# Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial


• **Objective:** A randomised clinical trial (n=42) compared the effectiveness of two approaches to debriding chronic leg ulcers: TenderWet 24, which is designed to support the autolytic degradation process, and Iruxol N (Santyl), an enzymatic treatment claimed to enhance the degradation process.
• **Method:** Patients were randomly assigned to one of the two treatment groups for three weeks. Wounds were evaluated weekly for the amount of eschar/slough, the area of healthy granulation and the re-epithelialised area.
• **Results:** During days 1–14 slough within the groups was reduced by almost 19% for TenderWet 24 and by 9% for Iruxol N, followed by an increase of 26% and 10% respectively in granulation tissue. These effects were less accentuated during days 7–21. There was a further 11% improvement in tissue debridement for the TenderWet 24 group and a relapse (+9.1%) in the Iruxol N group.
• **Conclusion:** Although TenderWet 24 appeared to be more efficient in a few cases, the general efficacy of the two products appeared to be almost the same as no statistically significant superiority of either product was found.
• **Declaration of interest:** This study was sponsored by Paul Hartmann AG, Heidenheim, Germany.


TenderWet 24; Iruxol N (Santyl); enzymatic debridement; autolytic debridement; venous leg ulcer

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Chronic wounds such as venous ulcers require effective debridement and a moist wound environment to heal. Effective compression therapy is also needed.[1-3] Wound debris such as slough and necrotic tissue causes hypoxia in the wound area, inhibits development of granulation tissue and slows re-epithelialisation. Furthermore, wounds with necrotic tissue and eschar often have high levels of bacteria and toxins, prolonging the inflammatory response and increasing the risk of infection.[4] Debridement is therefore required to facilitate healing.

Surgical debridement is the quickest method of removing superficially indurated and poorly vascularised tissue, and thus of facilitating the next step of the healing process.[5] Where surgical debridement is inappropriate or presents too great a risk to the patient, removal of wound debris can be done by less invasive means. One approach, which is widely used in Germany, is debridement with locally applied enzyme preparations, which are intended to accelerate the digestion of abundant, non-viable tissue.[6]

In contrast, the aim of moist wound healing[7,8] is to provide a physiological wound environment in which the body can exert its own debriding capacity.[9] This autolytic debridement can be found to some extent in every wound. By releasing endogenous proteolytic enzymes and activating phagocytes, necrotic tissue and slough are digested and separated from healthy tissue.[9]

The moisture-activated polyacrylate dressing pad, TenderWet 24 (IVF Hartmann, Switzerland), supports the autolytic debridement of the wound itself.[10] TenderWet 24:
• Attracts and permanently removes proteins from necrotic tissue
• Attracts and retains toxins and bacteria
• Provides a moist and physiological environment for enzymatic autolysis by collagenases, elastases, myeloperoxidases, hydroxylases and activation of phagocytes.[11,12]

This randomised controlled trial was designed to compare the efficacy of the 'pharmaceutical' (enzymatic) and the 'natural' (autolytic) approaches to the debridement of chronic leg ulcers.

## Method

Forty-two outpatients attending the wound healing unit at the Department of Dermatology, University of Freiburg, Germany, and who met the inclusion criteria (Table 1), were randomised by computer-generated list to one of the two treatments:
• 15 patients received TenderWet 24
• 27 patients received Iruxol N and dry gauze. (Iruxol N is branded as Santyl in North America, and is not distributed in the UK.)

Patients were informed about their rights and obligations within the study according to good clinical practice. Oral consent was obtained for every case.

To facilitate equal starting conditions for debride-

**Table 1. Main patient-selection criteria**

| Inclusion criteria |
|---|
| Patients suffering from venous ulcers with proven chronic venous insufficiency, where the current wound had persisted for at least six weeks |
| Outpatients aged over 18 years old |
| Able to perform self-care of their wound and to apply compression independently |
| **Exclusion criteria** |
| Concomitant diseases suggesting impediments to healing:<br>• Disabling disease such as malignant tumours, tuberculosis and HIV etc<br>• Administration of steroids (>8mg prednisolone daily)<br>• Peripheral arterial occlusive disease from Fontaine's stage IIa |

ment, a wash-out period of seven days was established. All patients unable to credibly declare that they did not use any unknown external applications such as ointments, rinses, soaks or other topical treatments were asked to avoid using them during the pre-phase of the study. Patients were told how to apply the dressing they were assigned.

Iruxol N is an enzymatic debriding ointment containing collagenase, which is derived from *Clostridium* spp., and digests collagen and necrotic tissue. According to the manufacturer's instructions, it is indicated for chronic dermal ulcers and severely burned areas. The manufacturer says it can be applied either directly, or indirectly by a sterile gauze pad applied to the wound.

The polyacrylate dressing pad TenderWet 24 must be activated before use with Ringer's solution. Patients were advised to change dressings every 24 hours.

Patients treated with Iruxol N were instructed to anoint their wounds completely with the enzymatic ointment and to change the dry gauze every 24 hours. According to the manufacturers' instructions, both TenderWet 24 and Iruxol N should be applied or changed once daily to ensure an efficient debridement performance. The daily dressing changes also prevent TenderWet 24 drying out.

In addition, patients in both groups were trained to use short-stretch compression bandages during the day for their chronic venous insufficiency. It was not recorded if they had been using short-stretch bandages before entering the study.

Over the course of the study, a dermatologist and second assessor from the wound-healing unit undertook weekly assessments that comprised of:

- Recording adverse events
- Digital imaging
- Subjective description of the wound with respect to percentage reduction of slough/eschar, development of granulation tissue and epithelialisation. An assessment tool was not used as the two investigators were experienced in the assessment and treatment of chronic wounds; furthermore, they had participated in previous studies in which subjective assessment proved to be effective. The same two clinicians assessed all 42 patients; a single clinician subjectively assessed concordance with compression therapy. The two assessors received the same training on the assessment of wound parameters before the study to help them collect comparable data. The relative amounts of the visually assessed properties of the wound bed were compared with the digital images to improve the validity of the assessed parameters.

### Statistical analysis

As outpatients attending the wound healing unit tend to be older people with comorbidities, the target population was advanced in years. In many cases concordance with self-care of wounds and independent application of compression could not be guaranteed. Additionally, many patients had concomitant diseases that impede wound healing. Therefore, only 42 patients complied with the inclusion criteria (Table 1) and so could be enrolled into this study. The figure of 58 patients (29 per each group) per protocol calculated in advance as necessary to show superiority of at least 30% for any product could not be achieved.

This and the fact that we did not use block-randomisation resulted in unequal numbers in the therapeutic groups. Because parametric tests did not fulfil the statistical qualifications, longitudinal evaluations within groups were run with the non-parametric Wilcoxon matched-pairs test. Sectional comparisons between groups were carried out with the independent pairs U-test.

## Results

The patients' average age was 71.7 years (female: 72.4; male: 71.7). Some two-thirds were female.

Inconsistent responses to therapy and the subjective nature of the visual wound assessments may have caused immense variations within the data set, which soon made it unlikely that meaningful results would be observed in a time period as short as 14 days. (A 14-day study period was selected because, in the investigators' experience, TenderWet 24 and Iruxol N normally result in improvements within 10 days.) Therefore, we continued to evaluate after the initial 14 days (days 1–14), extending the next evaluation from seven to 21 days (days 7–21).

The critical wound parameters improved significantly in both groups and debridement took place predominantly within the first days of initiating therapy, as is expected if effective measures are in place to enhance this process (Tables 2 and 3).

During the first period (days 1–14) slough reduced by almost 20% in the TenderWet 24 group and 10% in the Iruxol N group (Fig 1), followed by a simulta-


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**Table 2. Patients treated with TenderWet 24: characteristics of wounds and percentage changes**

**Percentage of wound area**

| Day | Slough/eschar | Granulation tissue | Epithelialised area |
|---|---|---|---|
| Day 0 (n=15) | 47.5% | 36.3% | 6.9% |
| Day 1–14 (n=15) | 28.8% | 63.0% | 16.2% |
| Percentage changes | -18.7% | +26.7% | +9.3% |
| p value* | **0.01** | **0.01** | **0.04** |
| Day 7–21 (n=11) | 17.9% | 73.9% | 24.3% |
| Percentage changes | -10.9% | +10.9% | +8.1% |
| p value* | 0.15 | 0.15 | **0.03** |

*Wilcoxon matched-pairs test (significant results are in bold)

**Table 3. Patients treated with Iruxol N: characteristics of wounds and percentage changes**

**Percentage of wound area**

| Day | Slough/eschar | Granulation tissue | Epithelialised area |
|---|---|---|---|
| Day 0 (n=27) | 55.2% | 34.9% | 0.3% |
| Day 1–14 (n=27) | 46.7% | 45.3% | 7.0% |
| Percentage changes | -8.5% | +10.4% | +6.7% |
| p value* | **0.04** | **0.02** | **0.02** |
| Day 7–21 (n=11) | 55.8% | 47.1% | 8.8% |
| Percentage changes | +9.1% | +1.8% | +1.8% |
| p value* | 0.29 | 0.72 | – |

*Wilcoxon matched-pairs test (significant results are in bold)

neous increase of 25% (TenderWet 24) and 10% (Iruxol N) in granulation tissue (Fig 2). These effects were less accentuated in the second period (days 7–21). There was about an 11% further improvement in tissue debridement in the TenderWet 24 group and a relapse (+9.1%) in the Iruxol N group (Fig 1). Percentage changes of epithelialisation are given in Fig 3.

Eighteen patients given Iruxol N and six treated with TenderWet 24 who did not respond to the therapy in the 21 days received the alternative therapy. The objective was to find out if these wounds would not respond to either treatment. That more patients crossed from Iruxol N to TenderWet 24 was at least partly due to an intangible effect of the different patient numbers in the two groups. Outcomes were not recorded due to the small numbers involved.

A differential efficacy in debridement between the two approaches could not be shown. Thus, compar-

**Fig 1. Percentage changes of slough/eschar in the TenderWet 24 and Iruxol N groups respectively**

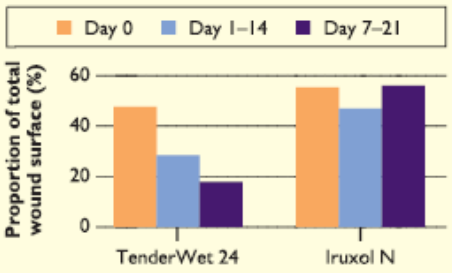



**Fig 2. Percentage changes of granulation tissue in the TenderWet 24 and Iruxol N groups respectively**

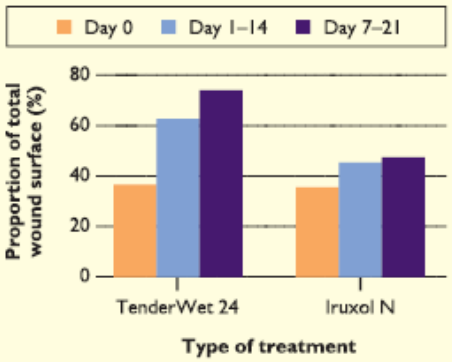
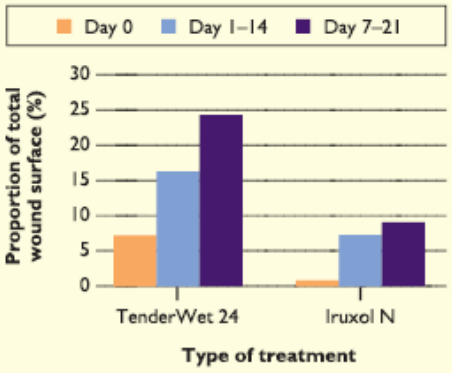



**Fig 3. Percentage changes of epithelialisation in the TenderWet 24 and Iruxol N groups respectively**



ison between the groups resulted in equivalence with respect to the critical parameters. This was partly also a consequence of excessive variation within the data as the response to both therapies was also inconsistent within each respective group.

Our findings appear to favour TenderWet 24, but the statistical results do not substantiate this.

**Table 4. Assessed parameters displayed in 14-day periods**

| | TenderWet 24 | | Iruxol N | | |
|---|---|---|---|---|---|
| | No. | Mean | No. | Mean | p-value* |
| **Days 1–14** | | | | | |
| Slough/eschar | 15 | -18.7 | 27 | -8.5 | 0.30 |
| Granulation | 15 | +26.7 | 27 | +10.4 | 0.07 |
| Epithelialisation | 15 | +9.3 | 27 | +6.7 | 0.95 |
| **Days 7–21** | | | | | |
| Slough/eschar | 11 | -10.9 | 11 | +9.1 | 0.07 |
| Granulation | 11 | +10.9 | 11 | +1.8 | 0.47 |
| Epithelialisation | 11 | +8.1 | 11 | +1.8 | 0.08 |

*U-test

## Discussion

Several underlying factors aggravate the venous ulcer and its progression — among them concordance with effective, permanent compression therapy looms large.[13,14] Another important factor is wound treatment, starting with effective debridement. Although it is widely recognised that debridement is a key element in wound healing, there are few randomised controlled studies showing its benefits.[11,15,16] There is also insufficient evidence to promote the use of one debriding agent over another.[11]

These results are consistent with the data from our trial, which found no statistically significant differences in efficacy of enzymatic and autolytic debridement. In the first observation period the two approaches worked as desired and performed equally with respect to debridement, as reflected by the increased area of removed slough. Later in the course of the trial the effectiveness of the enzyme seemed to decrease when compared with TenderWet 24.

On considering this observation, we felt the apparently decreased effectiveness in the debriding action of Iruxol N may not necessarily have reflected a lack of product effectiveness, but rather could represent a requirement for more thorough wound rinsing on dressing changes. The fact that an ointment cannot exert significant absorbent properties and therefore will be dependent on the secondary dressing used seems trivial. However, the definite and visible advantage of TenderWet 24 over Iruxol N must be deemed to be the result of better incorporation and removal of degraded material than is possible with dry gauze, which was applied with the latter treatment.

Our perception was that TenderWet 24 wounds benefited from the specifically designed absorbent core of the product as they generally appeared cleaner. This may be because the core of TenderWet 24 is designed to absorb more of the degraded tissue than is the enzyme, which is in an ointment format and requires an absorbent secondary dressing, as recommended by the manufacturer. This may have led the investigators to a subjective judgement of the superiority of the moist therapy provided by TenderWet 24 in a greater number of cases as statistical analysis could not significantly confirm this. Also, the number of adverse drug reactions was not significant enough to imply a lack of safety for Iruxol N. On the other hand, there was no compelling evidence suggesting superior degrading potency of either product.

The extent of newly developed, visible and assessable granulation tissue was limited by the amount of slough covering the wound beds. Hence, more effective removal of surface debris may have considerably influenced the investigators' judgement of the quality and quantity of neat granulation. Indeed, post hoc statistical analysis showed the two parameters (neat granulation tissue and slough) were closely and inversely correlated. Moreover, 'granulation tissue' was perceived and recorded less distinctly and was less reproducible — and thus less valid. Decrease or absence of slough in several cases was mistakenly paralleled by the impression of increasing granulation tissue. Therefore, we felt that debridement was over-defined using both parameters, in terms of measuring their effectiveness in debridement.

## Conclusion

Even though TenderWet 24 appeared to be more efficient, both approaches proved to be equally effective and their performance could not be quantitatively differentiated by statistical means. Enzymatic debridement was not superior to moist autolytic wound debridement in our setting. We therefore consider them as comparable treatments.

Iruxol N was easily handled and safe, although dry conditions may be less favourable to the overall outcome in wound cleansing and healing, requiring more effort in dressing changes (extensive and thorough wound irrigation to effectively loosen surface wound debris). In contrast, TenderWet 24 allowed for a 'one-step removal' of slough, performed once daily. Its major properties (removal of slough, provision of moisture, absorption and protection) are exerted simultaneously, thus avoiding the potential adverse effects of topical enzymes in wound tissue, while also improving quality of life in patients with chronic venous leg ulcers. ■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