Clinically relevant pain relief with an ibuprofen-releasing foam dressing: Results from a randomized, controlled, double-blind clinical trial in exuding, painful venous leg ulcers

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ABSTRACT

The objective of this 6-week, 120-patient, double-blind, randomized, controlled trial was to investigate if a foam dressing with ibuprofen provided clinically relevant pain relief (PAR) for exuding, painful venous leg ulcers in comparison with a similar foam dressing without ibuprofen. Primary outcome parameter was PAR compared with baseline pain during the first 5 days of the investigation. PAR was registered by the patient morning and evening. Main end point was proportion of patients reporting a summed PAR score of at least 50% of the total maximum PAR (i.e., responders) and the corresponding number needed to treat (NNT). Wound-related parameters such as ulcer healing, ulcer area reduction, and peri-ulcer skin condition as well as adverse events were recorded during all 6 weeks of the investigation. PAR was significantly greater in the ibuprofen foam group than the comparator group (p = 0.0438). There were 34% responders in the ibuprofen foam group vs. 19% in the comparator group (NNT = 6.8). When evening data were analyzed separately to evaluate PAR over daytime, NNT was 5.3. Wound healing parameters and adverse events were comparable. In conclusion, in this study, the ibuprofen foam dressing provided clinically relevant PAR for patients with exuding, painful venous ulcers.

Patients may suffer from, often recurrent, chronic wounds such as venous leg ulcers for a long period.1 As many as six out of 10 persons with chronic wounds suffer from persistent wound pain.2–4 The pain from chronic wounds can be extremely severe and wound pain is consistently reported by patients as the most prominent symptom of chronic venous leg ulcers.1,5–8 A qualitative study investigating the experience of pain in patients with chronic venous leg ulcers reported that the patients’ lives were dominated by pain originating from their ulcer.1 Reduction of pain is frequently cited as the highest treatment priority from the patient’s perspective.5,9 The importance of managing the pain associated with chronic wounds is increasingly recognized in clinical practice because it can significantly improve a patient’s quality of life and may indirectly promote healing by improving appetite and sleep.10,11

Clinical studies have shown that, in addition to moist wound healing, a foam dressing with added ibuprofen (Biatain Ibu, Coloplast, Humlebæk, Denmark) may reduce wound pain during wear time and at dressing change.12–16 A safe, low dose of ibuprofen is released from the ibuprofen foam dressing in response to the uptake of wound exudate into the dressing.17 To our knowledge, this is the only topical treatment aimed at reducing persistent wound pain, while topical anesthetics such as EMLA cream (2.5% lidocaine, 2.5% prilocaine) are widely used in connection with dressing change procedures and have been shown to reduce pain during debridement of venous leg ulcers.18,19 For persistent wound pain, oral analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used. However, systemic NSAID treatment can cause serious gastrointestinal and cardiovascular side effects,20,21 especially in elderly people treated with multiple drugs.20,22–25

Topical treatment of wound pain is not expected to elicit gastrointestinal or cardiovascular side effects. When wound
exudate and blood were analyzed for content of ibuprofen after 5 days of continuous use of the ibuprofen foam dressing, ibuprofen had a clinically relevant concentration in wound exudate but was not detectable in blood plasma.14

Previously, two randomized controlled trials (RCTs) investigating the efficacy and safety of the ibuprofen foam dressing were published. One study was a double-blind RCT in patients with painful, venous leg ulcers comparing the ibuprofen foam dressing to a similar foam dressing without added ibuprofen.15,16 In this study, significantly more pain relief (PAR) was observed in the ibuprofen foam group when measured over the first 7 days of the study than in the comparator group. PAR was observed already in the first evening after study start. Wound healing over 6 weeks was similar in the two groups, and no difference in adverse events or safety-related parameters was observed. These data were confirmed by a 7-day RCT comparing the ibuprofen foam dressing with local best treatment practice for a variety of chronic and traumatic exuding, painful wounds.15 Recently, a secondary analysis of this study was published.16 When clinical relevant PAR was analyzed for each etiology group separately, the ibuprofen foam dressing was shown to consistently relieve wound pain in chronic and acute wounds across etiologies, irrespective of basal pain intensity. Number needed to treat (NNT, i.e., the average number of patients who need to be treated for one patient to benefit from the treatment who would not have benefitted from placebo26) was calculated for each etiology subgroup. Responders to treatment were defined as at least 50% of maximal possible PAR over the full treatment period. NNTs ranged from 3.1 to 6.2 for the various wound etiology subgroup. For venous leg ulcers, NNT was 5.2, which was in the same order of magnitude as commonly used oral analgesics for chronic pain states.27,28

The aim of this study was to investigate if a foam dressing with ibuprofen provided clinically relevant PAR for exuding, painful, chronic venous leg ulcers in comparison with a similar foam dressing without ibuprofen. This 120-patient, double-blind RCT will extend the existing evidence for the efficacy of the ibuprofen foam dressing.

**METHODS**

**Study design and patients**

This was a multicenter, double-blind RCT conducted in order to compare the performance of an ibuprofen foam dressing with a comparator foam dressing without added ibuprofen. The study period was 6 weeks. Participants were patients (≥18 years of age) with a painful, moderately to highly exuding, chronic venous leg ulcer (ankle/brachial index ≥0.8) on the lower leg (ulcer duration ≥8 weeks). Pain intensity in the study ulcer should be at least 4 on an 11-point numerical rating scale (0 = no pain to 10 = worst possible pain), and ulcer size should be minimum of 1.6 cm and maximum of 11 cm in any direction. Furthermore, the participants should have been treated with moist wound-healing dressings and adequate compression therapy during the past 2 weeks prior to inclusion. Use of per need medication for the past 3 days before study start was an exclusion criterion. Other exclusion criteria were: painful ulcer resistant to analgesics for the past 6 months or more, known and verified hypersensitivity to any content of the products used in the investigation, local infection (bacterial imbalanced wound) or clinical infection in the study ulcer, vasculitis, erysipelas, cellulitis of the peri-ulcer skin, diseases and conditions where ibuprofen or other analgesics are contraindicated, diabetes mellitus, concomitant treatment with systemic antibiotics other than nitrofurantoin, corticosteroids (more than 10 mg/day prednisolone or equivalent) or other immunosuppressants within 1 month prior to inclusion, concomitant treatment with cancer chemotherapeutics, pregnant or lactating women.

PAR was registered in the morning and evening during the first 5 days of the study. During this period, any medication had to be kept constant regarding dose, intake, and way of administration. Per need medication was not allowed.

Use of compression therapy was mandatory throughout the study period. It was up to the investigator to select an adequate compression bandage for the study ulcer leg. A patient should not change the type of compression bandage during the first 5 days of the investigation.

The study was conducted according to local regulations, the Declaration of Helsinki II,29 the EC Medical Device Directive,30 and the international ISO standard on clinical investigation of medical devices for human subjects.31 Approval was granted from the relevant local ethics committees, and written informed consent was obtained from all patients.

**Interventions**

The test dressing (Biatain Ibu Non-Adhesive, Coloplast A/S) is designed to provide a moist wound healing environment and manage exudate. It consists of a soft, hydrophilic polyurethane foam with ibuprofen homogeneously dispersed throughout the foam (ibuprofen concentration: 0.5 mg/cm²). One dressing (15 × 15 cm) contains 112.5 mg of ibuprofen.17 The foam is bound to a semipermeable polyurethane film. In the presence of exudate, ibuprofen is continuously released into the wound bed. The comparator dressing was identical to the test dressing, but ibuprofen was not incorporated (Biatain Non-Adhesive, Coloplast A/S).

**Randomization**

Patients were randomized using an interactive voice response system (IVRS), which is a telephone system designed to facilitate and simplify the process of randomizing subjects into a study. The system was provided by an external company (Premier Research Group PLC, Workingham, Berkshire, United Kingdom). By using the IVRS, the subjects were centrally randomized and allocated to one of the two treatment groups. The IVRS system was set up based on a randomization list. The randomization was stratified into two levels of pain intensity at inclusion (Level 1: pain intensity 4–6; Level 2: pain intensity 7–10).

**Blinding**

The dressings were specially designed for this study to be anonymous by the use of top films without print. The color and texture of the dressings were identical so it was not possible to visually distinguish the test dressing from the
The study population consisted of 120 patients (60 patients in each treatment group) with chronic, exuding, painful venous leg ulcers on the lower limb. Patients were recruited from hospitals, community, and wound care centers in four countries (Denmark, France, Germany, and Spain) between March 2008 and March 2009. Baseline demographics are shown in Table 1. There was a statistically significant difference in ulcer size at baseline \( (p = 0.0009) \).

**Outcome parameters**

**PAR**

PAR was significantly greater in the treatment group than in the comparator group \( (p = 0.0438) \) with odds ratio = 1.73 \( (1.02–2.96) \) for treatment. Figure 1 illustrates percent responders at cutoff points ranging from 0% to 100% of maxTOTPAR. There were 34% responders at the 50% cutoff point (patients with at least 50% PAR) in the treatment group and 19% in the comparator group. This corresponds with an NNT of 6.8 (CI: 3.3–14.1). The Wilcoxon test revealed a significant group difference in favor of the treatment group \( (p = 0.039) \).

When evening data were analyzed separately, there was a significant difference between responder rates in the two treatment groups in favor of the ibuprofen foam group \( (p = 0.006, \text{ Figure 2}) \). NNT was 5.3 (CI: 2.9–9.6) based on responders in the evening at the 50% cutoff point (35% in the treatment group, 16% in the comparator group). The corresponding 95% confidence interval (CI) was derived from a binomial CI.

Furthermore, the evening data set was analyzed separately by the same method in order to use evening data to evaluate PAR during daytime.

Differences in pain intensity at inclusion and ulcer area between study groups were analyzed with the Wilcoxon–Mann–Whitney test. Differences in observed numbers of ulcers healed and adverse events between study groups were tested using Fisher’s exact test. Differences in reductions in absolute and relative ulcer areas between study groups were analyzed using analysis of variance. Reduction in ulcer area was analyzed with last observation carried forward. All data analyses were carried out on the intention-to-treat population.

**RESULTS**

**Demographics**

The study population consisted of 120 patients (60 patients in each treatment group) with chronic, exuding, painful venous leg ulcers on the lower limb. Patients were recruited from hospitals, community, and wound care centers in four countries (Denmark, France, Germany, and Spain) between March 2008 and March 2009. Baseline demographics are shown in Table 1. There was a statistically significant difference in ulcer size at baseline \( (p = 0.0009) \).

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As illustrated in Figure 2 and Table 2, the percentage of participants with clinically relevant PAR (2: “moderate,” 3: “marked,” or 4: “complete” PAR) increased over time in both groups, especially in the treatment group.
Ulcer healing and ulcer area

Nine ulcers healed in the treatment group and 11 in the comparator group during the study period ($p = 0.8071$). There was no statistically significant difference in relative ulcer area reduction between the groups (59% in the treatment group and 50% in the comparator group, $p = 0.0651$) nor in absolute ulcer area reduction (from baseline 4.82 to 2.44 cm$^2$ on day 43 in the treatment group and from 8.18 to 3.35 cm$^2$ in the comparator group, $p = 0.6943$).

Because of the odd distribution of ulcer sizes between the two treatment groups at baseline, the Gilman method of linear wound healing rates (LWHRs) was applied. Using the LWHR method, ulcer size at baseline and the shapes of the ulcers will not influence the results. Table 3 shows the LWHRs with healed ulcers calculated as 0. There was no significant difference in the healing rates between the two groups ($t$-test, $p = 0.4978$).

Peri-ulcer skin condition

The number of participants in each treatment group who experienced maceration, erythema, eczema, and petechiae decreased from study start to study termination in both treatment groups as illustrated in Figure 3. Only descriptive statistics were performed.

Adverse events and withdrawals

Fourteen adverse events were reported in the treatment group, of which four were reported as related or possibly related to the use of the dressing (two had eczema and two had infection.

Table 1. Demographics of patients

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Ibuprofen foam</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>71.6 ± 12.8</td>
</tr>
<tr>
<td>Gender</td>
<td>Female n (%)</td>
<td>42 (70)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean ± SD</td>
<td>168.6 ± 9.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ± SD</td>
<td>81.2 ± 19.3</td>
</tr>
<tr>
<td>Ulcer size (cm$^2$)</td>
<td>Mean ± SD</td>
<td>9.1 ± 10.9</td>
</tr>
<tr>
<td>Ulcer size (cm$^2$) Median (range)</td>
<td>4.82 (1.09–57.6)</td>
<td>8.18 (0.93–40.1)</td>
</tr>
<tr>
<td>Duration of ulcer (years)</td>
<td>Mean ± SD</td>
<td>1.5 ± 3.0</td>
</tr>
<tr>
<td>Type of compression therapy (%)</td>
<td>Short stretch/Long stretch/4 layer/Other*</td>
<td>48/32/15/15</td>
</tr>
</tbody>
</table>

* “Other” was mainly compression stockings.

Figure 1. The figure presents observed data and fitted curves for the percentage of responders at 0–100% of the maximal possible pain relief (maxTOTPAR). NNT were calculated from the 50% cutoff point.

Figure 2. The figure shows the percentage of participants with clinically relevant PAR (2: “moderate,” 3: “marked,” or 4: “complete”) at each evening measure (day 1 to 4).
Table 3. Linear wound healing rates

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>LWHR (mean/4 weeks)</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen foam</td>
<td>58</td>
<td>0.23 cm</td>
<td>0.40</td>
<td>−0.63</td>
<td>1.72</td>
</tr>
<tr>
<td>Comparator</td>
<td>59</td>
<td>0.27 cm</td>
<td>0.31</td>
<td>−0.47</td>
<td>1.04</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This double-blind, randomized, comparative, 120-patient, 6-week trial compared a foam dressing with ibuprofen with a similar foam dressing without ibuprofen for treatment of exuding, painful chronic venous leg ulcers. PAR measured during the first 5 days of the study was significantly greater in the treatment group than in the comparator group, both day by day and calculated as total PAR over the 5-day period. Thirty-four percent of the patients in the ibuprofen foam group reported a summed PAR score of at least 50% of maxTOTPAR (35% in the evening dataset) compared with 19% in the comparator group (16% in the evening dataset), corresponding to an NNT of 6.8 (5.3 in the evening). Wound healing parameters and numbers of adverse events were comparable for the two groups. This is comparable to the results from a previous RCT comparing the ibuprofen foam with local best treatment practice, where NNT for leg ulcers based on evening measures at 50%maxTOTPAR was 5.2 (p = 0.0003). Ulcer healing was not influenced by the ibuprofen foam neither in the present study nor in the two previously reported RCTs. Thus, the present study confirmed results from several previous studies showing that in addition to moist wound healing, the ibuprofen foam may reduce wound pain during dressing wear time while maintaining a beneficial safety profile.

The main end point of the analysis was the proportion of patients who from day 1 to day 5 reported a summed PAR score of at least 50% of the total maximum PAR score (maxTOTPAR) and the corresponding NNT. A cumulative responder analysis can present pain data over a range of cutoff points and NNTs can be calculated for all cutoff points. It has been argued that 50% PAR is clinically relevant and intuitively understood by doctors and patients. The Initiative on Methods, Measurement, and Pain in Clinical Trials consensus recommended interpretations of 15–20% decrease as minimally important, at least 30% as moderately important, and at least 50% as a substantial improvement. Thus, 50% of maxTOTPAR is a conservative view on clinically relevant PAR and commonly used in meta-analyses of analgesic efficacy to derive relevant NNTs. Oral analgesics for acute PAR have NNTs in the region of 2 to 4 compared with placebo (based on a 50% cutoff point). One recent meta-analysis of studies reporting on commonly used over-the-counter analgesics for acute pain reported NNTs—based on participants with at least 50%maxTOTPAR for active treatment and placebo—to range from 2.6 to 7.6. For chronic pain states, NNTs for oral analgesics are in the region of 3 to 5. A review of publications of topically applied analgesics for acute pain over 1 week reported NNTs for ibuprofen at 4.1 (2.9 to 6.9). In an analysis of trials of topical NSAIDs in chronic musculoskeletal pain, an NNT of 4.6 (95% CI: 3.8–5.9) was reported. Thus, the NNT found in this study (6.8) is comparable to NNTs from studies of oral and topically applied analgesics, especially considering that both the test and comparator dressings are modern moist wound-healing dressings that, combined with appropriate venous compression therapy, may have a pain relieving effect in itself. The evening data were specifically strong (NNT = 5.3). Venous leg ulcer pain as well as edema are relieved, when the legs are elevated, e.g., during nighttime. Therefore, it is most critical to relieve venous leg ulcer pain during the day or in the evening, when the patient is more up and about than in the morning when the legs have been rested during nighttime.

In this study, the patients in the ibuprofen foam group had smaller ulcers at baseline than the comparator group. Area-based comparisons of the ulcer could therefore have the potential to bias the results. A comparison of the linear healing parameter was performed as it would not be affected by the difference in baseline wound area. Using this method (as well as mean area), no difference in wound healing between the ibuprofen foam and the comparator group was...
found during the 6-week treatment period. Furthermore, in a previous double-blinded RCT, contrary to this study, the ibuprofen foam group had larger ulcers than the comparator group, and, also, in that study, no differences were observed in ulcer healing between groups.\(^\text{13}\)

Six infections were reported in the ibuprofen foam group whereas two were classified as device or possibly device related, while no infections were reported in the comparator group. Estimations based on previous studies (13 and an unpublished comparative study) found that 5.8 infections would be expected with a CI of 1.23–10.39 within 95% probability. Therefore, between 2 and 10 infections were expected in the ibuprofen foam group in the present study, and the six infections in this group were within the expected range. Between one and eight infections were expected in the comparator group in the present study. However, no infections were observed in the comparator group in the present study. This indicates that the difference between groups was caused by an unexpected low number in the comparator group.

The results from this double-blind RCT confirms and extends previous findings from a similar 120-patient double-blind RCT\(^\text{12,13}\) comparing the ibuprofen foam dressing with a similar foam dressing without ibuprofen for treatment of exuding, painful venous leg ulcers.

The ibuprofen foam dressing provided clinically relevant PAR for patients with painful, exuding venous leg ulcers with an NNT of 6.8. This result is comparable to a previous RCT\(^\text{27,28,39,41}\) for patients with painful, exuding venous leg ulcers with chronic pain.\(^\text{27,28,39,41}\) An important perspective of the results of this investigation is the additional analgesic intake compared with the control group. This indicates that the difference between groups was caused by an unexpected low number in the comparator group.

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In conclusion, the ibuprofen foam dressing provided clinically relevant PAR for patients with exuding, painful venous leg ulcers. The study confirmed results from previously published studies showing that in addition to moist wound healing, the ibuprofen foam may reduce wound pain during dressing wear time while maintaining a beneficial safety profile.\(^\text{12,16}\)

**ACKNOWLEDGMENTS**

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