Normobaric Oxygen Therapy in Acute Stroke: A Systematic Review and Meta-Analysis

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Keywords

Acute stroke · Oxygen therapy · Neuroprotection in stroke · Systematic reviews

Abstract

Purpose: Normobaric oxygen (NBO) is potentially a readily accessible neuroprotective therapy. We undertook a systematic review to assess NBO in acute stroke. **Methods:** MEDLINE, EMBASE, and CENTRAL databases were searched to December 2020. Randomized controlled trials of NBO administered <7 days after stroke to normoxic patients with no other indication for oxygen were identified. Data on early neurological recovery; functional outcome; mortality; oxygen saturation, and imaging markers were collected. **Findings:** Fifteen publications involving 12 cohorts and 9,255 participants were identified. One study with 8,003 participants had low risk of bias, but the designs of smaller trials had limitations. Ninety-seven per cent of participants were in studies of low-flow oxygen (≤ 4 L/min). 82.8% had ischaemic stroke. Median time to treatment was 19.3 h. Meta-analysis demonstrated no significant effect on: reduction in National Institutes of Health Stroke Scale at 7 days in all stroke or ischaemic stroke only (mean difference -0.16 [-1.11 to 0.80] and -0.73 [-3.54 to 2.08], respectively); modified Rankin scale at 3–6 months of follow-up (combined stan-

dardized mean difference [SMD] -0.08 [-0.38 to 0.22]; 3 months SMD -0.01 [-0.03 to 0.029]; 6-month SMD -0.20 [-1.49 to 1.09]), or mortality (odds ratio 1.15 [0.87 – 1.53]). **Discussion:** The majority of patients were administered low-flow oxygen in the sub-acute phase. Intervention strategies targeted at modification of early tissue survival (higher oxygen delivery and administration at early time points when significant volumes of viable tissue persist) have not been tested adequately. **Conclusion:** Studies of NBO have shown no significant effect on early neurological recovery, functional outcome, or mortality in acute stroke. Oxygen has been predominantly low-flow and commenced in the sub-acute phase.

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Introduction

Low tissue oxygen delivery resulting from vessel occlusion is central to the bioenergetic failure that characterizes acute ischaemic stroke. Reflecting limited clinical data, current guidelines from the European Stroke Organization [1] and American Heart Association [2] do not advocate the routine use of supplemental oxygen for non-hypoxic patients (those in whom oxygen saturation is $\geq 95\%$). Reperfusion with thrombolytic drugs or endovas-

cular mechanical thrombectomy is highly effective but benefit is time-dependent and times to effect reperfusion may be several hours after treatment initiation. A treatment that is able to retard or prevent hypoxic cell death may therefore have potential value as a neuroprotectant in this population, as well as those for whom reperfusion is not indicated or is ineffective. Supplemental normobaric oxygen (NBO) is usually a readily available resource in acute hospital environments. In animal models, low levels of tissue oxygen pressure in the ischaemic penumbra are significantly improved by NBO therapy despite only mild increases in arterial oxygen content [3] indicating therapeutic potential even in the absence of restoring blood flow. In rodent models of permanent focal ischaemia, 100% oxygen commenced 5 min after induction of transient ischaemia (up to 3 h duration) resulted in smaller final infarct volumes than control [4], possibly due to persistence of salvageable penumbra. NBO-treated rats have shown attenuation of DWI lesions and smaller infarct size, and the combination of NBO and intravenous thrombolysis has been shown to be safe and effective in a rat model of stroke with near complete reperfusion, small infarct volumes and no difference in rates of haemorrhage and brain swelling [5, 6]. This review aimed to identify all randomized controlled trials of NBO in patients diagnosed with acute stroke and examined the effect on early recovery, functional outcome, and mortality.

Methods

The protocol for the review has been registered with PROSPERO (CRD42018116250). MEDLINE, EMBASE, and CENTRAL databases were searched using MeSH terms and Boolean operators from inception to December 2020, search criteria are available in online supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000521027). Studies were identified by 2 researchers independently (A.M. and S.N.) by screening titles and abstracts, a third researcher (V.B.) resolved any discrepancies. The following inclusion and exclusion criteria were used:

- Population – patients with stroke in the last 7 days entered into randomized controlled trials of NBO. Quasi-randomized trials (e.g., allocation by date of birth) were accepted but clinical trials without randomization were excluded.
- Intervention – NBO administered <7 days after stroke (ischaemic or haemorrhagic) to normoxic patients with no other indication for oxygen therapy. This included NBO at any concentration or flow rate and for any length of time. Oxygen treatment at 2–4 L/min delivered by nasal cannula was considered low flow; higher rates by mask were considered high flow.
- Comparison – control groups receiving either no oxygen or oxygen only given if clinically indicated
- Outcome – data were collected from published abstracts, articles, or clinical trials databases on study design, details of oxy-

gen therapy, time to treatment from stroke onset, early recovery within 7 days; functional outcome within 9 months; mortality; oxygen saturation and imaging markers. Data from multiple publications from the same cohort were combined rather than being treated separately. Efforts were made to contact authors where initially retrieved data were insufficient.

For the purposes of meta-analysis, mean difference or standardized mean difference was calculated for functional outcome, early neurological recovery, and oxygen saturation; and odds ratio was calculated for mortality. A subgroup analysis for ischaemic stroke only was carried out for these outcomes where data allowed. The following statistical transformations were employed. Mean and variance were calculated from median, range, and IQR as per the methodology of Hozo et al. [7] and Luo et al. [8]. Pooled standard deviation was calculated as per the Cochrane Handbook [9]. Standard deviation was calculated from mean and *p* value using the RevMan calculator [10]. Odds ratio was converted to standardized mean difference as per Hasselblad and Hedges [11]. Calculation of statistics and meta-analysis were performed using StatsDirect [12] and Meta-Essentials [13]. Random effects models (DerSimonian Laird method) were utilized due to the heterogeneity of the interventions among studies.

Assessment of bias was performed using the Cochrane risk of bias assessment tool [9]. Two researchers (A.M. and S.N.) assessed risk of bias of each included study in 6 domains: random sequence generation; allocation concealment; blinding of participant; blinding of outcome assessment; incomplete outcome; and selective reporting. Any discrepancies were resolved by a third researcher (V.B.). Publication bias for the main outcomes was analysed by Egger's test [14] calculated by StatsDirect.

Results

The literature search process is summarized below in Figure 1. After screening of titles and abstracts, 19 publications were identified. Fifteen publications involving 12 cohorts were included in the final analysis, these are summarized in Table 1 [15–29]; 4 were excluded (3 due to no available data [30–32], 1 due to lack of randomization [33]). Seven publications included outcomes that could be analysed in meta-analysis.

Baseline Population

The total number of participants was 9,255, 8,003 (86%) of whom were in 1 trial (Roffe et al. [15]). The mean age of participants (where provided) was 72.2 years. The proportion of patients with ischaemic stroke was 82.8% (range 61–100%); the rate of stroke mimics was only declared in the Roffe et al. [15] study (3.5%). Mean NIHSS across all patients was 7. Oxygen regimes ranged from 2 L/min via nasal cannula nocturnally to 45 L/min via face-mask for 8 h from randomization. Ninety-seven per cent of participants were involved in studies of low-flow oxygen (≤ 4 L/min). Most protocols aimed to begin treatment

Fig. 1. Literature search.

within the first 24 h following symptom onset. The median time to treatment was 19.3 h. A summary of trial protocols is presented in Table 2.

Bias Assessment

The risk of bias assessment is shown in Table 3. Many studies had high risk of bias in at least one domain although the Roffe et al. [15] trial which enrolled the majority of patients did not. Insufficient methodological detail was published to allow determination of risk of bias for a number of smaller studies. Singhal [19] was not published and was evaluated on the basis of conference abstracts and a clinical trial registry. Egger's test had p value >0.05 indicating a low risk of publication bias for all outcomes other than follow-up modified Rankin scale (mRS) though this result may be due to heterogeneity of studies rather than true publication bias. Funnel plot symmetry was seen in all other outcomes; however, the interpretation of this was cautious given the low number of studies.

Outcomes

Trials used similar and well-established measures of outcomes, but the timing of assessments varied. Trials

broadly fell into 2 categories – large trials of low-flow oxygen used in the first 24–72 h primarily assessing functional outcomes; or smaller trials of high-flow oxygen used in the first 12–24 h primarily assessing early neurological recovery. Outcomes examined, the timing of their assessment, and numbers of participants for each are summarized in Table 4.

Early Neurological Recovery

Assessment of recovery in the first 7 days following stroke was measured using the National Institute of Health Stroke Scale (NIHSS). Six trials [15, 17, 18, 24, 27, 28], including the largest study, measured baseline and day 7 NIHSS. Meta-analysis (Fig. 2) of 5 of 6 studies demonstrated no significant difference in reduction in NIHSS at 7 days in all stroke (mean difference = -0.16 [-1.11 to 0.80]). The remaining study [27] was not included in the meta-analysis due to insufficient data. Two small trials [19, 28] measured NIHSS at early time points (0, 4, and 24 h); high-flow oxygen was found to improve NIHSS at 24 h in one study [28] but had no effect in the other [19]. Four studies also measured neurological recovery using the Scandinavian Stroke Scale (SSS), 2 studies [20, 23] in

Table 1. Summary of studies

First author	Title	Journal	Year	Patients, n	Inclusion criteria	Therapy to experimental groups	Time to treatment	Control group therapy	Main outcome measures
Roffe et al. [15]	Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke the stroke oxygen study randomized clinical trial	JAMA	2017	8,003	Acute stroke <24 h, no contraindication to oxygen treatment	Oxygen via NC, 2 L/min if sats >93% or 3 L/min if sats ≤93% (1) for 72 h (2) overnight 21:00–07:00 for 3 nights	<24 h	Room air or oxygen only if clinically indicated	mRS at 90 days and NIHSS at day 7
Ronning and Guldvog [16]	Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial	Stroke	1999	550	All patients with acute stroke	100% oxygen 3 L/min for 24 h	<24 h	Room air	Mortality and SSS
Roffe et al. [17]/ Ali et al. [18]*	The stroke oxygen pilot study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke – effect on key outcomes at 6 months	PLoS One	2011 + 2013	301	Acute stroke <24 h, no contraindication to oxygen treatment	Oxygen via NC for 72 h, 2 L/min if sats >93% or 3 L/min if sats ≤93%	<24 h	Room air or oxygen only if clinically indicated	NIHSS and SSS at 1 week and mRS at 6 months
Singhal [19]	NBO therapy in acute ischaemic stroke trial	Unpublished (conference Abstract)	2013	85	Age >18, onset <9 h, NIHSS ≥ 4	Oxygen 30–45 L/min for 8 h	<9 h	Room air 30–45 L/min for 8 h	NIHSS at 4 and 24 h
Roffe et al. [20]	A randomized controlled trial of the effect of fixed-dose routine nocturnal oxygen supplementation on oxygen saturation in patients with acute stroke	J Stroke Cerebrovasc Dis	2010	63	Acute stroke within 72 h. Not moribund and no other clinical need for oxygen	Oxygen 2 L/min via NC for 12 h overnight for first night	<72 h	No oxygen supplementation unless clinically indicated	Desaturations, lowest SpO ₂ , feasibility, SSS
Mazdeh et al. [21]	Effects of normobaric hyperoxia in severe acute stroke: a randomized controlled clinical trial study	Acta Med Iran	2014	52	Aged 40–70, ischaemic or haemorrhagic stroke within 12 h, NIHSS 7–9	Venturi 50% for 12 h	<12 h	No oxygen supplementation	mRS at 6 months, BI
Sills et al. [22]	The effect of oxygen on sleep in stroke patients	Age Ageing	2004	50	Acute stroke patients within 72 h	2 L/min via NC for 12 h overnight for first night	<72 h	Room air	Oxygen saturation and quality of sleep
Roffe et al. [23]	The effect of short-term nocturnal oxygen treatment on early neurological scores after stroke	Age Ageing	2005	44	Acute stroke within 72 h	2 L/min via NC for one night	<72 h	No oxygen supplementation	Overnight oxygen saturation, SSS
Padma et al. [24]	NBO therapy in acute ischaemic stroke: a pilot study in Indian patients	Ann Indian Acad Neurol	2010	40	Onset <12 h, NIHSS > 4, not for tPA, DWI-PWI mismatch	Oxygen 10 L/min for 12 h	<12 h	Room air or O ₂ via face mask to maintain sats >95%	NIHSS, mRS, BI, MRI lesion volume
Wiboonsirichai [25]	Effects of high flow oxygen therapy on oxygen desaturation index in patients with acute ischaemic stroke	Respirology	2017	30	Acute stroke <72 h with NIHSS ≥ 5	24% O ₂ at 20 L/min via optiflow versus O ₂ via NC 2 L/min	<72 h	No oxygen supplementation	Oxygen desaturation index, mean oxygen sat, lowest oxygen sat, improvement in NIHSS by day 7
Wu et al. [26]**	Evaluating effects of NBO therapy in acute stroke with MRI-based predictive models	Med Gas Res	2012	19	Anterior circulation (non-lacunar) stroke within 12 h, or last seen well <15 h, not for tPA, NIHSS ≥ 4, mRS ≤ 1, DWI-PWI mismatch	45 L/min for 8 h	<12 h	Room air or O ₂ 1–3 L/min to maintain sats >95%	DWI lesion growth
Shi et al. [27]	Normobaric hyperoxia reduces blood occludin fragments in rats and patients with acute ischaemic stroke	Stroke	2017	18	Aged >18, AIS eligible for thrombolysis, NIHSS 4–25, mRS < 1	10 L/min via face mask for 24 h	<4.5 h	Room air	NIHSS in first week, blood occludin and claudin-5 levels

Table 1 (continued)

First author	Title	Journal	Year	Patients, n	Inclusion criteria	Therapy to experimental groups	Time to treatment	Control group therapy	Main outcome measures
Singhal et al. [28]**	A pilot study of NBO therapy in acute ischaemic stroke	Stroke	2005	16	Anterior circulation (non-lacunar) stroke within 12 h, or last seen well <15 h, not for tPA, NIHSS ≥ 4 , mRS ≤ 1 , DWI-PWI mismatch	45 L/min for 8 h	<12 h	Room air or O ₂ 1–3 L/min to maintain sats >95%	NIHSS and MRI at 0, 4, 24 h, and 7 days, mRS and SSS at 0 h and 3 months
Gonzalez et al. [29]**	Stability of large diffusion/perfusion mismatch in anterior circulation strokes for 4 or more hours	BMC Neurol	2010	14	Anterior circulation (non-lacunar) stroke within 12 h, or last seen well <15 h, not for tPA, NIHSS ≥ 4 , mRS ≤ 1 , DWI-PWI mismatch	45 L/min for 8 h	<12 h	Room air or O ₂ 1–3 L/min to maintain sats >95%	Persistence of DWI-PWI mismatch

NIHSS, National Institute for Health Stroke Scale; mRS, modified Rankin scale; SSS, Scandinavian Stroke Scale; tPA, tissue plasminogen activator (thrombolysis); NC, nasal cannula; DWI, diffusion weighted imaging; PWI, perfusion weighted imaging; NBO, normobaric oxygen. * Data from same cohort published at 2 time points. ** Studies performed with same cohort.

Table 2. Summary of trial protocols

	Trials, n	Participants, n
<i>Oxygen regimen</i>		
2–3 L/min via nasal cannula	6	9,011
50% via Venturi mask	1	52
10–20 L/min via face mask	3	88
30–45 L/min via face mask	4	104
<i>Time to treatment</i>		
<12, h	7	214
<24, h	3	8,854
<72, h	4	187

the early time period (48 h) and the others at 3 [28] and 7 months [16], respectively. No study found a difference in recovery measured by SSS between oxygen and control.

Functional Outcome

Longer term outcomes in functional ability following stroke were measured using mRS and Barthel Index (BI). mRS was measured at 3 months in 3 studies [15, 24, 28] and 6 months in 2 studies [18, 21]. Meta-analysis of 4 studies (the 5th [24] had insufficient data) for each time point and combined for both time points found no effect of NBO on mRS outcome (combined standardized mean difference [SMD] = -0.08 [-0.38 to 0.22]; 3-month SMD = -0.01 [-0.03 to 0.029]; 6-month SMD = -0.20 [-1.49 to 1.09]). BI was measured at 3 months [15, 24], 6 months [17, 18, 21], or 7 months [16] with no significant effect of NBO on BI outcome found in any study.

Mortality

Mortality was assessed at 7 days [15], 3 months [15], 6 months [18, 21], and 1 year [16]. Meta-analysis for combined 3-, 6-, and 12-month data demonstrated no significant effect of NBO on mortality (odds ratio = 1.15 [0.87 – 1.53]). One study [19] was stopped early due to excess mortality in the NBO group; however, a blinded reviewer concluded that 1 death in each group was “probably” related to treatment allocation and all other deaths were unrelated.

Oxygen Saturation

Baseline oxygen saturation was >94% in 4 studies [15, 18, 20, 23]. Oxygen therapy was associated with raised oxygen saturation [15], reduced likelihood of desaturation [20], and higher nocturnal oxygen saturation [20, 22, 23].

Early neurological recovery - NIHSS

Study name / Subgroup name	Effect Size	CI LL	CI UL	Weight	I ²
Roffe 2017	0.00	-0.11	0.11	97.27%	
Roffe/Ali 2013	-0.13	-0.79	0.52	2.73%	
All stroke	0.00	-0.27	0.27	99.27%	0.00%
Singhal 2005	-1.33	-4.03	1.37	5.54%	
Padma 2010	0.22	-0.57	1.01	58.47%	
Singhal 2013	0.20	-0.79	1.19	35.98%	
Ischaemic stroke only	0.13	-0.95	1.20	0.73%	0.00%
Combined effect size	0.00	-0.03	0.03		0.00%

Functional outcome - modified Rankin scale

Study name / Subgroup name	Effect Size	CI LL	CI UL	Weight	I ²
Singhal 2005	-0.47	-1.49	0.56	0.25%	
Roffe 2017	-0.01	-0.05	0.04	99.75%	
3 months mRS	-0.01	-0.30	0.29	62.68%	0.00%
Mazdeh 2014	-0.33	-0.76	0.09	38.41%	
Roffe/Ali 2013	-0.12	-0.45	0.20	61.59%	
6 months mRS	-0.20	-1.49	1.09	37.32%	0.00%
Combined effect size	-0.08	-0.38	0.22		19.38%

Mortality

Study name	Effect size	CI Lower limit	CI Upper limit	Weight	I ²
Mazdeh 2014	0.13	-0.66	0.93	0.60%	
Roffe 2017	0.00	-0.05	0.05	51.78%	
Roffe/Ali 2013	0.02	-0.13	0.17	13.43%	
Ronning 1999	-0.05	-0.14	0.04	29.61%	
Singhal 2013	0.28	0.00	0.56	4.58%	
Combined effect size	0.00	-0.09	0.09		24.35%

Fig. 2. Meta-analysis – left shift favours NBO, right shift favours control. NBO, normobaric oxygen; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; LL, lower limit; UL, upper limit.

Table 3. Risk of bias assessment

	Random sequence generation	Allocation concealment	Blinding of participant	Blinding of outcome assessment	Incomplete outcome	Selective reporting
Roffe et al. [15]	Low	Low	Low	Low	Low	Low
Ronning Guldvog [16]	High	High	Low	Low	Low	High
Roffe et al. [17]/Ali et al. [18]	Low	Low	Unknown	Unknown	Low	Low
Singhal [19]	Unknown	Low	Low	Low	Low	Low
Roffe et al. [20]	Low	Low	Low	High	Low	Low
Mazdeh et al. [21]	Unknown	Unknown	High	High	High	High
Sills et al. [22]	Unknown	Unknown	Low	High	Unknown	Unknown
Roffe et al. [23]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Padma et al. [24]	Low	Unknown	Low	High	Unknown	High
Wiboonsirichai [25]	Unknown	Unknown	Low	High	Unknown	Unknown
Wu et al. [26]	Low	Low	Low	Low	Low	Low
Shi et al. [27]	High	Unknown	High	High	Unknown	Unknown
Singhal et al. [28]	Low	Low	Low	Low	Low	Low
Gonzalez et al. [29]	Low	Low	Low	Low	Low	Low

Table 4. Numbers included for trial outcome measures and timing of assessment

	Baseline	4 h	24 h	48 h	72 h	7 days	Discharge	3 months	6 months	7 months	1 year
Neurological recovery											
NIHSS	8,493 (15, 17, 18, 24, 25, 27, 28)	101 (19, 28)	119 (19, 27, 28)		18 (27)	8,408 (15, 17, 18, 24, 25, 27, 28)		16 (28)			
SSS	673 (16, 20, 23, 28)			107 (20, 23)				16 (28)		550 (16)	
Functional outcome											
MRS	56 (24, 28)						52 (21)	8,059 (15, 24, 28)	353 (17, 18, 21)		
BI	590 (16, 24)					8,003 (15)	52 (21)	8,043 (15, 24)	353 (17, 18, 21)	550 (16)	
Mortality								8,003 (15)	353 (17, 18, 21)		550 (16)
Oxygen saturation	8,354 (15, 17, 18, 22)					16 (28, 29)					
MRI lesion growth	19 (26, 28, 29)	19 (26, 28, 29)	19 (26, 28, 29)				19 (26)	16 (28)			
Blood markers	18 (27)		18 (27)		18 (27)						

Each square shows the number of individuals examined for each outcome measure at a given time point across all trials. Blank squares signify no measurement of the outcome at that time point. n (x), number of participants (studies including this measure); NIHSS, National Institute of Health Stroke Scale; SSS, Scandinavian Stroke Scale; mRS, modified Rankin scale; BI, Barthel Index.

Imaging Outcomes

Imaging outcomes were studied in 2 cohorts [19, 26, 28, 29], reporting reduction in DWI lesion volume with NBO at 4 h but not 24 h in one study [28], and no significant difference in DWI lesion growth in the other cohort [19].

Adverse Events

Three trials reported adverse outcomes. In the largest trial of 8,003 patients [15], no oxygen-related adverse events were reported and the total number of serious adverse events was lower in the nocturnal oxygen group than in the continuous oxygen and control groups. In a study of 289 patients [17], there was no significant difference in peak heart rate, peak blood pressure, peak temperature, or proportions requiring antibiotics or sedatives. One study [19] was stopped early due to excess mortality in the experimental group; however, independent review determined that 1 death in each group was related to the intervention and all other deaths were unrelated.

Subgroup Analysis

The majority of studies reported outcomes jointly for ischaemic and haemorrhagic stroke though 3 studies examined ischaemic stroke only [19, 24, 28], all of which also used high-flow oxygen. The only outcome reported with sufficient data across all 3 studies was NIHSS at baseline and 7 days. The difference in reduction in NIHSS at 7 days was not significant (mean difference -0.73 [-3.54 to 2.08], respectively).

Discussion

Our systematic review and meta-analysis found no effect of NBO on any outcome, including early neurological improvement and functional outcome at 3–6 months. Protocols varied widely amongst trials, but the majority of data (6/12 trials and 9,011/9,255 patients) relate to low-flow oxygen (2–4 L/min via nasal cannula) commenced predominantly in the 12–24 h period after stroke onset, establishing the safety of low-flow oxygen in acute stroke patients. Animal data have explored the potential for NBO supplementation to improve tissue oxygenation in the ischaemic penumbra as a means of delaying irreversible metabolic failure in ischaemic tissue pending definitive reperfusion, a concept termed “penumbral freezing” [34]. Completed clinical trials have not adequately tested this concept, having delivered insufficient supplementary oxygen predominantly at time points well be-

yond those when substantial volumes of penumbra typically persist.

Advantages of therapeutic oxygen supplementation over conventional pharmacological approaches to neuroprotection include low cost; familiarity and universal availability in healthcare systems; few adverse effects and contraindications; and potential for application in pre-hospital care. Use of oxygen carrying molecules such as perfluorocarbons (PFCs) could further increase oxygen delivery to ischaemic tissues. Previous animal studies of PFCs combined with NBO in models of transient and permanent middle cerebral artery occlusion have found reduction in infarct size [35, 36] or delay in infarct growth [37], though infarct size was determined very early (4–6 h) in some of the studies. Further animal studies have demonstrated combined use of PFCs and NBO to identify areas of penumbral tissue using T2* MRI blood oxygen level dependent imaging in a combined therapeutic and diagnostic approach [38]. Early phase human trials of an alternative PFC (administered without NBO) have demonstrated safety and further trials are planned [39].

Reperfusion therapies address the underlying cause of tissue ischaemia but the requirement for diagnostic confirmation and imaging, currently overwhelmingly hospital-based, incurs inevitable delay. The time from symptom onset to initiation of treatment was 240 ± 72 min in a meta-analysis of the alteplase thrombolysis trials, [40], and the time period from symptom onset to arterial puncture was 250.4 ± 95.6 min in the mechanical thrombectomy trials of the HERMES group [41]. Dependent on factors including clot burden, reperfusion may not be achieved for some time after treatment initiation, and both drug treatment and thrombectomy may fail to effect reperfusion in a moderate to high proportion of patients treated. In countries with well-equipped ambulance services, delivery of NBO is feasible from the point of provisional diagnosis in the field and could be continued during hospital transfers whilst suitability for reperfusion therapies is determined by clinical evaluation and neuroimaging. Pre-hospital paramedic-delivered clinical trials in acute stroke have been shown to be feasible in the UK (RIGHT-2 [42]) and USA (FAST-MAG [43]) though rates of mimics can be high (26% in RIGHT-2 compared with 3.9% in FAST-MAG) and a significant proportion have haemorrhagic stroke (13% in RIGHT-2, 22.8% in FAST-MAG). The safety of NBO in haemorrhagic stroke and common mimics would ideally need to be established in this pre-hospital setting, but there is wide experience of supplemental oxygen in a broad range of clinical situations; animal studies of NBO in haemorrhagic stroke

have shown no effect [44] or clinical improvement [45] compared to control. Oxygen saturations have been found to decrease during intra-hospital transfers, e.g., to CT or MRI scanning [46]. Inter-hospital transfers are commonly required in order to access mechanical thrombectomy, often following initiation of thrombolysis. Animal studies have suggested NBO and thrombolysis are safe in combination [6]. Any potential “penumbral freezing” effect of NBO would be advantageous for patients travelling to another site for mechanical thrombectomy.

Of the participants included in the trials in this review only 2% ($n = 192$) received oxygen over 10 L/min. The largest trial of high-flow oxygen [19] (>30 L/min) in a hyperacute population was halted early due to excess mortality in the experimental group; however, independent review determined that the effect was not due to the intervention. Some concerns have been raised previously about the potential toxicity of high-flow oxygen in the acute stroke period due to factors such as formation of reactive oxygen species [47] and risk of hyperoxic acute lung injury [48]. While hyperoxia causes cerebral vasoconstriction, this does not reduce brain perfusion significantly in healthy individuals [49]. Whether hyperoxic vasoconstriction may compromise critically perfused brain regions in the setting of acute ischaemic stroke or intracerebral haemorrhage is uncertain, and the balance of any change in blood flow against increased oxygen delivery is challenging to determine. A study [50] of patients intubated prior to mechanical thrombectomy for acute ischaemic stroke with subsequent intensive care admission found patients with $\text{PaO}_2 > 120$ mm Hg (16 kPa) had a poorer functional outcome as measured by the mRS than those < 120 mm Hg. This was, however, an observational study. A recent systematic review [47] identified that unfavourable outcome had been found in retrospective studies of intracerebral haemorrhage or subarachnoid haemorrhage but not ischaemic stroke and there were few prospective studies. The tolerability of high-flow oxygen via mask compared to low-flow oxygen via nasal cannula is poorer [51, 52] and may present an additional challenge.

Only 2.3% of participants were in trials aiming to deliver NBO within 12 h of symptom onset. Median interval from stroke onset to treatment initiation was 19 h. As highlighted above the period from symptom onset to initiation of revascularisation therapy has been approximately 4 h in clinical trials meaning that based on current data on NBO we are unable to draw conclusions regarding its potential role in penumbral freezing and neuroprotection. Initiation of treatment beyond the hyperacute

window has been proposed as the primary reason for the neutral results of trials of neuroprotective agents in stroke to date [53].

Additionally, the inclusion criteria for the majority of the trials permitted a wide selection of acute stroke patients including haemorrhagic stroke. In order to test the penumbral freezing hypothesis, selection of reperfusion-eligible patients with appropriate imaging features likely offers the most efficient design for future trials such as proposed in the upcoming PROOF trial [54] which will select patients with large vessel occlusion and compare NBO ≥ 40 L/min versus standard care within 3 h of symptom onset. Completed trials lack sufficient data on physiological brain imaging and timing or effectiveness of reperfusion therapies (if permitted) to allow even exploratory analysis.

The major limitation of this systematic review and meta-analysis is the large proportion of participants contributed by a single trial. Meta-analysis therefore largely reflects the results of this trial. Analyses of other sub-groups such as hyperacute populations or high-flow oxygen are limited by the small numbers in trials using such protocols. Detailed methodology was not available for several smaller clinical trials some of which had a high risk of bias often due to lack of blinding in outcome assessment. These factors highlight the lack of data for high-flow oxygen during the hyperacute period after stroke onset.

Conclusions

Studies to date of NBO have shown no significant effect on early recovery, functional outcome, or mortality in acute stroke. Study protocols and populations have varied considerably. Populations have included signifi-

cant numbers of non-ischaemic stroke and stroke mimics. Oxygen has been predominantly low flow commenced in the sub-acute phase. Further study of high-flow oxygen in the hyperacute period may be warranted.

Statement of Ethics

The article is exempt from Ethical Committee approval as it is a systematic review of publicly available data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.M. and S.N. carried out the literature search and identified suitable studies. V.B. resolved any conflicts in study inclusion. A.M. developed the protocol, carried out the analysis, and wrote the first draft. K.M. reviewed and edited the protocol and drafts. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/q4sv2/?view_only=6f96ca6aaba24d9f9bef0b76c187ac58.

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