

## **PB-PG-0407-11433 – NIHR Research for Patient Benefit Programme – Final report**

**Project title:** The Stroke Oxygen Supplementation (SOS) study

### **Authors:**

Professor Christine Roffe - North Staffordshire Combined Healthcare NHS Trust

Professor Peter Crome - Keele University

Professor Richard Gray - Birmingham University

Professor Peter Jones - Keele University

Mrs Linda Handy - Strokes R Us

### **Plain language summary**

Stroke is a common and disabling condition. The introduction of stroke units has improved clinical care and recovery. However, it is not known which of the treatments given on the stroke unit lead to better outcomes. Breathing problems are common after the stroke, and blood oxygen levels may fall below normal which can easily be missed, especially at night. Oxygen treatment could prevent falls in blood oxygen levels and subsequent worsening of the brain damage. It is safe, cheap, and easily available. Therefore many clinicians use it even in patients with normal oxygen levels. There has been little research to support this practice, and one small trial of routine oxygen treatment given over 24 hours has shown no benefit.

The aim of this trial is to determine if patients benefit from routine oxygen supplementation and to examine whether routine oxygen supplementation at night only is as effective as continuous oxygen supplementation. Adult patients with an acute stroke who have no definite need for oxygen treatment are invited to participate in the study within 24 hours of hospital admission. Participants are randomised to be given oxygen continuously, at night only or not at all, unless a clinical need arose, for a period of 72 hours. Baseline assessments include demographic details, blood oxygen levels, and a neurological assessment. After 1 week the neurological assessment is repeated, and indicators of potential complications assessed. Oxygen use outside the protocol for medical reasons is recorded. Outcomes at 3, 6 and 12 months are assessed by postal questionnaire with questions assessing the level of disability and quality of life.

Six thousand six-hundred patients will have to be recruited to this study to show whether routine oxygen treatment after acute stroke improves short and long-term recovery from the stroke. RfPB-funded the start-up phase for this trial. The aim of this was to set up at least 30 study sites throughout the UK, to randomise the first 1000 participants, to test and fine-tune trial procedures, to establish whether it is feasible to recruit 6600 patients, and to apply for funding to complete the study. The RfPB-funded start-up phase has achieved all its aims and more. We recruited over 100 centres and more than 3500 participants. Trial procedures and follow-up are running well. We now have confirmation of funding from the NIHR HTA to complete the full study.

### **Keywords**

Stroke, Oxygen, Hypoxia, Acute stroke treatment, Acute stroke care, Randomized controlled, trial, Modified Rankin scale, Quality of Life

## Summary of research findings

### Background

Stroke is a common and disabling condition. Hypoxia after stroke is common, often missed, has significant adverse effects on the ischaemic brain, and is associated with worse outcome. Oxygen (O<sub>2</sub>) supplementation could prevent hypoxia and related brain damage. However, there is some evidence from preclinical studies that hyperoxia may be neurotoxic, and a small clinical study of short-term fixed dose O<sub>2</sub> supplementation did not show overall benefit. Current guidelines on O<sub>2</sub> supplementation are not based on evidence from clinical trials and differ between countries and organizations. A survey of British stroke physicians has shown that there is uncertainty about O<sub>2</sub> treatment after stroke. It is therefore important to produce reliable evidence on the balance of benefits and risks of O<sub>2</sub> supplementation.

### Aims and Objectives

To:

- determine if patients benefit from routine O<sub>2</sub> supplementation after stroke.
- establish whether nocturnal O<sub>2</sub> supplementation is as effective as, or more so than, continuous O<sub>2</sub> supplementation.

This study has 2 stages:

- stage one (start-up) is funded by the RfPB grant and aims to:
- recruit 1000 participants
- test and fine-tune study design and procedures
- establish the feasibility of large-scale multicentre recruitment
- secure funding to support the second phase (study completion)

### Methods

This is a multi-centre prospective randomized open blinded-endpoint study of routine O<sub>2</sub> supplementation after acute stroke. All adult patients with an acute stroke are eligible to be considered for study participation if they have a clinical diagnosis of acute stroke (WHO criteria) and have not been in hospital for longer than 24 hours.

Patients are excluded if the responsible doctor considers the patient to have definite indications for or contraindications to O<sub>2</sub> treatment at a rate of 2-3 L/min. The decision is left to the responsible clinician. Patients are also excluded if the stroke is not the main clinical problem, or if they have another serious life-threatening illness likely to lead to death within the next few months.

Participants are randomized in a 1:1:1 ratio into either:

- no routine O<sub>2</sub> supplementation during the first 3 days after randomization
- O<sub>2</sub> per nasal cannula overnight (21:00-7:00) for the first 3 nights after randomization. At 2 L/min if baseline O<sub>2</sub> saturation >93%; if ≤ 93% than 3 L/min
- O<sub>2</sub> per nasal cannula continuously (day and night) during the first 3 days after randomization using the same flow rates as above

Randomization is via a web-based randomization and data entry system developed by the Birmingham Clinical Trials Unit. This uses minimization based on a validated prognostic score (based on age, living alone, independence pre-stroke, normal verbal component of the Glasgow Coma Scale, ability to lift both arms, ability to walk), time from stroke to

randomization, whether or not the participant was given routine O2 treatment during ambulance transfer, and baseline O2 saturation.

Follow up is on day 7 after randomization, to confirm the final diagnosis, check compliance with the intervention, monitor complications and recovery, and at 3, 6 and 12 months by postal questionnaire. The questionnaire contains standard validated assessment tools: Modified Rankin Score (mRS), Barthel and Nottingham Extended Activities of Daily Living Index, EuroQuol.

Main outcome for the full study is death and disability (mRS score) at 3 months. Secondary outcomes at 1 week are neurological deterioration (NIHSS score) and at 3 months are mortality or severe disability (mRS>3) and the percentage of patients living at home.

### Key Findings

The RfPB funded set-up stage for the Stroke Oxygen study achieved all its aims and more.

#### Set-Up

We planned to recruit and open 30 study centres throughout the UK within the time period of the grant. The identification of suitable centres and their involvement in the study was greatly aided by the Stroke Research Network. Local SRN managers alerted their research centres to the study and several local SRNs invited us to present the study at their team meetings. This enabled the promotion and awareness of the study right across the SRN and from this local network managers and individual centres contacted us to express an interest. This actually meant that we had a far greater number of interested centres than was predicted on the original application. We were recruiting and setting-up new centres from the first day of the RfPB grant, rather than the predicted 3rd month. By month 5 of the funding we had become multi-centred and we had the predicted 30 centres open by month 8, by the end of this funding we had 107 collaborating centres.

#### Feasibility

The study itself had always been designed to be a pragmatic study and as such consultation with other stroke research centres in the design of the protocol and data capture had been sought very early on, as had the patient and public involvement. This enabled very clear and a workable study to be developed. As mentioned previously the feasibility of conducting the study at each centre was assessed by the local SRN and their research facilitators before these centres expressed an interest. Several of our centres were new to stroke research and with the support of their local SRN they became involved in the SOS – the local SRNs favoured them starting stroke research with SOS due to its simple and workable structure. Many of these centres have since opened other stroke research studies as they have gained experience and confidence in stroke research.

We intended to randomize 1000 participants within the 3 years of the RfPB grant. We achieved this milestone within 17 months and recruited over 3500 participants in total during the RfPB funding part of the study. The higher than expected number of centres participating and the very high recruitment rate has been made possible by the excellent research infrastructure created by the Stroke Research Network and the enthusiastic support of the local research staff. This also highlights that the feasibility of the study – from the actual centre to the recruitment and randomisation is successful, more so than predicted.

Study procedures are running smoothly. Only minor changes were required to the randomization website, the data collection forms and the procedures for follow-up. Follow-up data completion is at a rate 99% for day 7, 92% at 3 months, 95% at 6 months, and 86% at 12 months. Feedback from research teams was that they liked the study because they felt that the research question is important and relevant to the day to day care of the stroke patient. Many patients have views on oxygen and are also interested to find out the results. Local research staff appreciated the wide inclusion criteria and the simplicity of the enrolment and follow-up procedures. The development of hyperacute stroke centres with short length of stay and early repatriation of patients to other centres at times caused problems with follow-up of recruited participants transferred to outlying hospitals in different trusts. This problem was addressed by making the receiving hospitals into supplementary study centres for follow-up purposes.

#### Evaluation of Large Effect Sizes

Data from the RfPB funded start-up phase of the Stroke Oxygen Study was used to establish the number of participants required to reliably detect or exclude a treatment effect. Many previous acute stroke studies have been underpowered because the expected treatment effect was unrealistically large. The main objective of SO2S is to show that oxygen treatment improves functional outcome (mRS) at 3 months after stroke. Each point difference in the mRS represents a major difference in the level of disability (e.g. from severe to mild disability) (8). As the study is to be analysed by non-parametric methods, the minimum relevant difference needs to be calculated in terms of odds ratios per mRS level. An 0.8 reduction in the odds of an adverse outcome (higher mRS Score) would be clinically important and has been taken as the minimum relevant difference in this study. Analysis of the SOS Pilot study confirms that an effect of this size is plausible.

For this application it was originally believed that if the study was feasible in total 6000 participants would be required. During the recruitment of this stage of the trial this was re-evaluated. Recruitment of 6600 participants (2,200 in each of the 3 groups), based on the percentages within each level of the mRS, will provide at least 90% power at 5% significance level to detect an odds ratio of 0.83 for a more adverse outcome (higher mRS score) for the primary comparison of no O<sub>2</sub> (n=2,200) vs O<sub>2</sub> (n=4,400; continuous and night only groups combined). For the secondary comparison of O<sub>2</sub> at night only versus continuous oxygen we will have 90% power to detect a difference of this size at 5% significance level. These sample sizes allow for a 10% rate of missing outcome data (gives a safe margin, target would be less than 3%).

#### Expected impact on the relevant field and conclusion

The Stroke Oxygen Study start-up phase has raised awareness of the problem of hypoxia in stroke units throughout the UK and is likely to have contributed to better care.

Many of the research centres and local investigators contributing to SOS had previously no or very little practical experience in clinical research. Participation in SOS has given many of our collaborators the confidence and skills to introduce clinical research into day to day care of patients.

Evidence of successful start-up and a study size calculation based on the blinded results so far allowed us to apply for funding from NIHR HTA to enable us to complete the study and

answer the research question. We have recently had confirmation that this has been granted and will start on 01.09.2011. The RfPB start-up grant has helped us to put all the procedures in place to make this study a success.

### **Patient and public involvement**

While developing the protocol we conducted focus group meetings with stroke groups in the region (Dysphasia Support Stafford, Strokes R Us Stoke-on-Trent, and Dysphasia Support Cannock) (45). Group members were consulted on the relevance of the research and study design. Outcome assessments were also discussed. While there was agreement with the standard tools suggested (Rankin, Barthel, EuroQuol), group members were particularly interested in finding out about effects of the treatment on softer outcomes such as memory, speech, and sleep, which are not usually addressed in follow-up questionnaires for multicentre trials. We have therefore included questions relating to these in the data collection. The content and layout of the patient and relative information forms was reviewed and edited by members of Strokes R Us and Different Strokes (Coventry) and this has made the forms easier to read and understand.

While the study has been active we have received feedback from participants, either by telephone or written communication, on the questionnaires we send out. The main focus is the lack of detail on how their eyesight is (if it has improved or deteriorated) and as such for the second stage of the trial this question will be incorporated into the questionnaires. The common comments we receive back are that they welcome the opportunity to feedback how they are and to have participated in the research.

We have attended various events, the UK Stroke Forum (as an exhibitor) and local Stroke Research Network events (either presenting or as an exhibitor) where we have met members of the public and patients to discuss the study.

### **Data sharing statement**

See link

[\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

### **Disclaimer**

This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0407-11433). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This project was carried out between 01 September 2008 and August 2011. This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.