomized controlled trial	38 cases, 36 controls	35	NR	Ulnar and median	Traumatic nerve injury	Mechanical
Elshinnawy, 2021[25]	Egypt	Randomized controlled trial	21 cases, 21 controls	54	28 males, 14 females	Sural and peroneal	Diabetic peripheral neuropathy	Ischemic
Kiralp, 2004[26]	Turkey	Randomized controlled trial	37 cases, 34 controls	29	NR	Various	Complex regional pain syndrome	Ischemic
Cundall, 2003[27]	UK	Prospective cohort	13 cases	52	1 male, 12 females	Pudendal nerve	Chronic pudendal neuropathy	Ischemic/ compression
Pritchard, 2001[28]	UK	Randomized controlled trial	17 cases, 17 controls	NR	NR	Brachial plexus	Radiation-induced brachial plexopathy	Ischemic
Jordan, 1998[29]	USA	Prospective cohort	22 cases	NR	NR	NR	Drug-induced peripheral neuropathy	Chemical

NR, not reported.

Table 2 A descriptive overview of (human) case reports included in the review, including patient descriptions and peripheral nerve injury details

Study	Country	Age (years)	Sex	Nerve distribution	Mechanism of injury	Category
Song, 2020[30]	China	24	Female	Distributed	Guillain-Barre Syndrome	Autoimmune
Binkley, 2020[20]	Canada	50	Female	Distributed	Complex regional pain syndrome	Mechanical
Katznelson, 2016[21]	Canada	41	Male	Left leg	Complex regional pain syndrome	Mechanical
Rahmani, 2013[31]	Morocco	42	Male	Brachial plexus	Carbon monoxide poisoning-induced peripheral neuropathy	Chemical
Williams, 2009[32]	UK	48	Male	Ankle	Complex regional pain syndrome	Mechanical

Etiology

The six human trials describe different mechanisms of PNI, including trauma,[24] diabetic neuropathy,[25] complex regional pain syndrome,[26] idiopathic chronic pudendal neuropathy,[27] radiation-induced,[28] and drug-induced,[29] as summarized in table 1. The five case reports describe HBOT in the treatment of complex regional pain syndrome,[20 21 32] Guillain-Barre syndrome (autoimmune),[30] and carbon monoxide-induced peripheral neuropathy (table 2).[31] Collectively, these report the use of HBOT for mechanical (4), ischemic (3), chemical (2), autoimmune (1), and ischemic/compressive (1) nerve injuries.

Among animal studies (table 3), the mechanisms of iatrogenic PNI include chronic neural constriction injury,[11 37 41–44 47 49–51 53 55] crush injury,[9 52 54 58 59 63 66 67 69 72] nerve transection[6 33 46 48 56 60 70] chemotherapy-induced neuropathy with paclitaxel,[3 34 36 40] or cisplatin,[1 35] nerve ligation,[3 38 45 61] diabetic neuropathy,[1 62] neurotoxic injury with clioquinol,[1 71] vascular embolization,[1 68] burn injury,[1 39] or a combination of these mechanisms.[57 64 65] Most of these reports described either mechanical (12) or ischemic/compressive (10) nerve injuries, or a combination of these (10), while the remainder described chemical (5) or ischemic (2) injuries.

HBOT regimens

Among human clinical trials, three described HBOT initiated during the acute period of nerve regeneration (range of <72 hours to 3 months)[24 26 29] and three as a delayed treatment (range of 2–11 years) (table 4).[25 27 28] All trials used a treatment pressure between 2.0 and 2.5 ATA, although there was wide variation in treatment duration ranging from five daily 120 min treatments[24] to 10–30 treatments of 60–120 min each over the course of several weeks or months.[25–29] Giving each trial equal weight, the average number of treatments was 19 and the average length of each treatment was 79 min. Case reports describe three patients treated in the acute period,[30–32] and two receiving HBOT as a delayed therapy (table 5).[20 21] Collectively, they describe treatment regimens of 10–73 serial treatments of 30–90 min each (average of 29 treatments of 68 min each), at 2.0–2.4 ATA,[21 30 32] although treatment pressure and total duration was not specified in one report.[31] All human studies which reported a fraction of inspired oxygen used 100%.[21 25–30 32]

HBOT regimens used in animal studies were highly heterogeneous, and are reviewed in table 6. A majority of these (39) described HBOT in the acute treatment of nerve injury, while just one described its use later than 3 months after injury.[71] Many studies describe brief hyperbaric exposures of 1–5 daily, 60 min sessions with 90%–100% oxygen applied at 2.0–3.5 ATA.[36 37 39–47 50 53] Another common protocol was 7 daily, 60–120 min treatments at 2.0–2.5 ATA.[34 35 38 49 51 54 55 58 68] Some studies applied much greater cumulative hyperoxic exposure, using protocols of 20–40 treatments, between once and twice daily, at 2.0–3.5 ATA.[48 52 56 60 65 69 71 72] The average number of treatments among animal studies was 10.8, with an average duration of 71 min each. The total duration of HBOT treatment among animal studies ranged from a single day[36 40 53] to 150 days.[33]

Follow-up

In human studies, the latest follow-up ranged from 2 weeks[25] to 12 months[24 28] from the final HBOT session (tables 4 and 5). Follow-up duration among animal studies ranged from 5 days[57 61] to 1 year,[71] with an average follow-up of approximately 6 weeks after treatment (table 6).

Outcomes

Five of the six human trials reported benefit from the use of HBOT,[24–27 29] and one did not.[28] Measures of nerve function, described in table 4, included electroneuromyography, motor and sensory latencies/amplitudes and thresholds, and pain. Similarly, four of five case reports detailed in table 5 ascribed benefit to HBOT,[20 21 30 31] and one did not,[32] using a variety of subjective, functional, and objective measures to measure recovery.

Mechanical and thermal thresholds were the most frequently applied measure of nerve function among animal studies, but some studies also used functional indices such as the Sciatic Function Index, nerve stimulation and conduction tests, pinch tests, gait analyses, and a variety of behavior scores. A majority of animal studies (36/40; 90%) reported a clinical benefit attributable to HBOT.[33–61 63 64 67 68 70–72] Of the remaining four studies, one described short-term benefits of HBOT (ie, faster recovery) but clinical equipoise at later time points.[65] Three studies reported no benefit of HBOT in the treatment of nerve injury.[62 66 69]

Complications

Only two of the included human studies reported complications of HBOT. One study describes reversible myopia in one patient, and severe sinus pain in another[27]; the other study describes claustrophobia experienced in the HBOT treatment chamber.[20] None of the animal studies attributed any complications to HBOT.

DISCUSSION

Our scoping review of the literature demonstrated that, among 51 animal and human studies, the vast majority (45; 88%) attribute a primary outcome benefit to HBOT in the treatment of PNI. Disaggregated by study type, HBOT was reported as beneficial in 5/6 (83%) human trials, 4/5 (80%) human case reports, and 35/40 (90%) animal studies. Collectively, the available literature describes beneficial effects of HBOT protocols ranging from 1 to 73 individual treatments of 30–120 min at pressures of 1.5–3.5 ATA. These studies report a positive effect of HBOT for PNI caused by various mechanisms including transection, crush injury, constriction/ligation, and chemotherapy-induced or radiation-induced neuropathies. No included studies reported

Table 3 A descriptive overview of non-human/animal studies included in the review, including experimental samples and peripheral nerve injury details

Study	Country	Sample size	Nerve type	Mechanism of injury	Category
Chou, 2021[34]	Taiwan	12 cases, 12 controls	Not applicable	Chemotherapy-induced peripheral neuropathy with paclitaxel	Chemical
Toledo, 2021[33]	Brazil	24 cases, 21 controls	Sciatic nerve	Traumatic (transection)	Mechanical
Brewer, 2020[36]	USA	28–36 cases, 91–99 controls	Not applicable	Chemotherapy-induced peripheral neuropathy with paclitaxel	Chemical
Khademi, 2020[35]	Iran	10 cases, 30 controls	Not applicable	Chemotherapy-induced peripheral neuropathy with cisplatin	Chemical
Kun, 2019[37]	China	36 cases, 72 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Liu, 2019[38]	China	5 cases, 10 controls	Left L5 spinal nerve	Traumatic (ligation)	Mechanical
Wu, 2019[39]	Taiwan	12 cases, 18 controls	Unspecified (right hind paw burn)	Traumatic (burn)	Mechanical
Zhang, 2019[40]	USA	35 cases, 35 controls	Not applicable	Chemotherapy-induced peripheral neuropathy with paclitaxel	Chemical
Ding, 2018[41]	China	6 cases, 12 controls	Sciatic nerve	Chronic neural constriction injury	Ischemic /compression
Ding, 2018[42]	China	48 cases, 96 controls	Sciatic nerve	Chronic neural constriction injury	Ischemic /compression
Ding, 2017[43]	China	36 cases, 6 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Han, 2017[44]	China	20 cases, 60 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Liu, 2017[45]	China	Not reported	Left L5 spinal nerve	Ligation	Mechanical
Shams, 2017[46]	Iran	28 cases, 32 controls	Sciatic nerve	Transection	Mechanical
Zhao, 2017[47]	China	12 cases, 24 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Ince, 2016[48]	Turkey	30 cases, 10 controls	Sciatic nerve	Transection	Mechanical
Hu, 2015[49]	USA	16 cases, 32 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Zhao, 2015[50]	China	24 cases, 16 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Zhao, 2014[51]	China	12 cases, 12 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Gibbons, 2013[52]	USA	16–18 cases, 16–18 controls	Sciatic nerve	Crush injury	Mechanical
Han, 2013[53]	China	16 cases, 24 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Gu, 2012[54]	China	40 cases, 40 controls	Sciatic nerve	Crush injury	Mechanical, Ischemic /compression
Li, 2011[55]	USA	18 cases, 24 controls	Sciatic nerve	Chronic neural construction injury	Ischemic /compression
Oroglu, 2011[56]	Turkey	8 cases, 8 controls	Sciatic nerve	Transection	Mechanical
Thompson, 2010[57]	USA	22 cases, 20 controls	L5 spinal nerve (ligation) and sciatic nerve (chronic constriction injury)	Ligation and chronic neural constriction injury	Mechanical, ischemic /compression
Pan, 2009[58]	Taiwan	63 cases, 60 controls	Sciatic nerve	Crush injury	Mechanical, ischemic /compression
Müller, 2008[59]	USA	5 cases, 15 controls	Cavernous nerve	Crush injury	Mechanical, ischemic /compression
Eguiluz-Ordoñez, 2006[60]	Mexico	20 cases, 20 controls	Sciatic nerve	Transection	Mechanical
Mychaskiw, 2005[61]	USA	8 cases, 16 controls	Sciatic nerve	Ligation	Mechanical
Aydin, 2004[62]	Turkey	10 cases, 30 controls	Sciatic nerve	Diabetic neuropathy	Ischemic
Bajrović, 2002[63]	Slovenia	7 cases, 14 controls	Sciatic nerve	Crush injury	Mechanical, ischemic /compression
Haapaniemi, 2002[64]	Sweden	24 cases, 72 controls	Sciatic nerve	Transection and crush injury	Mechanical, ischemic /compression
Santos, 2000[65]	USA	24 cases, 24 controls	Peroneal nerve	Transection and crush injury	Mechanical, ischemic /compression
Tuma, 1999[66]	Brazil	5 cases, 8 controls	Sciatic nerve	Crush injury	Mechanical, ischemic /compression
Haapaniemi, 1998[67]	Sweden	43 cases, 32 controls	Sciatic nerve	Crush injury	Mechanical, ischemic /compression
Bradshaw, 1996[72]	USA	25 cases, 5 controls	Sciatic nerve	Crush injury	Mechanical
Kihara, 1995[68]	USA	18 cases, 18 controls	Sciatic nerve	Other: embolization of nerve-supplying arteries	Ischemic
Santos, 1995[69]	USA	17 cases, 51 controls	Peroneal nerve	Crush injury	Mechanical, ischemic /compression
Zamboni, 1995[70]	USA	16 cases, 20 controls	Sciatic nerve	Transection	Mechanical

Continued

Table 3 Continued

Study	Country	Sample size	Nerve type	Mechanism of injury	Category
Mukoyama, 1975[71]	UK	7 cases, 15 controls	Not applicable (although the study included biopsies of the posterior tibial nerve)	Other: neurotoxic peripheral nerve damage via clioquinol (a neurotoxin)	Chemical

All studies describe rodent models of nerve injury with the exception of two (Mukoyama *et al* and Bradshaw *et al)*, which used a rabbit model.

that HBOT resulted in worse outcomes after PNI, there were no major complications reported after treatment, and only three minor complications of HBOT were described.

Notably, the only human trial included herein which did not ascribe benefit to HBOT initiated treatment 11 years, on average, after initial nerve insult (radiation-induced brachial plexopathy),[28] which is a very late time point for any intervention. The remaining five studies (four animal model experiments and one case report) which did not favor HBOT described treatment initiated during the acute injury period,[32 62 65 69] and only one described HBOT during a 'hyperacute period' within 6 hours of PNI.[66] One possible explanation for the observed lack of effect in these studies is small sample sizes: the human trial in this subgroup describes 17 patients undergoing HBOT,[28] and the animal studies' experimental groups range in size from 5 to 24 animals.[62 65 66 69] These samples were smaller than the cohort averages of 25 (13 – 38) for human studies and 21 (5–63) for animal studies and, in some cases, a larger sample size may have demonstrated statistical significance. For example, one study evaluating a model of hypoxic PNI found that 24 HBOT-treated animals had a 12% improvement in nerve function after five daily treatments, but no statistically significant long-term benefit or histopathological changes at later time points (despite a noted increase in myelinated axonal areas and myelin

Table 4 Overview of hyperbaric oxygen therapy protocols applied among human trials included in the review, including outcomes of nerve injury treatment

Study	Elapsed time from injury to hyperbaric oxygen therapy	Hyperbaric oxygen therapy protocol	Complications	Follow-up duration	Outcomes	Benefit (yes/no)
Ince, 2022[24]	Acute (within 96 hours)	5×120 min sessions at 2.0 ATA, over 5 days	Not reported	12 months (select cases followed 36 months)	Primary: Electromyography (conduction velocity)	Yes
					Secondary: Nerve-related muscle strength	Yes
					Secondary: Two-point discrimination (fingertip)	Yes
					Secondary: Two-point discrimination (thenar, hypothenar surfaces)	No
Elshinnawy, 2021[25]	Delayed (average 7.92 years)	10×60 min sessions at 100% O2 and 2.5 ATA, over 2 weeks	None	Two weeks	Primary: Motor and sensory latencies	Yes
					Secondary: Michigan Neuropathy Questionnaire	Yes
Kiralp, 2004[26]	Acute (approximately 1.5 months)	15×90 min sessions at 100% O2 and 2.4 ATA over 3 weeks	Not reported	45 days	Primary: Pain	Yes
					Secondary: wrist range of motion	Yes
					Secondary: wrist edema (circumference)	Yes
Cundall, 2003[27]	Delayed (2 years or more)	30×90 min sessions at 100% O2 and 2.4 ATA, over 6 weeks	Reversible myopia in one patient, severe sinus pain in another	6 months	Primary: Pudendal nerve terminal motor latency	Yes
					Secondary: Fecal incontinence quality of life scale	No (after 1 month)
					Secondary: Anal sphincter resting and squeeze pressures	No
Pritchard, 2001[28]	Delayed (11 years after insult)	30×100 min sessions, each with two 5 min air breaks, at 100% O2 and 2.4 ATA, over 6 weeks	Not reported	12–24 months	Primary: Warm and cold sensory threshold	No
					Secondary: Arm lymphoedema	Yes
Jordan, 1998[29]	Acute (0 to 3 months)	24×120 min sessions at 100% O2 and 2.0 ATA, over 3 months	Not reported	6 months	Primary: Frequency of neuropathy	Yes
					Secondary: Karnofsky functional impairment score	Yes
					Secondary: Patient subjective assessment scores	Yes

ATA, atmosphere absolute.

Table 5 Overview of hyperbaric oxygen therapy protocols applied among (human) case reports included in the review, including outcomes of nerve injury treatment

Study	Elapsed time from injury to hyperbaric oxygen therapy	Hyperbaric oxygen therapy protocol	Complications	Follow-up intervals	Outcomes	Benefit (yes/no)
Song, 2020[30]	Acute (approximately 2.5 months)	30×40 min sessions at 100% O2 and 220 kPa (2.17 ATA), over 34 days	None	1 month	Primary: Functional recovery	Yes
					Secondary: Muscle strength	Yes
Binkley, 2020[20]	Delayed (more than 3 months)	73×90 min sessions, each with a 5 min air break, at 2.4 and 2.0 ATA, over 1 year	Claustrophobia	Approximately 5 months	Primary: Complex regional pain syndrome pain	Yes
					Secondary: Skin integrity	Yes
					Secondary: Quality of life	Yes
Katznelson, 2016[21]	Delayed (more than 3 months)	15×90 min sessions at 100% O2 and 2.4 ATA over 3 weeks	None	NR	Primary: Complex regional pain syndrome pain	Yes
					Secondary: skin swelling/color	Yes
					Secondary: Resolution of Tinel's sign	Yes
					Secondary: Ankle range of motion	Yes
					Secondary: Depression and anxiety scores	Yes
Rahmani, 2013[31]	Acute (approximately 23 days)	10×30 min sessions	None	NR	Primary: Electromyography	Yes
Williams, 2009[32]	Acute (3.5 weeks)	19×90 min sessions, each with a 5 min air break, at 100% O2 and 2.2 ATA, over 4 weeks	None	Approximately 5 months	Primary: wound healing; prevention of complex regional pain syndrome	No

ATA, atmosphere absolute.

thickness).[65] Another possible explanation relates to mechanisms of injury, as this subgroup contains several reports of PNI caused by crush injury or diabetic neuropathy. Three studies showed no effect of HBOT initiated immediately after crush injury of the sciatic nerve[66 69] or peroneal nerve[65] in rats, although the authors suggested that the mechanism of crush injury may differ from other models of nerve transection as functional impairment may normalize within several weeks of nerve crush without any therapeutic intervention. This was observed in control group animals, and likely accounts for the lack of HBOT benefit in crush injury models of PNI.[66] In contrast, spontaneous regeneration is less likely in models of nerve transection, which may explain why a therapeutic benefit of HBOT is more evident in studies of this mechanism.[33 46]

It must also be noted that HBOT has the potential to increase oxidative stress if applied at the wrong time point or in a suboptimal dose, and this may contribute to the lack of benefit seen in six of the included studies. The optimal time to initiate HBOT for PNI is currently unknown; however, it has been suggested that the therapeutic window for benefit may be within the first 6 hours after acute injury.[13] During this time, HBOT may improve ischemia, swelling, and microcirculation in the injured nerves to promote the salvation of jeopardized tissue. We speculate that the therapeutic window for HBOT in PNI may be bimodal, with potential for enhanced tissue regeneration in this early stage as well as later, in the chronic stage of healing. Between these phases, a subacute window (the exact bounds of which have yet to be defined) may present enhanced vulnerability of injured tissues to reactive oxygen species, and the benefits of HBOT during this stage may be offset by increased oxidative stress to provide little if any benefit or even potentially exacerbate tissue damage. This mechanism can help explain the lack of HBOT benefit in models of early-stage diabetic neuropathy, such as that reported by Aydin *et al*,[62] who similarly suggested that HBOT might cause further oxidative damage. We hypothesize that, in this trial, HBOT was applied too late to benefit acute injury and too early to stimulate neurogenesis and angiogenesis in injured nervous tissue at a later regenerative stage. However, several included studies also reported positive results with HBOT initiated at similar time points,[24 33 34 38 40 44 45 47 51 55 58] and more research is needed to support this hypothesis. The optimal dose for HBOT in the treatment of acute PNI is similarly unknown, but Holbach *et al* have demonstrated an impairment of ATP production with higher treatment pressures (2.0 ATA) compared with lower ones (1.5 ATA).[73] This may explain why less favorable results are seen in some human and animal studies which apply HBOT at pressures exceeding 2.0 ATA.[28 32 62 65 66 69] Very high concentrations of oxygen, at higher treatment pressures, may generate an excess of reactive oxygen species that injured tissues' antioxidant capacities cannot overcome.

Our findings are consistent with one prior review article on this subject, which highlights the neuroprotective role of HBOT,[18] but which is limited by a narrower view of the literature, including only a subset of the extant animal-model studies—and no human studies—of PNI. One strength of the present review is its comprehensive overview of the extant literature relating to HBOT in the treatment of PNI. None of the included human studies evaluated HBOT in the treatment of perioperative PNI specifically, but many of the studied PNI mechanisms can be expected to overlap with the pathophysiology of neurological injury in the surgical patient. Furthermore, the overwhelming support for HBOT in PNI treatment among included studies supports the proposition that ischemia may be a common link between many or all distinct mechanisms of PNI. Currently, there are insufficient data to support any specific clinical protocol of HBOT timing, duration, or treatment pressure that should be prescribed in the setting of acute or delayed PNI. However, HBOT is a non-invasive intervention with an appealing safety profile and few contraindications or side effects,[74] which should be carefully considered as a therapeutic option in PNI when other interventions have failed or are otherwise unavailable. Potential cost represents an important barrier to the routine application of HBOT in practice, and the setup costs associated with hyperbaric chambers should be considered.

Table 6 Overview of hyperbaric oxygen therapy protocols applied among non-human/animal studies included in the review, including outcomes of nerve injury treatment

Study	Elapsed time from injury to hyperbaric oxygen therapy	Hyperbaric oxygen therapy protocol	Follow-up duration	Outcomes	Benefit (yes/no)
Chou, 2021[34]	Acute (0–1 days)	7×60 min sessions at 2.5 ATA, over 7 days	2 weeks	Primary: Mechanical and thermal thresholds	Yes
Toledo, 2021[33]	Acute (1 day)	10×105 min sessions, over 150 days	150 days	Primary: Functional testing	Yes
				Secondary: Histological and morphometric analysis	Yes
Brewer, 2020[36]	Acute (7 to 10 days)	1 or 4×60 min sessions at 100% O2 and 3.5 ATA, over 1 or 4 days	45 days	Primary: Mechanical and thermal thresholds	Yes
Khademi, 2020[35]	Acute (preceding injury and continuing for 4 weeks)	7×60 min sessions at 100% O2 and 2.0 ATA, over 7 days	4 weeks	Primary: Von Frey nociception assay (mechanical thresholds)	Yes
				Secondary: Histopathology	Yes
Kun, 2019[37]	Acute (6 hours)	5×60 min sessions at 90% O2 and 0.25 mPa (2.47 ATA), over 7 days	7 days	Primary: Mechanical and thermal thresholds	Yes
				Secondary: Microscopy	Yes
Liu, 2019[38]	Acute (24 hours)	7×60 min sessions at 2.0 ATA, over 7 days	7 days	Primary: Mechanical and thermal thresholds	Yes
				Secondary: Microscopy	Yes
Wu, 2019[39]	Acute (3–4 weeks)	5 or 10×60 min sessions at 100% O2 and 2.5 ATA, over 7 or 14 days	13 weeks	Primary: Mechanical and thermal thresholds	Yes
Zhang, 2019[40]	Acute (1 day)	1 or 4×60 min sessions at 100% O2 and 3.5 ATA, over 1 or 4 days	24 days	Primary: Mechanical and thermal thresholds	Yes
Ding, 2018[41]	Acute (within 4 hours)	5×60 min sessions at 2.5 ATA, over 5 days	15 days	Primary: Mechanical and thermal thresholds	Yes
Ding, 2018[42]	Acute (6 days)	5×60 min sessions at 2.5 ATA, over 5 days	15 days	Primary: Mechanical and thermal thresholds	Yes
Ding, 2017[43]	Acute (0–14 days)	5×60 min sessions at >90% O2 and 2.5 ATA, over 5 days	15 days	Primary: Mechanical and thermal thresholds	Yes
Han, 2017[44]	Acute (1 day)	5×60 min sessions at >90% O2 and 0.25 mPa (2.47 ATA), over 5 days	7 days	Primary: Mechanical and thermal thresholds	Yes
				Secondary: Histopathology	Yes
Liu, 2017[45]	Acute (24 hours)	5×60 min sessions at 2.0 ATA, over 5 days	7 days	Primary: Mechanical thresholds	Yes
				Secondary: Histopathology	Yes
Shams, 2017[46]	Acute (1 day before or immediately after)	5×60 min sessions at 100% O2 and 2.0 ATA, over 5 days	4 weeks	Primary: Biochemical	Yes
				Secondary: Histopathology	Yes
				Secondary: Tunel staining	Yes
Zhao, 2017[47]	Acute (1 day)	5×60 min sessions at 100% O2 and 2.0 ATA, over 5 days	7 days	Primary: Mechanical and thermal thresholds	Yes
				Secondary: Histopathology	Yes
Ince, 2016[48]	Acute (1 hour, 1 week, or 2 weeks)	21×90 min sessions at 100% O2 and 2.4 ATA, over 21 days	16 weeks	Primary: Sciatic function index	Yes
				Secondary: Nerve histology	Yes
Hu, 2015[49]	Acute (6 hours)	7×60 min sessions at 100% O2 and 2.4 ATA, over 7 days	7 days	Primary: Mechanical thresholds	Yes
				Secondary: immunohistochemistry	Yes
Zhao, 2015[50]	Acute (1, 6, or 11 days)	5×60 min sessions at 100% O2 and 2.0 ATA, over 5 days	21 days	Primary: Mechanical and thermal thresholds	Yes
				Secondary: Histopathology	Yes
Zhao, 2014[51]	Acute (1 day)	7×60 min sessions at 100% O2 and 2.0 or 2.5 ATA, over 7 days	7 days	Primary: Mechanical and thermal thresholds	Yes
				Secondary: Histopathology	Yes
Gibbons, 2013[52]	Acute (7 days)	29×60 sessions at 3.5 ATA, over 29 days	30 days	Primary: Mechanical thresholds	Yes
				Secondary: Allodynia	Yes
Han, 2013[53]	Acute (12 hours before or after)	1×60 min session at >90% O2 and 0.25 mPa (2.47 ATA)	4 weeks	Primary: Mechanical thresholds	Yes
				Secondary: Histopathology	Yes
Gu, 2012[54]	Acute (30 min)	7×70 min sessions at >98% O2 and 1.5–3.0 ATA, over 7 days	35 days	Primary: Mechanical thresholds	Yes
				Secondary: Histopathology	Yes
Li, 2011[55]	Acute (1 day)	7×60 min sessions at >98% O2 and 2.4 ATA, over 7 days	7 days	Primary: Mechanical thresholds	Yes
				Secondary: Microscopy	Yes

Continued

Table 6 Continued

Study	Elapsed time from injury to hyperbaric oxygen therapy	Hyperbaric oxygen therapy protocol	Follow-up duration	Outcomes	Benefit (yes/no)
Oroglu, 2011[56]	Acute (2 hours)	30×60 min sessions at 100% O2 and 2.5 ATA, over 21 days	22 days	Primary: Sciatic function index	Yes
				Secondary: Nerve histopathology	Yes
				Secondary: Electrophysiology	No
Thompson, 2010[57]	Acute (2 weeks or more)	6×90 min sessions at 100% O2 and 2.4 ATA, over 6 days	5 days	Primary: Mechanical paw withdrawal threshold testing	Yes
Pan, 2009[58]	Acute (12 hours)	7×60 min sessions at 100% O2 and 2.0 ATA, over 7 days	28 days	Primary: Sciatic function index	Yes
				Secondary: Histopathology	Yes
Müller, 2008[59]	Acute (within 24 hours)	10×90 min sessions at 100% O2 and 3.0 ATA, over 10 days	10 days	Primary: Maximal intracavernosal pressure/mean arterial pressure	Yes
				Secondary: Histopathological analysis	Yes
Eguiluz-Ordoñez, 2006[60]	Acute (within 3 hours)	20×90 min sessions at 100% O2 and 2.0 ATA, over 10 days	14 weeks	Primary: Motor latency	Yes
				Secondary: Ankle-foot angles	Yes
				Secondary: Nerve amplitudes	Yes
				Secondary: Nerve axons	Yes
				Secondary: Nerve blood vessels	Yes
Mychaskiw, 2005[61]	Acute (immediately after)	5×120 min sessions at 100% O2 and 3.0 ATA, over 5 days	5 days	Primary: Tissue edema	Yes
				Secondary: Nerve cellular structure	Yes
				Secondary: Skin blood flow	Yes
				Secondary: Muscle and neuronal ultrastructural integrity	Yes
Aydin, 2004[62]	Acute (24 hours)	10×60 min sessions at >95% O2 and 2.5 ATA, over 10 days	12 weeks	Primary: Sciatic function index	No
				Secondary: Mean axon diameter	No
				Secondary: Myelin sheath diameter	No
				Secondary: Axonal count per area	No
Bajrović, 2002[63]	Acute (2 to 8 hours)	6×90 min sessions at 100% or 21% O2 and 2.5 or 0.5 ATA, over 6 days	1 week	Primary: Pinch test	Yes
Haapaniemi, 2002[64]	Acute (within 60 min)	14×90 min sessions at 100% O2 and 2.5 ATA, over 7 days	84 to 90 days	Primary: Walking track analysis	Yes
				Secondary: Axonal outgrowth in nerve grafts	Yes
Santos, 2000[65]	Acute (within 1 month)	21×90 min sessions at 100% O2 and 2.5 ATA, over 14 days	120 days	Primary: Tension transduction testing	No
				Secondary: Gait analysis	No
				Secondary: Histology	No
Tuma, 1999[66]	Acute (1 hour)	6×30 min sessions at 100% O2 and 2.8 ATA, over 3 days	30 days	Primary: Sciatic function index	No
Haapaniemi, 1998[67]	Acute (immediately after)	5–16 × 45 min sessions at 100% O2 and 3.3 ATA, over 5 days	35 days	Primary: Pinch reflex test	Yes
				Secondary: Neurofilament staining	Yes
Bradshaw, 1996[72]	Acute (4 days)	35×90 min sessions at 100% O2 and 2.0, 2.4, or 3.0 ATM, over 7 weeks	7 weeks	Primary: Morphological/histological analysis	Yes
				Secondary: Subjective grading of edema	Yes
Kihara, 1995[68]	Acute (within 30 min)	7×120 min sessions at 2.5 ATA, over 7 days	6 to 7 days	Primary: Behavior score	Yes
				Secondary: Electrophysiology	Yes
				Secondary: Neuropathology	Yes
Santos, 1995[69]	Acute (within 3 months)	21×90 min sessions at 100% O2 and 2.5 ATA, over 14 days	28 days	Primary: Gait analysis	No
				Secondary: Nerve stimulation	No
				Secondary: Muscle force	No
Zamboni, 1995[70]	Acute (within 3 months)	14×105 min sessions at 100% O2 and 2.5 ATA, over 7 days	10 weeks	Primary: Sciatic function index	Yes
Mukoyama, 1975[71]	Delayed (greater than 3 months)	40×60 min sessions at 2.0 ATA, over 40 days	12 months	Primary: Nerve testing	Yes

ATA, atmosphere absolute.

However, hyperbaric treatment facilitates already exist within many large North American centers and across Europe, and while a cost–benefit analysis of HBOT for PNI has not yet been performed, we suggest that the marginal cost of treatment can be readily justified by the potential for material PNI improvement, relative to surgical management which bears a high cost and limited effectiveness for many nerve injuries.

The foremost limitation of the present review is the heterogeneity within and between study populations, study settings, study design, HBOT regimens, and mechanisms of PNI. However, it is reasonable

to assume that while the settings and specific mechanisms of injury may differ, nerve ischemia is a common essential feature of PNI regardless of mechanism and setting. Importantly, since the majority of studies included herein describe the use of HBOT for rat models of PNI, the findings of these studies may not accurately reflect the oxidative stress conditions in human PNI repair, and do not allow for study of subjective experiences of pain. Similarly, while animal model studies can provide evidence supporting a statistical benefit of HBOT for PNI, they are limited in their ability to establish clinical significance for patients. Additional shortcomings likely include publication bias, as it is possible that reports which ascribe no benefit of HBOT in PNI treatment remain disproportionately unpublished. Lastly, these studies may not have identified adverse effects that occur in longer term follow-up, with many studies ceasing study observation on or shortly after HBOT completion.

The present scoping review suggests that HBOT may confer important therapeutic benefits in the setting of PNI, and also identifies a need for high-quality studies to further characterize its effect as an adjunct treatment for human patients. Because the diagnosis of perioperative PNI is often delayed, the validation of HBOT for hyperacute-phase injury in this setting will need to occur in clinical circumstances wherein PNI can be immediately recognized (eg, witnessed nerve transection or change in intraoperative neuromonitoring signal). Other perioperative PNI which we propose as worthwhile targets for future study with HBOT are those sustained, recognized, and/or attributable to peripheral nerve blockade, as well as single-nerve injuries resulting from retraction or intraoperative positioning. Randomized controlled trials of HBOT are often not pragmatic because long courses of hyperbaric treatment require specially trained personnel and infrastructure which is not available in all centers, and because the inclusion of a high-fidelity negative control group would require randomizing some patients to spend impractical lengths of time in a sealed chamber containing regular air. Well-designed randomized controlled trials of patients with PNI are similarly difficult to conduct for a variety of clinical and technical reasons, but these studies are needed to establish the role of HBOT for PNI, which has few other efficacious therapies.

The available evidence suggests treatment protocols characterized by 1.5–2.0 ATA and administered during either the hyperacute (<6 hours from injury) or delayed phase of PNI treatment may be a useful starting point in the design of future clinical trials. Situating this evidence within current clinical treatment pathways for PNI like the ASRA practice guideline for neurological complication,[7] HBOT might be considered as an adjunct therapy offered in parallel to traditional management in the hyperacute phase of PNI, rather than simply as a treatment of last resort when others such as physical therapy or surgery have failed to provide adequate improvement. For the purposes of discussion, presented with a case of PNI sustained in an operative setting which was either (1) recognized within this hyperacute period, or (2) identified outside of this brief window but not fully resolved after 3 months despite traditional conservative and/or surgical management, we would consider offering a trial of 20 daily, 90 min sessions of HBOT at 1.8–2.0 ATA at our home institution. Important future direction for this work include: (1) prospective studies comparing several unique HBOT regimens and/or time points of treatment to identify the optimal application of HBOT for PNI; (2) high-quality studies applying HBOT at very late time points (eg, years) following PNI to determine when, if ever, it is too late to derive benefit; (3) cost–benefit analyses to determine the cost-effectiveness of HBOT for PNI relative to other management strategies; (4) the collection of data specific to HBOT in the treatment of PNI experienced in the course of perioperative care; and (5) the description of long-term outcomes of patients undergoing treatment of perioperative PNI with HBOT, in order to distinguish accelerated recovery from overall improvement in functional outcomes, as well as allow for the identification of potential complications of treatment.

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