Effects of hyperbaric oxygen therapy initiation latency on auditory outcomes following acute acoustic trauma

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Abstract
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Introduction: Hyperbaric oxygen (HBO) is a potential adjunct treatment to improve hearing following acute acoustic trauma. However, the optimal time frame for HBO initiation has not been elucidated.

Methods: Patients exposed to intense noise as part of active military service that met our audiometric criteria were referred for combined HBO (253 kPa for 80 min, treatment numbers titrated to response) and corticosteroid treatment. The primary outcome was defined as an improvement of at least 10 dB in any of the measured high pure tone frequencies (3, 4, 6 or 8 kHz). Additional outcomes included the absolute change in high pure tone (3, 4, 6 and 8 kHz) summation (HPTS), relative change in HPTS compared to baseline (rHPTS) and the proportion of patients returned to auditory combat readiness.

Results: Of 129 ears (103 patients) included in the final analysis, 59/67 (88%) of the patients treated within seven days but only 14/25 (56%) of patients treated 21 days or more from exposure met the primary outcome (Bonferroni adjusted $P = 0.002$). Similarly, HPTS improvement (55 dB vs -5dB), rHPTS improvement (55% vs 3%) and return to combat readiness (32/56 (57%) vs 3/20 (15%)) were significantly ($P < 0.001$, $P < 0.001$ and $P = 0.017$, respectively) more pronounced in patients treated earlier. These results were unchanged despite adjusting to age, degree of initial hearing loss and the mechanism of injury.

Conclusions: Early initiation of HBO following acute acoustic trauma is associated with improved response to therapy. The optimal treatment latency appears to be within seven days from injury, with response rates dropping when treatment is delayed beyond three weeks.

Introduction

Acute acoustic trauma (AAT) is the leading cause of newly diagnosed preventable hearing disability in young adults.[1] Beyond direct mechanical damage to the cochlear hair bundles, the acoustic overstimulation at the heart of this condition leads to massive neurotransmitters and cytokine release.[2] The resultant inflammation and decreased cochlear blood flow cause inner ear hypoxia, furthering the damage through free radicals and proinflammatory cytokines, in a vicious cycle propagating the sensory neuronal damage. This damage often manifests clinically as any combination of sensorineural hearing loss, tinnitus, hyperacusis or auricular fullness.[3,4]

Consequently, several studies have examined the efficacy of hyperbaric oxygen (HBO) therapy for AAT, as an adjunct to well-established standard of care of oral, intravenous or intratympanic glucocorticoids.[5–7] The timing of HBO therapy initiation after AAT seems to be of utmost importance, as demonstrated in studies comparing early (up to two days) versus late treatment.[8,9] Limited data from animal models showed HBO treatment to be most efficacious when initiated 1–7 days post exposure.[3] However, there is a paucity of evidence regarding the optimal initiation time for HBO treatment for AAT in humans.

One study described patients treated within one week from exposure, in whom improvement was significant and seemed to be more pronounced with earlier initiation within this timeframe.[8,10] Another reported a significant improvement in hearing thresholds when HBO was initiated within five days from exposure in a small sample of 22 ears.[11] A third found that initiation of treatment (steroids with or without HBO) within seven days from injury was more effective compared to later treatment (74% versus 53% of ears showed significant audiometric improvement). However, in this work only patients failing to improve with pharmacological

treatment received HBO therapy, thus the exact contribution of HBO therapy remains undetermined.[12]

Other works included only patients treated very shortly after (up to 43 hours)[13] or within four days[14] from noise exposure. Most of the aforementioned studies were conducted in the setting of a professional army during peace-time, and were therefore limited in sample size and in patients' age-range. We aimed to elucidate the relationship between HBO therapy initiation latency and hearing improvement in AAT, accounting for other potential factors such as patient age and corticosteroid treatment latency.

Methods

This human study was approved by our institutional ethics committee (approval #2280-2021). A requirement for consent was waived due to the retrospective nature of this study.

POPULATION AND SETTING

Patients who reported themselves as being potentially exposed to intense noise as part of active (conscription or reserve) military service were evaluated by audiometry. Intense noise was very broadly defined to include any subjective exposure, including any explosion or shooting that caused discomfort to the service member regardless of the presence of auditory protection. All such service members were encouraged to undergo a full auditory evaluation by a speech therapist at the earliest operationally feasible time. Since audiometry is only performed at baseline for very few professions as required by law (e.g., pilots and divers), hearing was assumed to be normal at baseline unless contrary evidence was available (as detailed below). Otoscopy was performed in all patients before referral. Audiometry was deferred to at least 48 h post-exposure for practical reasons.[8] If a recent (i.e., performed over the previous 72 h) audiogram was not available, a repeated audiogram was completed upon admission.

Since this process was initiated by the patient and performed outside the theater of operations, the delay to the initial evaluation (and as a consequence, the HBO therapy latency) was highly variable. While prone to selection bias (e.g., patients with very severe injuries were more likely to be evacuated promptly), this variability served as an important inference point in our data.

Those deemed potentially suitable for HBO therapy at initial assessment were prescribed oral prednisone for a total of 14 days (see regimen below), and were concomitantly referred to further evaluation at the Israeli Naval Medical Institute (INMI). We recommended the addition of HBO therapy in the following instances: 1) a sensorineural hearing threshold of ≥ 45 dB in at least one pure tone frequency; 2) a sensorineural hearing threshold of ≥ 40 dB in at least two frequencies; or 3) a sensorineural hearing threshold of ≥ 35 dB in at least three frequencies. As per current policy, audiometry is not performed at baseline for the absolute majority of conscripts. In the rare cases where previous audiograms were available, we only considered the change from the previous examination – i.e., a worsening of at least 45 dB in one, 40 dB in two or 35 dB in three frequencies compared to baseline justified treatment. Patients who had not already been prescribed with oral prednisone received it in line with the aforementioned protocol upon admission. Contraindications to HBO therapy included the inability to equalise middle ear pressure; severe pulmonary pathology that could result in pneumothorax; and lack of patient consent.

Inability to comply with treatment protocol for any reason (e.g., withdrawal of consent, adverse reactions to HBO or prednisone) led to the discontinuation of HBO therapy. Patients unable to complete the full course of recommended treatment sessions were excluded from the final analysis. In view of the mounting evidence of a distinct and dissimilar pathophysiology,[15] patients with sudden sensorineural hearing loss patterns consistent with sudden idiopathic hearing loss – i.e., diffuse sensorineural loss and discordant exposure history, that is no noise exposure whatsoever – were excluded from this analysis despite being treated with HBO.

TREATMENT PROTOCOL

All patients were prescribed a course of oral prednisone (60 $mg \cdot d^{-1}$ for seven days, followed by 40 $mg \cdot d^{-1}$ for three days, 20 $mg \cdot d^{-1}$ for two days and 10 $mg \cdot d^{-1}$ for two days). This glucocorticoid treatment regimen was started prior or concomitantly with HBO administration and continued for 14 days (including tapering down), irrespective of the duration of HBO therapy. Patients were pressurised to 253 kPa (2.5 atmospheres absolute), followed by four intervals of pure oxygen breathing for 20 minutes each, separated by 5 minutes of air breathing. Repeat audiometry was performed every five treatments. Treatments were continued until a return to baseline (assumed to be normal, i.e., thresholds below 20 dB in all pure tone frequencies) or no meaningful (≥ 10 dB) change in any frequency on two consecutive audiograms was observed. The air breaks were included to address the risk of central-nervous-system oxygen toxicity, shown to be higher in patients treated with corticosteroids.[12]

OUTCOME MEASURES

All audiograms were performed by a certified speech therapist in a calibrated audiometer (AC40 Interacoustics, Denmark). The primary outcome of minimal response to therapy was defined as an increase of at least 10 dB in any of the high pure tone frequencies measured (3, 4, 6 or 8 kHz).[11] Secondary outcomes included the absolute change in the high pure tone summation (HPTS), i.e., the sum of change in the pure tone thresholds of 3, 4, 6 and 8 kHz; the relative change in high pure tone summation ratio (rHPTS),

defined as the ratio of HPTS/[sum of 3, 4, 6 and 8 kHz on the initial audiometry][8] and the proportion of soldiers returned to auditory combat readiness (defined as maximal bone conduction thresholds of 25 dB on 3–4 kHz or 60 dB in 6–8 kHz).

STATISTICAL ANALYSIS

Standard descriptive statistics were used to summarise population characteristics. We used a Chi-square test for categorical variables, Mann-Whitney U test for nonparametric variables and student's unpaired *t*-test for normally distributed continuous variables. Fisher's least significant difference correction was applied when applicable to adjust for multiple comparisons. Categorical variables were described using proportions and percentages, non-parametric variables with median and interquartile range (IQR) and normally distributed continuous variables as mean with standard deviation (SD).

Multivariate logistic regression modeling was performed using Pearl and Reed's method, with a generalised linear model (GLM) implemented for the uni and multivariate analysis of normally distributed outcome measures. The Shapiro-Wilk method was used to test for the normality of distribution of residuals. We used the Pearson correlation coefficient to determine possible correlations between independent variables; only variables not co-related ($r \leq 0.7$) to other predictors and which significantly predicted the outcome measure ($P > 0.1$) on univariate analysis were included in the model. A two-sided $P < 0.05$ was considered statistically significant for all tests. All statistical analysis was performed using R software version 4.2.1.

Results

Of 138 patients referred for our evaluation, 111 met the criteria for HBO therapy in combination with steroids. Twenty-seven were not included due to difficulty equalising middle ear pressures (n = 5) or refusal of treatment (n = 22), and eight were excluded due to inability to follow the treatment protocol. A total of 129 ears (103 patients) were included in the final analysis. Of these, 64 (62.1%) were reservists and 39 were either conscripts or professional servicemen. None had any previously documented or self-reported prior AAT or any other auditory problem. HBO therapy began within seven days after noise exposure in 67 ears (52%), 8–14 days post exposure in 24 ears (19%), 15–21 days after in 13 ears (10%) and more than three weeks after exposure in 25 ears (19%). A Consolidated Standards of Reporting Trials (CONSORT) diagram summarising the data mining and filtering process is presented in Figure 1, with the study groups' baseline characteristics and symptoms upon presentation outlined in Table 1. Signs upon presentation, including otoscopy and audiometry, are summarised in Table 2 and presented in Figure 2.

Figure 1

Study phases presented according to CONSORT guidelines; [1]see text of HBO treatment criteria [2]see text for definition of sudden sensorineural hearing loss (SSNHL); HBO – hyperbaric oxygen, INMI – Israel Naval Medical Institute

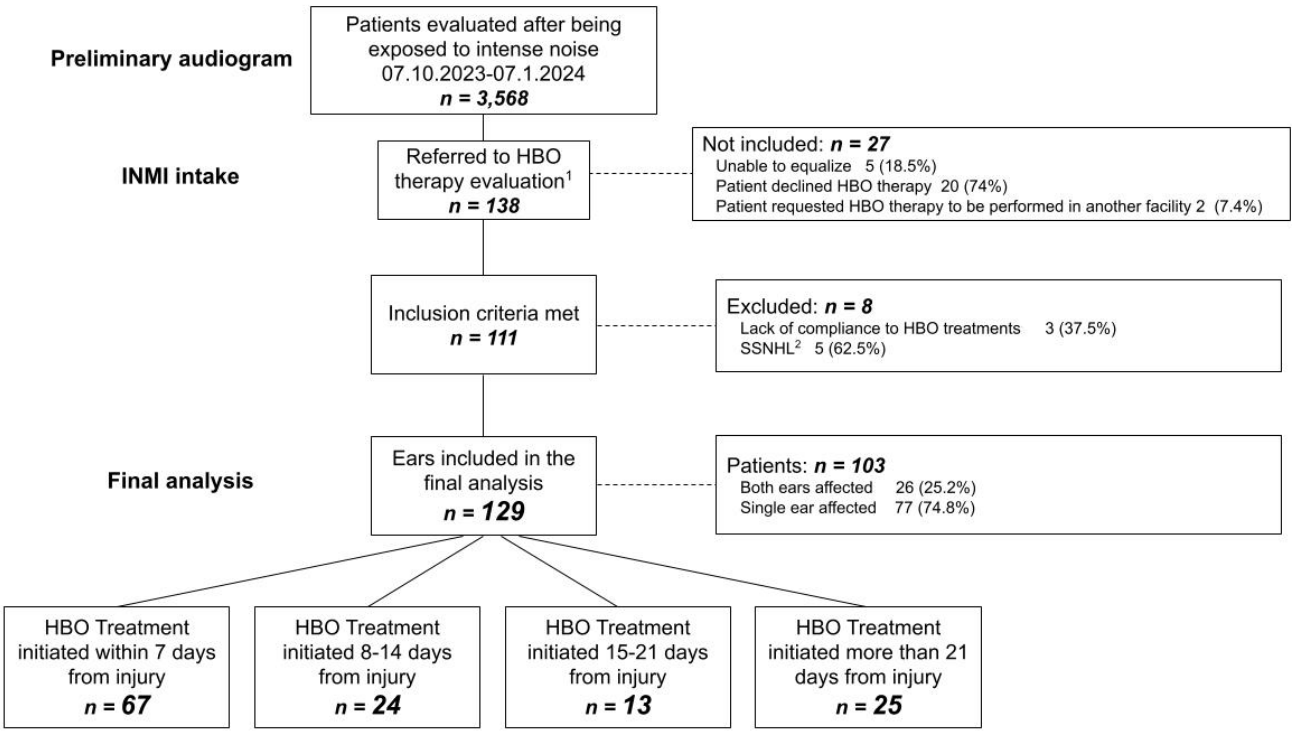


Table 1

Baseline characteristics and symptoms upon presentation for subjects stratified according to latency from noise exposure to hyperbaric oxygen (HBO) treatment; IQR – interquartile range

Characteristic	Overall *n* = 129	≤ 7 days *n* = 67	8–14 days *n* = 24	15–21 days *n* = 13	> 3 weeks *n* = 25
Age, Median (IQR)	23 (20–30)	22 (20–29)	29 (21–32)	24 (21–30)	23 (22–36)
Left ear, *n* (%)	72 (56)	37 (55)	13 (54)	8 (62)	14 (56)
Days from exposure to steroid initiation, Median (IQR)	5 (3–12)	3 (2–4)	10 (6–12)	15 (8–18)	23 (12–28)
Days from exposure to HBO therapy initiation, Median (IQR)	7 (4–17)	4 (3–6)	12 (10–14)	17 (17–19)	25 (23–28)
Tinnitus at admission, *n* (%)	112 (87)	59 (88)	22 (92)	12 (92)	19 (76)
Subjective feeling of auricular fullness on initial evaluation, *n* (%)	58 (45)	35 (52)	8 (33)	7 (54)	8 (32)
Subjective perception of impaired hearing at admission, *n* (%)	83 (64)	44 (66)	14 (58)	6 (46)	19 (76)
Auricular pain on initial evaluation, *n* (%)	14 (11)	7 (10)	5 (21)	2 (15)	0 (0)
Hyperacusis at admission, *n* (%)	21 (16)	11 (16)	4 (17)	3 (23)	3 (12)
Dizziness or vertigo on initial evaluation, *n* (%)	10 (7.8)	9 (13)	1 (4.2)	0 (0)	0 (0)

Table 2

Signs and findings upon presentation

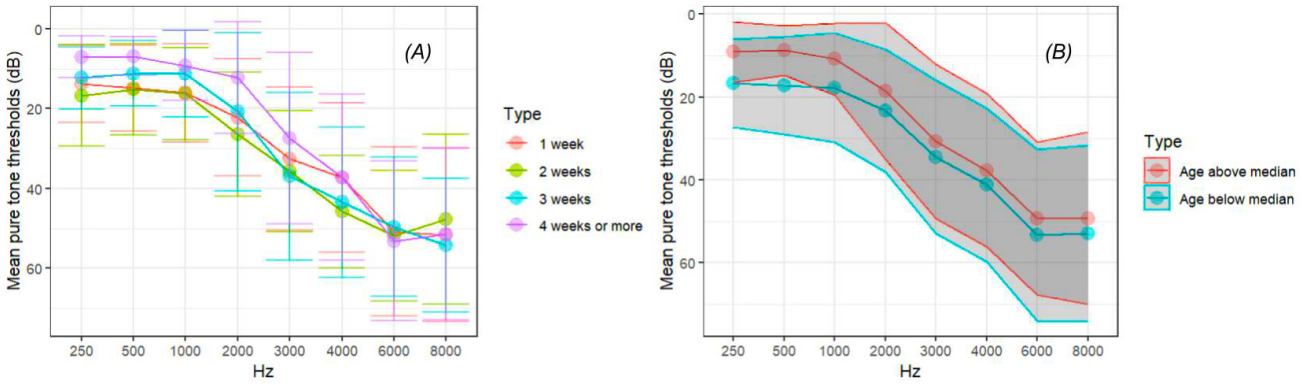
The baseline signs upon initial presentation, including otoscopy, audiometry, and occupational fitness (determined solely based on objective findings) are summarised in the table below. All numbers except combat readiness describe ears, not patients. Combat readiness is calculated as a percentage of patients in each group. HTPA – high pure tone average; IQR – interquartile range

Characteristic	Overall *n* = 129	≤ 7 days *n* = 67	8–14 days *n* = 24	15–21 days *n* = 13	> 3 weeks *n* = 25
Findings on initial otoscopic evaluation, *n* (%)					
Bullous myringitis	1 (0.8)	0 (0)	0 (0)	1 (7.7)	0 (0)
Clouded	3 (2.3)	2 (3.0)	1 (4.2)	0 (0)	0 (0)
Haemotympanum	2 (1.6)	2 (3.0)	0 (0)	0 (0)	0 (0)
Mild redness	3 (2.3)	3 (4.5)	0 (0)	0 (0)	0 (0)
Myringosclerosis	5 (3.9)	1 (1.5)	0 (0)	1 (7.7)	3 (12)
Normal	109 (84)	55 (82)	21 (88)	11 (85)	22 (88)
Perforations	3 (2.3)	1 (1.5)	2 (8.3)	0 (0)	0 (0)
Small perforation	2 (1.6)	2 (3.0)	0 (0)	0 (0)	0 (0)
Serous otitis media	1 (0.8)	1 (1.5)	0 (0)	0 (0)	0 (0)
Fit for combat on initial evaluation, *n* (%)	20 (16)	11 (16)	1 (4.2)	3 (23)	5 (20)
HTPA on initial evaluation, Median (IQR)	45 (35–57)	43 (35–57)	46 (40–55)	48 (42–53)	45 (35–57)

Looking at the primary outcome, 59 of 67 patients (88%) treated within seven days met the criterion for minimal response of 10 dB improvement in at least one of 3–8 KHZ frequencies. Only 56% of patients who began treatment more than 21 days after exposure met this criterion (Table 3).

The absolute change in high pure tone summation (HPTS) was significantly greater in patients treated within seven days from exposure in comparison to later treatment (55 dB vs. 5, 15 and -5 dB, $P = 0.01$, 0.024 and < 0.001 compared to treatment initiation latency of 8–14 days, 15–21 days and more than three weeks after exposure, respectively). Similar

Figure 2
Pure tone threshold averages before treatment
Average pure tone thresholds (with the 95% confidence interval marked by error bars) are presented in (A) by the time passed from injury to initial HBO and in (B) by age group (younger half of the cohort versus older half)



trends were noted when looking at the relative change from audiometry upon presentation, with a significantly greater improvement of 55% in the rHPTS when HBO therapy was initiated within seven days from injury (compared with 10% for week two and three and only 3% when over three weeks have passed; $P = 0.011$, 0.033 and < 0.001 respectively).

Regarding combat readiness, 109 of 129 ears were deemed unfit for combat upon admission. Of those, 57% of ears treated within seven days restored combat readiness after treatment. This percentage decreased with prolonged treatment latency. This difference was significant when comparing treatment within seven days from injury (57%) to treatment after 14–21 days (10%) and more than 21 days (15%) from injury (Bonferroni adjusted $P = 0.012$ and 0.017, respectively).

Examining the whole study population, the average improvement following HBO treatment for each of the high pure tone frequencies (3,000–8,000 Hz) was not statistically significant (at $\alpha = 0.05$, Figure 3A). However, on a week-by-week analysis, as can be seen in Figure 3, there was a noticeable difference between groups regarding the improvement in each of the high pure tone frequencies. Patients treated within seven days of exposure improved more than patients treated later (Figure 3 B, C, D). Patients receiving HBO therapy within seven days of exposure were younger (mean age 24.7 vs 27.8, mean difference -3.1 years, 95% CI -0.4 to -5.8). Patients treated more than three weeks after noise exposure did not significantly improve in any of the high tone frequencies (Figure 4).

On univariate analysis, only age, time from injury to glucocorticoid initiation (steroid latency), and time from injury to HBO therapy initiation (HBO latency) were found to significantly predict either the primary or any of the secondary outcomes.

Adjusting for age, in a logistic regression model each additional day of steroid initiation delay significantly decreased the likelihood of the primary outcome of minimal response to therapy (RR -0.01, 95% CI -0.02 to 0.00) or the restoration of combat readiness (RR -0.01, 95% CI -0.02 to 0.00). In other words, each day of steroids delay decreased the likelihood of these outcomes by about 2% and 1%, respectively. Similarly, a linear regression model showed steroid latency to be inversely associated with the improvement in HPTS (RR -2.2, 95% CI -3.3 to -1.2) and rHPTS (RR -2%, 95% CI -3% to -1%).

Likewise, the age-adjusted relative risk predicted by a logistic regression model of any additional day from injury to HBO therapy initiation was -0.01 (95% CI -0.02 to -0.01) for minimal response and -0.01 (95% CI -0.02 to -0.01) for the restoration of combat readiness. Implementing a linear regression model the age-adjusted relative risk was -2.0 (95% CI -3.0 to -1.0) for HPTS, and -2% (95% CI -3% to -1%) for rHPTS. However, a mixed model accounting for both HBO latency and steroid latency (in addition to age), showed only HBO therapy latency to be a significant predictor of minimal response (RR -0.02, 95% CI -0.03 to 0.00), or of restoration of combat readiness (RR -0.02, 95% CI -0.04 to 0.00), or of rHPTS (linear regression predicted RR -1%, 95% CI -3% to -0.2%). These models are presented in Table 4.

Recorded adverse effects and treatment complications were minimal. Middle ear barotrauma was recorded in nine patients (one ear each), with minimal clinical significance (Teed's grade 1). In these cases, HBO therapy was paused for 1–3 treatments, with return to treatment and completion of a full HBO course once a repeat otoscopy showed improvement. There were no cases of central oxygen toxicity in our cohort. No other adverse effects of pressure changes or the administration of high partial pressure of oxygen were recorded.

Table 3

Primary and secondary outcomes; post hoc between-group comparisons is Bonferroni corrected for multiple comparisons. No comparisons between weeks 2, 3 and 4 or over showed any significant differences. [1]Fisher's exact test; Kruskal-Wallis rank sum test. [2] Bonferroni adjusted pairwise comparison; HPTS – high pure tone sum; IQR – interquartile range; rHPTS – relative high pure tone sum

Characteristic	Overall *n* = 129	≤ 7 days *n* = 67	8–14 days *n* = 24	15–21 days *n* = 13	> 3 weeks *n* = 25	*P*-value[1]	1 vs 2 weeks[2]	1 vs 3 weeks[2]	1 vs 4 weeks[2]
Minimal response, *n* (%)	102 (79)	59 (88)	18 (75)	11 (85)	14 (56)	**0.010**	0.184	0.662	**0.002**
Delta HPTS, Median (IQR)	25 (-10–70)	55 (23–85)	5 (-11– 3)	15 (0– 0)	-5 (-15–20)	< 0.001	**0.010**	**0.024**	**< 0.001**
rHPTS, Median (IQR)	25% (-3%–70%)	55% (23%–80%)	10% (-5%–46%)	10% (-2%– 8%)	3% (-13%–17%)	< 0.001	**0.011**	**0.033**	**< 0.001**
Cases not fit for combat at admission Combat readiness restored, *n* (%)	109 44 (40)	56 32 (57)	23 8 (35)	10 1 (10)	20 3 (15)	< 0.001	0.086	**0.012**	**0.017**

Discussion

Acute acoustic trauma is a leading cause of a high tone sensorineural hearing loss, damaging the cochlea and causing hearing loss both by mechanical and metabolic pathways. This is by far the largest cohort of acute acoustic trauma receiving HBO therapy thus far reported.[8,12] The small and centralised nature of military healthcare in the IDF ensured all acoustic trauma cases evaluated by any caregiver were referred to our consideration. Selection bias is thus primarily limited only to cases where patients sought absolutely no professional health care whatsoever, a scenario we deem to be diminishingly rare. Although theoretically patients with worse injuries could be biased towards seeking help earlier, in our cohort there was no major difference in the initial audiometry between the different presentation latency groups.

In this study, we sought to evaluate whether a delay in HBO is associated with a poorer response to HBO treatment after acute acoustic trauma. Our data show a clear association between the delay in HBO therapy initiation and a decreased improvement in high pure tone thresholds. This association is maintained across all our pre-specified outcome measures. Most importantly, this association is maintained even when adjusted to glucocorticoid therapy initiation time and patient's age. Our data indicates that HBO therapy initiated within seven days from injury is associated with the most significant improvement, when looking at higher (3–8 kHz) pure tone hearing thresholds, that are most commonly impaired by noise exposure. These findings are consistent with what was previously described by Holy et al.[12] In our study, when accounting for both HBO latency and steroid latency, steroid latency was not found to contribute significantly to hearing improvement. This can be accounted for by the fact that according to the IDF acoustic trauma treatment protocol – both treatments, corticosteroids and HBO, are initiated approximately at the same time. Therefore, we were limited in our ability to isolate the sole impact of steroid initiation time, and it can be assumed that the impact of HBO initiation time represents the efficacy of combined treatment, both HBO and steroids.

Acute acoustic trauma is associated with multifactorial changes, both mechanical and metabolic. Vasospasm of microcirculation and hypoxia of sensory cells occur, to prevent metabolic imbalance. These processes have been shown to be most significant in the first days after injury.[2,16] We propose that HBO therapy acts primarily by reversing these processes and increasing blood oxygen through an increase in the arterial partial pressure of oxygen, which results in better oxygen diffusion to compromised areas.[13,17] Hence, the association between its therapeutic benefits and time elapsed from injury are in line with our mechanistic understanding.

Age appears to be a significant predictor of HBO-associated hearing improvement in AAT. This could be, at least

Figure 3

Average pre- and post-HBO pure tone thresholds (with the 95% confidence interval shaded in gray); (A) for the entire study cohort; (B) in patients where HBO was initiated within seven days from injury; (C) in patients where HBO was delayed beyond seven days from injury; (D) shows mean before vs after HBO differences (with 95% confidence intervals) in pure tone thresholds by groups (within or later than seven days)

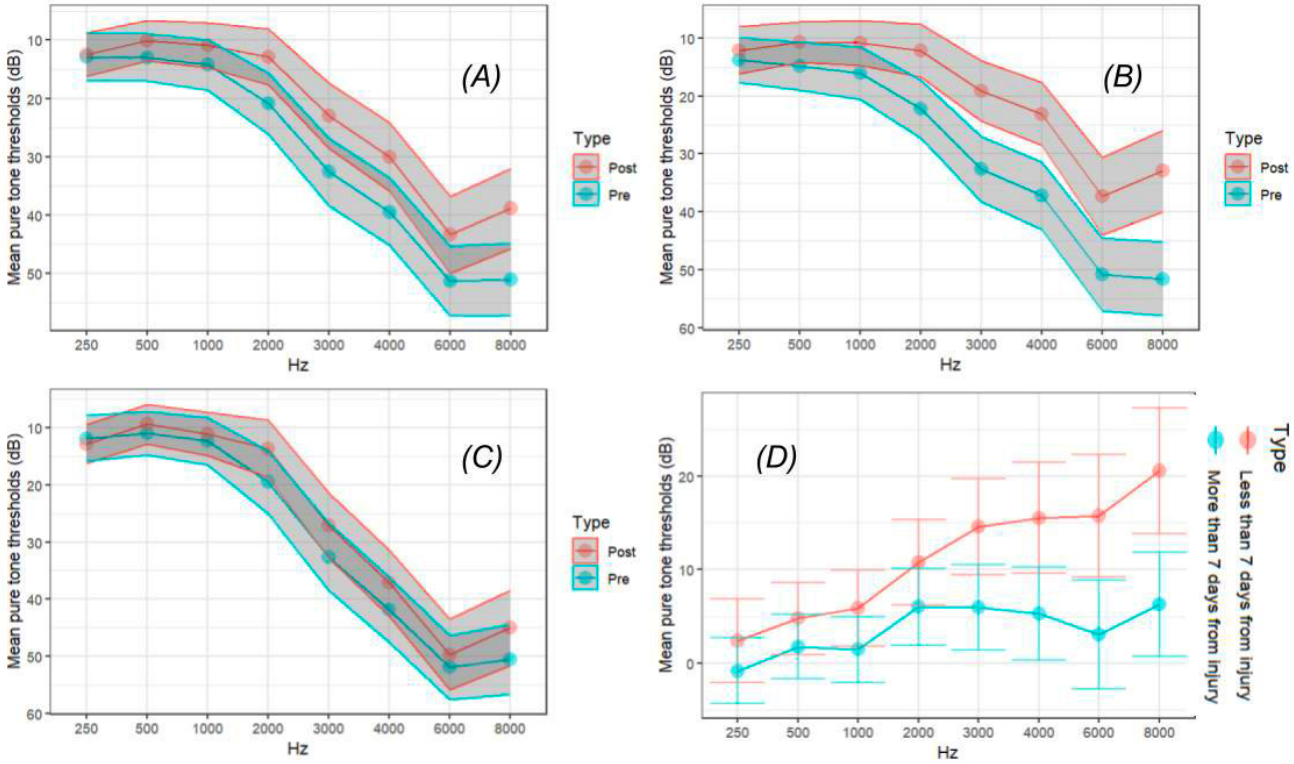
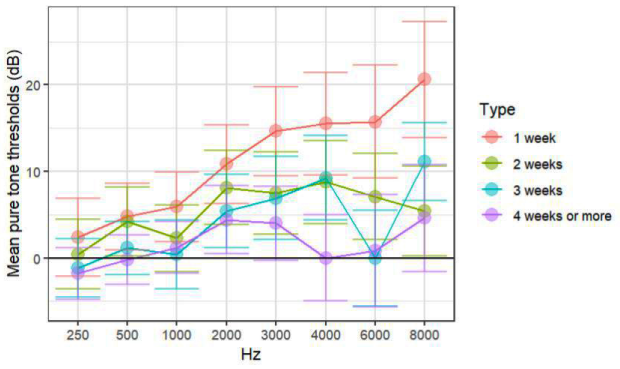


Figure 4

Average pure tone threshold changes (with error bars indicating a 95% confidence interval) by week of HBO initiation



in part, attributed to a higher incidence of underlying (chronic) sensorineural hearing loss in older individuals. The true magnitude of this potentially confounding effect is impossible to ascertain in our study population, since we had no recent baseline (pre-AAT) audiogram in the majority of cases. We acknowledge that this is a significant limitation in our study. Moreover, previous studies support the notion that age might mechanistically influence the degree of improvement under HBO therapy. Chen et al.[18] report a similar pattern of strong association between treatment outcomes and age (as well as treatment delay) in sensorineural hearing loss. This may be attributed to decreased inner ear oxygen supply due to microangiopathic changes that are not uncommon with older age.[18] Similar findings were reported by Wu et al. in a larger, more recent cohort.[19]

Patients referred for evaluation earlier after injury had a higher incidence of complaints of dizziness. However, no vestibular dysfunction was found on vestibular evaluation in any of the patients referred to HBO therapy following AAT. This presentation was not associated with decreased improvement under HBO therapy.

Despite the physiological plausibility of different injury mechanisms when looking at blast versus noise exposure, we deemed patient recollection not significantly reliable to discriminate between the mechanisms.[20] Additionally, most patients referred to our institute reported repeated loud noise exposure, as expected during war. Therefore, we could not discriminate reliably between noise and blast exposure types.

LIMITATIONS

The retrospective nature of this analysis limits our ability to infer causality/treatment efficacy. Since the chance of spontaneous hearing restoration might be decreased

Table 4

Multivariate regression model; multivariate regression models were constructed incorporating age with steroid latency, hyperbaric oxygen treatment (HBOT) latency or both for the primary (minimal response) and each of the secondary outcomes. For binary outcomes (minimal response and combat readiness) the relative risk (RR) describes a change of the probability of reaching this outcome with each year of age or additional day of delaying therapy. For Delta HPTS and rHPTS the RR describes the change in HPTS in dB (Delta HPTS) or percent from initial audiometry (rHPTS) with each additional year of age or day of delaying therapy. CI – confidence interval; Delta HPTS average – difference in the high pure tone sum average; rHPTS – relative high pure tone sum

Characteristic	Minimal response		Combat readiness restored		Delta HPTS		rHPTS	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
HBOT latency and age only								
Age	-0.01 (-0.02 to 0.00)	**0.033**	-0.02 (-0.03 to -0.01)	**< 0.001**	-2.4 (-3.5 to -1.3)	**< 0.001**	-2% (-3% to -1%)	**< 0.001**
Days from injury to HBOT initiation	-0.01 (-0.02 to -0.01)	**< 0.001**	-0.01 (-0.02 to -0.01)	**< 0.001**	-2.0 (-3.0 to -1.0)	**< 0.001**	-2% (-3% to -1%)	**< 0.001**
Steroid latency and age only								
Age	-0.01 (-0.02 to 0.00)	0.064	-0.02 (-0.03 to -0.01)	**< 0.001**	-2.2 (-3.3 to -1.0)	**< 0.001**	-2% (-3% to -1%)	**< 0.001**
Days from injury to steroid initiation	-0.01 (-0.02 to 0.00)	**0.004**	-0.01 (-0.02 to 0.00)	**0.004**	-2.2 (-3.3 to -1.2)	**< 0.001**	-2% (-3% to -1%)	**0.002**
HBO latency, Steroid latency, and age								
Age	-0.01 (-0.02 to 0.00)	**0.026**	-0.02 (-0.03 to -0.01)	**< 0.001**	-2.3 (-3.4 to -1.1)	**< 0.001**	-2% (-3% to -1%)	**< 0.001**
Days from injury to steroid initiation	0.01 (-0.02 to 0.03)	0.51	-0.01 (-0.04 to 0.02)	0.44	-1.3 (-4.3 to 1.6)	0.37	-2% (-3% to 1%)	0.46
Days from injury to HBOT initiation	-0.02 (-0.03 to 0.00)	**0.033**	-0.02 (-0.04 to 0.00)	**0.028**	-1.1 (-3.2 to 0.98)	0.29	-1% (-3% to -0.2%)	**0.015**

with time, patients evaluated later might have inherently less chances of improvement, with or without treatment. However, in view of the mounting evidence of diminished effect when treatment is delayed, a prospective comparison of early versus delayed HBO therapy for acute acoustic trauma of any etiology seems unethical. Moreover, a retrospective approach can still yield important clinical guidance as to the success rates, and resultant justification of the cost and potential side effects of HBO, once patient presentation is delayed.

Conclusions

Early initiation of HBO therapy is associated with improved response to therapy in AAT. The rate of improvement when therapy is delayed beyond three weeks seems to be particularly low, raising the question of overall justification in view of the cost of HBO therapy. Larger cohorts are needed to fully elucidate the temporal limits of HBO therapy latency in AAT.

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