

# Findings from an expert panel meeting on NATROX® Oxygen Wound Therapy

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A group of key opinion leaders met in Windsor, UK, on September 19, 2019 to discuss their use of NATROX® Oxygen Wound Therapy (Inotec AMD Ltd) and agree on tips for best practice. NATROX is clinically proven as an effective, practical and patient-friendly treatment (Wounds UK, 2017; Wounds International, 2018a; Wounds UK, 2019). The focus of the discussion was on optimising outcomes through patient selection and tips for best usage in practice.

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It is well established that oxygen is vital to wound healing (Castilla et al, 2012; Eisenbud, 2012; Wounds UK, 2018). While oxygen therapy has been used in various forms for decades (Yarbrough and Behnke, 1939), NATROX (Inotec) has represented a new practical solution that is able to widen usage in practice (Wounds UK, 2018). Hyperbaric oxygen therapy has been found to benefit patients and still represents an effective treatment in appropriate cases, but can be impractical and costly for some patients and healthcare settings (Tawfick and Sultan, 2009; Wounds UK, 2017). One of the main aims of NATROX is to offer a patient-friendly device that can maintain continuous oxygen therapy 24 hours a day, 7 days a week, to achieve complete re-epithelialisation.

NATROX Oxygen Wound Therapy consists of a lightweight, portable device (the patient can easily carry it in their pocket): the oxygen generator, and an oxygen delivery system that delivers the oxygen directly to the wound bed [Figure 1]. The device is battery-operated, discreet and silent, enabling the patient to continue with their daily activities with minimal disruption.

### Why use NATROX?

NATROX has been found to be effective in a range of wounds, particularly challenging wounds in which standard treatment has not been successful; there has been evidence of

chronic, non-healing wounds going on to heal with NATROX therapy (Yu et al, 2016; Kaufman, 2016; Wounds UK, 2019). During a meeting of key opinion leaders in Windsor, UK, the expert panel noted that NATROX is particularly good for patients who are not suitable for hyperbaric oxygen therapy, or do not have access to it.

It was also noted that NATROX is suitable not only on a variety of challenging wounds but also anatomical locations: for instance, the panel reported use in complex scalp wounds and for ischaemic nipples in breast reconstruction.

NATROX has been shown to work in clinical practice; emerging research also shows that it has an effect on bacteria, so is beneficial in managing wounds with suspected biofilm (Wounds International, 2018b). It is well established that lack of oxygen results in decreased antimicrobial activity and impairs the ability of immune cells to kill bacteria that colonise wounds, increasing the risk of biofilm formation (Wounds International, 2018b).

### Agreed effects of NATROX observed in practice.

- Reduced time to healing
- Reduced scarring
- Reduced pain
- Increased exudate levels observed in responders (in first 2–3 weeks of treatment)
- Increased oxygen diffusion
- Increased ROS
- Reduced anaerobes/bacterial load
- Increased patient engagement.

Figure 1. NATROX Oxygen Wound Therapy.



Biofilm is now strongly associated with wound chronicity and has been found to be present in the vast majority of chronic, non-healing wounds (WUWHS, 2016; Wounds International, 2018b).

It is suggested that oxygen therapy affects bacteria/biofilm growth: a 'significant' effect has been observed in practice, which requires further investigation. Future research is in progress in this area, as the effect of oxygen on wounds is a current key area of focus.

### **NATROX and quality of healing**

Enhanced quality of healing tissue is often reported with NATROX, as well as reduced scarring and improved appearance resulting in better function in healed tissue. Oxygen levels have been found to improve quality of healing, through the influence of oxygen on increased collagen production (Kominsky et al, 2010). Oxygen improves both the rate of collagen production, and the tensile strength and quality of the collagen produced, which improves the quality, appearance and function of healed tissue (Gordillo and Sen, 2003). The message is 'we can do better for patients than just getting the wound healed'.

Anecdotally, NATROX was used on a patient who would have normally received NPWT for a partially dehisced abdominal wound. The clinician reported that the wound healed with better quality tissue and less scarring than would have been expected if NPWT had been used. NATROX has been found to be beneficial in all phases of healing, however, it is particularly good at stimulating granulation tissue and epithelialisation. For larger/deeper wounds,

NPWT might be more appropriate, however NATROX can result in better-quality healing and improved tissue function and appearance. Additional studies are planned to explore the use of NATROX in surgery, including cosmetic due to the observed positive effect on scarring.

### **Focus on patient selection**

The expert panel reported extremely positive results with NATROX, but agreed that patient selection is a key element to successful treatment. It was noted that NATROX works well on 'nearly all patients'; however, there are some it does not, and the panel agreed it was important to focus on patient selection in order to optimise results.

When using advanced treatments, such as NATROX, there can be a tendency to consider it a 'last resort' treatment in extremely challenging, complex cases. While NATROX may work on many of these cases, and 'in some patients, NATROX is all that works', success is not guaranteed if appropriate patient selection is not considered.

In practice if, for example, a patient has other issues/comorbidities that are not being appropriately managed, healing will fail; there can be a tendency in these cases to blame the product or treatment, when in fact nothing would have worked. However, in order to make the best use of resources and optimise outcomes, there is a need to identify appropriate patients and give the treatment the best chance of working.

This highlights the need for thorough, holistic assessment and to make sure that any other issues or comorbidities are also dealt

with. In patients who are selected for treatment with NATROX, it is important that treatment is monitored and measured.

## Patient selection criteria

The panel discussed broad criteria for patient selection in order to optimise treatment and outcomes. It is important to remember that the differing scope may be huge for different wound types and locations.

As such, before treating with NATROX, the following points should be considered:

- A full holistic assessment of the patient and their wound is necessary before starting treatment
- The wound bed should be properly prepared before starting treatment — debridement is needed but this does not need to be aggressive (consider ‘aggressive cleansing’ or ‘conservative debridement’ as a guideline)
- In cases of osteomyelitis, treatment should commence prior to initiation of NATROX. Soft tissue infection can also be treated simultaneously (e.g. combined with antimicrobial dressing)
- In chronic wounds, consider NATROX in line with current biofilm guidelines: if the wound is not healing, biofilm must be suspected and the most effective therapies selected accordingly (e.g. antimicrobial dressings in conjunction with NATROX); resolve biofilm and reassess
- Patient compliance to a full treatment regimen is an important element (e.g. in diabetic foot ulcers, NATROX should be used in conjunction with offloading)
- Patient engagement and self-care is key: NATROX is easy to use in the home setting and this can represent an opportunity for patient empowerment and involvement in their own treatment
- Do not leave NATROX as a last-resort treatment!

## Optimising the impact of NATROX

In order for NATROX to work effectively, it is vital that wound bed preparation (WBP) is optimised before treatment begins. A structured WBP framework should be used, tailored to the individual patient and their wound, such as the TIME framework (Dowsett and Newton, 2005).

The panel discussed key points in terms of WBP and agreed upon the following points:

- Slough can impede oxygen absorption, so in such cases appropriate debridement is needed
- Gentle cleansing/debridement is key, so as not to disturb healing tissue
- Balance between sufficient debridement and not disturbing healing tissue is key, and

- should be emphasised and closely monitored
- Bleeding should be monitored, while bearing in mind that granulation tissue does bleed — in general, pinpoint bleeding is acceptable and not cause for concern, but bleeding should not be excessive as this might indicate that the tissue has been damaged
- Experience suggests that NATROX may reduce the need for debridement as it encourages the wound bed to improve.

## Monitoring treatment

Identifying biomarkers for treatment response, and measuring outcomes, is key to successful use of NATROX. Use in practice has shown an initial increase in exudate, which indicates healing response, as the wound environment is changing. Anecdotal evidence suggests that the increased exudate should be seen within the first 2–3 weeks of treatment to indicate that it is working. If this response is not seen during this initial period, experience suggests that NATROX will not work at all on this patient and other treatments (or treating underlying causes and comorbidities) should be considered.

It is also important that realistic expectations are set in terms of healing timeframes, which should be communicated to the patient — e.g. treatment duration may be from 6 weeks to 3 months. It is important for patients to be informed and be able to plan their lives. The panel noted that patient feedback around NATROX has been very positive: patients love the device, finding it very convenient, and tend to like the simplicity of the treatment; however, in some patients there may be some anxiety around change and using a new treatment, so it is vital to communicate and educate the patient. As noted, sometimes treatment can take longer before the full benefits can be seen, but the overall result and tissue quality will be improved; communicating this to the patient, in terms of the rationale behind treatment selection, may be helpful.

## The future

The encouraging results observed in use of NATROX on challenging, complex wounds opens up the scope for a great deal of future study and potential areas of use. In complex cases, there is scope for using NATROX in conjunction with other advanced therapies and it was agreed that investigating potential synergistic effects may be very beneficial.

In measuring the effects of NATROX, investigation is also needed into the exudate being produced by the wound during

#### Tips for use in practice.

- Barrier creams can be used if there is any concern about maceration and leaving the device on
- Caution should be exercised in positioning the tubing — no specific issues have been reported around this but clinician judgement should be used if there are concerns around irritation or pressure damage (e.g. varying the angle of the tubing, using suitable adhesives to hold it in place). Reported experience demonstrates that some clinicians try to vary the angle of the tubing and, conversely, some try to match the same angle each time — no difference has been observed in outcomes
- In small or hard-to-access areas (such as the toes in the case of DFUs), NATROX can be folded or positioned in various ways, in order to simplify application. There are no adverse effects of NATROX being placed over intact periwound skin.

treatment; it was agreed that it would be useful to assess dressings for exudate composition to investigate this cellular level response.

Further study into the effects on NATROX will help to determine patient selection criteria, identifying which patients and wounds will be effective responders to treatment.

#### Service provision

It is important that NATROX is used appropriately in order to utilise resources in the most effective way, and to improve outcomes for suitable patients, which will also result in overall savings in cost and clinician time. Time to healing has been shown to be improved in suitable cases, and patients are able to use NATROX effectively at home, engaging and participating in their own treatment.

Further health economic data are required to analyse the benefits of NATROX and identify how best it can be utilised to improve outcomes. Measuring outcomes is key to produce value-based data. Key issues are to be identified in all treatment areas, in order to use experience effectively to guide future practice. Examples of effective cost-saving markers may include:

- Reduction in amputation for DFU treatment
- Reducing surgical site infection (e.g. tracking 30/60/90-day outcomes)
- Comparison to nearest alternative treatment, such as NPWT in suitable cases
- In some geographical areas and healthcare systems, hyperbaric oxygen therapy may be used as the alternative (although this does not apply in all areas)
- In the US, relating treatment to reimbursement issues.

In terms of the health economic aspect, it is important that NATROX is appropriately

positioned in the treatment landscape and used as such. NATROX should be viewed as a 'therapeutic intervention', rather than a dressing.

It is important that all key stakeholders are engaged and involved in treatment decisions. As key decision-makers, nurses should be involved in business cases where possible, as they are delivering care and have key knowledge relating to patients and their needs.

#### Educational needs

In order to increase appropriate use of topical oxygen therapy and improve outcomes, there is a need for education. This involves both hands-on clinical training in patient selection criteria and markers to look for, and education about the mode of action and role of oxygen.

Published evidence is required at all levels, including randomised controlled trial (RCT) evidence, although this is not the sole form of evidence. This includes evidence around:

- Mode of action
- Clinical efficacy
- Cost.

Documentation is key, both for clinical best practice and to track outcomes in NATROX use. Data can then be extrapolated and disseminated, in order to aid improved outcomes and to improve knowledge on optimum use.

Oxygen therapy is a key area in wound care, and evidence is growing of its efficacy, particularly now that NATROX has enabled wider practical usage. Therefore, increased knowledge is needed around the benefits of oxygen and how this can be applied in patient care. The panel agreed that oxygen therapy has huge potential to improve outcomes

## Key learning points.

- Oxygen is vital to wound healing and NATROX provides a practical solution to delivering oxygen therapy across healthcare settings
- NATROX is suitable for use across a range of wound types, although it is important to focus on appropriate patient selection and managing any underlying causes and comorbidities
- Emerging evidence demonstrates that NATROX has an effect on bacteria and is effective in preventing and managing biofilm
- NATROX has shown improved healing tissue, both in appearance (i.e. reduced scarring) and improved function
- Increased education is required around the benefits of oxygen therapy and how this can best be applied in practice in order to improve outcomes.

and patient lives when used in suitable cases. Currently, this varies across geographical regions and healthcare settings — for example, in Malaysia, compulsory training in wound care includes information around oxygen therapy. Increased knowledge and development of guidelines should enable this level of knowledge and application across global areas.

It is important to keep the patient at the heart of all care; it was agreed by the panel that overall education on the importance of wound care, and the reality of being a patient living with a chronic wound, deserves a higher profile.

**WINT**

## References

- Castilla DM, Liu Z-J, Velasquez OC (2012) Oxygen: Implications for healing. *Adv Wound Care* 1(6): 225-30
- Dowsett C, Newton H (2005) Wound bed preparation: TIME in practice. *Wounds UK* 1(3): 58-70
- Eisenbud DE (2012) Oxygen in wound healing: Nutrient, antibiotic, signalling molecule and therapeutic agent. *Clin Plastic Surg* 39: 293-310
- Gordillo GM, Sen CK (2003) Revisiting the essential role of oxygen in wound healing. *Amer J Surg* 186: 259-63
- Kaufman H (2016) A new approach in oxygen wound therapy: an overview of NATROX experience in Israel. Abstract and presentation. World Union of Wound Healing Societies, Florence
- Kominsky DJ, Campbell EL, Colgan SP (2010) Metabolic shifts in immunity and inflammation. *J Immunol* 184(8): 4062-8
- Tawfik WA, Sultan S (2009) Does topical wound oxygen (TWO2) offer an improved outcome over conventional compression dressings (CCD) in the management of refractory venous ulcers (RVU)? A parallel observational comparative study. *Eur J Endovasc Surg* 38(1): 125-32
- World Union of Wound Healing Societies (2016) Congress position document: Management of biofilm. Available at: <https://www.woundsinternational.com/resources/details/position-document-management-biofilm> (accessed 10.12.2019)
- Wounds International (2018a) Consensus round table meeting: Portable topical oxygen therapy for healing complex wounds. Available at: <https://www.woundsinternational.com/resources/details/consensus-round-table-meeting-portable-topical-oxygen-therapy-for-healing-complex-wounds> (accessed 10.12.2019)
- Wounds International (2018b) Challenging wounds, improving outcomes: Biofilm management with topical oxygen therapy. Available at: [https://www.woundsinternational.com/resources/all/0/date/desc/cont\\_type/49](https://www.woundsinternational.com/resources/all/0/date/desc/cont_type/49) (accessed 10.12.2019)
- Wounds UK (2017) Consensus round table meeting: Clinical pathway for using topical oxygen therapy in practice. Available at: <https://www.wounds-uk.com/resources/details/consensus-round-table-meeting-clinical-pathway-using-topical-oxygen-therapy-practice> (accessed 10.12.2019)
- Wounds UK (2019) Case series: Using NATROX Oxygen Wound Therapy in the management of diabetic foot ulcers. Available at: <https://www.wounds-uk.com/resources/details/case-series-using-natrox-oxygen-wound-therapy-management-diabetic-foot-ulcers> (accessed 10.12.2019)
- Yarbrough OK, Behnke AR (1939) Treatment of compressed air illness utilizing oxygen. *J Indust Hyg Toxicol* 21: 213-8
- Yu J, Lu S, McLaren A-M et al (2016) Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. *J Vasc Surg* 24(6): 1536