Normobaric hyperoxia combined with endovascular treatment for acute ischaemic stroke in China (OPENS-2 trial): a multicentre, randomised, single-blind, sham-controlled trial

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Summary

Background Endovascular treatment improves the recanalisation rate for patients with acute ischaemic stroke; however, even with endovascular treatment, approximately half of patients do not have a favourable functional outcome. We aimed to evaluate the effect of normobaric hyperoxia combined with endovascular treatment on functional outcomes up to 90 days after treatment in patients who had an acute ischaemic stroke with large-vessel occlusion.

Methods In this multicentre, randomised, single-blind, sham-controlled trial, patients aged 18–80 years presenting within 6 h of acute ischaemic stroke attributed to large-vessel occlusion in anterior circulation, who were candidates for endovascular treatment, were recruited from 26 comprehensive stroke centres in China. Eligible patients were randomly assigned (1:1), with an Interactive Web Response System on the basis of a minimisation process to balance assignment at each participating site both overall and according to age, sex, occlusion location, and use of intravenous thrombolytics, to receive either normobaric hyperoxia combined with endovascular treatment or sham normobaric hyperoxia combined with endovascular treatment. Participants and assessors were blinded to treatment assignment. Normobaric hyperoxia treatment involved inhaling 100% oxygen at a flow rate of 10 L/min through a non-rebreather mask for 4 h, or an inspiratory oxygen fraction (FiO_2) of 1·0 in participants for whom intubation was necessary. Sham treatment was 100% oxygen delivered at a flow rate of 1 L/min or an FiO_2 of 0·3. The primary outcome was the comparison of the ordinal scores on the modified Rankin Scale (mRS) at 90 days assessed in the intention-to-treat population (including all patients randomly assigned to treatment). Safety was assessed in all patients who received any oxygen therapy. This trial is registered with ClinicalTrials.gov, NCT04681651, and is now complete.

Findings Between April 22, 2021, and Feb 5, 2023, 473 patients were screened, of whom 282 were randomly assigned to either normobaric hyperoxia plus endovascular treatment (n=140) or sham normobaric hyperoxia plus endovascular treatment (n=142; intention-to-treat population). The median age was 65 years (IQR 57–71), 75 (27%) of 282 participants were female, 207 (73%) were male, and 282 (100%) of participants were of Chinese Han ethnicity. At 90 days, the median score on the mRS for the normobaric hyperoxia group was 2 (IQR 1–4) and it was 3 (1–4) in the sham normobaric hyperoxia group (adjusted common odds ratio 1·65 [95% CI 1·09–2·50]; p=0·018). At 90 days, 14 (10%) of 140 patients in the normobaric hyperoxia group and 17 (12%) of 142 in the sham normobaric hyperoxia group died (adjusted risk difference –0·02 [95% CI –0·09 to 0·06]) and 28 (20%) and 33 (23%) had serious adverse events (adjusted risk difference –0·03 [–0·12 to 0·07]).

Interpretation In patients with acute ischaemic stroke caused by large-vessel occlusion in the anterior circulation who were candidates for endovascular treatment, normobaric hyperoxia yielded superior functional outcomes at 90 days compared with the sham normobaric hyperoxia, without raising safety concerns.

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Introduction

Endovascular treatment has emerged as the standard of care for patients with acute ischaemic stroke caused by large-vessel occlusion in the anterior circulation.[1–5] Despite this advancement, a substantial challenge remains: approximately half of patients who undergo endovascular treatment do not have a favourable functional outcome, defined by a modified Rankin

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published from database inception to July 30, 2024, evaluating normobaric hyperoxia in patients with ischaemic stroke, using terms ("normobaric hyperoxia" OR "normobaric oxygen") AND "ischemic stroke", without language restrictions. We identified four small clinical trials conducted before the endovascular thrombectomy era that had mixed results for normobaric hyperoxia, primarily showing temporary benefits or neutral outcomes in patients with stroke who did not receive adequate reperfusion. The only large-scale clinical trial at that time, which was terminated early, also showed no effect on the primary outcome measure. We identified three pilot clinical trials examining the combination of normobaric hyperoxia with endovascular treatment since the advent of the endovascular treatment era: the OPENS-1 trial, a dose-escalation trial, and a trial delivering normobaric hyperoxia after endovascular treatment. All three of these trials showed primary efficacy outcomes that favoured the use of normobaric hyperoxia. To provide sufficient evidence on normobaric hyperoxia combined with endovascular treatment in patients with ischaemic stroke, two multicentre, large-scale clinical trials were conducted in parallel with different protocols of normobaric hyperoxia: OPENS-2 trial (this study) and the PROOF trial.

Added value of this study

To our knowledge, the OPENS-2 trial is the first multicentre, large trial completed to evaluate normobaric hyperoxia combined with endovascular treatment in patients with ischaemic stroke in anterior circulation. At 90 days, normobaric hyperoxia resulted in a significantly favourable shift in the distribution of scores on the modified Rankin Scale, indicating better functional outcomes compared with the sham normobaric hyperoxia group. The rates of mortality and serious adverse events did not significantly differ between the two groups, suggesting a similar safety profile.

Implications of all the available evidence

The results of this trial support normobaric hyperoxia combined with endovascular treatment in patients with acute ischaemic stroke caused by large-vessel occlusion in the anterior circulation who were candidates for endovascular treatment. Future trials should confirm our results in different populations and explore whether normobaric hyperoxia can be used to improve functional outcome after stroke in pre-hospital settings or in later time windows.

Scale (mRS) score of 0–2 at 90 days.[6] These poor outcomes are attributed to the fact that, although reperfusion therapies are designed to salvage the ischaemic penumbra and reduce infarct volume, the penumbra can evolve into the ischaemic core over time, potentially becoming too small or even absent by the time reperfusion occurs. Consequently, a crucial advancement is needed to "freeze the penumbra" by integrating cerebral-protective strategies with reperfusion therapies.[7,8]

Before the era of endovascular treatment, clinical trials often did not show substantial benefits due to low recanalisation rates.[9–14] Although endovascular treatment now allows higher rates of recanalisation, trials such as ESCAPE-NA1[15] and ESCAPE-NEXT[16] have yet to find an effective cerebral-protective therapy because they are hindered by the challenge of drug delivery to the ischaemic penumbra, among other reasons.

Normobaric hyperoxia is an exception. Its diffusive properties enable it to reach the penumbra before reperfusion, potentially providing effective concentrations.[17] The benefits of normobaric hyperoxia include low cost, wide availability, and ease of use, making it suitable for diverse health-care settings worldwide, irrespective of economic status.

Preclinical stroke models have demonstrated the capacity of normobaric hyperoxia to preserve the penumbra by elevating the partial pressure of oxygen, thereby reducing infarct volume and enhancing neurological outcomes.[18–21] The first clinical trial investigating the effect of normobaric hyperoxia on individuals with stroke enrolled 16 participants with perfusion-diffusion mismatch and found that normobaric hyperoxia ameliorated US National Institutes of Health Stroke Scale (NIHSS) scores, curtailed infarct volume with enhanced penumbral salvage, and augmented aerobic metabolism during treatment, albeit without sustained effects at later timepoints.[22,23] Encouraged by these preliminary findings, a more comprehensive clinical trial run by Singhal and colleagues was registered to assess the safety and efficacy of normobaric hyperoxia versus room air, anticipating a cohort of 240 patients with acute ischaemic stroke (NCT00414726). Unfortunately, this trial was discontinued after enrolling 85 patients due to an unexpectedly high mortality rate in the normobaric hyperoxia group. However, subsequent analysis from this trial indicated that this increase in deaths was not related to normobaric hyperoxia treatment. The primary outcome, the NIHSS scores from baseline to 24 h, showed no significant differences between the normobaric treatment group and the room air group. Additional small-scale trials have yielded mixed results: one study reported no improvements in NIHSS, mRS, or Barthel Index scores at various timepoints;[24] another study had a numerical reduction in deaths and comorbidities among patients with severe stroke, although the reduction was not significant;[25] and a third study indicated improvements in mRS scores at 6 months without corresponding changes in Barthel Index scores

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See **Online** for appendix

For more on the **trial by Singhal and colleagues, the reasons for termination, and subsequent analysis** see https://clinicaltrials.gov/study/NCT00414726

at discharge.[26] A large-scale clinical trial that recruited 8003 patients with acute stroke also showed that low-dose oxygen supplementation did not reduce the risk of death or disability at 3 months.[27]

All aforementioned trials involved patients with acute stroke who did not receive endovascular treatment (because it was not the standard of care at the time) or had very low rates of intravenous thrombolysis reperfusion therapy, where normobaric hyperoxia demonstrated only transient benefits or no clinically meaningful benefits. These findings might be attributed to the lack of reperfusion, under which normobaric hyperoxia could only delay but not stop the deterioration of the penumbra into infarction. These findings parallel preclinical studies on neuroprotectants, which suggest that permanent ischaemic models are less responsive to treatment than are transient ones, with significant negative correlation identified between the effect on infarct volume reduction of normobaric hyperoxia and duration of ischaemia.[8]

The contemporary reperfusion era presents a unique opportunity for evaluating normobaric hyperoxia in the context of successful vessel recanalisation, akin to the ischaemia-reperfusion models in preclinical research. In light of this, a pilot single-centre OPENS-1 trial was conducted, which found that the combination of normobaric hyperoxia with endovascular treatment could reduce infarct volume and improve functional outcomes with a satisfactory safety profile compared with endovascular treatment alone.[28] Encouraged by these findings, we initiated the multicentre OPENS-2 trial to validate the efficacy and safety of normobaric hyperoxia plus endovascular treatment, in comparison with sham normobaric hyperoxia plus endovascular treatment, among patients with acute ischaemic stroke due to large-vessel occlusion in the anterior circulation who met criteria for endovascular treatment.

Methods

Study design and participants

The OPENS-2 trial was an investigator-initiated, multicentre, randomised, single-blind, sham-controlled trial conducted in 26 comprehensive stroke centres in China (appendix pp 2–3).

Patients were eligible for enrolment if they had an acute ischaemic stroke due to large-vessel occlusion in the internal carotid artery or the first segment of middle cerebral artery, with less than a third of the middle cerebral artery territory involved, as confirmed by CT or MRI. Additionally, patients had to be aged 18–80 years, have indications to receive endovascular treatment, and be eligible to undergo random assignment to treatment within 6 h of stroke onset. Eligible patients also had a pre-stroke score of 0 or 1 on the mRS (which ranges from 0 to 6, with higher scores indicating more severe disability and 6 indicating death), a score of 10 to 18 on the NIHSS (which ranges from 0 to 42, with higher scores indicating more severe deficit), and a 6 or higher on the Alberta Stroke Program Early CT Score (ASPECTS;[29] which ranges from 0 to 10, with higher scores indicating a lower infarct burden). Because of slow recruitment during the COVID-19 pandemic, after enrolment of 78 patients, the inclusion criteria were expanded as part of a protocol amendment (protocol version 3.0; Feb 8, 2022) to allow for enrolment of patients with a score of 10–20 on the NIHSS. Patients were ineligible if they had active chronic obstructive pulmonary disease or acute respiratory distress syndrome, required more than 3 L/min of oxygen to maintain arterial oxygen saturation higher than 94%, could not cooperate to inhale oxygen with the mask, or had a life expectancy of less than 90 days. A complete list of eligibility criteria is in the appendix (pp 8–9).

The protocol and statistical analysis plan are in the appendix (pp 45–194). The protocol was approved by the Ethics Committee of Xuanwu Hospital Capital Medical University (approval number [2020]124). The protocol underwent two substantial revisions. First, on Feb 8, 2022 (protocol version 3.0), the inclusion criteria were broadened to encompass a baseline NIHSS score range of 10–20, up from the initial 10–18. Second, the requirement for baseline arterial blood gas analysis was introduced in on Aug 4, 2022, in protocol version 4.0. Written informed consent was obtained before enrolment either from the patient or their legally authorised representative. The trial was monitored by an independent data and safety monitoring board. This trial is registered with ClinicalTrials.gov, NCT04681651, and is now complete.

Randomisation and masking

Eligible patients were randomly assigned (1:1) by the site investigators to receive either normobaric hyperoxia plus endovascular treatment (the normobaric hyperoxia group) or sham normobaric hyperoxia plus endovascular treatment (the sham group). Treatment allocation was done with an Interactive Web Response System on the basis of a minimisation process to balance assignment at each participating site both overall and according to the baseline categories of age (<70 years or ≥70 years), sex (male or female), occlusion location (internal carotid artery or middle cerebral artery), and use of intravenous thrombolytics (yes or no). Participants were blinded to treatment group assignment, because both groups received oxygen therapy via the non-rebreather mask and the flow meter was out of their line of sight. Outcome assessors in each participating site and the members of the clinical events committee and core imaging laboratory were blinded to study group assignment The site investigators and the treating neuro-interventionalists were not blinded to the treatment allocation.

Procedures

Certified neuro-interventionalists involved in the study were required to have at least 2 years of training in

diagnostic angiography and endovascular treatment at a comprehensive stroke centre and they were required to have participated in more than 200 angiographies and 150 endovascular treatments (appendix p 43).

Oxygen therapy was administered to participants as soon as possible and within 30 min after treatment allocation. Normobaric hyperoxia was delivered by the inhalation of 100% oxygen at a flow rate of 10 L/min via a non-rebreather mask with reservoir for 4 h, or with an inspiratory oxygen fraction (FiO_2) of 1·0 if intubation was required. Sham normobaric hyperoxia was delivered with 100% oxygen at a flow rate of 1 L/min via an identical non-rebreather mask that had the bilateral side valves open for the same duration, or with FiO_2 of 0·3 if the participant was intubated. All participants received endovascular treatment and standard medical treatments according to the 2019 American Heart Association or American Stroke Association guidelines.[30] Endovascular treatment was recommended to be performed under conscious sedation unless general anaesthesia was necessary.

Sex and ethnicity of participants were determined via birth record data, which are the same as the information provided on individuals' ID cards issued by the Chinese Government. Participants were followed up at the end of oxygen therapy and at 24 h (±6), 72 h (±24), 7 days (±2), 30 days (±7), and 90 days (±14) after randomisation. mRS scores were collected at 30 days (±7) and 90 days (±14), with assessments done via structured interviews by local assessors who were blinded to treatment assignment and were not involved in endovascular treatment and stroke management. In-person interview was recommended, and if the patient could not attend the follow-up visit, the scores were collected by telephone interview. Written reports of mRS were sent to an independent blinded clinical events committee for central adjudication. In case of disagreement between the local and the central evaluation, the scores adjudicated by central assessors were considered as the correct score. More details are in the appendix (p 10).

All angiograms and imaging data were collected and uploaded to the independent blinded imaging core laboratory (Beijing Chaoyang Hospital, Beijing, China) for central adjudication.

Patients were followed up for safety during the endovascular treatment procedure, at the end of oxygen therapy, and at 24 h (±6), 72 h (±24), 7 days (±2), 30 days (±7), and 90 days (±14) after randomisation. Adverse events were categorised using Common Terminology Criteria for Adverse Events version 5.0.

Outcomes

The primary efficacy outcome was the comparison of the ordinal mRS score at 90 days (±14) after randomisation between the treatment groups (appendix p 10).

Secondary outcomes were infarct volume at 24–48 h on MRI or CT (MRI preferred); mRS scores of 0–1, 0–2, and 4–6 at 90 days, which were evaluated as dichotomous outcomes; NIHSS score at 24 h, 72 h, and 7 days; early neurological improvement at 24 h, defined as a reduction of at least 4 points on the NIHSS from baseline; successful vessel recanalisation on post-procedural angiogram, defined as grade 2b, 2c, or 3 on the extended Thrombolysis in Cerebral Infarction scale[31] (scores range from 0 to 3, with higher grades indicating increased reperfusion); recanalisation of the occluded vessel at 24–48 h, defined as grade 2 or 3 on Arterial Occlusive Lesion[32] (range from grade 0 to 3, with higher grade indicating better recanalisation); arterial partial pressure of oxygen at the end of oxygen therapy; score on Barthel Index (which ranges from 0 to 100, with a score of 95 to 100 indicating no disability that interferes with

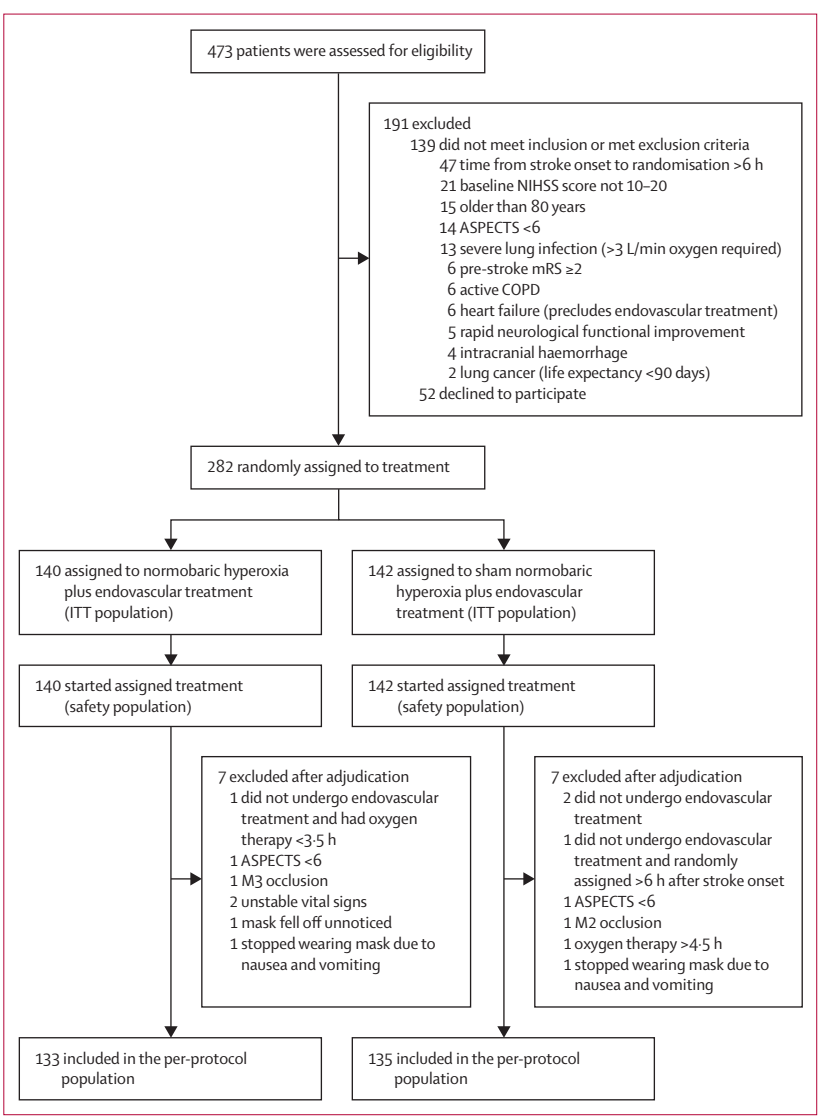

Figure 1: **Trial profile**
ASPECTS=Alberta Stroke Program Early CT Score. COPD=chronic obstructive pulmonary disease. ITT=intention-to-treat. M2=second segment of middle cerebral artery. M3=third segment of middle cerebral artery. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale.

daily activities) at 90 days; score on EQ-5D visual analogue scale (range from 0 to 100, with higher score indicating better quality of life) at 90 days; and duration of hospital stay.

Safety outcomes were all-cause death, stroke-related death (defined as death related to the index stroke or to systemic complications associated with the index stroke or a new stroke), and serious adverse events within 90 days; oxygen-related adverse events within 90 days (including severe lung infection, pneumothorax, atelectasis, respiratory failure, acute respiratory distress syndrome, and cardiopulmonary arrest); adverse events of special interest within 90 days (including malignant brain oedema, perioperative myocardial infarction, and acute heart failure); symptomatic intracranial haemorrhage and any intracranial haemorrhage within 24 h, defined as any type of intracranial haemorrhage that was associated with an increase of at least 4 points on the NIHSS or death and was judged to be the predominant cause of neurological deterioration; early neurological deterioration at 24 h, defined as an increase of at least 4 points on the NIHSS from baseline; vital signs at the end of oxygen therapy and at 24 h; and arterial blood gas analysis at the end of oxygen therapy.

	Normobaric hyperoxia group (N=140)	Sham normobaric hyperoxia group (N=142)
Demographics		
Age, years	65 (57–70)	66 (57–72)
Sex		
Female	35 (25%)	40 (28%)
Male	105 (75%)	102 (72%)
Ethnicity		
Chinese Han	140 (100%)	142 (100%)
Clinical		
Medical history		
Previous ischaemic stroke	24 (17%)	22 (15%)
Hypertension	69 (49%)	82 (58%)
Diabetes	28 (20%)	34 (24%)
Hyperlipidaemia	10 (7%)	7 (5%)
Atrial fibrillation	41 (29%)	53 (37%)
Respiratory system disease	16 (11%)	17 (12%)
Current smoker	49 (35%)	55 (39%)
NIHSS score*	14 (12–16·2)	14 (12–16·8)
ASPECTS†		
Median	8 (7–10)	8 (7–9)
<8	44 (31%)	54 (38%)
≥8	96 (69%)	88 (62%)
Intravenous thrombolysis		
Yes	61 (44%)	64 (45%)
No	79 (56%)	78 (55%)
Site of occlusion‡		
Internal carotid artery	51 (36%)	50 (35%)
Middle cerebral artery	89 (64%)	92 (65%)
Stroke subtype§		
Large-artery atherosclerosis	69 (49%)	67 (47%)
Cardioembolism	61 (44%)	61 (43%)
Other aetiology	2 (1%)	2 (1%)
Undetermined aetiology	8 (6%)	12 (8%)
Procedural		
Method of oxygen delivery		
Non-rebreather mask (conscious sedation)	111 (79%)	110 (77%)
Intubation (general anaesthesia)¶	29 (21%)	32 (23%)
Oxygen therapy non-compliance	3 (2%)	2 (1%)
Time from stroke onset to randomisation, h	4·2 (2·7–5·2)	4·4 (3·2–5·1)
Time from stroke onset to oxygen delivery, h	4·3 (2·8–5·3)	4·4 (3·2–5·2)
Time from stroke onset to groin puncture, h‖	4·7 (3·4–6·1)	5·0 (3·5–5·9)
Time from stroke onset to revascularisation, h‖	5·6 (4·3–6·7)	5·8 (4·4–6·8)
Time from oxygen delivery to revascularisation, h‖	1·3 (1·0–1·9)	1·3 (1·0–1·9)

(Table 1 continues on next page)

Statistical analysis

We determined the sample size for our trial on the basis of the distribution of mRS scores from the normobaric hyperoxia and control groups in the OPENS-1 trial.[28] The relative risk estimates between the treatment and control groups were 1·55, 1·45, and 1·28 for the dichotomised 90-day mRS of 0–1, 0–2, and 0–3, respectively. Via simulation, we estimated that a sample of 198 patients would provide 90% power to detect a significant shift in the mRS score distribution at a two-sided α level of 0·05. To account for potential losses to follow-up and to ensure a conservative approach regarding the treatment effect observed in OPENS-1, we increased the final sample size to 280 patients.

Our analysis of both primary and secondary outcomes included patients in the intention-to-treat population, defined as all participants randomly assigned to treatment. Safety was assessed in all participants who received any amount of oxygen therapy. Additionally, a prespecified per-protocol analysis of the primary and secondary efficacy outcomes was conducted in the per-protocol population, which comprised participants who met the eligibility criteria, received the assigned treatment, and had no major protocol deviations. For participants with missing 90-day mRS values, we imputed these with the 30-day mRS values. When both timepoints were missing, we used multiple imputation models. Secondary and safety outcomes with missing values were excluded from the regression analysis, and the numbers of missing values were reported.

In the primary efficacy analysis, the proportional odds assumption was validated using a Brant test. We reported the common odds ratio with its associated 95% CI and p value, using ordinal regression as the primary measure of the primary outcome. In post-hoc analyses, we also used a mixed-effects proportional odds model to account for clustering within sites(appendix pp 11–12). In further post-hoc analyses, we calculated the number needed to treat for one additional patient to be functionally

independent, with its associated 95% CI. The secondary efficacy and safety analyses included both quantitative and binary variables. For quantitative variables, we applied the Student's *t* test or the Wilcoxon rank-sum test, as appropriate. Binary variables were compared using the χ^2 test or Fisher's exact test, as suitable. We calculated the risk ratio, mean difference, or risk difference with their corresponding 95% CI for secondary and safety outcomes. A prespecified Kaplan–Meier analysis was conducted to assess mortality at 90 days for each group. Both unadjusted and adjusted analyses were performed for efficacy and safety outcomes, with adjustments for age (<70 years or ≥70 years), sex (male or female), occlusion location (internal carotid artery or middle cerebral artery), and use of intravenous thrombolytics (yes or no). We did not adjust the CI widths for secondary outcomes due to multiple comparisons; therefore, no definitive conclusions were drawn from these results. We also did a prespecified subgroup analysis of the proportion of participants who had mRS scores of 0–2 at 90 days by age (<70 years *vs* ≥70 years), sex (female *vs* male), history of atrial fibrillation (yes *vs* no), use of intravenous thrombolysis (yes *vs* no), occlusion location (internal carotid artery *vs* middle cerebral artery), method of oxygen delivery (non-rebreather mask *vs* intubation), baseline ASPECTS (<8 *vs* ≥8), and stroke subtype (large artery atherosclerosis *vs* cardioembolism *vs* other or undetermined aetiology); and in post-hoc subgroups by time from stroke onset to randomisation (0–3 h *vs* ≥3 h) and smoking status (no *vs* yes). The p-interaction was calculated for each of these subgroup analyses. Post-hoc subgroup analysis was conducted to calculate the duration from stroke onset to groin puncture or revascularisation in the patients receiving intravenous thrombolysis or not.

Post-hoc sensitivity analysis using mRS based on local assessments was performed to assess the robustness of the mRS-related efficacy analysis. Additionally, a post-hoc sensitivity analysis was performed to assess the robustness of the secondary efficacy analysis, where the missing data in the treatment group were imputed by applying the median outcome from the control group, and this process was reciprocally applied to the sham normobaric hyperoxia group using the median from the normobaric hyperoxia group.

All statistical analyses were done using R version 4.3.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 22, 2021, and Feb 5, 2023, 473 patients were screened, and 282 were enrolled and assigned to either the normobaric hyperoxia group (n=140) or the sham normobaric hyperoxia group (n=142; intention-to-treat population; figure 1; appendix p 15), all of whom started oxygen therapy and were included in the safety analysis population. In the normobaric hyperoxia group, one patient did not complete the 90-day follow-up, and their outcome was estimated using the 30-day mRS score. At baseline, the two groups were similar in their characteristics (table 1; appendix pp 26–27). The median age was 65 years (IQR 57–71), 75 (27%) of 282 participants were female, 207 (73%) were male, and 282 (100%) participants were of Chinese Han ethnicity.

124 (89%) of 140 patients in the normobaric hyperoxia group and 126 (89%) of 142 in the sham normobaric hyperoxia group initiated oxygen therapy before groin puncture, and all patients received oxygen therapy before revascularisation. However, in the normobaric hyperoxia group, oxygen therapy was concluded before revascularisation in four (3%) of 140 patients compared with two (1%) of 142 in the sham normobaric hyperoxia group. The therapy was administered via a

	Normobaric hyperoxia group (N=140)	Sham normobaric hyperoxia group (N=142)
(Continued from previous page)		
Time from groin puncture to revascularisation, h‖	0·8 (0·6–1·2)	0·8 (0·5–1·1)
Time from revascularisation to end of oxygen therapy, h‖	2·7 (2·1–3·0)	2·7 (2·1–3·0)
Duration of oxygen therapy, h	4·0 (4·0–4·0)	4·0 (4·0–4·0)

Data are median (IQR) or n (%). ASPECTS=Alberta Stroke Program Early CT Score. NIHSS=National Institutes of Health Stroke Scale. *Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe deficits. †ASPECTS ranges from 0 to 10, with higher scores indicating fewer early ischaemic changes. ‡Patients who had occlusion of the internal carotid artery might also have had occlusion of the first segment of the middle cerebral artery; all occlusions of the middle cerebral artery involved the first segment (M1), except in one patient who had an occlusion involving the third segment (M3) in the normobaric hyperoxia group and in one patient involving the second segment (M2) in the sham normobaric hyperoxia group. §The subtype of stroke was evaluated according to the medical history, clinical characteristics, and imaging results. ¶Patients who received oxygen therapy via intubation were initially administered oxygen with non-rebreather mask before general anaesthesia. ‖Revascularisation was defined as the first visualisation of successful reperfusion, as indicated by an extended Thrombolysis in Cerebral Infarction score of 2b, 2c, or 3 (on a scale from 0 [no reperfusion] to 3 [complete reperfusion]); data were missing for two patients in the normobaric hyperoxia group and for 3 in the sham normobaric hyperoxia group.

Table 1: **Baseline characteristics and clinical procedural characteristics, intention-to-treat population**

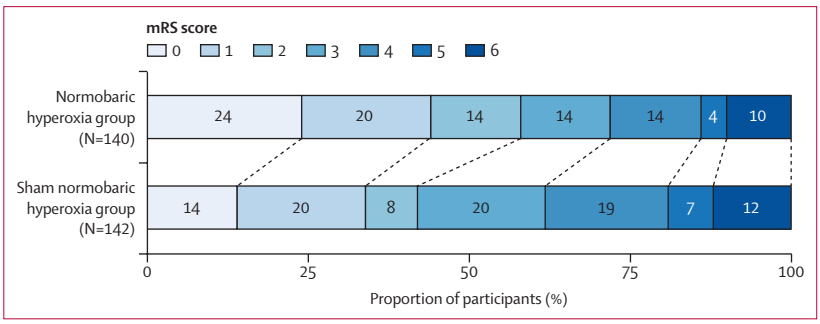

Figure 2: **Distribution of modified Rankin Scale scores at 90 days, intention-to-treat population**
Scores ranged from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The numbers in the bars are proportions of patients who had each score; the percentages might not sum to 100 due to rounding. Data were missing for one patient in the normobaric hyperoxia group, which were imputed using the 30-day score.

non-rebreather mask to 111 (79%) patients in the normobaric hyperoxia group and 110 (77%) in the sham normobaric hyperoxia group; the remaining patients were intubated (table 1). Although all participants underwent groin puncture, four did not proceed to endovascular treatment (one [1%] in the normobaric hyperoxia group and three [2%] in the sham normobaric hyperoxia group). Protocol deviations were noted in 14 patients overall, with seven occurrences in each group, such that the per-protocol population comprised 268 participants (133 in the normobaric hyperoxia group and 135 in the sham normobaric hyperoxia group; figure 1; baseline characteristics in the appendix [pp 29–30]).

At 90 days (±14), the median score on the mRS was 2 (IQR 1–4) for the normobaric hyperoxia group and 3 (1–4) for the sham normobaric hyperoxia group. The ordinal logistic regression model met the proportional odds assumption in both unadjusted and adjusted analyses, validating the use of the common odds ratio as a key measure for the primary efficacy analysis. The adjusted common odds ratio was 1·65 (95% CI 1·09–2·50; p=0·018; figure 2, table 2; appendix pp 33–34). The number needed to treat for one additional patient to be functionally independent is 6·25 (95% CI 3·37–43·11; post hoc). In post-hoc analyses, we used a mixed-effects proportional odds model to account for clustering within sites, and the result was similar (adjusted common odds ratio 1·66 [95% CI 1·09–2·52]; appendix pp 11–12). The per-protocol analysis gave similar results, with an adjusted common odds ratio of 1·71 (95% CI 1·12–2·62; p=0·014; appendix pp 16, 31–32). Prespecified and post-hoc subgroup analyses of the primary outcome are shown in figure 3 and the appendix (pp 18–25). Post-hoc sensitivity analysis using mRS based on local assessments showed similar results to that using mRS based on central adjudication (appendix p 37).

Secondary outcomes are shown in table 2, with unadjusted estimates shown in the appendix (pp 33–34), and per-protocol analysis results shown in the appendix (pp 31–32). Post-hoc sensitivity analysis in which the missing data in both groups were imputed by applying the median outcome from the other group showed

	Normobaric hyperoxia group (N=140)	Sham normobaric hyperoxia group (N=142)	Measure of effect	Adjusted value (95% CI)*†
Primary outcome				
mRS at 90 days‡	2 (1 to 4)	3 (1 to 4)	Common odds ratio	1·65 (1·09 to 2·50)§
Secondary outcomes				
Infarct volume at 24–48 h, mL¶	19 (9 to 37)	27 (12 to 78)	Mean difference	−18·02 (−30·33 to −5·72)
Score on mRS at 90 days‖				
0–1	61/139 (44%)	49/142 (35%)	Risk ratio	1·22 (0·92 to 1·62)
0–2	81/139 (58%)	60/142 (42%)	Risk ratio	1·30 (1·03 to 1·63)
4–6	39/139 (28%)	54/142 (38%)	Risk ratio	0·76 (0·55 to 1·05)
NIHSS score**				
At 24 h	10 (5 to 14)	12 (7 to 16)	Mean difference	−2·10 (−3·85 to −0·15)
At 72 h	8 (3 to 13)	11 (4 to 17)	Mean difference	−2·72 (−4·78 to −0·43)
At 7 days	7 (2 to 12)	8 (3 to 15)	Mean difference	−2·21 (−4·53 to 0·43)
Early neurological improvement††	75/137 (55%)	55/137 (40%)	Risk ratio	1·34 (1·04 to 1·71)
Successful reperfusion on post-procedural angiogram	126 (90%)	129 (91%)	Risk ratio	1·00 (0·94 to 1·07)
Recanalisation of occluded vessel at 24–48 h‡‡	91/122 (75%)	89/118 (75%)	Risk ratio	1·00 (0·87 to 1·16)
Arterial partial pressure of oxygen at the end of therapy, mm Hg§§	156 (111 to 231)	106 (84 to 131)	Mean difference	69·85 (51·41 to 88·85)
Barthel Index score of 95 or 100 at 90 days¶¶	76/139 (55%)	60/142 (42%)	Risk ratio	1·23 (0·97 to 1·55)
EQ-5D visual analogue scale score at 90 days‖‖	80 (60 to 94)	72 (40 to 90)	Mean difference	4·49 (−3·52 to 11·02)
Duration of hospital stay, days	10 (8 to 14)	11 (8 to 18)	Mean difference	−1·93 (−4·44 to 0·60)

Data are median (IQR), n (%), or n/N (%) if the analysable population differed from the intention-to-treat population, unless otherwise stated. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *The reported confidence intervals for secondary outcomes were not adjusted for multiple comparisons, and no clinical inferences can be drawn from these results. †Adjustments were made to estimates for age (<70 years or ≥70 years), sex (male or female), occlusion location (internal carotid artery or middle cerebral artery), and use of intravenous thrombolysis (yes or no); unadjusted results of efficacy outcomes in the intention-to-treat population are shown in the appendix (pp 33–34). ‡Data were missing for one patient in normobaric hyperoxia group, which were imputed using the 30-day mRS score. §p=0·018. ¶Data were missing for three patients in normobaric hyperoxia group and for four patients in sham normobaric hyperoxia group. ‖Data were missing for one patient in the normobaric hyperoxia group and were not imputed. **The worst scores were assigned for patients who died; data were missing for three patients and five patients at 24 h, two patients and four patients at 72 h, and one patient and four patients at 7 days in the normobaric hyperoxia group and in the sham normobaric hyperoxia group, respectively. ††Data were missing for three patients in the normobaric hyperoxia group and for five patients in the sham normobaric hyperoxia group. ‡‡Data were missing for 18 patients in the normobaric hyperoxia group and for 24 in the sham normobaric hyperoxia group. §§Data were missing for nine patients in the normobaric hyperoxia group and for 15 in the sham normobaric hyperoxia group. ¶¶The worst scores were assigned for patients who died; data were missing for one patient in the normobaric hyperoxia group. ‖‖The worst scores were assigned for patients who died; data were missing for one patient in the normobaric hyperoxia group.

Table 2: **Primary and secondary efficacy outcomes, intention-to-treat population**

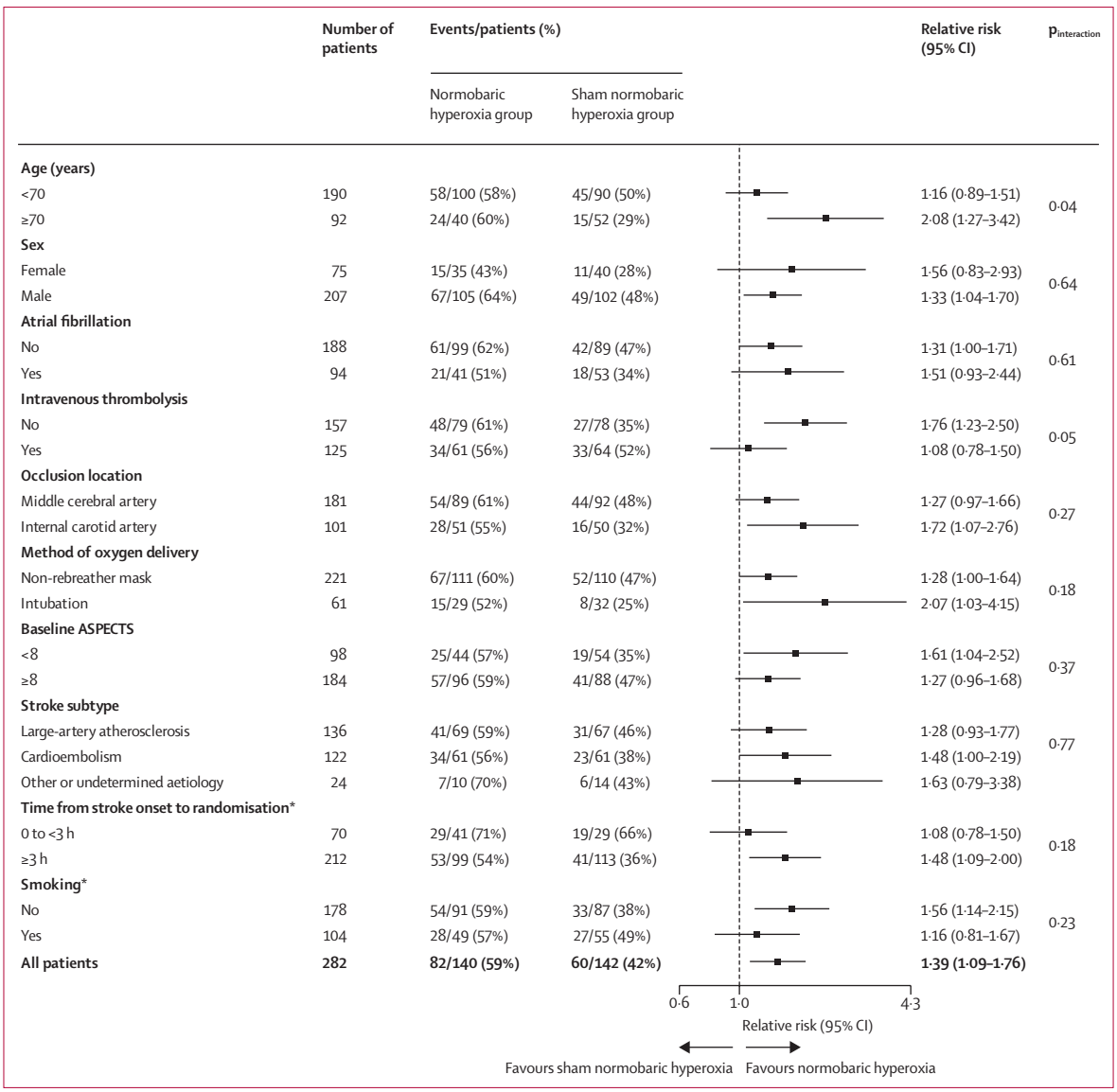

Figure 3: **Subgroup analyses of modified Rankin Scale score 0–2 at 90 days**
ASPECTS=Alberta Stroke Program Early CT Score. *Post-hoc analysis. The trial was not powered for and had no prespecified correction for multiple comparisons for a definitive analysis of subgroups.

similar results to all the results of secondary outcomes (appendix pp 38–39).

A post-hoc subgroup analysis shows that the duration from stroke onset to groin puncture or revascularisation was shorter in patients who received intravenous thrombolysis than in patients not receiving intravenous thrombolysis (appendix p 41).

Safety analyses showed no significant differences between the normobaric hyperoxia group and the sham normobaric hyperoxia group in prespecified safety outcomes (table 3; data for vital signs and arterial blood gas analyses are in the appendix [pp 26–27]). At 90 days, 14 (10%) of 140 patients in the normobaric hyperoxia group and 17 (12%) of 142 in the sham normobaric hyperoxia group died (table 2; appendix p 17), and serious adverse events had occurred in 28 (20%) and 33 (23%) patients, respectively (appendix p 28). The incidence rate of oxygen-related adverse events within 90 days of treatment was similar between groups. A lower proportion of patients in the normobaric hyperoxia group than in the sham normobaric hyperoxia group had symptomatic intracranial haemorrhage within 24 h (six [4%] of 140 *vs* 11 [8%] of 142) and any intracranial haemorrhage within 24 h (30 [21%] *vs* 46 [32%]; table 3).

Discussion

We found superior functional outcomes as measured by mRS at 90 days for patients with acute ischaemic stroke

	Normobaric hyperoxia group (N=140)	Sham normobaric hyperoxia group (N=142)	Adjusted risk difference (95% CI)*
Oxygen-related adverse events within 90 days			
Severe lung infection	2 (1%)	5 (4%)	−0·02 (−0·06 to 0·02)
Atelectasis	0	1 (1%)	−0·01 (−0·02 to 0·01)
Pneumothorax	0	0	NA
Respiratory failure	0	3 (2%)	−0·02 (−0·04 to 0·01)
Acute respiratory distress syndrome	0	0	NA
Cardiopulmonary arrest	0	1 (1%)	−0·01 (−0·02 to 0·01)
Adverse events of special interest within 90 days			
Malignant brain oedema	1 (1%)	1 (1%)	0·00 (−0·02 to 0·02)
Perioperative myocardial infarction	0	2 (1%)	−0·01 (−0·03 to 0·00)
Acute heart failure	1 (1%)	2 (1%)	−0·01 (−0·03 to 0·02)
All-cause death within 90 days	14 (10%)	17 (12%)	−0·02 (−0·09 to 0·06)
Serious adverse events within 90 days	28 (20%)	33 (23%)	−0·03 (−0·12 to 0·07)
Stroke-related death within 90 days	11 (8%)	9 (6%)	0·02 (−0·04 to 0·08)
Symptomatic intracranial haemorrhage within 24 h	6 (4%)	11 (8%)	−0·03 (−0·09 to 0·02)
Any intracranial haemorrhage within 24 h	30 (21%)	46 (32%)	−0·11 (−0·21 to 0·00)
Early neurological deterioration†	13/137 (10%)	20/137 (15%)	−0·05 (−0·13 to 0·03)

Data are n (%) or n/N (%), unless otherwise stated. Data for the safety endpoints of vital signs at the end of oxygen therapy and at 24 h, and the results of arterial blood gas analysis at the end of oxygen therapy are in the appendix (pp 26–27). NA=not applicable. *Adjustments were made for age (<70 or ≥70 years), sex (male or female), occlusion location (internal carotid artery or middle cerebral artery), and use of intravenous thrombolysis (yes or no); unadjusted results are shown in the appendix (pp 35–36). †Data were missing for three patients in the normobaric hyperoxia group and for five patients in the sham normobaric hyperoxia group.

Table 3: **Select safety outcomes, safety population**

due to large-vessel occlusion in the anterior circulation when treated with normobaric hyperoxia plus endovascular treatment compared with sham normobaric hyperoxia plus endovascular treatment. Secondary outcomes also generally favoured the normobaric hyperoxia group. Notably, the two groups had similar rates of mortality and serious adverse events.

Clinical trials from before the endovascular treatment era showed the mixed results of normobaric hyperoxia, which were mostly temporary benefits or no clinically meaningful benefits.[22–26] The only large-scale clinical trial at that time, conducted by Singhal and colleagues (NCT00414726) and that was terminated early, also showed no effect on the primary outcome. Our findings contrast with these normobaric hyperoxia trials which primarily involved patients who did not have access to or who were not eligible for reperfusion therapies.[22–26] A probable reason for these contrasting findings is that at least 90% of patients in our study had successful reperfusion. We also selected patients within 6 h after stroke onset, with ASPECTS scores of 6 or higher, indicating a substantial salvageable ischaemic penumbra. These inclusion criteria are a departure from previous trials that have often included patients up to 12 h after onset of stroke and without specific imaging to assess the penumbra and core infarct. Our strategy to focus on a specific stroke type—large-vessel occlusion in the anterior circulation—and to target patients with baseline NIHSS scores of 10–20 probably contributed to the enhanced outcomes, as opposed to the broader NIHSS range in earlier studies.

The 4 h normobaric hyperoxia treatment period, which spanned before (median of approximately 1·3 h) and after reperfusion (median of approximately 2·7 h), was justified by previous animal studies that showed reduced infarct volume with normobaric hyperoxia applied throughout the ischaemic and reperfusion phases.[33,34] A previous clinical trial also supported the safety and efficacy of post-reperfusion normobaric hyperoxia.[35] The proposed mechanism of action for normobaric hyperoxia is the stabilisation of the ischaemic penumbra during ischaemia[19,22] and suppression of neuronal apoptosis post-reperfusion.[33]

We found that a lower proportion of participants in the normobaric hyperoxia than in the sham normobaric hyperoxia group had intracranial haemorrhage. This reduction might be attributed to the mitigation of damage to the blood–brain barrier via normobaric hyperoxia, as evidenced by decreased levels of blood occludin, a biomarker for such damage, in patients who received thrombolysis.[36,37] These findings hint at the potential of normobaric hyperoxia to alleviate reperfusion injury and thereby contribute to improved functional outcomes.

Notably, although we found a general improvement in functional outcomes, quality of life outcomes were similar between treatment groups. Due to a lack of statistical power, results for secondary measures such as quality of life scores are only descriptive and so should be considered to be hypothesis generating. Nonetheless, numerically, the normobaric hyperoxia group had greater quality of life improvements than did the sham normobaric hyperoxia group and we hypothesise that an increased sample size could potentially identify significant improvements in quality of life. To this end, we are planning a large-scale, multicentre, randomised controlled trial (AN-O2-Trans; NCT06666764) to thoroughly assess the effectiveness of normobaric hyperoxia.

The subgroup analysis revealed several intriguing findings. Intervention efficacy, as measured by an mRS score of 0–2 at 90 days, was lower in patients who underwent intravenous thrombolysis than in those who did not, possibly due to the quicker time to revascularisation (post-hoc analysis). Additionally, the dual benefits of both endovascular treatment and intravenous thrombolysis in this group might have overshadowed the effects of normobaric hyperoxia. Patients who were intubated had a more pronounced response to normobaric hyperoxia, although the analysis was underpowered. Patients aged 70 years and older, with an upper limit of 80 years in this study, also benefited more from normobaric hyperoxia than did those younger than 70 years, such that further investigation into the efficacy of treatment in those older than 80 years could be

justified. Patients with lower ASPECTS and those arriving within the 3–6 h after stroke onset (post-hoc analysis) benefited more from normobaric hyperoxia than their comparator groups. Although these subgroup analyses were not the main focus of our trial and lack statistical power, they merit further exploration. We have planned future clinical trials to test these hypotheses and verify our preliminary observations, particularly for sicker patients, as identified by these variables.

Singhal and colleagues' trial that was terminated early (NCT00414726) raised some safety concerns with normobaric hyperoxia; however, a subsequent analysis found that the observed increase in mortality was not directly related to normobaric hyperoxia, suggesting that clinicians should be cautious when considering patients with severe strokes for this treatment.[8] Our trial's shorter enrolment window of 6 h after stroke onset and the high success rate of endovascular reperfusion probably reduced the incidence of severe strokes. Additionally, the 4 h duration of oxygen therapy in our study, as opposed to the 8 h regimen in Singhal and colleagues' trial (NCT00414726), might have minimised the risks associated with prolonged, high-flow oxygen administration.[8] In another study,[35] 6 h of normobaric hyperoxia that was delivered after endovascular treatment did not increase mortality in patients with acute stroke, and this supported our use of the 4 h regimen as being safe in patients with stroke.

In the pre-endovascular treatment era, large-scale, multicentre clinical trials did not demonstrate significant benefits from neuroprotectants, despite positive findings in earlier small-scale studies.[9–14] In the conceptualisation stage of the OPENS-2 trial, our primary objective was to establish the efficacy of normobaric hyperoxia. Patients with milder strokes might have satisfactory functional outcomes without the need for normobaric hyperoxia, potentially masking its benefits. The findings of Singhal and colleagues' aforementioned clinical trial that was terminated early (NCT00414726) could suggest that patients with severe strokes should be excluded from future trials of normobaric hyperoxia.[8] Additionally, we analysed data from the OPENS-1 trial,[28] which indicated that normobaric hyperoxia had a greater treatment effect in patients with an NIHSS score of 10–20, and this result informed our choice of this range as an inclusion criterion. For the criterion of age up to 80 years, we were concerned that very old patients (ie, older than 80 years) might present safety concerns with normobaric hyperoxia due to its potential effects on the cardiopulmonary system. Previous clinical trials on normobaric hyperoxia also set the age range of 18–80 years as an inclusion criterion, including the OPENS-1 trial,[28,35] and we maintained the age limit of 18–80 years to confirm the safety of normobaric hyperoxia before broadening the demographic scope.

In ischaemic stroke, the affected brain tissue loses essential oxygen and glucose due to vessel occlusion. Although normobaric hyperoxia can temporarily supply oxygen and sustain metabolism, the loss of glucose limits its protective effect to the short term. This transient nature of the intervention probably explains the neutral long-term outcomes observed in normobaric hyperoxia trials before thrombectomy's efficacy was established.[22–26] Our trial innovates by using normobaric hyperoxia to protect the penumbra from further damage during the wait for endovascular treatment, followed by endovascular treatment to restore the blood flow. The novelty of our study design is its dual focus on cerebral protection before and after endovascular treatment, prioritising the pre-reperfusion phase, aiming to maximise the benefits of normobaric hyperoxia as a bridge to endovascular treatment and ensure brain tissue gets the necessary oxygen until the blood flow is restored.

Given the high incidence of patients with stroke in China, the enrolment rate of this study was relatively slow. This trial was an investigator-initiated study without the support of industry sponsors, which constrained our ability to offer substantial financial incentives generally, including incentives to patients, that might have sped up recruitment. Additionally, the trial was conducted during the COVID-19 pandemic, and the unpredictable nature of the pandemic further hindered our recruitment efforts.

The potential for between-centre heterogeneity prompted us to stratify patients by centre during random assignment to mitigate any disparities between the treatment groups. We acknowledge that, in retrospect, the average enrolment per centre was modest. Nevertheless, patients' baseline characteristics were well balanced across centres, which ensured that the validity of our study findings remains robust and is not compromised by these factors.

Our study had a small proportion of missing data, which could theoretically influence the results. However, we conducted a post-hoc sensitivity analysis, in which we imputed missing data for the normobaric hyperoxia group using the median outcome from the sham normobaric hyperoxia group, and vice versa, under a pessimistic scenario. The results of this analysis suggested that our conclusions remained consistent, even in the presence of missing data.

At the 2023 World Stroke Conference, findings from the PROOF trial[38] and our study were presented. Although PROOF also examined the effect of combining normobaric hyperoxia with endovascular treatment, its interim analysis reported neutral outcomes, contrasting with our positive results. Several methodological differences account for this discrepancy. PROOF included patients with a baseline NIHSS score of 6 or higher, by contrast with our trial's stricter criteria of 10–20. Furthermore, PROOF applied normobaric hyperoxia at a higher flow rate of 40 L/min solely before reperfusion, whereas we administered normobaric hyperoxia at 10 L/min for 4 h, encompassing the periods before and after reperfusion. This broader application of normobaric hyperoxia might

provide enhanced protection.[33,34] A dose-escalation study indicated minimal benefits when normobaric hyperoxia is limited to 2 h,[39] emphasising the importance of the duration employed here. Additionally, PROOF enrolled older patients (mean 72 years *vs* median 65 years in our study) and used non-rebreather masks less frequently than our study (120 [54%] of 223 *vs* 221 [78%] of 282).[40]

The potential of normobaric hyperoxia to extend the therapeutic window for reperfusion and mitigate reperfusion injury could broaden its applicability. Combining normobaric hyperoxia with other neuroprotectants might further optimise outcomes. For patients without proximal arterial occlusion, adjunctive normobaric hyperoxia with intravenous thrombolysis is under investigation in an ongoing large-scale trial (NCT05965687).

Our trial has several limitations. First, given our enrolment criteria of a baseline NIHSS score of 10–20 and treatment initiation within 6 h of stroke onset, our findings might not be generalisable to patients treated beyond this window or with varying stroke severities. However, we are addressing this gap with a randomised trial that extends enrolment to 24 h after stroke onset, analysis for which is ongoing (NCT05128422). Second, the median duration of administration of normobaric hyperoxia before recanalisation was relatively brief, at 1·3 h (IQR 1·0–1·9), suggesting that initiating normobaric hyperoxia earlier, potentially in a pre-hospital setting, could be a valuable direction for future research. Third, a notable limitation of our study is the low proportion of participants who were female, accounting for just 27% of the population. We ensured an unbiased enrolment process and are uncertain of the reasons behind this disparity. In subgroup analyses, although the treatment effect for female patients was in favour of normobaric hyperoxia, the 95% CI was very wide due to the small sample size, crossing 1. Fourth, our study's population was exclusively of Chinese Han ethnicity, which might raise questions about the generalisability of our findings to patients of other ethnicities or races. Nevertheless, we believe that normobaric hyperoxia, being a low-cost and widely available treatment in all hospitals, has substantial potential for broad applicability across different populations. Fifth, baseline arterial blood gas data were missing for 100 patients in the normobaric hyperoxia group and 112 in the sham normobaric hyperoxia group because collection was mandated only from protocol version 4.0 onwards. However, the arterial blood gas analysis at the conclusion of oxygen therapy was completed and was available for the majority of patients. Sixth, our blinding design was somewhat cumbersome. Eligible patients for this trial might be too sick to be fully aware of the endovascular treatment process, and the approach in the sham group to blind patients to treatment being received might have been overly complex with limited additional benefit. In our subsequent normobaric hyperoxia trial (OPENS-3 trial, which is currently recruiting; NCT05965687), we have discontinued the use of non-rebreather masks in the control group, similarly to all the previous open-labelled trials of normobaric hyperoxia including the two large trials (NCT00414726 [which was terminated early] and PROOF).[22–26] In summary, our findings indicate that for patients with acute ischaemic stroke resulting from large-vessel occlusion in the anterior circulation who are candidates for endovascular treatment, normobaric hyperoxia plus endovascular treatment led to superior functional outcomes as measured by mRS at 90 days and did so without raising safety concerns, compared with sham normobaric hyperoxia plus endovascular treatment.

Contributors

XJ, WL, JL, MW, and KJL designed the trial. WC, SL, XY, QD, HY, ZG, XW, CW, TL, CJ, DL, ZC, JS, WS, JY, YQ, and BL contributed to data collection. LL wrote the statistical analysis plan. LL and CH did the statistical analysis. WL, JL, MW, and LL wrote the first draft of the manuscript. XJ, ZQ, CL, LJ, QY, MF, and WF provided critical revisions to the manuscript. XJ, WL, and MW accessed and verified the underlying data. All authors approved the final manuscript for submission and had final responsibility for the decision to submit the manuscript for publication. All authors had full access to data in this trial including those not involved in patient recruitment and non-Chinese members of the committees.

Declaration of interests

XJ reports grants from Beijing Municipal Education Commission, Beijing Municipal Bureau of Finance, and National Natural Science Foundation of China. WL reports grants from China Postdoctoral Science Foundation. JL reports grants from National Natural Science Foundation of China. MW reports grants from Beijing Postdoctoral Research Foundation. LL reports personal fees from Medtronic, outside the submitted work. MF reports consulting fees from Lumosa, Sincere USA, and Revalesio; honoraria for lectures and support for attending meetings or travel from Chinese Stroke Association; participation on a Data Safety Monitoring Board or Advisory Board for US National Institute of Neurological Disorders and Stroke, Moleac, NoNo; and serves in a leadership or fiduciary role as President of the World Stroke Organisation, without compensation. All other authors declare no competing interests.

Data sharing

Collected data, including individual de-identified participant data and a data dictionary defining each field in the set, will be made available to investigators whose proposed use of the data has been approved by the steering committee. Requests for access to the data can be made by email to the corresponding author.

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