

NATROX oxygen wound therapy for managing diabetic foot ulcers and complex or chronic non-healing wounds

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is NATROX. It is used to treat chronic non-healing and complex wounds, including diabetic foot ulcers.
- The **innovative aspects** are that the device delivers 98% humidified oxygen directly to the wound bed to stimulate and improve wound healing.
- The intended **place in therapy** would be in addition to standard care in people with chronic non-healing wounds.

- The **main points from the evidence** summarised in this briefing are from 3 studies, a randomised controlled trial and 2 observational studies – a total of 172 adults in secondary care. They show that NATROX effectively treats a range of chronic wounds, and is more effective than standard care in people with grade 2 and grade 3 diabetic foot ulcers.
- **Key uncertainties** around the evidence or technology are the small sample size of the randomised controlled trial and the heterogenous population in the larger observational studies. These limit the value of the findings.
- The **cost** of NATROX ranges from £300 to £500 per 12-week treatment. The cost reflects the average number of oxygen delivery system devices bought for a 12-week treatment in the UK; the reusable generator is included in the cost.

The technology

NATROX (Inotec AMD) consists of a rechargeable, battery-operated oxygen generator and an oxygen delivery system (ODS). The oxygen generator is reusable so can be used again on different patients. It's a portable device about the size and weight of a mobile phone (107 g). The ODS is a sterile, single-use, web-like device which is placed directly onto the wound bed beneath the wound dressing. This allows any exudate to be managed as normal with the appropriate secondary dressing. Oxygen is delivered continuously to the wound through a flexible tube from the portable oxygen generator. NATROX can be used with other advanced wound therapies and dressings and is supplied with 2 rechargeable batteries.

Innovations

NATROX claims to be the only portable continuous oxygen delivery device for managing wounds available in the UK. It delivers 98% humidified oxygen directly to the wound bed with the aim of stimulating and improving wound healing. Previously, oxygen delivery to wounds has been through hyperbaric oxygen therapy, which is costly and requires people to be confined to either a full body or limb chamber for treatment.

Current care pathway

Wound care depends on the type of wound. Standard care is cleaning and dressing it. The

best dressing to use depends on things like wound size and depth, and amount of exudate.

More complicated wounds, for example surgical site infections, diabetic foot problems, venous leg ulcers and pressure ulcers, can result in chronic non-healing wounds and need more advanced care. Care of these types of wounds aims to promote healing and minimise the risk of further complications. For diabetic foot or venous leg ulcer, healthcare professionals record the depth and position of the ulcer and offload or treat it with compression therapy to promote healing. If a non-healing wound is thought to be infected, healthcare professionals take a microbiological sample and prescribe an antibiotic to treat the infection. The wound is cleaned and debrided regularly, and dressed. Clinical staff choose a dressing that will promote healing and manage exudate based on the individual wound. Dressings should be changed or removed using aseptic non-touch technique. Some wounds are treated with topical negative pressure therapy. Chronic non-healing wounds typically need more advanced dressings. People may be referred to a specialist for multidisciplinary care, depending on wound aetiology. Tissue viability nurses assess wounds if they are seriously infected, if there is a differential diagnosis, or if the person has complex comorbidities.

The following guidelines have been identified as relevant to this care pathway:

- [NICE guideline on surgical site infections: prevention and treatment](#)
- [NICE guideline on diabetic foot problems: prevention and management](#)
- [NICE guideline on pressure ulcers: prevention and management](#).

Population, setting and intended user

NATROX can be used in primary and secondary care by different healthcare professionals, including tissue viability nurses, surgeons and podiatrists in secondary care, and community nurses and podiatrists in primary care. People using the device at home are responsible for ensuring the rechargeable oxygen generator remains charged between dressing and ODS changes. The company says NATROX can be managed by people and their carers at home. Some training is needed. Each treatment lasts 12 weeks, needing 20 to 30 ODS devices.

Costs

Technology costs

NATROX therapy costs between £300 and £500 per 12-week treatment, depending on the number of ODS needed. The reusable oxygen generator is provided on loan for free, as long as ongoing purchases of the ODS devices are made. The company will loan extra oxygen generators, provided enough ODS devices are bought for further patients. The company reclaims the oxygen generator if ODS devices are no longer ordered. The cost of the technology is in addition to standard care, but the company claims the technology improves healing outcomes and so reduces the resource burden of chronic non-healing and complex wounds.

Costs of standard care

Different dressings are available as standard care for non-healing and complex wounds, priced according to size:

- soft polymer dressing £0.19 to £39.83
- hydrocolloid fibrous dressing £0.97 to £10.37
- antimicrobial dressing £0.18 to £64.13
- PICO negative pressure wound dressings £127.06 to £145.68
- VAC Veraflo treatment £82.06 per wound per day.

The average cost of treating a diabetic foot ulcer with an interactive dressing is £2,990 (based on 77 dressing changes), and £3,380 for non-interactive dressings (based on 118 dressing changes; [figures from a report by the NICE resource and impact team](#)). The national tariff for single amputation stump or partial foot amputation procedure for diabetes ranges from £1,692 to £12,767.

Resource consequences

NATROX is used in addition to standard care and so costs more than standard care alone. The company claims the technology could result in savings later on because of improved healing rates and fewer further interventions. Healthcare professionals and people using

the device need training to use it, but this is included in the cost of the device.

Regulatory information

NATROX is a CE-marked class 2b medical device.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

NATROX should not be used to treat malignant tissue. Someone with cancer is legally considered to be disabled and is protected under the 2010 Equalities Act.

NATROX is intended for use in people with non-healing wounds. Elderly people, people with heart conditions, and people with diabetes are at an increased risk of non-healing wounds and may benefit from this technology. In some cases, diabetes and heart conditions can be considered a disability. Age and disability are protected characteristics under the 2010 Equalities Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 3 studies summarised in this briefing. They included 172 patients, 162 of whom received NATROX therapy.

The evidence indicates oxygen therapy could be effective for non-healing wounds. But more clinical evidence on larger cohorts of patients is needed from controlled trials and

larger real-world populations to establish its effectiveness. Studies in 1 wound type would establish which wounds benefit most from the technology.

Overall assessment of the evidence

There is not much good-quality evidence: 1 small, high-quality randomised controlled trial and 2 larger observational studies. There are several abstracts and other publications describing individual cases, but these do not add to the substantive studies below.

The evidence shows an effect from the NATROX device, but the relatively small numbers of patients and heterogeneous populations means definitive conclusions are difficult. Only 1 study includes NHS data, but non-NHS pathways and the epidemiology of non-healing wounds and diabetic foot ulcers appear similar across all sources.

Yu et al. (2016)

Study size, design and location

Randomised controlled trial including 20 patients with diabetic foot ulcers, Canada.

Intervention and comparator(s)

NATROX compared with 'standard best practice'; NATROX used once a week for 8 weeks.

Key outcomes

Ulcer surface area over time was analysed using standardised digital imaging software. Wound size was significantly reduced compared with baseline in the NATROX group (F [2.238, 20.146] 58.885, $p < 0.001$) and not significant in the control group (F [1.186, 10.674] 51.447, $p < 0.262$). Ulcers were present without healing for a mean duration of 76 weeks before the study. All grade 1 ulcers in both groups healed (complete wound closure); all grade 2 ulcers in the NATROX group healed compared with none in the control group; 50% of grade 3 ulcers healed with NATROX compared with none in the control group.

Strengths and limitations

This was a high-quality study with well-defined interventions and patient groups. Ulcers

were graded with the widely used University of Texas diabetic foot ulcer classification. A limitation was its small size, with only 10 patients receiving the intervention. Generalisability to the UK is not clear as the study was in Canada.

Kaufman et al. (2018)

Study size, design and location

Real-world observational study on 100 consecutive cases, Israel.

Intervention and comparator(s)

Continuous oxygen delivery using NATROX for an average duration of 40.3 days; no comparator.

Key outcomes

The cases included 48 venous leg ulcers, 27 arterial ulcers, 13 diabetic foot ulcers and 12 others (trauma, burns, post-op and pressure ulcers). Adherence with the treatment was 88% and there was a mean reduction in wound area of 7% per week. For patients treated for more than 25 days, 31 of 65 wounds healed completely. There were no statistically significant differences between the groups, but non-healing ulcers tended to be larger and have a longer duration.

Strengths and limitations

This study is of low methodological quality but includes important real-world data from consecutive cases, although it is a relatively small real-world study. The mixture of types and duration of wounds and patients make clear conclusions difficult. Generalisability to the UK is not clear as the study was undertaken in Israel.

Hayes (2017)

Study size, design and location

Multicentre observational study on 52 diabetic foot ulcer cases, UK.

Intervention and comparator(s)

Continuous oxygen delivery using NATROX for an average duration of 24 weeks; no comparator.

Key outcomes

The median duration of diabetic foot ulcer before the trial was 12 months. The median ulcer size decreased from 1.8 cm² to 0.15 cm² over 24 weeks. At 8 weeks the median ulcer size reduction was 48%. At 12 weeks 42% of ulcers had healed completely and 14% showed more than 80% re-epithelialisation.

Strengths and limitations

This study included 18 UK NHS tertiary care sites. Standardised digital images were used to report wound size. The study is reported as an abstract and is limited in methodological detail; patient demographic data are not reported. Only descriptive statistics were reported, and the lack of a comparator limits the usefulness of these data. The abstract does not reference NATROX specifically, however, these are preliminary data from a randomised controlled trial in the UK investigating NATROX in diabetic foot ulcers.

Sustainability

The company states the NATROX Oxygen Generator is reusable and can be recycled at an appropriate facility, or through the company. The NATROX device complies with all relevant medical device disposal directives.

Recent and ongoing studies

- An observational clinical trial examining the effect of topical oxygen therapy (NATROX™) on the rates of healing of chronic diabetic foot ulcers. ClinicalTrials.gov identifier: NCT03863054. Status: recruiting. No results published. Estimated completion date: March 2020. Indication: diabetic foot ulcer. Devices: NATROX, Inotec AMD. Location: Singapore.

- The effect of NATROX® oxygen wound therapy on the healing rate of chronic diabetic foot ulcers. ClinicalTrials.gov identifier: NCT03905863. Status: active, not recruiting. No results published. Estimated completion date: March 2020. Indication: diabetic foot ulcer. Devices: NATROX, Inotec AMD. Location: USA.
- Topical oxygen and diabetic foot ulcers 2 (TODFU-2): a randomised, double-blind, placebo-controlled multicentre trial examining the effect of topical oxygen (NATROX) on the rates of healing for chronic diabetic foot ulcers 2. No ClinicalTrials.gov number reported. ISRCTN registry no. ISRCTN13815433. Status: completed, pending results, preliminary results reported as an abstract. Last updated: January 2019. Indication: diabetic foot ulcer. Devices: NATROX, Inotec AMD. Location: UK.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Four experts were familiar with and had used this technology before. Two continue to use the technology.

Level of innovation

Three experts consider the technology to be innovative. One believed it was a new variation on current methods of increasing oxygen to a wound. None of the experts believed the technology to have been superseded. Two noted alternative oxygen therapies, including hyperbaric oxygen therapy and a spray designed to deliver porcine haemoglobin to a wound bed. Neither of the alternative therapies mentioned are used in standard care.

Potential patient impact

Three experts believed the technology has the potential to reduce healing times in non-healing wounds. Two considered that the technology offers an alternative for people with complex wounds who have limited treatment options. One expert believed the technology might reduce pain and infection rate but felt there is little robust evidence to support this. Two believed the technology engages patients and may increase compliance. One

believed that NATROX results in better quality tissue closure and is less invasive than alternative therapies. All experts believed people with chronic non-healing wounds would most benefit from this technology.

Potential system impact

Two experts believed NATROX could reduce the number of hospital visits. One also said that antibiotic use and amputation could be reduced, with an overall reduction in secondary care costs. One expert believed NATROX could save nursing time because of faster healing and a need for fewer dressings. All experts considered that the technology will be cost saving if it reduces healing time. One expert commented that the technology could have a positive impact by introducing advanced wound therapies into the community care setting. Three believed the technology could reduce burden on the healthcare system. All agreed that only basic training is needed.

General comments

All experts agreed that this technology would be in addition to standard care. Two experts commented that occasionally the tubing kinks. One described accidental detachment when people have accidentally pulled the tubing. The company explained how to position the device to prevent kinking or pulling on the tube. Two experts also commented that charging the device overnight can be inconvenient, and some are not confident charging or wearing the device. Two experts believed an issue with using the device might be identifying patients that could manage it.

Expert commentators

The following clinicians contributed to this briefing:

- Ms Nicola Ivins, clinical research director, Welsh Wound Innovation Initiative. Declared no interests.
- Ms Deborah Joanne Wilson, lecturer in podiatry, Glasgow Caledonian University. Ms Wilson received financial reimbursement for involvement in a round paper discussion on the role of topical oxygen therapy in managing diabetic foot ulcer wounds. She has published case studies on NATROX and offered these data to the company. Ms Wilson has not received financial reimbursement from Inotec AMD.

- Mr David Russell, consultant vascular surgeon and honorary clinical associate professor, Leeds Teaching Hospitals NHS Foundation Trust. Declared no interests.
- Mr Ibbi Younis, consultant plastic surgeon, Royal Free and University College Hospitals. Mr Younis receives a retainer as a NATROX international advisory board member and has also received financial reimbursement from Inotec AMD for speaking engagements at a wound care conference.

Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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