Retinal vessel diameter changes after 6 months of treatment in the Idiopathic Intracranial Hypertension Treatment Trial

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ABSTRACT

Background/Aims Prior studies support an association between increased retinal venule diameter and elevated intracranial pressure (ICP). The purpose of this study was to test the hypothesis that retinal venule diameters decrease in association with long-term therapy for high ICP in subjects with idiopathic intracranial hypertension (IIH).

Methods This is a retrospective analysis of multicentre randomised controlled trial data. Standardised procedures were used to measure area of optic nerve head elevation (ONHA) and diameters of 4 arterioles and 4 venules 2.7 mm from the optic disc centre on fundus photos collected at baseline and after 6 months of randomised treatment with placebo+diet or acetazolamide+diet in subjects participating in the IIH Treatment Trial (IIHTT) (n=115). Change in arteriole (Da) and venule (Dv) diameters from baseline to 6 months was studied as a function of IIH, haemodynamic and demographic variables.

Results Dv decreased following 6 months of therapy (8.1 µm, 5.9%, p<0.0005) but Da did not change. Dv change was associated with ONHA change (p<0.0005, r=0.47) and this association persisted in multiple variable models.

Conclusions Retinal venule diameter decreased, and arteriole diameter did not change in association with treatment for elevated ICP with a weight loss intervention and placebo or acetazolamide in IIHTT participants. Further study is needed to determine how retinal vessel measurements can be combined with other clinical observations to inform disease management.

INTRODUCTION

High intracranial pressure (ICP) can be idiopathic (IIH) or due to secondary causes such as brain tumours, venous sinus thrombosis or meningitis. It typically causes optic nerve head swelling (papilledema), leading to vision loss in approximately half of those affected and permanent blindness in up to 10%.[1 2] Treatment is aimed at lowering ICP using medical and surgical approaches. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT, clinicaltrials.gov identifier NCT01003639) was a randomised controlled trial comparing 6 months of treatment with diet and acetazolamide to treatment with diet and placebo in 165 subjects with IIH, papilledema and mild vision loss. Both groups showed improvement in vision, papilledema and headache with acetazolamide showing a treatment effect for the primary outcome of perimetric mean deviation.[3] A planned interventional trial will compare cerebrospinal fluid (CSF) shunting with dural venous sinus stenting in IIH (clinical trials.gov identifier NCT02513914). Another planned IIH weight trial will compare surgical and non-surgical weight loss interventions for morbidly obese patients with IIH.[4]

A clinical challenge in the treatment of high ICP is monitoring response to treatment. Direct measures of ICP are invasive and indirect markers used in clinical practice, such as papilledema reduction, apparent on clinical examination, fundus photography and optical coherence tomography (OCT) imaging, and vision improvement has delayed response following ICP changes.[5] Retinal vascular changes, specifically a decrease in retinal venule diameter associated with decrease in ICP, have been demonstrated to occur within 1 hour following ICP lowering by lumbar puncture with CSF drainage in individuals with high ICP.[6] Similar changes in the longer term have been reported in a small case series of nine patients undergoing optic nerve sheath fenestration[7] and four patients with IIH after long term therapy.[8] Increase in retinal venule diameter has been reported in animals with experimental acute ICP elevation[9 10] and in humans with acute ICP change due to subarachnoid haemorrhage and other acute intracranial events.[11 12] On the basis of these results, retinal venule size is a promising biomarker for IIH treatment response. An important next step is verification of the association in a larger cohort.

As part of the IIHTT, standardised photos of the optic disc were obtained at baseline and subsequent study visits. Trial analysis included measurements of disc elevation area and diameters of the four primary retinal arterioles and venules in each eye. OCT images were obtained in a subset of subjects who participated in the OCT substudy. Optic disc photography results were previously reported for baseline visit, demonstrating a decreased A:V ratio that was associated with area of disc elevation.[13] The aim of this study was to evaluate change in retinal venule and arteriole diameter between baseline and study end-point at 6 months in the IIHTT. We hypothesised that retinal venule diameter decrease would be associated with treatment of IIH. A secondary aim was to assess potential associations between retinal vessel diameters, measures of papilledema and treatment.

MATERIALS AND METHODS

Subjects

Subjects for this study were participants in the IIHTT, a multi-centre randomised, double-masked,

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placebo-controlled study, full details and other results of which were reported elsewhere.[3] Briefly, 165 subjects with IIH and mild vision loss (perimetric mean deviation between −2 dB and −7 dB) were enrolled at 38 North American centres between 2010 and 2012. Two subjects had diabetes. All participants were offered a dietary plan and lifestyle modification programme and were randomised to either maximally tolerated acetazolamide (maximum 4 g/day) or placebo for the study duration (6 months). The research adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards of each centre. Informed consent was collected from all participants in this study after they were notified of the nature and potential outcomes and consequences of the study. The current study was conducted using data from the IIHTT. It did not collect any new data and data was provided in a deidentified manner such that the identity of subjects could not be determined directly or indirectly. Therefore, the current study was exempt from IRB review (45 CFR part 46 requirements) under 45 CFR 46.101(b)(4).

Eyes included in this study were study eyes as defined at time of trial entry (one per subject) with optic disc photographs collected as part of the IIHTT at baseline and 6 months with measurement of at least one retinal arteriole or venule at both time points. Due to these inclusion criteria, subjects not completing follow-up and treatment failures were excluded from this study. Availability of OCT images was not a criterion for inclusion since these were collected only in participants in the OCT substudy (see below).

Fundus photography

Optic nerve photographs collected as part of the IIHTT protocol at baseline and at 6 months were the basis for measurements analysed in this study. The photography protocol consisted of digital fundus images obtained through pharmacologically dilated pupils of at least 6 mm in diameter. Two stereo pairs of 30° or 35° images were centred on the optic nerve: one pair was focused on the dome of the disc and the other at the base of the disc. Photograph acquisition including colour and magnification calibration was standardised across sites and personalised based on best corrected visual acuity refraction as previously described.[13]

Image analysis

Image analysis was performed per trial protocol at the IIHTT photographic reading centre at the University of Rochester as previously described.[13] Briefly, using stereo-paired images of each eyes for each subject at each time point, two raters independently measured elevated optic nerve head area (ONHA) comprised of a central brighter component, which is the reflective area of ganglion cell oedema, and a peripheral darker component, which is the surrounding area of less reflective retinal elevation characterised by change in retinal vessel direction. For this analysis, we used the total area of optic nerve head swelling. To measure retinal vessels, a 5.4 mm diameter circular grid divided into four sectors was overlaid on the image and centred on the optic disc. The diameter of the major venule and arteriole in each quadrant 2.7 mm from the optic disc centre were measured independently by two raters masked to treatment group (figure 1). Photographs from different visits were measured in separate analysis sessions and were not compared. Measurements differing between raters by more than 10% were resolved by discussion. Measurements were averaged between raters to generate the measurements for that vessel at that time point. Change in diameter for each vessel was calculated as the difference between baseline and 6 months measurements, both in µm (absolute) and normalised to baseline diameter (proportional). Changes in each individual vessel were averaged within eyes to generate average venule diameter change and average arteriole diameter change for that eye.

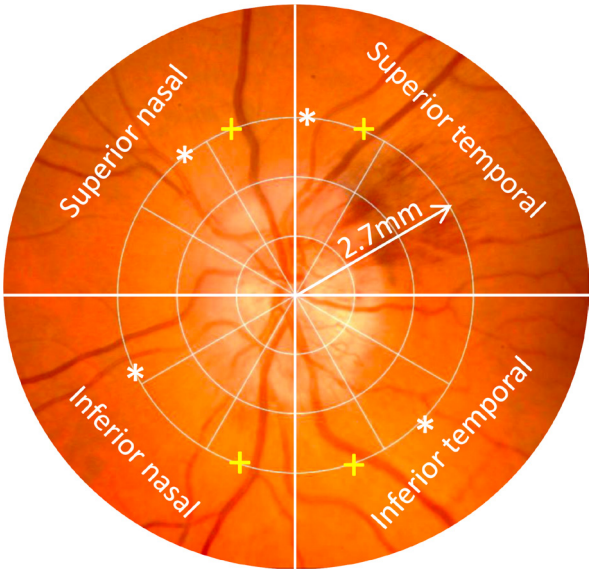

Figure 1 Location of retinal vessel diameter measurements from fundus photographs in the IIHTT. The most prominent vessel of each type (arteriole (*), venule (+)) in each quadrant (superior/inferior, nasal/temporal) was selected along a 2.7 mm diameter ring centred on the optic disc. IIHTT, Idiopathic Intracranial Hypertension Treatment Trial.

Optical coherence tomography

Spectral domain OCT scans (Cirrus, Zeiss Meditech) were collected in a subset of IIHTT subjects (n=126) as part of the IIHTT OCT substudy. Optic nerve head volume (ONHV) was calculated as the tissue volume between the internal limiting membrane and retinal pigment epithelium in circle with a radius of 1.73 mm centred on the optic nerve head. Image acquisition and analysis techniques are detailed elsewhere.[14]

Statistical analysis

For each subject, the study eye, as enrolled in the IIHTT, was analysed. The primary outcome was change from baseline in average size of arterioles and venules in study eyes following 6 months of treatment of IIH which was compared with a null hypothesis of no change (change=0) using a one sample t-test. Effect of treatment group was evaluated by applying t-test for independent samples to the change in vessel diameter grouped by treatment group (placebo, acetazolamide). Both absolute diameter change (in μm) and proportional diameter change (normalised to baseline diameter) were studied.

Correlations between vessel change in study eyes and potential associated variables including age, baseline intraocular pressure, baseline mean arterial pressure, baseline CSF pressure, baseline ONHA (photograph derived), baseline ONHV (OCT derived), intraocular pressure change, mean arterial pressure change, CSF pressure change, ONHA change and ONHV change were evaluated using linear regression and Pearson correlation. Gender was not studied as a variable due to the small number of men in the study. Exploratory analysis with scatter plots was applied to ensure that linear analysis was appropriate. Number of subjects for each correlation varied according to missing data.

Multiple variable models of the outcomes were constructed to evaluate the relationships of variables associated with $p<0.1$

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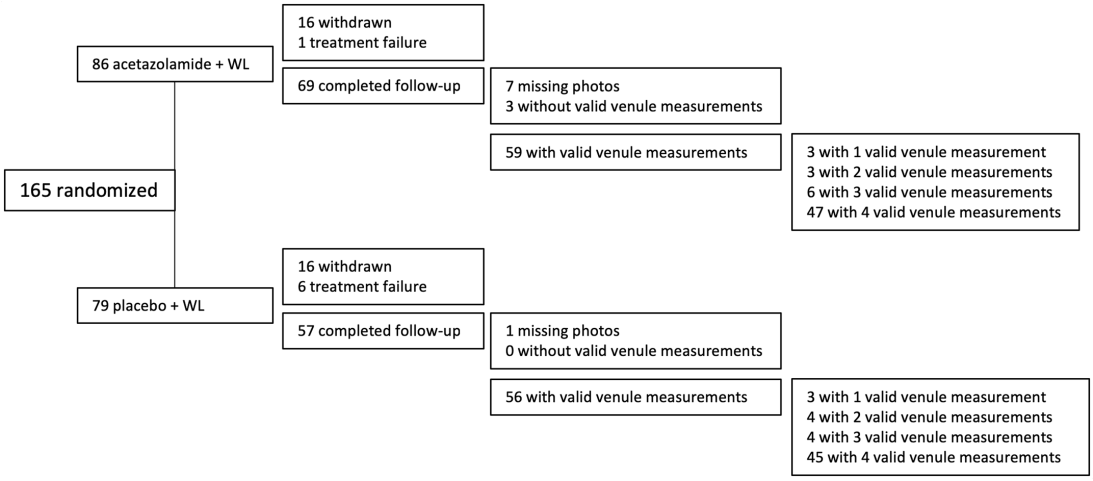

Figure 2 IIHTT subjects included in change in retinal vessel analysis. IIHTT, Idiopathic Intracranial Hypertension Treatment Trial; WL, weight loss.

in correlation analysis as well as specific variables of interest (ONHV, ONHA, ICP) using multiple variable linear regression. Due to their known correlation, ONHV and ONHA were studied in separate models.[15] Frisèn papilledema grade was not studied because it is subjective, not a continuous variable and correlated with ONHA is the baseline analysis of this trial.[13] Similar analyses were completed at the eye level using generalised estimating equations to account for within subject correlation. The results were similar and are not shown. Analysis results excluding the two diabetic subjects were similar and are not reported. Analysis was performed using SPSS 24 (IBM).

RESULTS

A total of 230 eyes (115 study eyes) had at least one venule measured at both baseline and 6 months (figure 2) and 220 eyes (109 study eyes) had at least one arteriole measured at both time points (n=6, 15, 19, 69 for 1, 2, 3, 4 arterioles, respectively). The included subjects were 29.5±7.8 years old and 98% (n=115) were female, which is similar to the entire IIHTT cohort. Fifty-nine were randomised to acetazolamide and diet and 56 to placebo and diet.

Average retinal venule size decreased 8.1 µm (95% CI (–10.6 to 5.6), p<0.0005, single sample t-test) or 5.9% ((–7.8 to –3.9), p<0.0005, single sample t-test) between baseline and 6 months. Average retinal arteriole size increased 0.9 µm ((−0.5 to 2.3), p=0.23, single sample t-test) or 2.2% ((0.2 to 4.4), p=0.04, single sample t-test) between baseline and 6 months, but this was of small magnitude and only statistically significant for the proportional outcome.

Acetazolamide treatment was associated with a larger magnitude of venule diameter decease, but this did not reach statistical significance (−4.0 µm (−9.0 to 1.0), p=0.121; −3.5% (–7.5 to 0.4), p=0.062, t-test for independent samples). Acetazolamide treatment was not associated with arterial diameter change (p=0.4 absolute, p=0.25 proportional, t-test for independent samples).

Bivariate relationships between outcomes of venule diameter and arterial diameter change between baseline and 6 months and other potentially relevant baseline and change variables are shown in tables 1 and 2 for absolute venule and arteriole change, respectively. Of note are highly significant associations between change in retinal venule size but not retinal arteriole size and baseline measures of papilledema (ONHV, ONHA) and change in papilledema (ONHV, ONHA) (figure 1). There was not a significant association between CSF opening pressure change and retinal venule diameter change (p=0.33, linear regression), though there was a borderline association for retinal arterial diameter change (p=0.07, linear regression) (figure 3). Relationships for proportional venule and arteriole change were similar and are not shown.

In multiple variable models of average retinal venule diameter change including baseline and change in papilledema parameters to adjust for the other, measures of papilledema change, but not baseline papilledema remained significantly associated with retinal venule diameter change (photo model, n=108, ONHA change p<0.0005, ONHA baseline p=0.34; OCT model, n=80, ONHV change p<0.0005, ONHV baseline p=0.5, p=0.27, multiple variable linear regression). ONHA change and ONHV

Table 1 Linear associations between venule diameter change (absolute) after 6 months of treatment for IIH and variables of interest in study eyes of subjects in the IIHTT

Variable	% missing (n=115)	R (Pearson correlation)	P value (linear regression)
Age	0	0.08	0.396
Baseline			
IOP	0	0.07	0.441
Mean arterial pressure	0	0.062	0.509
Perfusion pressure	0	0.042	0.656
CSF opening pressure	0	0.155	0.098
ONHA (photo)	6% (n=7)	0.250	0.009
ONHV (OCT)	30% (n=34)	0.256	0.021
Change (baseline–6 months)			
IOP	0.9% (n=1)	0.071	0.455
Mean arterial pressure	0	0.107	0.255
Perfusion pressure	0.9% (n=1)	0.088	0.349
CSF opening pressure	36% (n=41)	0.013	0.333
ONHA (photo)	6% (n=7)	0.472	<0.0005
ONHV (OCT)	30% (n=35)	0.422	<0.0005

CSF, cerebrospinal fluid; IIHTT, Idiopathic Intracranial Hypertension Treatment Trial; IOP, intraocular pressure; ONHA, optic nerve head area; ONHV, optic nerve head volume.

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Table 2 Linear associations between arteriole diameter change (absolute) after 6 months of treatment for IIH and variables of interest in study eyes of subjects in the IIHTT

Variable	% missing (n=109)	R^2 (Pearson correlation)	P value (linear regression)
Age	0	0.057	0.554
Baseline			
IOP	0	0.065	0.503
Mean arterial pressure	0	0.081	0.403
Perfusion pressure	0	0.062	0.524
CSF opening pressure	0	0.094	0.333
ONHA (photo)	6% (n=7)	0.110	0.270
ONHV (OCT)	28% (n=31)	0.065	0.572
Change (baseline–6 months)			
IOP	1% (n=1)	0.069	0.476
Mean arterial pressure	0	0.111	0.253
Perfusion pressure	1% (n=1)	0.089	0.358
CSF opening pressure	35% (n=38)	0.214	0.073
ONHA (photo)	6% (n=7)	0.088	0.381
ONHV (OCT)	29% (n=32)	0.051	0.663

CSF, cerebrospinal fluid; IIHTT, Idiopathic Intracranial Hypertension Treatment Trial; IOP, intraocular pressure; ONHA, optic nerve head area; ONHV, optic nerve head volume.

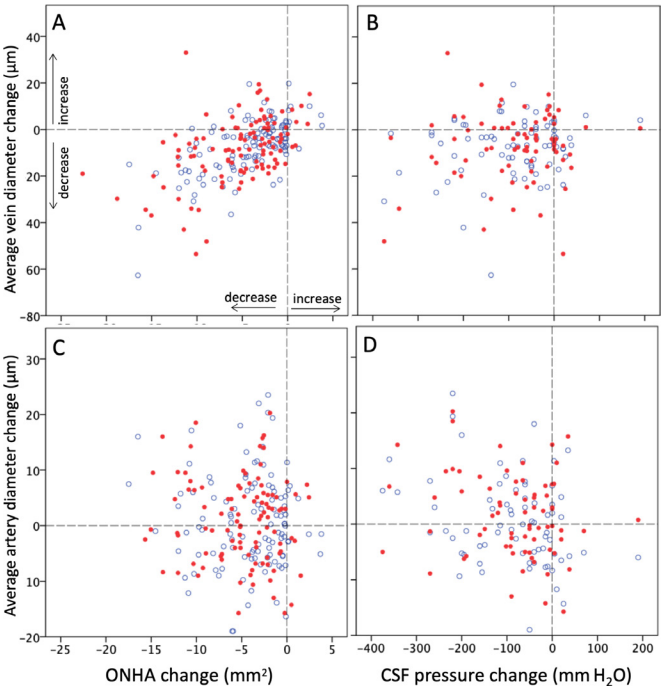

Figure 3 Retinal vessel diameter change in IIH subjects following 6 months of treatment in the Idiopathic Intracranial Hypertension Treatment Trial. Average retinal venule diameter change at 6 months as a function of (A) optic nerve head area change and (B) CSF pressure change. Average retinal arteriole diameter change at 6 months relative to baseline as a function of (C) optic nerve head area change and (D) CSF pressure change. Each marker represents an eye. Marker style and colour indicate study eye (solid red) or fellow eye (blue outline). CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension; ONHA, optic nerve head area.

change remained associated with average retinal venule diameter change when CSF opening pressure change was included in the models (photo model, n=69, ONHA change p<0.0005, ONHA baseline p=0.44, CSF pressure change p=0.54; OCT model n=48, ONHV change p=0.048, ONHV baseline p=0.53, CSF pressure change p=0.61, multiple variable linear regression). Results were similar for models of proportional retinal venule and arteriole diameter change and are not shown.

DISCUSSION

In IIH subjects with papilledema and mild vision loss, retinal venule diameter decreased over 6 months in association with treatment with a weight loss intervention combined with either acetazolamide or placebo. A corresponding change in retinal arteriole diameter was not observed. This is the largest study of retinal vessel diameter change in subjects with high ICP undergoing treatment. Other strengths include standardised prospective image collection and analysis as part of a randomised controlled trial.

The observed changes are in agreement with what has previously been reported in humans with high ICP undergoing short-term and long-term ICP lowering[6–8] and are the expected inverse of what has been described in animals undergoing acute ICP elevation.[9 10] Presumably, the larger venule diameters when ICP is elevated reflect higher retinal venule pressures.[16] This is supported by prior observations of correlation between ICP and retinal venous pressures measured with ophthalmodynanometry.[17]

The correlation between retinal venule diameter change and two different measures of optic nerve head swelling, one photograph derived and one OCT derived, support a major contribution of compressive force of the swollen optic nerve acting on the central retinal venule to increase outflow resistance. This adds to baseline data from the IIHTT showing association between ONHA and ICP.[13] Clinical observations of retinal venous engorgement in states of optic disc oedema (such as anterior ischaemic optic neuropathy) not associated with high ICP support a contribution of increased downstream resistance due to compression of vessels by a swollen optic nerve head.

Another possible contributing factor to higher retinal venule pressures might include altered dural venous hemodynamics in high ICP states.[18 19] It is possible that there are elevated cerebral venous pressures that contribute directly to higher upstream pressure in the retinal venules as well as to higher ICP due to change in pressure gradient across the arachnoid villi. Published observations of increased retinal venous diameter following acute increase in ICP before papilledema forms[9 10] suggest that cerebral CSF and hemodynamics are a relevant factor. Our analysis does not support ICP as a relevant independent factor in retinal venule size change beyond its role in causing papilledema. The lack of correlation with ICP change is also informative because it emphasises the difference between intraoptic nerve sheath ICP (relevant to papilledema and ganglion cell injury) and lumbar subarachnoid ICP measured during lumbar puncture. However, further study is needed since the sample size available for analysis was substantially less in the models with ICP change due to the amount of missing data for ICP at 6 months. Interestingly, retinal arteriole diameter change had a borderline association with change in ICP but not papilledema measures. This may reflect altered cerebral hemodynamics in IIH.[18]

Age and baseline blood pressure have been previously shown to be associated with retinal vessel diameter in cohort studies[20 21] but were not in our study. Similarly, perfusion

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pressure is a known factor in ocular hemodynamics, but was not associated with vessel diameter change in our study. This may be due to a dominant association with measures of papilledema. Though acetazolamide treated eyes had greater retinal venule diameter decrease than those in placebo treated eyes this did not reach statistical significance. Furthermore, this difference was not detected when adjusting for disc oedema change and thus may simply reflect the differential effect size of acetazolamide on disc oedema, which was previously reported.[22]

Limitations of this study include the possibility of error introduced by the use of subject based calibration factors to obtain absolute measurement of retinal vessels. However, similar results obtained using proportional measurements suggests that this did not impact the results. A previously raised concern regarding measurement of retinal vessels from photographs is that globe flattening could bring vessels closer to the camera and make them appear larger.[8] However, if this were the case, one would expect similar changes in both venules and arterioles which was not observed. Missing data may introduce bias if it is not missing at random, for example, if measurements could not be made in high grade papilledema cases.

In conclusion, we demonstrate decrease in size of retinal venules but not arterioles in subjects with IIH and mild vision loss following 6 months of treatment with either acetazolamide and weight loss or weight loss alone. Our analysis is an important one that contributes longitudinal analysis of retinal vessel change using the largest IIH treatment cohort available. We are also the first to examine correlations with other measures of treatment response. This result builds on prior literature regarding retinal vascular changes associated with ICP changes and more broadly to scientific understanding of ophthalmic changes associated with ICP, the latter having potential application as biomarkers of ICP. Though we do not know whether retinal venule diameter measurement provides additional clinical value over optic disc swelling, this is an important area for investigation. It would have an application if it changed faster, since we know that disc swelling changes are delayed following ICP changes. Further study is needed to determine if vessel changes in the early phases of treatment have predictive or prognostic implications.

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Contributors Conception or design of the work: HEM and SEF. Acquisition, analysis or interpretation of data: HEM, RAH, WSF and SEF. All authors contributed to drafting the work or revising it critically for important intellectual content and have approved the final version.

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Competing interests SEF is a consultant to Association of University Professors of Ophthalmology and a Trustee of Doheny Eye Institute.

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Data availability statement Data were obtained from IIHTT study management, to whom any requests for study data should be referred.

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