Original articles

Hyperbaric Oxygen for Lower Limb Trauma (HOLLT): an international multi-centre randomised clinical trial

Ian L Millar[1,2], Folke G Lind[3], Karl-Åke Jansson[4], Michal Hájek[5,6], David R Smart[7,8], Tiago D Fernandes[9], Rosemary A McGinnes[2], Owen D Williamson[2], Russell K Miller[10], Catherine A Martin[2], Belinda J Gabbe[11,12], Paul S Myles[13], Peter A Cameron[11], for the HOLLT investigator group

[1] *Department of Intensive Care and Hyperbaric Medicine, Alfred Health, Melbourne, Victoria, Australia*
[2] *Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia*
[3] *Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institutet at Karolinska University Hospital, Stockholm, Sweden*
[4] *Department of Molecular Medicine and Surgery, Karolinska Institutet at Karolinska University Hospital, Stockholm, Sweden*
[5] *Centre of Hyperbaric Medicine, Ostrava City Hospital, Ostrava, Czech Republic*
[6] *Department of Biomedical Sciences, Faculty of Medicine, University of Ostrava, Ostrava-Zabreh, Czech Republic*
[7] *Department of Diving and Hyperbaric Medicine, Royal Hobart Hospital, Hobart, Tasmania, Australia*
[8] *School of Medicine, University of Tasmania, Tasmania, Australia*
[9] *Hyperbaric Medicine Unit, Department of Anesthesia, Hospital Pedro Hispano, Matosinhos, Portugal*
[10] *Department of Orthopaedic Surgery, Alfred Health, Melbourne, Victoria, Australia*
[11] *Prehospital, Emergency and Trauma Research Unit, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia*
[12] *Health Data Research UK, Swansea University, Swansea, United Kingdom*
[13] *Department of Anaesthesiology and Perioperative Medicine, Alfred Health and Monash University, Melbourne, Victoria, Australia*

Corresponding author: *Dr Ian Millar, The Alfred Hyperbaric Service, PO Box 315, Prahran, Victoria 3181, Australia*
i.millar@alfred.org.au

Keywords
Fractures; Hyperbaric oxygen treatment; Injuries; Musculo-skeletal; Orthopaedics; Outcome; Wounds

Abstract
(Millar IL, Lind FG, Jansson K-A, Hájek M, Smart DR, Fernandes TD, McGinnes RA, Williamson OD, Miller RK, Martin CA, Gabbe BJ, Myles PS, Cameron PA. Hyperbaric Oxygen for Lower Limb Trauma (HOLLT): an international multi-centre randomised clinical trial. Diving and Hyperbaric Medicine. 2022 30 September;52(3):164–174. doi: 10.28920/dhm52.3.164-174. PMID: 36100927.)

Introduction: Hyperbaric oxygen treatment (HBOT) is sometimes used in the management of open fractures and severe soft tissue crush injury, aiming to reduce complications and improve outcomes.

Methods: Patients with open tibial fractures were randomly assigned within 48 hours of injury to receive standard trauma care or standard care plus 12 sessions of HBOT. The primary outcome was the incidence of necrosis or infection or both occurring within 14 days of injury.

Results: One-hundred and twenty patients were enrolled. Intention to treat primary outcome occurred in 25/58 HBOT assigned patients and 34/59 controls (43% vs 58%, odds ratio (OR) 0.55, 95% confidence interval (CI) 0.25 to 1.18, $P = 0.12$). Tissue necrosis occurred in 29% of HBOT patients and 53% of controls (OR 0.35, 95% CI 0.16 to 0.78, $P = 0.01$). There were fewer late complications in patients receiving HBOT (6/53 vs 18/52, OR 0.22, 95% CI 0.08 to 0.64, $P = 0.007$) including delayed fracture union (5/53 vs 13/52, OR 0.31, 95% CI 0.10 to 0.95, $P = 0.04$). Quality of life measures at one and two years were superior in HBOT patients. The mean score difference in short form 36 was 2.90, 95% CI 1.03 to 4.77, $P = 0.002$, in the short musculoskeletal function assessment (SMFA) was 2.54, 95% CI 0.62 to 4.46, $P = 0.01$; and in SMFA daily activities was 19.51, 95% CI 0.06 to 21.08, $P = 0.05$.

Conclusions: In severe lower limb trauma, early HBOT reduces tissue necrosis and the likelihood of long-term complications, and improves functional outcomes. Future research should focus on optimal dosage and whether HBOT has benefits for other injury types.

Introduction

Hyperbaric oxygen treatment (HBOT) has long been advocated for acute traumatic injury but is little used in practice.[1–4] Animal models, case series and two small randomised trials suggest potential benefit but the evidence to date has been inadequate to support wider use of this treatment in the setting of severe trauma.[5–11]

Complex open fractures with severe soft tissue injury are associated with complication rates ranging from 10% to 100%.[12,13] Late complications such as deep infection and delayed union often require multiple additional interventions, adding to the burden of hospitalisation and disability that follows orthopaedic injury.[14–16]

Hyperbaric oxygen has therapeutic effects that should be of value in such injuries. These include anti-infective actions that are additive or synergistic with antibiotics, reductions in oedema and ischaemic necrosis, mitigation of reperfusion injury, and the potential to accelerate healing of bone, nerve, tendon, muscle, and skin.[8,17–26]

We conducted an international multicentre clinical trial of early HBOT in patients suffering an open tibial fracture with severe associated soft tissue injury.

Our hypothesis was that adding HBOT to the care of complex open tibial fractures would reduce the rates of acute wound necrosis and/or infection and that this would be associated with improved late outcomes.

Methods

Human research ethics approval was given by The Alfred Health Human Ethics Committee (206/04) and the Monash University Human Research Ethics Committee (CF07/4208). Approval was also obtained from the institutional human research ethics committee at each participating site. The protocol was registered with ClinicalTrials.gov (NCT 00264511) and on the Australian New Zealand Clinical Trials Registry (12607000559415).

STUDY DESIGN

This was an open label, pragmatic randomised trial with blinded outcome arbitration.

The study was conducted according to our previously published protocol[27] at 10 hospitals located in Australia, Sweden, the Czech Republic, Portugal, Chile, Italy, Austria, India and the United States.

There was no involvement of patients or the public in the design processes, conduct, oversight, or analysis of this trial.

INCLUSION AND EXCLUSION CRITERIA

Adult trauma patients with an open tibial fracture were eligible if their injuries were judged by the treating surgeon to be sufficiently severe to carry a high risk of major complications. Gustilo 3 grading was used as a guideline noting that soft tissue injury severity is a qualitative judgement and host factors play a part in risk such that some Gustilo 2 fractures might be considered 'high risk'.[12] Patients were excluded only if other injuries or trauma care requirements precluded HBOT, or if major contraindications to HBOT were identified. The enrolment window was 48 hours from time of injury.

ENROLMENT AND RANDOMISATION

Consent for participation was sought from patients, or for non-competent patients from a third party as allowed by local law and human research ethics committee approvals. Randomisation was via internet access to computer-based assignment of the intervention group and a study identification number, stratified by site and with treatment assignment allocated one to one in randomly selected and non-viewable blocks of six or eight.

INTERVENTIONS

Trauma care and HBOT sessions were provided to participants in accordance with the practices of each site, without any trial-related standardisation.

Hyperbaric oxygen treatment sessions involved pressurisation to 243 kPa or 284 kPa (2.4 or 2.8 atmospheres absolute) with total oxygen breathing durations of 80 to 100 minutes. Both multiplace and monoplace chambers were utilised. The trial protocol called for HBOT-assigned patients to receive 12 treatment sessions over approximately nine days, commencing as soon as possible after enrolment and after the initial fracture and wound management surgery.

DATA COLLECTION AND BLINDING

Baseline health data and demographics, injury characteristics and data on initial surgical management were collected at or soon after enrolment. Early-outcome data were nominally collected at 14 days post injury with a range of 12–15 days considered acceptable. Follow up was conducted at three, six, nine, 12, 18, and 24 months to collect pre-defined longer-term events and outcomes.

Data were entered into a centralised database via a secure internet-based interface which tracked entries and modifications. The database incorporated data validation and user assistance features. Access to each patient's data was restricted to the site investigator or data collector entering their own patient's data, and the project manager. Surgeons

initially operating upon patients were blinded to the trial group allocation. Clinicians and data collectors were not subsequently blinded.

Final fracture grading and all outcome measures involving qualitative scoring were adjudicated independently by two experienced orthopaedic specialists blinded to patient identity, site and trial group allocation. Investigators other than the project manager were unable to access the randomisation allocation and hyperbaric treatment section of the database until after the data set was 'locked' and provided to the study biostatisticians following closure of follow-up data entries.

OUTCOME MEASURES

The outcome measures reported were defined *a priori* and determined from the collected patient data according to procedures and guidance notes that are further detailed in the hyperbaric oxygen in lower limb trauma (HOLLT) protocol[27] and the statistical analysis plan. All derived, scored and arbitrated outcomes were determined with blinding to patient identity, intervention group allocation and the enrolling site. Where the two orthopaedic specialists arbitrating outcomes were not initially in agreement, they conferred to come to a decision. The primary outcome was the occurrence of infection or necrosis or both during the period from initial surgery to the 14-day assessment date. This was determined as follows. Enrolling centres were asked to record their determination of clinical episodes of 'infection' and 'necrosis' according to the study criteria. The definitive determination of primary outcome events was confirmed after blinded review of all available data including surgical debridements, other surgical findings and procedures, antibiotics prescribed, microbiology, wound data and photos where available. The US Centre for Disease Control wound infection guidelines were used in assessing infection events. The trial outcome of necrosis excluded minimal wound edge necrosis and debridements to 'clean up wound edges'. When patients were discharged early, data from the three-month review were also reviewed.

The components of the primary outcome were also assessed separately in accordance with our study hypothesis that HBOT would reduce the rates of acute wound necrosis and/or infection. Other pre-specified early secondary outcomes included identification of those acute complications that were clinically severe according to *a priori* guidelines. Characteristics of clinical care provided were assessed, including whether HBOT commenced within 24 hours or not and whether the number of HBOT sessions achieved met the arbitrarily chosen six that was defined as a 'therapeutic course'. Multivariate analysis was undertaken to assess whether there might be any inter-group difference after adjustment for any risk factor differences between groups based on injury severity.

Late outcome data included measures of wound healing, infections, bone grafts and non-union assessed at three-month intervals up to 12 months after injury. Radiological image files and records of hospital re-admissions and surgical procedures were also recorded. These data were reviewed and arbitrated by the blinded adjudicators as meeting or not meeting criteria for being recorded as a 'problem wound', a 'deep infection', 'osteomyelitis', or 'delayed union' using pre-determined guidelines. 'Problem wounds' were identified by the blinded assessors considering the same guidance factors used to determine 'clinically severe' acute infections and necrosis, as well as any prolonged hospitalisation or re-admission, requirement for additional surgical procedures and whether an open wound was associated with late wound related deep infections and necrosis. 'Osteomyelitis' was recorded if the treating centre had made that diagnosis and this was confirmed by checking for antibiotic use and surgical procedures. Determinations of 'delayed union' were based upon clinician diagnosis of non-union at nine or 12 months or a bone graft having been performed or scheduled for non-union or pseudo-arthrosis.

The reported measure 'incidence of significant late complications' is a composite of the above measures (occurrence of either a problem wound or a deep infection or osteomyelitis or delayed union or any combinations).

Questionnaire-based functional and quality of life assessments were administered at 12 and 24 months using the language specific short form 36 (SF36v2) and the lower limb components of the short musculoskeletal function assessment (SMFA).[28]

SAMPLE SIZE AND STATISTICAL ANALYSIS

An original sample size of 250 participants was selected to provide 80% power to detect a reduction in the incidence of the composite outcome of acute infection and/or necrosis from 30% to 15% at $P = 0.05$. The analysis of outcome data was undertaken in accordance with a pre-decided statistical analysis plan (see supplementary material).

The primary analysis was on an unadjusted intention-to-treat basis. Secondary outcomes analysis included using mixed effects logistic regression to adjust for any potential differences in risk of complications between treatment allocation groups, with injury severity grading as a fixed effect and recruiting centre as a random effect. Centres that recruited fewer than 10 patients were combined as a single 'other centre' to avoid instability in the model estimation procedure. The injury severity factors adjusted for were Gustilo grade, severe contamination and muscle loss.

Time to surgical wound closure and time to definitive fracture fixation were compared using a competing risk survival analysis with amputation as a competing risk.

For the SF36v2, SMFA and pain scores, mixed effects linear regression models, accounting for time since injury, were used.

Stata Statistical Software: Release 13 (StataCorp LP, College Station TX, USA) was used to analyse the data. A two-sided *P*-value < 0.05 was considered statistically significant with no adjustment made to *P*-values for the assessment of multiple secondary outcomes since they were pre-specified.

CHANGES TO TRIAL DESIGN

The trial was originally conceived as enrolling patients within 24 hours of injury. This time window was increased to 48 hours in response to difficulties in achieving early enrolments.

A futility analysis was performed by the data safety and monitoring committee after only 44 patients were enrolled in the first 3.5 years of the study. Without un-blinding, this identified a higher-than-expected incidence of recorded acute complications, leading to the prediction that a revised enrolment target of 120 subjects had reasonable prospects to demonstrate significant study outcomes.

STUDY SITE CHARACTERISTICS

Most sites were academic hospitals associated with Level 1 trauma centres. All hyperbaric centres were physically and organisationally integrated into a hospital.

Results

A total of 120 patients were enrolled over the period 13 February 2007 to 18 August 2014.

PATIENT CHARACTERISTICS

The group allocation ratio was exactly one to one. One patient allocated to the HBOT group had bilateral eligible fractures and these were evaluated as one injury, with the worst outcomes used for analysis.

There were no significant differences between the groups in patient or injury characteristics (Table 1).

SURGICAL MANAGEMENT

The characteristics of initial surgery performed did not differ between groups (Table 2).

There was no difference in time to surgical wound closure (hazard ratio 1.42, 95% confidence interval [CI] 0.84 to 2.39; $P = 0.19$) or time to definitive internal fixation (hazard ratio 1.31, 95% CI 0.83 to 2.07; $P = 0.25$).

For more information on surgical management and timing, see *sections S5, S8, S9 and S12 in the online supplementary material .

LOSSES AND EXCLUSIONS

Two patients in the HBOT group withdrew from the study. One withdrew prior to any treatment and one after an initial HBOT session. Both declined follow-up. One patient in the control group had insufficient data recorded for meaningful analysis. Acute outcomes are therefore reported for 117 (98%) patients. A CONSORT diagram appears on page 41 of the supplementary material.

HYPERBARIC OXYGEN TREATMENT

In total, 619 HBOT sessions were provided to 65 enrolled patients during the conduct of the HOLLT trial. The median time to commencing HBOT was 21.6 h (interquartile range 18.7 to 28.6), with 37 patients (65%) receiving their first session within 24 h of enrolment. There was no significant difference in clinically severe complications for those commencing treatment on the first versus the second post injury day (see supplementary Table S7).

Of 60 patients allocated to HBOT, 51 (85%) received the six or more HBOT sessions that were *a priori* considered a therapeutic course. Seven (12%) were intolerant, with three failing to complete their first pressurisation and four receiving only one treatment. One patient underwent amputation after five sessions for complications of a severe Gustilo 3C fracture and another with a Gustilo 2 fracture refused further treatments after receiving four sessions (see supplementary Table S22).

PRIMARY OUTCOME (INTENTION TO TREAT)

We found no statistically significant difference between groups in the incidence of the composite primary outcome of one or more acute phase complications (infection and/or necrosis), with 25 events (43%) in the HBOT group and 34 events (58%) in the control group (odds ratio [OR] 0.55, 95% CI 0.25 to 1.18; $P = 0.12$).

PRIMARY OUTCOME COMPONENTS

Necrosis was reduced in the HBOT group (29% vs 53%; OR 0.35, 95% CI 0.16 to 0.78; $P = 0.01$).

Footnote: *Supplementary material is available on the DHM Journal website: https://www.dhmjournal.com/images/Appendices/52_3/Millar_HOLLT_Supplementary_material_2022-523_2.pdf

Table 1
Characteristics of patients enrolled and randomised; data are *n* (%) or median (interquartile range); BMI – body mass index; HBOT – hyperbaric oxygen treatment

Parameter	HBOT (*n* = 60)	Control (*n* = 60)
Age (years)	40 (31.0–55.5)	40 (27.0–53.0)
Male	50 (83%)	47 (78%)
BMI kg·m^{-2}	26.5 (23.7–29.4)	25.2 (23.7–29.6)
Current Smoker	18 (30%)	15 (26%)
Diabetes	2 (3%)	2 (3%)
Injury severity score	13.5 (9–18)	10 (9–18)
Fracture location(s)		
Plateau	5 (8%)	6 (10%)
Proximal shaft	13 (22%)	7 (12%)
Mid shaft	21 (35%)	21 (35%)
Distal shaft	30 (50%)	31 (52%)
Pilon / Ankle joint	7 (12%)	9 (15%)
Multi-site	16 (27%)	14 (23%)
Fracture type		
Transverse	16 (27%)	12 (20%)
Spiral	7 (12%)	5 (8%)
Segmental	7 (12%)	5 (8%)
Comminuted	39 (65%)	43 (72%)
Wound characteristics		
Signif. contamination	14 (23%)	7 (11%)
Skin loss	26 (43%)	23 (38%)
Muscle loss	15 (25%)	9 (15%)
Bone loss	13 (22%)	10 (17%)
Arbitrated Gustilo grading		
Grade 1	1 (2%)	2 (3%)
Grade 2	13 (22%)	11 (18%)
Grade 3A	27 (45%)	28 (47%)
Grade 3B	16 (27%)	15 (25%)
Grade 3C	3 (5%)	3 (5%)

There was no statistically significant difference in the acute infection rate (22% vs 32%; unadjusted OR 0.61, 95% CI 0.26 to 1.43; $P = 0.26$).

Fewer patients in the HBOT group experienced the problem of having both infection AND necrosis (9% vs 27%; unadjusted OR 0.23, 95% CI 0.08 to 0.70; $P = 0.01$).

SECONDARY OUTCOMES

The primary outcome measures were analysed with multivariate adjustment for the baseline injury severity factors (Gustilo grade, contamination and hospital) in accordance with the statistical analysis plan. The statistical relationship between HBOT allocation and the incidence of acute infection and/or necrosis strengthened but remained non-significant (adjusted OR 0.43, 95% CI 0.17 to 1.09; $P = 0.08$), and the same occurred with respect to infection (adjusted OR 0.46, 95% CI 0.17 to 1.28; $P = 0.14$). The association between HBOT allocation and reduced necrosis was stronger (adjusted OR 0.28, 95% CI 0.11 to 0.72; $P = 0.008$), as was the association between HBOT allocation and the combination of infection and necrosis (adjusted OR 0.16, 95% CI 0.04 to 0.61; $P = 0.007$).

There were no differences in any of the other planned acute secondary outcomes (Table 3). There were fewer severe infections and severe necrosis events in the HBOT group but this was not statistically significant. Further detail is provided in supplementary material (S11).

At 12 months, nine of 117 (7.7%) patients had been lost to follow-up. The four patients who underwent early amputation were excluded from the following analysis of late limb injury complications.

Over the 14 day to 12 month period, patients receiving HBOT were less likely to suffer a defined late complication (6/52 vs 18/52; 12% vs 35%; OR 0.24, 95% CI 0.08 to 0.68; $P = 0.007$).

Table 2

Characteristics of acute care including initial (blinded) surgery; data are n (%) or median (interquartile range); *multiple methods used in some cases; ICU – intensive care unit; IM – intramedullary; HBOT – hyperbaric oxygen treatment

Parameter	HBOT (*n* = 60)	Control (*n* = 60)
Time from injury to surgery (hours)	5.4 (3.6–8.3)	5.1 (3.2–7.3)
Fasciotomy performed	6 (10%)	5 (8%)
Debridement performed	47 (78%)	43 (72%)
Major skin excision	5 (8%)	3 (5%)
Significant deep debridement	10 (17%)	9 (15%)
Length of stay (days)	15 (10–22)	15 (10–24)
ICU admission	10 (17.5%)	19 (32.2%)
Fracture management*		
Intramedullary nail	18 (30%)	19 (32%)
Internal fixation (other than IM nail)	13 (22%)	14 (23%)
External fixation	38 (63%)	37 (62%)
Splint	7 (12%)	7 (12%)

Table 3

Acute outcomes (up to 14-day assessment); no adjustments made for multiple measures of pre-specified secondary outcomes; *predefined primary outcome measure 'infection AND/OR necrosis'; **fasciotomy performed at surgery subsequent to initial surgery

Outcome components	HBOT (*n* = 58)	Control (*n* = 59)	OR [95% CI] *P*-value
Primary outcomes			
≥ 1 wound complication*	25 (43%)	34 (58%)	0.55 [0.25 to 1.18] 0·12
Necrosis	17 (29%)	31 (53%)	0.35 [0.16 to 0.78] 0·01
Infection	13 (22%)	19 (32%)	0.61 [0.26 to 1.43] 0·26
Infection AND necrosis	5 (9%)	16 (27%)	0.23 [0.08 to 0.70] 0·01
Secondary outcomes			
≥ 1 wound complication – multivariate baseline risk adjusted			0.4 [0.17 to 1.09] 0.08
Necrosis – multivariate baseline risk adjusted			0.28 [0.11 to 0.72] 0.008
Infection – multivariate baseline risk adjusted			0.46 [0.17 to 1.28] 0.14
Clinically severe necrosis	12 (21%)	17 (29%)	0.61 [0.25 to 1.48] 0.28
Clinically severe infection	9 (16%)	14 (24%)	0.58 [0.30 to 1.50] 0.26
Fasciotomy required**	2	3	
Amputation	1	3	
Subsequent surgery – patients	39 (67%)	33 (56%)	
Subsequent surgery – procedures (mean number per patient)	96 (2.5)	114 (3.3)	

Fewer patients receiving HBOT were observed to have an open wound at each of the three-monthly reviews. At six months, only one HBOT patient had an open wound, compared with 10 in the control group. There were no wounds in HBOT patients that were arbitrated as 'problem wounds' by blinded assessors whilst there were seven such problem wounds identified in the control group. The odds of wounds being healed at review over the 12 months were higher for HBOT patients compared to controls (mixed effects logistic regression OR 1.65, 95% CI 1.07 to 2.53; $P = 0.02$).

Delayed union was lower in the HBOT group; 10% vs 25% (OR 0.31, 95% CI 0.10 to 0.95; $P = 0.04$) (Table 4).

HEALTH-RELATED QUALITY OF LIFE OUTCOMES

Complete SF36v2 and SMFA lower limb subscale data were available for 74 (62%) patients at 12 months (35/60 HBOT, 39/60 Control) and for 60 (50%) at 24 months (29/60 HBOT, 31/60 Control). Assessments were not available from patients who declined participation and where enrolling centre resources did not enable administration of the

Table 4

Twelve month arbitrated outcomes (day 14 through to 12 months); no adjustment for multiple measures of pre-specified secondary outcomes; *delayed union AND/OR deep infection AND/OR problem wound; **not able to be analysed in a manner consistent with the *a priori* plan to determine odds ratios due to zero number in HBOT group (Fishers exact test statistic 0.006); ***non-united at nine or 12 months and/or bone graft performed for non-union or pseudarthrosis (early amputation cases not included); HBOT – hyperbaric oxygen treatment; N/A – not applicable; OR – odds ratio

Complication	HBOT	Control	OR [95% CI] *P*-value
≥ one serious complication*	6/52 (12%)	18/52 (35%)	0.24 [0.08 to 0.68] 0.007
Problem wound	0/53	7/52 (13%)	OR analysis N/A**
Deep infection	4/53 (8%)	8/52 (15%)	0.43 [0.12 to 1.56] 0.20
Delayed union***	5/52 (10%)	13/51 (25%)	0.31 [0.10 to 0.95] 0.04
Closed wounds at review			
14 days	37/58 (64%)	34/59 (56%)	
3 months	44/52 (87%)	39/52 (77%)	
6 months	50/51 (98%)	38/48 (79%)	
9 months	48/49 (98%)	38/44 (86%)	
12 months	43/44 (98%)	38/41 (93%)	
Mixed effects logistic regression comparison over 12 months: OR 1.65, 95% CI 1.07 to 2.53; *P* = 0.02			

Table 5

Patient reported quality of life measures at 12 and 24 months; CI – confidence interval; HBOT – hyperbaric oxygen treatment; SF36 – language specific short form 36; SMFA – short musculoskeletal function assessment

Scale	Group	Mean score (SD)		Mean difference, [95% CI] mixed effects regression using time from injury	*P*-value
		12 months	24 months		
SF36 physical function (higher is better)	HBOT	38.5 (9.7)	40.3 (11.2)	+2.90, [1.03 to 4.77]	0.002
	Control	34.2 (12.7)	40.3 (13.3)		
SMFA function index (lower is better)	HBOT	21.8 (13.6)	17.3 (14.1)	-2.54, [-4.46 to -0.62]	0.01
	Control	29.3 (20.1)	22.2 (18.4)		
SMFA daily activities (lower is better)	HBOT	26.8 (20.1)	20.4 (21.9)	-19.51, [-21.08 to 0.06]	0.05
	Control	38.2 (27.4)	26.0 (24.2)		

questionnaires. There was no differential loss to follow up between trial allocation groups at 12 months (X^2_1 = 0.56, *P* = 0.45) or 24 months (X^2_1 = 0.71, *P* = 0.71).

Hyperbaric oxygen patients reported better mean scores of physical functioning, less impairment of daily activities and lower mean pain scores at follow-up. One control group patient opted for elective amputation at 24 months (Table 5 and supplementary Table S20).

CROSS OVERS AND AS PER TREATMENT RECEIVED ANALYSIS

Six patients allocated to the control group received one or more HBOT sessions. Five of the six commenced HBOT late on day two or on day three post injury. All experienced necrosis and three developed infection. None received sufficient HBOT sessions to meet the 'therapeutic course' criteria and all were considered by their primary surgeon to need HBOT in view of incipient or actual complications of severe injury. All of these patients were included when 'as per treatment received' data analysis was undertaken, despite being a group with high likelihood of complications and late or insufficient sessions of HBOT. One patient started HBOT on day eight when assessed as being at high risk of postoperative wound breakdown due to age and diabetes. He did not experience complications and was not included in the 'as per treatment received' analysis due to the late commencement. In this 'as per treatment received' analysis, there were no statistically significant differences identified between treatment allocation groups.

ADVERSE EVENTS

There were no major complications of HBOT although treatment was prematurely discontinued for minor ear

barotrauma in two cases and for coincident nausea, vomiting, pain, agitation or anxiety in a further nine instances (15% of HBOT cases). See supplementary material for further detail.

One serious adverse event was notified: a patient allocated to the HBOT group experienced a free-flap failure due to irreversible venous thrombosis. The relevant hospital's clinical review committee concluded that this complication was unrelated to the study protocol or conduct. The patient did not receive further HBOT sessions following flap failure but underwent a second tissue transfer procedure which was successful.

Discussion

Our group has successfully completed the first multi-centre randomised clinical trial of HBOT in acute musculoskeletal trauma, confirming that it is possible to safely deliver HBOT during the acute care phase. The allocated groups were well matched and our 12-month outcome analysis is based upon a 92% follow up rate of wound healing, infection and orthopaedic procedure data.

The demographic, gender and injury patterns of the HOLLT patients were similar to those reported from advanced economy nations, with motor transport related injury and falls from heights predominant. Our study had many of the characteristics of what are considered 'pragmatic trials', with few exclusion criteria and normal clinical practises followed. Although most enrolling centres did not record the number of potentially eligible patients not approached for enrolment, there were reportedly very few, if any, identified patients who were excluded for reasons of unsuitability for HBOT. We therefore expect our findings should be generalisable to other centres.[29]

It is notable that HBOT patients had lower numbers of complications of every recorded type, in every sub-category. Importantly, the severity of acute phase complications appears reduced in the HBOT group, with a lower incidence of soft tissue necrosis and an associated reduction in the likelihood of wounds developing the concerning problem of co-incident infection and necrosis.

Severe open fractures of the tibia are well known for high rates of long-term complications.[12–15] Our study suggests HBOT can significantly reduce the risk of such complications. Over 12 months post-injury, there was a reduced incidence of complications overall and a reduction in the specific problems of delayed union and persistence of open wounds. Based upon 12- and 24-month health-related quality of life and function measures, HBOT patients had superior functional outcomes. These effects are all biologically plausible and consistent with the effects of hyperbaric oxygen in animal models and previous studies in crush injury and in wounds and soft tissue infections in other settings.

Our results are consistent with our *a priori* hypothesis that adding HBOT to conventional modern care of complex open tibial fractures would reduce acute wound complications and that this would be associated with improved late outcomes. It is likely that our positive results are generalisable to other severe musculoskeletal injuries at other anatomical locations, consistent with claims by others.[8,9,30–33]

Our positive results arise predominantly from the data for patients with Gustilo 3A and 3B fractures. Although all enrolled patients were judged by clinicians to have severity factors indicating a high risk of complications, our study supports the predictive power of Gustilo grading, with low rates of complications following injuries arbitrated as Gustilo 2. All three patients who received HBOT for Gustilo 3C fractures avoided amputation. The case for using HBOT seems stronger in more severe injuries, with local or systemic risk factors probably more relevant considerations in lower severity injuries.

Although we believe the morbidity and complications of HBOT were acceptable in this study setting, it should be noted that it can be challenging to provide HBOT to acute post-injury and post-operative patients.

These findings may have significant implications worldwide, demanding further research and evaluation of the feasibility of delivering HBOT to a higher proportion of acute trauma patients.

LIMITATIONS

Our selection of a composite of acute complication measures as primary outcome was based upon the assumption this would be a more sensitive measure than the more clinically important 12-month complication rate. We were also concerned about the practicality of achieving acceptable follow up over 12 months. When slow enrolment necessitated revising the original enrolment target from 250 to 120 subjects, this likely made the study underpowered for our chosen primary outcome. The two acute soft tissue complications of injury upon which our primary outcome was based have a complex interaction – infection or necrosis can occur in isolation, or infection can develop and lead to necrosis, or necrosis can occur which becomes infected. In hindsight, we would not recommend this composite outcome for future studies.

Although the lack of blinding of patients and their carers risks bias towards HBOT, we believe that this was unavoidable as sham hyperbaric treatments for control patients would have been potentially negative for the quality of their care and thus also a potential bias against the control allocation to 'standard care'. It is hoped that the use of objective measures and blinded arbitrators has minimised any significant bias in the study outcomes.

Conclusions

This multi-centre randomised trial of HBOT for severe open tibial fractures did not detect a statistically significant reduction in its pre-specified primary outcome measure of the overall number of acute complications of infection and/or necrosis, likely because it was underpowered following a reduction in its enrolment target from 250 to 120 due to slow recruitment. Nevertheless, the study hypothesis was validated by the findings that HBOT was associated with a reduction in acute tissue necrosis and infection, and subsequently, a reduction in problems with wound healing and bone union.

The ideal number and timing of HBOT sessions remains unknown, and it is possible that the optimal number may vary with injury severity. The 12 HBOT session target used in this study may be excessive for most cases. Studies to determine optimum dose and timing are indicated. It will be important to evaluate the costs of this moderately expensive and logistically complex treatment against clinical outcomes and health economics over a longer term.

References

1 James PB. Hyperbaric oxygen treatment for crush injury. BMJ. 1994;309(6967):1513. doi: 10.1136/bmj.309.6967.1513b. PMID: 7695727. PMCID: PMC2541636.

2 Myers RA. Hyperbaric oxygen therapy for trauma: crush injury, compartment syndrome, and other acute traumatic peripheral ischemias. Int Anesthesiol Clin. 2000;38(1):139–51. doi: 10.1097/00004311-200001000-00009. PMID: 10723673.

3 Myers RA, Schnitzer BM. Hyperbaric oxygen use. Update 1984. Postgrad Med. 1984;76(5):83–6, 89–91, 94–5. doi: 10.1080/00325481.1984.11698755. PMID: 6483698.

4 Greaves I, Porter K, Smith JE, et al. Consensus statement on the early management of crush injury and prevention of crush syndrome. J R Army Med Corps. 2003;149:255–9. doi: 10.1136/jramc-149-04-02. PMID: 15015795.

5 Ishii Y, Ushida T, Tateishi T, Shimojo H, Miyanaga Y. Effects of different exposures of hyperbaric oxygen on ligament healing in rats. J Orthop Res. 2002;20:353–6. doi: 10.1016/S0736-0266(01)00094-8. PMID: 11918316.

6 Zamboni WA, Brown RE, Roth AC, Mathur A, Stephenson LL. Functional evaluation of peripheral-nerve repair and the effect of hyperbaric oxygen. J Reconstr Microsurg. 1995;11:27–9. doi: 10.1055/s-2007-1006507. PMID: 7714876.

7 Zhao DW. Therapeutic effect of hyperbaric oxygen on recovery of surgically repaired peripheral nerve injury. Zhonghua Wai Ke Za Zhi. 1991;29:118–20, 43. PMID: 1864185. Chinese.

8 Strauss MB. The roles of hyperbaric oxygen in crush injury and other acute traumatic ischemias. In: Whelan HK, Kindwall EP, editors. Hyperbaric medicine practice, 4th ed. North Palm Beach: Best Publishing; 2017.

9 Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P. Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. J Trauma. 1996;41(2):333–39. doi: doi: 10.1097/00005373-199608000-00023. PMID: 8760546.

10 Lindstrom T, Gullichsen E, Lertola K, Niinikoski J. Effects of hyperbaric oxygen therapy on perfusion parameters and transcutaneous oxygen measurements in patients with intramedullary nailed tibial shaft fractures. Undersea Hyperb Med. 1998;25:87–91. PMID: 9670433.

11 Bennett MH SR, Turner R. Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union. Cochrane Database Syst Rev. 2012;12:CD004609. doi: 10.1002/14651858.CD004609.pub3. PMID: 23235612.

12 Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma. 1984;24:742–6. doi: 10.1097/00005373-198408000-00009. PMID: 6471139.

13 Court-Brown CM. The epidemiology of fractures. In: Rockwood CA, Bucholz RW, editors. Rockwood and Green's fractures in adults, 7th ed. Philadephia: Lippincott Williams and Wilkins; 2010. p. 53–8.

14 Lua J, Tan VH, Sivasubramanian H, Kwek E. Complications of open tibial fracture management: risk factors and treatment. Malays Orthop J. 2017;11:18–22. doi: 10.5704/MOJ.1703.006. PMID: 28435569. PMCID: PMC5393109.

15 Joveniaux P, Ohl X, Harisboure A, Berrichi A, Labatut L, Simon P, et al. Distal tibia fractures: management and complications of 101 cases. Int Orthop. 2010;34:583–8. doi: 10.1007/s00264-009-0832-z. PMID: 19554328. PMCID: PMC2903136.

16 Harris AM, Althausen PL, Kellam J, Bosse M, Castillo R, Lower Extremity Assessment Project (LEAP) Study Group. Complications following limb-threatening lower extremity trauma. J Orthop Trauma. 2009;23:1–6. doi: 10.1097/BOT.0b013e31818e43dd. PMID: 19104297.

17 Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. Plast Reconstr Surg. 2011;127(Suppl 1):131S–141S. doi: 10.1097/PRS.0b013e3181fbe2bf. PMID: 21200283. PMCID: PMC3058327.

18 Strauss MB. Why hyperbaric oxygen therapy may be useful in treating crush injuries and skeletal muscle-compartment syndrome. Undersea Hyperb Med. 2012;39:799–800. PMID: 22908835.

19 Cimsit M, Uzun G, Yildiz S. Hyperbaric oxygen therapy as an anti-infective agent. Expert Rev Anti Infect Ther. 2009;7:1015–26. doi: 10.1586/eri.09.76. PMID: 19803709.

20 Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. Emerg Med Clin North Am. 2008;26:571–95, xi. doi: 10.1016/j.emc.2008.01.005. PMID: 18406988.

21 Rocha FS, Gomes Moura CC, Rocha Rodrigues DB, Zanetta-Barbosa D, Nakamura Hiraki KR, Dechichi P. Influence of hyperbaric oxygen on the initial stages of bone healing. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120:581–7. doi: 10.1016/j.oooo.2015.06.039. PMID: 26324750.

22 Grassmann JP, Schneppendahl J, Hakimi AR, Herten M, Betsch M, Lögters TT, et al. Hyperbaric oxygen therapy improves angiogenesis and bone formation in critical sized diaphyseal defects. J Orthop Res. 2015;33:513–20. doi: 10.1002/jor.22805. PMID: 25640997.

23 Costa Maia MC, Camacho OF, Pinto Marques AF, Coelho PMB. Hyperbaric oxygen therapy treatment for the recovery of muscle injury induced in rats. Diving Hyperb Med. 2013;43:222–5. PMID: 24510328.

24 Francis A, Baynosa RC. Hyperbaric oxygen therapy for the compromised graft or flap. Adv Wound Care (New Rochelle). 2017;6:23–32. doi: 10.1089/wound.2016.0707. PMID: 28116225.

25 Lerche CJ, Christophersen LJ, Kolpen M, Nielsen PR, Trøstrup H, Thomsen K, et al. Hyperbaric oxygen therapy augments tobramycin efficacy in experimental Staphylococcus aureus endocarditis. Int J Antimicrob Agents. 2017;50:406–12. doi: 10.1016/j.ijantimicag.2017.04.025. PMID: 28669832.
26 Kolpen M, Mousavi N, Sams T, Bjarnsholt T, Ciofu O, Moser C, et al. Reinforcement of the bactericidal effect of ciprofloxacin on Pseudomonas aeruginosa biofilm by hyperbaric oxygen treatment. Int J Antimicrob Agents. 2016;47:163–7. doi: 10.1016/j.ijantimicag.2015.12.005. PMID: 26774522.
27 Millar IL, McGinnes RA, Williamson O, Lind F, Jansson K-A, Hajek M, et al. Hyperbaric oxygen in lower limb trauma (HOLLT); protocol for a randomised controlled trial. BMJ Open. 2015;5(6):e008381. doi: 10.1136/bmjopen-2015-008381. PMID: 26068515. PMCID: PMC4466757.
28 Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. J Bone Joint Surg Am. 1999;81:1245–60. doi: 10.2106/00004623-199909000-00006. PMID: 10505521.
29 Sox HC, Lewis RJ. Pragmatic trials: practical answers to "real world" questions. JAMA. 2016;316:1205–06. doi: 10.1001/jama.2016.11409. PMID: 27654606.
30 Roje Z, Roje Z, Eterović D, Druzijanić N, Petrićević A, Roje T, et al. Influence of adjuvant hyperbaric oxygen therapy on short-term complications during surgical reconstruction of upper and lower extremity war injuries: retrospective cohort study. Croat Med J. 2008;49:224–32. doi: 10.3325/cmj.2008.2.224. PMID: 18461678. PMCID: PMC2359875.
31 Huang KC, Tsai YH, Hsu RW. Hyperbaric oxygen therapy facilitates surgery on complex open elbow injuries: preliminary results. J Shoulder Elbow Surg. 2007;16:454–60. doi: 10.1016/j.jse.2006.10.011. PMID: 17507249.
32 Yamada N, Toyoda I, Doi T, Kumada K, Kato H, Yoshida S, et al. Hyperbaric oxygenation therapy for crush injuries reduces the risk of complications: research report. Undersea Hyperb Med. 2014;41:283–9. PMID: 25109081.
33 Chiang IH, Tzeng YS, Chang SC. Is hyperbaric oxygen therapy indispensable for saving mutilated hand injuries? Int Wound J. 2017;14:929–36. doi: 10.1111/iwj.12730. PMID: 28251838. PMCID: PMC7950024.

HOLLT investigator group

Alfred Health, Melbourne, Australia – Andrew Fock, Wei Ch'ng, Cate Venturoni, Virginia Cable, Anniki Hill; Karolinska University Hospital, Stockholm, Sweden – Folke Lind, Karl-Åke Jansson, Jorgos Sidiras, Ulrika Tampe; Ostrava City Hospital Ostrava, Czech Republic – Michal Hajek, Aleš Zatloukal, Jan Vrchovecky, Milan Lerch; Faculty Hospital of Ostrava, Ostrava, Czech Republic – Jan Stránský, Roman Madeja; Royal Hobart Hospital, Hobart, Australia – David Smart, Susannah Sherlock, Bebe Brown; Hospital Pedro Hispano, Matosinhos, Portugal – Tiago Fernandes, Óscar Camacho; Hospital del Trabajador, Santiago, Chile – Tania Capote, Luis Acuña; Policlinico Umberto 1, Rome, Italy – Monica Rocco; Univ. Klinik f. Unfallchirurgie, Graz, Austria – Herwig Hofer, Beatrice Ratzenhofer-Komenda; Indraprastha Apollo Hospital, New Delhi, India –Tarun Sahni; John Muir Trauma Center, Walnut Creek, California, USA – Peter Benson

Acknowledgements

The participation of each collaborating centre was only made possible through individual clinical leadership and the willingness of many staff at each site to contribute to an international clinical research effort.

Cate Venturoni was Research Nurse for the original Pilot Study conducted at The Alfred Hospital, and with Owen Williamson was central to establishing many practical aspects of this study and to the detailed design of the data collection instruments.

Armin Kemmer and the hyperbaric team at BG Unfallklinik Murnau, Germany, shared their extensive practical experience and enthusiasm for the use of HBOT in acute trauma care, and strongly supported us in designing and establishing this study.

An International Steering Group helped establish this study, advising on key design features and seeking potential collaborators: Folke Lind (Stockholm, Sweden), Lin Weaver (Salt Lake City, USA), Daniel Mathieu (Lille, France), Michael Bennett (Sydney, Australia), Armin Kemmer (Murnau, Germany) and Thomas Kossmann (Melbourne, Australia).

Andrew Forbes, Chris Reid and Michael Bennett formed the Data Safety and Monitoring Committee. Rory Wolfe provided valuable oversight and advice regarding statistical methods.

Bebe Brown facilitated recruitment, site data input, and follow-up of all subjects enrolled at Royal Hobart Hospital

Conflicts of interest and funding

The study received funding from Australia's National Health and Medical Council (NHMRC Project Grant 49096) and from the Victorian Trauma Foundation (Project Grant NV12), providing for project management, the operation of the data centre plus some partial support for data collection. The involvement of the Hobart site was made possible by a grant from the Tasmanian Motor Accident Insurance Board Injury Prevention Foundation.

Belinda Gabbe was supported by an Australian Research Council Future Fellowship and Paul Myles held an NHMRC Practitioner Fellowship.

All other study related costs and all clinical care and hyperbaric oxygen therapy costs were provided from within the budgets of each participating institution.

The funding sources had no role in the study design, conduct, analysis, writing or submission for publication. There were no commercial entities or interests involved in the trial. There are no identified conflicts of interest for any of the authors regarding the conduct and reporting of this study.

Data access

The Principal Investigator, Ian Millar, and the Project Manager, Rosemary McGinnes, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The Principal Investigator only gained access to the site raw data entries and group allocation after data entry

closed and data were extracted from the Web Entry Data System for transmission to the study statisticians for analysis. Most statistical analyses were performed by Catherine Martin, with patient reported outcome data analysed by Belinda Gabbe.

Transparency statement

As Principal Investigator, first author and guarantor, Ian Millar affirms that the manuscript is honest, accurate and a transparent account of the study being reported, with no important aspects omitted and discrepancies from original plans reported and explained within the manuscript.

Data sharing

A file of de-identified patient data can be made available to researchers upon reasonable request, subject to a research plan being communicated to the HOLLT investigators with assurance of the identity and credentials of the requesting researcher(s). This file includes de-identified data extracted from the HOLLT study Web Entry Data System and the results of arbitrated outcomes for each of the 120 study participants.

Monash University holds an archive of all study information, raw data and image files. This is de-identified healthcare data which is re-identifiable via the international collaborators and cannot be released due to privacy requirements and trial agreements between Monash University and the study collaborators. It was, however, envisaged that future researchers might wish to conduct further analyses based upon these data, by entering into a confidentiality agreement with the HOLLT investigators and obtaining Human Research Ethics approval from The Alfred and Monash Ethics Committee and the HOLLT collaborator group.

Submitted: 25 March 2022
Accepted after revision: 26 July 2022
