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THERAPEUTICS

Emergency oxygen use

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic for this series, please email us at practice@bmj.com.

A 60 year old man with chronic obstructive pulmonary disease (COPD) requiring long term home oxygen therapy called an ambulance because of severe breathlessness. With nasal oxygen therapy at 2 L/minute, his oxygen saturation was 88%. The paramedics administered nebulised salbutamol driven by oxygen (approximately 60% oxygen) and then gave oxygen via a reservoir mask (approximately 80% oxygen) during a 27 minute journey to hospital. He became drowsy before arrival in the emergency department, and blood gases showed evidence of respiratory acidosis with pH 7.19 (normal range 7.35-7.45), elevated CO_2 level at 11.3 kPa (normal range 4.5-6.0), elevated bicarbonate level at 32 mmol/L (normal range 21.0-28.0), and high oxygen partial pressure at PaO_2 18.5 kPa (normal range 12.0-15.0) with high oxygen saturation at 100% (normal range 95-98%). He required intubation and ventilation for acidotic hypercapnic respiratory failure, but he died on the second day of ventilation.

Emergency oxygen use

Oxygen is administered to about a third of emergency ambulance patients, and about 15% of UK hospital patients receive oxygen therapy on any given day.[1 2] Common indications for emergency oxygen therapy are shown in box 1, while box 2 shows some common conditions for which oxygen was given routinely in the past but is now recommended only if the patient is hypoxaemic. Patients with carbon monoxide or cyanide poisoning and patients with some diving or altitude emergencies benefit from hyperoxaemia, but the prevention of hypoxaemia is the goal of oxygen therapy in all other conditions. Several publications have raised concerns about the risks of either insufficient or excessive oxygen therapy.[3-9]

Box 1 | Medical emergencies where oxygen is likely to be required until patient is stable and within target saturation range[3]

Medical emergencies requiring high concentration oxygen in all cases
- Shock, sepsis, major trauma
- Cardiac arrest and during resuscitation
- Anaphylaxis
- Carbon monoxide or cyanide poisoning

Medical emergencies where patients are likely to need oxygen therapy (ranging from low to high concentration depending on disease severity), with target saturation range 94-98%
- Pneumonia
- Asthma
- Acute heart failure
- Pulmonary embolism

Medical emergencies where patients are likely to need controlled oxygen, with target saturation range 88-92%
- Acute exacerbation of chronic obstructive pulmonary disease (COPD)
- Acute illness in patients with cystic fibrosis
- Acute respiratory illness in patients with obesity hypoventilation syndrome or morbid obesity
- Acute respiratory illness in patients with chronic neuromuscular or musculoskeletal conditions

Box 2 | Common medical emergencies for which oxygen was given routinely in the past but is now advised only if the patient is hypoxaemic[3]
- Myocardial infarction or unstable coronary artery syndrome
- Stroke
- Ongoing management of survivors of cardiac arrest with restored spontaneous circulation
- Sickle cell crisis or acute anaemia
- Obstetric emergencies
- Most poisonings (other than carbon monoxide or cyanide poisoning)
- Metabolic and renal disorders with tachypnoea due to acidosis (Kussmaul breathing)

Medical oxygen, like other medical gases, is regarded as a drug in most countries and should usually be prescribed. However, like other drugs used in medical emergencies, it is appropriate to initiate oxygen therapy immediately in emergency situations and to document this therapy once the emergency condition has stabilised.[3] Yet half of UK hospital patients receiving supplementary oxygen therapy do not have a prescription for this treatment or valid written documentation; similar concerns have been raised in several other countries.[2 3]

How effective is emergency oxygen therapy?

Oxygen is often given with the intention of relieving breathlessness, but there is no evidence that oxygen can relieve breathlessness in non-hypoxaemic patients with acute illness, so the main indication for emergency oxygen therapy is to protect patients from potentially harmful consequences of hypoxaemia. A study of 25 healthy subjects exposed to acute hypoxaemia at altitude found that errors in mental tasks occurred at mean oxygen saturation of 64% (range 45-84%), and imminent loss of consciousness occurred at mean saturation of 56% (40-68%) and was reversed by oxygen therapy.[10] More sustained hypoxaemia can lead to hypoxic brain damage and potential damage to other organs such as the liver and kidneys.[3]

On the other hand, acclimatised mountaineers can tolerate short term exposure to oxygen saturation levels as low as 34%, and many patients with chronic lung disease are acclimatised to hypoxaemia.[4 11] The effectiveness of emergency oxygen therapy has not been evaluated in randomised trials involving hypoxaemic patients, so the benefits of oxygen therapy are not known in terms of numbers needed to treat (NNT) to avoid death or complications. The precise levels of hypoxaemia that are dangerous in particular disease states are not known, but four observational studies of critically ill patients have shown increased mortality among hypoxaemic patients in intensive care units with PaO_2 <8-9 kPa (equivalent to oxygen saturation <91-94%).[6 7 12 13]

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Previous articles in this series

- Laxatives for chronic constipation in adults (*BMJ* 2012;345:e6168)
- Inhaled corticosteroids for chronic obstructive pulmonary disease (*BMJ* 2012;345:e6843)
- Newer insulins in type 2 diabetes (*BMJ* 2012;345:e4611)
- Carbapenem antibiotics for serious infections (*BMJ* 2012;344:e3236)
- Bisphosphonates in the treatment of osteoporosis (*BMJ* 2012;344:e3211)

Box 3 | Devices for oxygen administration

Reservoir mask (non-rebreathing mask) for critical illness or severe hypoxaemia (fig1)

Venturi mask for controlled oxygen therapy (especially for oxygen sensitive patients) (figs 2 and 3)

Nasal cannulas for most medium dose oxygen therapy (adjust flow to increase or decrease blood oxygen level) (fig 4)

Simple facemask—works in a similar manner to nasal cannulas, but most patients prefer nasal cannulas to masks, and some rebreathing may occur (fig 5)

Tracheostomy masks for "neck breathing" patients (fig 6)

However, a Cochrane review of perioperative oximetry monitoring showed that correcting modest hypoxaemia did not reduce perioperative deaths or complications, although clinicians who had access to oximetry results believed that they had averted harm by correcting hypoxaemia.[14] There are no randomised trials to evaluate the effectiveness of oxygen therapy in critically ill patients who are not hypoxaemic. The recommendation to administer oxygen during the immediate management of all critically ill patients is based on expert advice that oxygen saturation measurements may be unreliable in critical illness, especially in prehospital care; a target saturation range should be set as soon as the patient has stabilised.

How safe is emergency oxygen therapy?

Too little oxygen or too much oxygen can cause death. A report by the UK National Patient Safety Association identified at least nine deaths (and potentially up to 35 deaths) between 2004 and 2009 that were attributable to incorrect oxygen therapy, including four cases of insufficient oxygen and four cases of excessive oxygen therapy.[8] Equipment failure such as empty or disconnected oxygen supplies or accidental connection to air outlets instead of oxygen outlets accounted for most of the incidents associated with underuse of oxygen. It is likely that these figures are gross underestimates, and many deaths related to oxygen therapy may not be easily recognised.

It was established more than 100 years ago that high concentrations of oxygen may cause lung injury.[15] Pure oxygen is irritating to mucous membranes and may generate tissue injury by causing release of free radicals.[3] Recent cohort studies have shown increased mortality associated with hyperoxaemia in the first 24 hours among survivors of cardiac arrest who were treated in intensive care units and among general intensive care patients.[6 7] Other authors also identified increased mortality associated with hyperoxaemia in cohort studies of intensive care patients and survivors of cardiac arrests, but these authors reported no residual excess mortality in the hyperoxaemic group after multivariable analysis.[12 13]

High concentration oxygen increases the risk of hypercapnic respiratory failure in acute exacerbations of COPD.[4] For example, the first randomised trial of controlled oxygen therapy in acute exacerbations of COPD found that mortality was 9% when high concentration oxygen was given, but mortality was only 4% when controlled oxygen was given with a target saturation range of 88-92%.[5] The British Thoracic Society's Emergency Oxygen Guideline recommends a near normal oxygen saturation target range of 94-98% for most acutely unwell patients and a target range of 88-92%

Fig 1 | High concentration reservoir mask (non-rebreathing mask). (Reproduced from O'Driscoll et al *Thorax* 2011[2])

Fig 2 | Venturi mask. (Reproduced from O'Driscoll et al *Thorax* 2011[2])

Fig 3 | Venturi mask barrels with range of oxygen concentrations available. (Reproduced from O'Driscoll et al *Thorax* 2011[2])

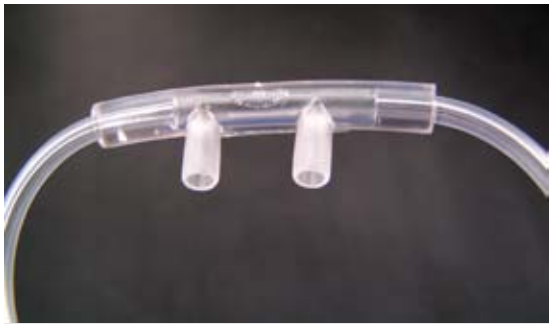

Fig 4 | Nasal cannulas. (Reproduced from O'Driscoll et al *Thorax* 2011[2])

Fig 5 | Simple facemask. (Reproduced from O'Driscoll et al *Thorax* 2011[2])

Fig 6 | Tracheostomy mask. (Reproduced from O'Driscoll et al *Thorax* 2011[2])

for most patients at risk of hypercapnic respiratory failure (the more appropriate course in our case scenario).[3]

A UK audit of 9716 cases of acute COPD exacerbation reported overall mortality of 7.7%: mortality was higher when >35% oxygen was given compared with that for lower concentrations of oxygen (11% *v* 7%); the need for ventilator support was also higher with >35% oxygen (22% *v* 9%).[16] These recent studies lend support to the recommendation in the British Thoracic Society Emergency Oxygen Guideline that oxygen therapy in acute exacerbations of COPD should be titrated to achieve an oxygen saturation level between 88% and 92%.[3]

Recent controlled trials have shown that high concentration oxygen is also associated with increased risk of hypercapnia in acute asthma and pneumonia and in obesity-hypoventilation syndrome.[17-19] In the acute asthma study, 106 patients were randomised to receive high concentration oxygen (8 L/min via simple facemask) or titrated oxygen therapy to achieve saturation targets of 93-95% for 60 minutes.[17] All 10 cases of hypercapnia in this trial occurred among the patients given high concentration oxygen. This raises the possibility that most cases of hypercapnic respiratory failure in acute asthma (near-fatal asthma) may be caused by excessive oxygen therapy.

What are the precautions?

Oxygen supports combustion, and there is a risk of fire or explosion, especially if patients or carers should smoke or light matches near the oxygen source. Oxygen is contraindicated in paraquat poisoning and in bleomycin lung injury because it accentuates lung damage in these conditions.[3]

Uncontrolled oxygen therapy and high concentration oxygen therapy are contraindicated in COPD and in other conditions such as morbid obesity or musculoskeletal or neurological conditions such as severe kyphoscoliosis or motor neurone disease, where oxygen may cause or aggravate hypercapnic respiratory failure.[3]

How cost effective is it?

The cost effectiveness of emergency oxygen therapy cannot be calculated because the clinical effectiveness of oxygen therapy has not been evaluated in controlled trials for most conditions where it is used. Oxygen is a cheap drug, but even short term use requires the use of a facemask or cannulas and tubing, which may cost more than the oxygen used. Audits in the UK and other countries have tended to report overuse rather than underuse.[1 2] The 2011 British Thoracic Society Emergency Oxygen Audit of 41 000 UK hospital patients found that only 32% of those patients using supplementary oxygen had a prescription or other written order for oxygen in 2008, rising to 48% by 2011; of those with a specified target oxygen saturation range, 10% were below this range but 23% were above it.[20] These audits suggest that cost effectiveness could be improved if oxygen therapy was restricted to those who require it, potentially avoiding hyperoxia and its complications.

How is it administered and monitored?

Oxygen delivery devices

Clinicians need to become familiar with four or five types of delivery device to deal with most emergency oxygen use

(see box 3). The advantages and disadvantages and special considerations for each of these devices are described in detail in the British Thoracic Society's Emergency Oxygen Guideline, which also provides advice about the use of different oxygen sources including piped oxygen and a wide range of cylinder sizes.[3]

Bedside monitoring

Unlike most drugs, emergency oxygen therapy should not be prescribed at a fixed dose. The prescribing clinician should specify the target oxygen saturation range that is safest for the patient (usually either 94-98% or 88-92%).[3] The administering team (usually nurses) should adjust the inspired oxygen concentration to achieve this target range and ensure that the oxygen delivery system is documented clearly as recommended in UK guidelines.[3] If oxygen requirements increase, patients require review by a doctor, as the cause of worsening hypoxaemia needs to be identified and treated. All patients requiring emergency oxygen therapy should have regular monitoring, ideally using a recognised "track and trigger" system such as a modified early warning score.[3] Some newer early warning scores include oximetry results, but patients with respiratory illnesses may need protection from hyperoxaemia as well as from hypoxaemia and may be harmed by a "normal" oxygen saturation level.[21] Future early warning scores will need to reflect this.

Saturation monitoring

Cheap and reliable finger oximeters are now available in almost all situations where emergency oxygen therapy is used. However, oximetry may not be possible in cases of shock, and it may be misleading in some circumstances, such as carbon monoxide poisoning (because carboxyhaemoglobin gives a similar signal to oxyhaemoglobin). Therefore, regularly monitor other vital signs, especially the respiratory rate; these signs may alert clinicians to clinical deterioration before any fall in the oxygen saturation level.

Avoid the precautionary use of oxygen in non-hypoxaemic patients, as the increase in blood oxygen content is minimal in normoxaemic patients while the artificially high oxygen level renders pulse oximetry almost useless as a means of monitoring ventilation and gas exchange and may delay recognition of clinical deterioration.[3 9]

Box 4 | Alternative methods to increase tissue oxygen delivery

- Safeguarding the airway
- Optimising circulating volume to maintain tissue perfusion
- Correcting severe anaemia
- Enhancing cardiac output
- Avoiding or reversing respiratory depressants such as benzodiazepines or opiates
- Increasing fraction of inspired oxygen (FIO_2) if the patient is hypoxaemic
- Establishing and treating the underlying cause of hypoxaemia (such as bronchospasm, heart failure)
- More specialised treatments, including non-invasive or invasive ventilation for seriously ill patients after assessment by senior clinicians

TIPS FOR PRESCRIBERS

- Advise patients not requiring oxygen and their families that oxygen was overused in the past and is not required in most circumstances unless the blood oxygen level is low, even if breathlessness is present
- Excessive oxygen therapy (hyperoxaemia) in seriously ill patients (such as survivors of cardiac arrest or those admitted to intensive care units), may be associated with increased mortality
- Aim for oxygen saturation of 94-98% for most patients and 88-92% for most patients at risk of hypercapnic respiratory failure (some hypercapnic patients may have a lower individualised target range based on previous blood gas results)
- Issue a personal "Oxygen Alert Card" and educational materials to patients with a history of hypercapnic respiratory failure to ensure that they are not endangered by excessive oxygen therapy[3]
- Prescribing oxygen to a target range is simple and safer than trying to prescribe a fixed "dose" of oxygen. The target range needs to be set just once for each patient, although the device and flow rate may need to be changed several times if the patient's condition changes. Document all such changes on the bedside observations chart alongside the oxygen saturation
- Allowing the clinicians who are administering oxygen to select the most appropriate device and flow rate while maintaining the patient within the desired saturation range enhances patient safety and patient comfort
- Ensure that bedside air outlets (which could be mistaken for an oxygen outlet in an emergency) are either removed, covered, or clearly labelled

Monitoring for toxicity and effectiveness

Hypoxaemic patients and those at risk of hypoxaemia need careful monitoring as described above. Effectiveness of oxygen therapy can be monitored directly by pulse oximetry and blood gas measurements and indirectly by improvement in other vital signs. Toxicity is best recognised among patients at risk of hypercapnic respiratory failure (such as those with COPD, obesity-hypoventilation, or chronic neuromuscular disease).[3-5]

Clinical signs of carbon dioxide retention include vasodilation, drowsiness, and flapping tremor, but the only reliable way to diagnose hypercapnia (and acidosis) is to check blood gases. For this reason, blood gases should be requested for all patients at risk of hypercapnic respiratory failure who require emergency oxygen therapy. Transcutaneous carbon dioxide sensors are not yet as reliable as finger oximeters, and they are not recommended for clinical use in the management of medical emergencies.[3]

How does oxygen compare with other drugs?

There are no other drugs for the specific indication of hypoxaemia, but there are several other methods to improve oxygen delivery to the tissues (box 4). For patients with modest hypoxaemia, these strategies may be more effective than simply increasing the concentration of inhaled oxygen.

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1 Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital emergency department. *Emerg Med J* 2008;25:773-6.
2 O'Driscoll BR, Howard LS, Bucknall C, Welham SA, Davison AG, British Thoracic Society. British Thoracic Society emergency oxygen audits. *Thorax* 2011;66:734-5.
3 O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008;63(suppl 6):vi1-68.
4 Murphy R, Driscoll P, O'Driscoll R. Emergency oxygen therapy for the COPD patient. *Emerg Med J* 2001;18:333-9.
5 Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ* 2010;341:c5462.
6 Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010;303:2165-71.
7 De Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12:R156.
8 National Patient Safety Agency. Rapid response report: Oxygen safety in hospitals (NPAS 2009/RRR2006). NPSA, 2009. www.nrls.npsa.nhs.uk/resources/?EntryId45=62811.
9 Downs JB. Has oxygen administration delayed appropriate respiratory care? Fallacies regarding oxygen therapy. *Respir Care* 2003;48:611-20.
10 Hoffman CE, Clark RT, Brown EB. Blood oxygen saturations and duration of consciousness in anoxia at high altitudes. *J Appl Physiol* 1946;145:685-92.
11 Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE, et al. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009;360:140-9.
12 Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Crit Care* 2011;15:R90.
13 Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med* 2012;38:91-8.
14 Pedersen T, Møller AM, Hovhannisyan K. Pulse oximetry for perioperative monitoring. *Cochrane Database Syst Rev* 2009;4:CD002013.
15 Lorrain Smith J. The pathological effects due to increase of oxygen tension in the air breathed. *J Physiol* 1899;24:19-35.
16 Roberts CM, Stone RA, Buckingham RJ, Pursey NA, Lowe D, National Chronic Obstructive Pulmonary Disease Resources and Outcomes Project implementation group. Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations. *Thorax* 2011;66:43-8.
17 Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax* 2011;66:937-41.
18 Wijesinghe M, Perrin K, Healy B, Weatherall M, Beasley R. Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia. *J R Soc Med* 2012;105:208-16.
19 Wijesinghe M, Williams M, Perrin K, Weatherall M, Beasley R. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study. *Chest* 2011;139:1018-24.
20 O'Driscoll BR. Emergency Oxygen use in UK Hospitals: BTS hospital oxygen audits 2008-2011. www.brit-thoracic.org.uk/Portals/0/Audit%20Tools/BTS%20Oxygen%20Audit%202008%202009%20and%202010%20and%202011.pdf.
21 O'Driscoll BR, Murphy P, Turkington PM. Acute monitoring of patients with chronic respiratory disease during hospital admission. *Clin Med* 2012;12:79-81.

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UNCERTAINTIES

Does routine oxygen supplementation in patients with acute stroke improve outcome?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Stroke is the third most common cause of death and the leading cause of long term disability in developed countries. Specialist care in stroke units is well established as being effective in preventing death and disability after stroke.[1] However, which aspects of stroke care are crucial for improving outcome remains unclear. Patients in a stroke unit are more likely than those on a non-specialised general ward to receive oxygen.[2] Bravata and colleagues found that treating all episodes of hypoxia with supplemental oxygen was one of three key processes associated with better outcome in acute stroke care.[3] Mild hypoxia is common in patients with stroke and may have substantial adverse effects on an ischaemic brain after stroke. Whereas healthy adults with normal cerebral circulation can compensate for mild hypoxia by an increase in cerebral blood flow, this is not possible in patients whose brain is already ischaemic after stroke.[4] Hypoxaemia in the first few hours after hospital admission is associated with an increased risk of death.[5]

Oxygen treatment is not without problems.[6] The tubing that connects the patient to the oxygen source impedes early mobilisation and could pose an infection risk. Physiological changes associated with oxygen treatment can include absorption atelectasis; worsening of ventilation-perfusion mismatch; coronary, cerebral, and systemic vasoconstriction; and a reduction in cardiac output.[7] Animal models and in vitro studies show that oxygen encourages the formation of toxic free radicals, leading to further damage to the ischaemic brain, especially during reperfusion. Oxidative stress has also been implicated in the activation of cell signalling pathways, which lead to apoptosis and neuronal cell death. Although some research points towards adverse effects of hyperoxia in the ischaemic brain, some evidence supports the notion that eubaric hyperoxia (hyperoxia induced by oxygen treatment at normal atmospheric pressure) may be neuroprotective.[8]

What is the evidence of the uncertainty?

We searched PubMed, Medline, and Embase databases and the Cochrane Library for randomised controlled trials comparing oxygen treatment with placebo or with no treatment in patients with acute stroke and other relevant literature using the search terms "oxygen" or "hypoxia" or

Recommendations for oxygen treatment in national and international guidelines

British Thoracic Society Guideline for Emergency Oxygen Use in Adult Patients

Supplementary oxygen should only be given to achieve a saturation of 94-98%, or 88-92% in patients at risk of type II respiratory failure (2008)

UK National Clinical Guidelines for Stroke

Arterial oxygen concentration should be maintained within normal limits (2004)
Give oxygen if saturation ‹95% (2008)

European Stroke Initiative and European Stroke Organization Recommendations for Stroke Management

Give oxygen at a rate of 2-4 L/min when indicated (2003)
Give oxygen if saturation ‹92% (2007)
Give oxygen if saturation ‹95% (2008)

American Stroke Association Guidelines

Give oxygen if saturation ‹95% (2003, 2005)
Give oxygen if saturation ‹93% (2007)

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Previous articles in this series

- Does mindfulness based cognitive therapy prevent relapse of depression? (*BMJ* 2012;345:e7194)
- Should selective digestive decontamination be used in critically ill patients? (*BMJ* 2010;345:e6697)
- What factors influence prognosis in children with acute cough and respiratory tract infection in primary care? (*BMJ* 2012;345:e6212)
- How effective are non-drug, non-surgical treatments for primary dysmenorrhoea? (*BMJ* 2012;344:e3011)
- Should we use individual cognitive stimulation therapy to improve cognitive function in people with dementia? (*BMJ* 2012;344:e633)

"anoxia" and "stroke" or "cerebrovascular accident". We included only articles on normobaric oxygen treatment. (Bennett and colleagues conducted a systematic review of hyperbaric oxygen for acute stroke.[9])

Should patients with acute stroke be given oxygen routinely?

We found one quasi-randomised and two randomised controlled pilot studies of oxygen supplementation after acute stroke. The quasi-randomised study enrolled 550 consecutive patients within 24 hours of acute stroke and treated them with either oxygen at a rate of 3 L/min via nasal cannulas or no routine oxygen during the first 24 hours. The findings showed no difference in survival at one year or disability at seven months. Subgroup analyses suggested a trend towards better outcomes with oxygen in patients with severe strokes and an adverse trend in those with mild strokes, but the study size was too small to define patients who are likely to derive benefit with certainty.[10] In the smaller of the two randomised controlled pilot studies, 16 patients received high flow humidified oxygen at 45 L/min via a simple face mask (using a flow meter that can deliver up to 75 L/min—such as Timeter Classic Series Flowmeter model 0-75, Allied Healthcare Products) or control treatment (room air) within 12 hours of symptom onset, for eight hours. Patients had potentially salvageable tissue in the ischaemic penumbra of the infarct, indicated by a perfusion-diffusion mismatch on magnetic resonance imaging. There was a trend towards better reperfusion on magnetic resonance imaging at 24 hours, but no long term clinical benefit at three months.[11] In the larger pilot study (Stroke Oxygen Pilot Study) 301 patients within 24 hours of admission with acute stroke were randomised to receive either oxygen supplementation for 72 hours at a flow rate of 2 L/min or 3 L/min, depending on baseline oxygen saturation, or no routine oxygen supplementation. After one week, their neurological outcome—according to the score on National Institutes for Health stroke scale—was the same in both groups, but the degree of recovery (difference in neurological scores between baseline and week 1) was significantly better in the group receiving oxygen supplementation.[12] The researchers found no difference in functional outcome at six months on direct comparison, although they found a trend for better outcome with oxygen after correction for differences in baseline stroke severity and prognostic factors. These results are promising but need confirmation in a much larger study. This is now in progress (see below).

Clinical guidelines on oxygen supplementation after stroke differ across countries and have changed over time without clear justification (box). None of the recommendations are based on evidence from controlled clinical trials. Not surprisingly, doctors treating patients with stroke are uncertain about which treatment approach to take and when to give oxygen. In a survey of British stroke physicians just over half stated they would start oxygen supplementation after stroke at an oxygen saturation below 95%,[13] a cut-off that was later included in UK and European guidelines on stroke (box).

How should oxygen be given in patients with stroke?

A small study (n=46) compared oxygen treatment via a venturi mask delivering 40% oxygen with nasal cannulas at a flow rate of 2 L/min within 48 hours of an acute middle cerebral artery infarct and found non-significant differences in mortality (6% *v* 24%, P=0.1) and complications.[14] When given the choice, patients with stroke prefer nasal cannulas to face masks (73% out of 21 asked).[15]

When should oxygen supplementation be given?

Hypoxia is common early after stroke, particularly while a patient is being moved from one ward to another or is in the head scanner,[5] and at night.[16] The mean nocturnal oxygen saturation is about 1% lower than "awake" oxygen saturation, both in patients with stroke and in controls. Twenty three per cent of patients with acute stroke who have normal oxygen saturation during the day spend more than 30 minutes with an oxygen saturation <90% at night.[13] Sleep apnoea has been reported in 60-70% of patients early after stroke.[17 18] A study in healthy volunteers found that hypoxaemia leads to a compensatory increase in cerebral blood flow during wakefulness but not during sleep and is therefore more likely to result in brain tissue hypoxia at night.[19] Oxygen supplementation is therefore probably more important at night than during the day. No studies of oxygen saturation or treatment in patients very early after the stroke (for example, in the ambulance) have been published.

For how long should oxygen be given?

Two studies giving oxygen for eight and 24 hours showed no benefit.[8 9] A pilot study of oxygen supplementation for 72 hours showed improved neurological recovery at one week, but no significant difference in functional outcomes at six months.[10] We currently do not know whether oxygen supplementation should be given routinely, how early to start, and for how long to continue treatment.

Is ongoing research likely to provide relevant evidence?

A search of the Current Controlled Trials Register (ISRCTN), the *meta*Register of Controlled Trials, and the US Government Clinical Trials Register using the terms

RECOMMENDATIONS FOR FUTURE RESEARCH

- How does intensive monitoring compare with routine treatment?
- How effective is night only supplementation compared with continuous supplementation?
- Does starting treatment very early (before hospital admission) improve outcome?
- If oxygen supplementation is effective, what is the optimal treatment dose and duration and the best mode of administration?
- Are there subgroups of patients who respond better (such as those with ischaemic stroke *v* haemorrhagic stroke; those receiving thrombolysis; those with a large difference in diffusion-perfusion deficit on magnetic resonance imaging)?
- Is there a cut-off in oxygen saturation beyond which oxygen supplementation is no longer effective?

"stroke" and "oxygen" identified one ongoing, one prematurely terminated, and one completed but unpublished study of oxygen treatment for acute stroke.

The Stroke Oxygen Study (ISRCTN52416964), an ongoing randomised controlled study in 6600 patients with acute ischaemic stroke, is comparing the effects of routine fixed dose supplementation (3 L/min if baseline oxygen saturation is ≤93%, and 2 L/min if baseline oxygen saturation is >93%) for 72 hours; routine fixed dose oxygen supplementation at night only, for three nights; and usual management (oxygen given only when needed) on neurological recovery at one week and functional outcome at three months.

The Normobaric Oxygen in Acute Ischaemic Stroke Trial (NCT00414726), a randomised controlled trial, compared high dose oxygen treatment (30-45 L/min via face mask) or control (room air at the same flow rate) for a period of eight hours on neurological recovery within four and 24 hours in patients within nine hours of acute ischaemic stroke. This trial had aimed to enrol 240 patients but was stopped early because of an imbalance of deaths in favour of the control group (17/43 on oxygen *v* 7/43 on room air). The results are available on the clinicaltrials.gov website but not published in a journal.

A randomised controlled study of the effect of low flow oxygen on capillary blood gases in 40 patients with acute stroke (ISRCTN75718175) is listed as completed but has not yet reported results on the ISRCTN website or in print.

What should we do in the light of the uncertainty?

Until evidence shows whether routine oxygen supplementation improves outcome, patients with acute stroke should only be given oxygen to maintain oxygen saturation within the normal range. Patients should be checked regularly for hypoxia, especially at night, during transfers between wards, and in the head scanner. It is important to remember that hypoxia is a symptom of an underlying problem in gas transfer or regulation of respiratory activity, and not a disease in itself. Blind treatment of hypoxia without further investigation risks masking an important warning sign of an underlying life threatening condition and delaying its detection and treatment. Before starting oxygen treatment, basic resuscitative measures, such as checking and clearing the airway and optimising patient positioning, should be taken. It is further important to establish and treat the cause of hypoxia. Secretions in the upper airways, pneumonia, pulmonary embolism, heart failure, and the effects of sedative medications on respiratory drive need to be managed in all stroke patients with low or falling oxygen saturation.

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1 Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2007;4:CD000197.
2 Indredavik B, Bakke F, Slordahl SA, Rosketh A, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit. *Stroke* 1999;30:917-23.
3 Bravata DM, Wells CK, Lo AC, Nadeau SE, Melillo J, Chodkowski D, et al. Processes of care associated with acute stroke outcomes. *Arch Intern Med* 2010;170:804-10.
4 Roffe C. Hypoxaemia and stroke. *Rev Clin Gerontol* 2001;11:323-35.
5 Rowat AM, Dennis MS, Wardlaw JM. Hypoxaemia in acute stroke is frequent and worsens outcome. *Cerebrovasc Dis* 2006;21:166-72.
6 Cornet AD, Kooter AJ, Peters MJ, Smulders YM. Supplemental oxygen therapy in medical emergencies: more harm than benefit? *Arch Intern Med* 2012;172:289-90.
7 O'Driscoll BR, Howard LS, Davison AG. British Thoracic Society guideline for emergency oxygen use in addult patients. *Thorax* 2008;63(suppl 6):vi1-68.
8 Singhal AB. Oxygen therapy in stroke: past, present, and future. *Int J Stroke* 2006;1:191-200.
9 Bennett MH, Wasiak J, Schnabel A, Kranke P, French C. Hyperbaric oxygen therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2005;3:CD004954.
10 Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* 1999;30:2033-7.
11 Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, et al. A pilot study of normobaric oxygen therapy in acute ischemic stroke. *Stroke* 2005;36:797-802.
12 Roffe C, Ali K, Warusevitane A, Sills S, Pountain S, Allen M, Hodsoll J, et al. The Stroke Oxygen Pilot Study. A RCT of the effect of routine oxygen supplementation early after stroke. Effect on recovery of neurological function at one week. *PLoS ONE* 2011;6(5):e19113.
13 Arora A, Gray R, Crome P, Roffe C. What do physicians with an interest in stroke consider to be best practice in the diagnosis and treatment of hypoxia after acute stroke? *Br J Cardiol* 2005;12:456-8.
14 Chiu EHH, Liu CS, Tan TY, Chang KC. Venturi mask adjuvant oxygen therapy in severe acute ischemic stroke. *Arch Neurol* 2006;63:741-4.
15 Ali K, Sills S, Roffe C. The effect of different doses and routes of oxygen administration on oxygen saturation in stroke patients. *Neurocritical Care* 2005;3:24-6.
16 Roffe C, Sills S, Halim M, Wilde K, Allen M, Jones PW, et al. Unexpected nocturnal hypoxia in patients with acute stroke. *Stroke* 2003;34:2641-5.
17 Bassetti CL, Milanova M, Gugger M. Sleep-disordered breathing and acute ischemic stroke: diagnosis, risk factors, treatment, evolution, and long-term clinical outcome. *Stroke* 2006;37:967-72.
18 Parra O, Arboix A, Bechich S, Garcia-Eroles L, Montserrat JM, Lopez JA, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med* 2000;161:375-80.
19 Meadows GE, O'Driscoll DM, Simonds AK, Morrell MJ, Corfield DR. Cerebral blood flow response to isocapnic hypoxia during slow-wave sleep and wakefulness. *J Appl Physiol* 2004;97:1343-8.