A Pilot Study of Oxygen Therapy for Acute Leg Ulcers

Background:

The concept of increasing the oxygen concentration in healing wounds developed originally with hyperbaric oxygen therapy and from the fact that oxygen is recognised as an essential element used during cellular metabolism. Hyperbaric therapy has shown only limited success in this field because it is only possible to use this for very short periods of the week (approx. 5%) therefore limiting its efficacy in raising oxygen levels in wounds for a prolonged period. In addition to this access is difficult, and it is also costly (Tawfick 2013). Smaller devices have become available which provide localised oxygen therapy to the wounds. These work by enclosing the area where the wound is present in a “box-type” device. Any dressings and bandages have to be removed and the patient has to interrupt their normal lifestyle to receive this therapy.

Natrox™ is a device designed to overcome a number of problems associated with previous methods of O₂ therapy, it delivers continuous oxygen to the wound bed through a dressing. The Natrox™ topical oxygen therapy system developed by Inotec AMD Limited employs a small battery-powered electrochemical ‘oxygen generator’ to concentrate atmospheric oxygen and feed the pure, moist, oxygen at a rate of around 15mL/hour through a fine, soft, tube to a dressing-like ‘oxygen distribution system’ that is placed over the wound and is held in place by a conventional dressing. The oxygen generator is worn in a holster on the waist or above the calf or is placed in a trouser pocket, thus enabling the patient to enjoy normal mobility (hence ‘ambulatory’) while receiving continuous treatment.

Why do we need Oxygen to heal a wound?

In order for a wound to heal the body metabolism needs to increase energy by 20% for a clean wound and 50% for infected wounds (Wild, Nutrition 2010), in terms of local cellular metabolism at the wound bed this needs to increase by 500%. Low wound oxygen levels significantly restrict energy production and therefore limits wound healing.

Energy production is created within the mitochondria from the metabolism of carbohydrates broken down into glucose and fats, oxygen is delivered via the haemoglobin carried in the arterial supply through the capillary bed. From here it diffuses through the tissues and is taken up into cellular mitochondria where it is used in the process of energy production. In a wound with deficient oxygen supply the energy production is greatly reduced. Wound healing works best when cells have enough energy to reproduce, make proteins and fight infection. When oxygen levels in a wound are low, one molecule of oxygen generates 2 molecules of energy. However, with plenty of oxygen around the process is 18 times more efficient, generating 36 molecules of energy. This generates an environment in which the cells can work much more efficiently and increases the speed of wound healing.

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Most leg ulcers occur in elderly patients, and many of these have an underlying problem that slows down or restricts the transfer of oxygen from the lungs to the wound tissue. Diabetes, hardening of the arteries and high blood pressure all mean that the wall of the arteries delivering the blood are much thicker than normal and this greatly reduces the oxygen reaching the wound. Vein problems cause damage to the tissues underlying the skin, making them thicker and tougher and so more resistant to oxygen moving through them. Leg swelling means that any oxygen released into the tissues is greatly diluted by all the water that is present.

It is clear that without sufficient oxygen, the healing cascade of inflammation, proliferation, and remodelling can become impaired, which can delay or “stall” wound healing. Vascular or endovascular interventions to correct macrovascular issues when present are useful, but this is not always possible, and sometimes in the elderly population, practical. Supplemental oxygen can be a relatively easy and cost effective method of aiding wound healing, and may reduce the time taken to heal wounds, or even prevent progression onto the formation of a chronic wound. This may ultimately reduce the costs associated with chronic, non-healing wounds.

Device

The Natrox™ Oxygen Delivery System (ODS) comprises the NatroxTM Oxygen Generator + NatroxTM ODS.

The device is supplied in a small carrying case, and consists of 2 small rechargeable batteries that operate an oxygen concentrator which generates 100% oxygen from water that is naturally present in the atmosphere. It employs a small battery-powered electromechanical ‘oxygen generator’ which splits the hydrogen and oxygen molecules that form water apart. The pure, moist, oxygen is delivered at a rate of around 15ml/hr through a fine, soft, tube to a specially designed dressing ‘oxygen distribution system’ (ODS) that is placed over the wound, the oxygen then diffuses evenly across the wound surface and is held in place by a conventional dressing. The dressing can be cut and shaped so that it matches the wound size. The oxygen generator is worn in a holster near the wound, on the waist or placed in a trouser pocket, thus enabling the patient to enjoy normal mobility (hence ‘ambulatory’) while receiving continuous treatment.

The rechargeable battery provides power for 30 hours and therefore will need changing on a daily basis. The used battery pack is then recharged in the charger which is provided with the Natrox™ system. An LED on the battery charger indicates the status – it flashes yellow when charging and becomes a solid light when the charge is complete.

The ODS is a single-use, sterile, oxygen delivery system with a fine tube for connection to the Natrox Oxygen generator. Moist oxygen flows through the tube to the ODS and through that to the ulcer bed. The design of the ODS ensures an even distribution of oxygen over the ulcer while allowing an absorbent dressing to be placed on top to manage the ulcer and wound fluid. When the Natrox™ Oxygen generator is switched on, the oxygen which is manufactured passes down the tube through the ODS to the damaged tissue. The ulcer area is then bathed in an oxygen rich environment which is considered to promote healing in long term ulcers, which include difficult to treat diabetic foot ulcers.
The Natrox™ system is designed to overcome a number of problems associated with previous methods of oxygen therapy, it delivers continuous oxygen to the ulcer bed through a dressing and because of its size and weight is portable. There is a flashing green LED light on the Natrox™ which gives positive indication that there is oxygen flow. The holster has a Velcro strap that allows the generator to be worn around the leg or there is a belt loop for it to be worn around the waist.

**Study Plan:**

A randomised trial of 60 patients with acute leg ulcers in a community setting. The trial will take place across 2 or 3 CCGs in the east of England and be based in leg ulcer clinics or General Practice facilities.

60 devices will be supplied, 30 that produce oxygen and 30 that appear identical but don’t function and will function as the placebo arm. The devices will be spread evenly across the chosen sites. The sites and patients will not know whether they have a functioning device or not. Each device will have a unique serial number for the trial that will identify the active and placebo devices. The serial number will be recorded in the trial electronic case record (eCRF), enabling unblinding to take place once the study is completed.

**Inclusion criteria:**

- Leg ulcers between 2 weeks and 3 months in duration.
- Ulcer size between 1cm² to 60cm²
- Ulcers located below the knee and above the ankle
- Ongoing active chemical or sharp wound debridement prior to, and during, the application of Natrox™ is very important. The presence of slough or necrotic tissue in the wound bed will impair the transfer of oxygen to the underlying tissues. This is particularly important for wound edges, to allow the metabolically active epithelial cells to begin migration across the wound.
- No limit on level of ischaemia. ABPIs are usually checked as standard of care and will be recorded.
- The patient is 18 years of age or older, and consents to the use of their data and images being stored and used for analysis at a later date.
- The patient is willing to complete >75% of follow-up evaluations required by the study protocol.
- The patient agrees to abstain from enrolment in any other clinical trial for the duration of the study.

**Exclusion criteria:**

- The subject has an invasive soft tissue infection at the time of baseline assessment, requiring oral or intravenous antibiotic therapy.
• Wounds were it is felt clinically necessary to cover the surface in gel or creams that would prevent the transmission of oxygen to the wounds surface
• Wounds where an underlying malignancy is suspected.
• Subjects with an ulcer which is >60cm² (it is possible to use more than one device to treat multiple wounds though)
• Exposed bone without soft tissue or granulation tissue across the surface;
• Diabetic patients with a glycated haemoglobin HbA1C of >12mmol mol⁻¹
• Subjects who have evidence of connective tissue disorders (e.g. vasculitis or rheumatoid arthritis) under active treatment. This would also include subjects being treated with immunosuppressive medication greater than 7.5mg prednisolone daily;
• The subject has other concurrent conditions that in the opinion of the investigator may compromise subject safety;
• The patient is a vulnerable or protected adult, or unable to provide consent.
• Inability to comply with dressing regime or manage the Natrox™ device.
• Subjects with a life expectancy <1 year, and those with disseminated malignancy.

Study objectives:

Primary: To assess the efficacy of NatroxTM in the management of acute leg ulcers.

Secondary:
• To evaluate the number of subjects with fully healed ulcers.
• To evaluate pain levels in subjects with acute leg ulcers
• To evaluate Quality of Life in subjects with acute lower limb ulcers
• To evaluate the impact on healthcare expenditure on acute ulcers

Study end points:

Primary: Percentage wound area reduction after 6 weeks of treatment

Secondary:
• Percentage of patients with fully healed ulcers at 6 weeks
• Median pain score measured on a visual analogue score across the study
• Change in the Charing Cross venous leg ulcer score
• Cost of healthcare team input into wound care, plus dressings used through the study period

Protocol for management

1. Appropriate local ethics committee and/or research and development office permissions will be in place.
2. Patients will be identified by local community teams, either from General Practice or Tissue Viability teams. They will be supplied with an ethics approved Patient Information sheet. After at least 24 hours, patients will be contacted again and their interest in being involved with the study confirmed. After checks of the inclusion and exclusion criteria, patient consent will be obtained.

3. Active wound debridement to remove as much slough and necrotic material as possible to maximise oxygen transfer to the wound surface.

4. Digital image recording with standardised size sticker in the image. The sticker has a space to record details such as patient initials, unique identifier and site name or code. The image should be taken from a position as perpendicular to the wound surface as possible, under good lighting conditions.

5. The sterile Oxygen Delivery System (ODS) can then be cut to size as needed and placed directly onto the wound surface white side down, with the tube orientated towards where the Oxygen Generator (OG) will be worn. The ODS is important as it diffuses the oxygen evenly across the wound surface.

6. The choice of the dressing to be placed over the upper, beige surface of the ODS is at the clinician’s discretion. Experience with the device has shown that over the first 7-10 days, the wound becomes very active and may produce a significantly increased level of exudate. This may need super-absorbent dressings to manage the fluid load and prevent maceration of the wound surface. It is also possible that the patient may need more frequent dressing changes in the early period, until the wound gets used to the increased levels of oxygen.

7. The dressings are then usually covered with an occlusive dressing, which helps to maintain an oxygen rich environment. In patients where wound maceration is an issue, it is acceptable to use porous dressing but this should be well padded if possible to try and maintain a good oxygen concentration close to the wound surface. An occlusive dressing should be returned to as soon as is clinically possible.

8. The process for attaching the ODS to the OG should then be demonstrated to the patient if this is the first time of use. A pre-charged battery should then be clipped into position on the OG and confirmation that the unit is working looked for by checking that the green light begins to flash. This may take up to one minute.

9. Depending on the position of the wound and how the patient chooses to carry the Natrox™ device, it may be necessary to use an extension tubing set to increase the length of tubing between the ODS and the OG.

10. If this is the first time the patient has been treated with Natrox, they should be supplied with information about the product so that community teams understand how the patient is being managed. It is also important that arrangements are made for early and regular wound review over the first week in order that wound edge maceration can be avoided. The patient needs to be supplied with an adequate number of ODS so that the community teams can manage the dressings until the next wound clinic review. This may be up to 7 in the first week.

11. Arrangements should be made for weekly follow up for at least the first 4 weeks. At each visit, the wound should be actively debrided and an image captured where possible. It is not unusual for wounds to exhibit a small increase in size over the first week or 2. The minimum period over which a measurable difference can be seen is at least 4 weeks, and may well be longer in very difficult chronic wounds.
12. The mode of action for Natrox means that better quality collagen is laid down in well oxygenated wounds. As this has the potential to reduce long term recurrence rates, it is recommended that treatment is continued until full wound closure is obtained.