

# Routine low-dose continuous or nocturnal oxygen for people with acute stroke: three-arm Stroke Oxygen Supplementation RCT

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## Scientific summary

### The Stroke Oxygen Study (SO<sub>2</sub>S)

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# Scientific summary

## Background

The introduction of specialist stroke units has reduced stroke-related mortality and disability. However, stroke is still the largest cause of complex disability, with half of all survivors requiring help with activities of daily living.

Mild hypoxia is not normally a problem in healthy adults, but it is common in stroke patients, and may result in further damage to an already ischaemic brain. Prophylactic oxygen therapy could prevent this additional deterioration by avoiding hypoxic events. However, oxygen treatment is not without side effects. There is an associated risk of infection with the therapy and a patient is confined to bed, impeding early mobilisation and rehabilitation.

Evidence from randomised controlled trials is conflicting, and insufficient to guide clinical practice. This is reflected in clinical uncertainty and conflicting guidelines based on the same evidence. An adequately powered study of routine oxygen supplementation (ROS) is needed to provide reliable information on which recommendations can be based.

## Objectives

1. To assess whether or not routine low-dose oxygen supplementation during the first few days following stroke improves patients' outcome compared with no oxygen.
2. To assess whether or not oxygen given at night only is more effective than continuous oxygen.

## Methods

The Stroke Oxygen Study (SO<sub>2</sub>S) is a multicentre, prospective, randomised, open, blinded-end point (PROBE) trial.

Participants were adult patients with a clinical diagnosis of acute stroke, who were within 24 hours of hospital admission and 48 hours of stroke onset. Patients were not eligible for the trial if they had any definite indications for, or contraindications to, oxygen treatment, or had another serious life-threatening condition that was likely to lead to death within the next 12 months.

Patients were recruited by clinicians and research nurses from 136 hospitals across England, Northern Ireland and Wales. Each hospital had an acute stroke unit. The research team at the recruiting centre randomised the patients via a computer-generated web-based system. Randomisation included a minimisation protocol, which allocated participants on a 1 : 1 : 1 basis to one of three trial arms:

1. Continuous oxygen: oxygen via nasal cannula continuously (day and night) for 72 hours after randomisation. The flow rate was set at 3 l/minute if baseline oxygen saturation was  $\leq 93\%$  or 2 l/minute if baseline saturation  $> 93\%$ .
2. Nocturnal oxygen: oxygen via nasal cannula overnight (21:00–07:00) for three consecutive nights. The flow rate was set at 3 l/minute if baseline oxygen saturation was  $\leq 93\%$  or 2 l/minute if the baseline saturation was  $> 93\%$ .
3. Control group: no ROS during the first 72 hours after randomisation unless required for other clinical reasons.

Patients' vital signs including oxygen saturation were monitored at least 6-hourly. Patients who developed clinical indications for oxygen treatment or needed a higher dose of oxygen than that delivered by the trial intervention were given additional oxygen, as determined by their treating physicians.

Baseline, randomisation and 1-week follow-up data were collected and entered online into the trial database by the research team based at the recruiting hospital. Baseline assessment included patient demographics, date and time of the stroke, oxygen therapy prior to randomisation, existing comorbidities, Glasgow Coma Scale (GCS), the Six Simple Variables (SSV) outcome prediction tool, the National Institutes of Health Stroke Scale (NIHSS) and consent details.

Patients were assessed by members of the local research team at week 1, or on the day of discharge, if sooner. The assessment included neurological function (NIHSS), vital status, adverse events, oxygen prescriptions for clinical indications in addition to the trial intervention, information on compliance, physiological variables, details of other treatments including antibiotics and sedatives, results of computerised tomography or magnetic resonance imaging head scans, the final diagnosis and contact details for follow-up.

The trial co-ordinating centre sent follow-up questionnaires via post to patients at 3, 6 and 12 months post randomisation. If the questionnaires were not returned, then patients or their preferred alternative contacts were telephoned to complete the questionnaire with a data assistant. The questionnaire booklet contained: the discharge date; current living arrangements; hospital readmissions; the modified Rankin Scale (mRS); the Barthel Index (BI); the European Quality of Life-5 Dimensions, three levels (EQ-5D-3L) and the European Quality of Life Visual Analogue Scale (EQ-VAS); the Nottingham Extended Activities of Daily Living (NEADL) scale; patient-reported outcome measures of sleep, eyesight, speech and memory; and which trial treatment they remembered receiving.

The primary outcome was disability assessed by the mRS (range from 0 = no disability to 5 = extreme disability) at 90 days post randomisation. Death was included as a score of 6. Secondary outcomes at day 7 included neurological improvement, NIHSS and mortality, and the lowest and highest oxygen saturations recorded during the 72-hour treatment period. Long-term outcomes were mortality, the number of patients alive and independent, the number of patients living at home, the BI, the EQ-5D-3L and EQ-VAS, and the NEADL, at the 3-, 6- and 12-month time points.

The original sample size calculation of 6000 patients was revised to 8000 patients in October 2012 to give a greater power to detect an interaction between stroke severity subgroups and the effect of oxygen compared with control.

Statistical analysis was by intention to treat. The primary outcome of mRS as a measure of disability at 90 days post randomisation was analysed using an ordinal logistic regression model. Analyses adjusted for age, sex, baseline NIHSS, baseline oxygen saturation and the SSV prognostic index for 6-month independence were also conducted. To avoid bias due to patients dying before the assessment point, the worst outcome on each of the scales was used for the analysis. Planned subgroup analyses were performed for the mRS only, based on a risk stratification approach. The subgroups were based on stroke severity (NIHSS at baseline), baseline oxygen saturation, oxygen treatment prior to randomisation, time since stroke onset, final diagnosis, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, GCS, age, comorbidities, thrombolysis and baseline SSV risk score for independence at 6 months.

To estimate the cost-effectiveness and cost-utility of ROS versus no oxygen supplementation, a within-trial economic evaluation was conducted. Additional analyses also compared all three trial arms. The cost per additional day of home time gained was calculated for the cost-effectiveness analysis and quality-adjusted life-years (QALYs) for the cost-utility analysis.

## Results

Between 24 April 2008 and 17 June 2013, 8003 patients were recruited to SO<sub>2</sub>S. Participants were randomised to the three trial arms, with 2668 in the control group, 2668 in the continuous oxygen group and 2667 in the nocturnal (night-time only) oxygen group.

Fully informed consent was given by 6991 (87%) of patients and assent given by a relative, carer or independent legal representative for 1012 (13%) patients. In total, over the 12-month participation, 89, 81 and 81 patients withdrew from the continuous oxygen, nocturnal oxygen and control groups, respectively.

Baseline characteristics were well balanced across the three trial arms. The overall mean age was 72 years [standard deviation (SD) 13 years] and 4398 (55%) patients were male. Of the 8003 patients, 7332 (92%) were independent in activities of daily living prior to their stroke, and this was equally distributed across the three groups. Medical history and comorbidities were also well matched, with ischaemic heart disease ( $n = 1602$ , 20%), heart failure ( $n = 657$ , 8%), atrial fibrillation ( $n = 1995$ , 25%) and chronic lung conditions ( $n = 812$ , 10%) recorded in each group. The median GCS score was 15 [interquartile range (IQR) 15–15] and the mean and median NIHSS scores were 7 and 5 (range 0–34), respectively. Ischaemic stroke was the final diagnosis in 82% of patients ( $n = 6555$ ), followed by primary intracerebral haemorrhage in 7% ( $n = 588$ ), transient ischaemic attack in 2% ( $n = 168$ ), and a non-stroke diagnosis in 4% ( $n = 292$ ). This information was unavailable for 106 patients (1%). The mean baseline oxygen saturation was 96.6% in the continuous (SD 1.7) and nocturnal oxygen (SD 1.6) groups and 96.7% (SD 1.7) in the control group. Oxygen therapy prior to randomisation was recorded in 20% of patients.

In the continuous oxygen arm 2158 (81%) patients completed the 72 hours of the trial intervention and 433 (16%) did not. Treatment adherence was similar in the nocturnal oxygen arm, with 2225 (83%) patients completing the three nights of oxygen therapy and 361 (14%) not doing so. Discharge from hospital was the most common reason for a patient not receiving the complete trial intervention. In the control group 2229 (84%) patients did not receive any ROS for the treatment of stroke. There were 23 (1%) patients who received oxygen therapy in the control group. This information was missing for 406 (15%) participants.

Routine oxygen supplementation did not improve functional outcome at 3 months compared with the control group. No statistically significant difference was recorded between the continuous oxygen and the nocturnal oxygen arms. The unadjusted odds ratio (OR) for a better outcome (lower mRS) was 0.97 [95% confidence interval (CI) 0.89 to 1.05;  $p = 0.5$ ] for oxygen (continuous and nocturnal combined) compared with the control, and 1.03 (95% CI 0.93 to 1.13;  $p = 0.6$ ) for continuous compared with nocturnal oxygen. The adjusted analyses yielded very similar results. For combined oxygen compared with control the OR was 0.97 (95% CI 0.89 to 1.06;  $p = 0.5$ ) and comparing the two oxygen interventions the OR was 1.01 (95% CI 0.92 to 1.12;  $p = 0.8$ ). No subgroups were identified that benefited from oxygen supplementation when the study population was divided based on the previously described parameters. Sensitivity analyses based on multiple imputation and an adherers-only analysis, aimed at investigating potential bias resulting from missing data, also revealed similar outcomes. Additional sensitivity analyses represented best- and worst-case scenarios, to set maximum plausible bounds for the effect of missing data.

Neurological improvement at week 1 did not differ between the three trial groups (median NIHSS score, 2; IQR, 1–6). Exploratory analyses of the data collected at the week 1 review did not show any appreciable differences for indicators of stress (highest heart rate, blood pressure and need for sedation), or for indicators of infection (antibiotic treatment and highest temperature). Highest and lowest oxygen saturations increased by 0.8% and 0.9%, respectively, in the continuous oxygen group when compared with the control group and by 0.5% and 0.4%, respectively, when compared with the nocturnal group ( $p < 0.001$  for all comparisons). Significantly more participants in the combined oxygen group than in the control group required oxygen for clinical reasons outside the trial intervention ( $p = 0.0008$ ). This was also the case in the continuous versus nocturnal oxygen groups ( $p = 0.03$ ).

Long-term functional outcome did not improve with oxygen therapy at any of the 3-, 6- and 12-month follow-up time points. The number of patients who were alive and independent and back in their own homes, the ability to perform basic activities of daily living (BI) or the Nottingham Extended Activities of Daily Living scale score and quality of life (EQ-5D-3L) at 90, 180 and 365 days were not increased by ROS. Mortality at 90 days was similar in the oxygen (both groups combined) and control group (hazard ratio 0.97, 99% CI 0.78 to 1.21;  $p = 0.8$ ), and for continuous oxygen versus oxygen at night only (hazard ratio 1.15, 99% CI 0.90 to 1.48;  $p = 0.1$ ). Neither patient-reported outcome measures nor the rate of readmission to hospital was improved by the trial interventions at any of the follow-up assessments. The number of serious adverse events did not differ at any of the three follow-up time points between the three trial arms.

The health economics analysis results were in line with the clinical findings. The trial treatment was associated with increased costs, as expected. Patients did not return home more quickly or experience more QALYs with either of the oxygen treatments. The cost-effectiveness analysis demonstrated a low probability of cost-effectiveness (31%) at £20,000/QALY.

## Conclusions

The results of the study have shown that low-dose oxygen supplementation in stroke patients who are not severely hypoxic does not confer any benefits either for the whole population or for any subgroups. This lack of benefit is consistent across all outcomes and for all time points up to 1 year. It also did not matter if the oxygen was given continuously or at night-time only. Future research should investigate the causes of hypoxia and explore ways of preventing desaturations in stroke patients.

## Trial registration

This trial is registered as Current Controlled Trials ISRCTN52416964 and European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2006-003479-11.

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