

ORIGINAL RESEARCH—CLINICAL SCIENCE

Reducing wound pain in venous leg ulcers with Biatain Ibu: A randomized, controlled double-blind clinical investigation on the performance and safety

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ABSTRACT

Six out of 10 patients with chronic wounds suffer from persistent wound pain. A multinational and multicenter randomized double-blind clinical investigation of 122 patients compared two moist wound healing dressings: a nonadhesive foam dressing with ibuprofen (62 patients randomized to Biatain Ibu Nonadhesive Coloplast A/S) and a nonadhesive foam without ibuprofen (60 patients to Biatain Non-Adhesive—comparator). Patients were recruited from September 2005 to April 2006. The ibuprofen foam was considered successful if the pain relief on a five-point Verbal Rating Scale was higher than the comparator without compromising safety including appropriate healing rate. Additional endpoints were change in persistent wound pain between dressing changes and pain at dressing change on days 1–5 (double blind) and days 43–47 (single blind). The primary response variable, persistent pain relief, was significantly higher in the ibuprofen-foam group, as compared with the comparator on day 1–5, with a quick onset of action ($p < 0.05$). Wound pain intensity was significantly reduced with the ibuprofen foam during day 1–5 with 40% from baseline, compared with 30% with the comparator ($p < 0.001$). At day 43–47, the patients in the ibuprofen-foam group had a significant ($p < 0.05$) reemergence of persistent pain and pain at dressing change ($p < 0.05$) when the active dressing was changed to the comparator. Wound healing was similar in the ibuprofen foam and comparator group. No difference in adverse events between the comparator and the ibuprofen foam with local sustained release of low-dose ibuprofen was observed in this study. It was generally found that women reported less pain intensity than men, and pain intensity decreased with increasing age. In addition, pain intensity increased with initial pain intensity and increasing wound size. This study has demonstrated that the ibuprofen-foam dressing provided pain relief and reduced pain intensity without compromising healing or other safety parameters.

Despite the fact that six out of 10 individuals with chronic wounds suffer from persistent wound pain,^{1–3} little is known about the effectiveness of local treatment interventions for persistent pain between dressing changes.⁴ Persistent pain associated with nonhealing wounds is caused by tissue (nociceptive) or nerve (neuropathic) damage and

is influenced by dressing changes and chronic inflammation. Chronic wounds take a long time to heal and patients may suffer from chronic wounds for many years.⁵

The pain from chronic wounds can be temporary and dressing related or may be persistent, affecting everyday life. The persistent pain can be extremely severe and thus it

causes both physical and mental debilitation. Patients may become immobile, which in turn can lead to social isolation, depression, and feelings of hopelessness.⁵ Wound pain is reported to reduce appetite,⁶ reduce mobility, induce a feeling of loneliness,⁷ and disturb sleep.⁸ The pain experienced by persons with chronic wounds has been described as a red raw feeling, a burning sensation, and like having acid thrown onto the skin.⁵

The application of compression bandaging is generally accepted to improve venous ulcer healing. In many cases patients with chronic venous ulceration find it difficult to tolerate high-compression bandaging (44%) because of the associated pain⁹ and this will adversely affect ulcer healing. The reduced quality of life and the reduced treatment adherence can lead to a general decrease in health status, and are barriers to wound healing.

Current treatment of total wound pain has been focused on temporary wound pain, while treatment of persistent pain has either been neglected or treated with pharmaceuticals.¹⁰ The aim of this clinical investigation was to investigate whether an ibuprofen-foam dressing relieves venous ulcer pain without compromising safety or the beneficial properties of moist wound healing.

MATERIALS AND METHODS

Design

This randomized, controlled double-blind, parallel-group, multicenter, and multinational clinical investigation was conducted in order to compare the performance and safety of an ibuprofen foam with a comparator. The study was double blind from days 1 to 42 and single blind from days 43 to 47. Study personnel and patients were blind to treatment from days 1 to 42 (double blind).

On days 43–47, the treatment was blinded (single-blind) to the patients only. For this last period all patients were changed to and treated with the comparator dressing, and the groups were named the “former ibuprofen-foam” group or the “comparator group.”

Both dressings were specially designed for this double-blind study to be anonymous with the use of top-films without any print. Randomization in closed envelopes took place after inclusion and before study initiation. The patients were randomized 1:1 either to the ibuprofen-foam group or to the comparator group. Block randomization was applied in blocks of 4. The randomization was carried out before packaging of the products, which were packed and labeled specifically for each patient due to the blinding. A patient was considered randomized when the informed consent form was signed and a number was allocated to the patient. An independent, certified company packed and distributed the test products at the investigator sites.

Patient characteristics

Independent ethic boards for each study site had approved this study according to internationally approved standards. The recruited patients had received both oral and written information about the study, and had signed consent. Patients were recruited from September 2005 to April 2006. The study subjects were older than 18 years of age

with painful chronic venous leg ulcers of more than 8 weeks duration. The diagnosis was based on an ankle brachial pressure index > 0.8 and one of the following: duplex scan, phlebography, and obvious clinical diagnosis (palpation, morphology, inspection, and anamnesis) in combination with or without toe pressure and palpable foot pulse.

The patients were required to receive compression therapy for at least 2 weeks before inclusion, as well as throughout the study period. At inclusion, the type of compression bandage was optional but had to be kept constant throughout the study. However, the selected compression bandage must produce adequate compression, defined by keeping a constant circumference at the ankle. A deviation $> \pm 15\%$ between two measurements in the circumference at the ankle was interpreted as if the compression state had changed. This was a minimal problem (seven out of 122 patients; see Results).

The ulcer was required to have a minimum length of 1.6 cm in any direction and a maximum area of 50 cm². The minimum leg ulcer pain score accepted for inclusion was moderate on a five-point Verbal Rating Scale (VRS) (none, slight, moderate, lots, complete). Exclusion criteria were: (1) painful ulcers that had been resistant to analgesic treatment over the past 6 months or more, (2) pregnant or lactating women, (3) clinical infection including erysipelas and cellulitis, (4) local infection or bacterial imbalance within or surrounding the study ulcer, (5) vasculitis, (6) allergy or other contraindication to ibuprofen or other related analgesics (nonsteroidal anti-inflammatory agents), (7) a history of asthma, rhinitis, or urticaria, (8) diabetes, (9) the use of unscheduled additional pain medication for 3 days before study admission (regular concomitant pain medication was acceptable for inclusion), (10) concomitant treatment with systemic antibiotics other than nitrofurantoin, (11) concomitant treatment with systemic corticosteroids (more than 10 mg/day of prednisolone or equivalent), (12) treatment with other immunosuppressant or cancer chemotherapeutic agents within 1 month before inclusion, (13) concomitant participation in other studies, and (14) previous participation in this study.

The study participants were to keep concomitant pain medication constant during pain assessment periods (days 1–5 and days 43–47).

Outcomes and assessments

The primary outcome was to compare the pain relieving effect of the ibuprofen foam against a nonactive foam at days 1–5. Secondary endpoints were reduction in pain intensity at days 1–5, ulcer area reduction, difference between groups in adverse events, and pain intensity at days 43–47. Other secondary endpoints were temporary pain at dressing change, occurrence of critical colonization, and selected activities of daily living indicators such as well-being, appetite, sleep, and mood. The ibuprofen foam was regarded as a therapeutically effective treatment if the pain relief was significantly higher and pain intensity ratings were significantly lower than the comparator product during days 1–5.

Persistent (relief and intensity) and temporary pain (dressing change related) were assessed at days 1–5 and at days 43–47 (Figure 1). The persistent pain was rated in the morning and evening by the patients between dressing changes in a diary. The pain relief was rated on a five-point

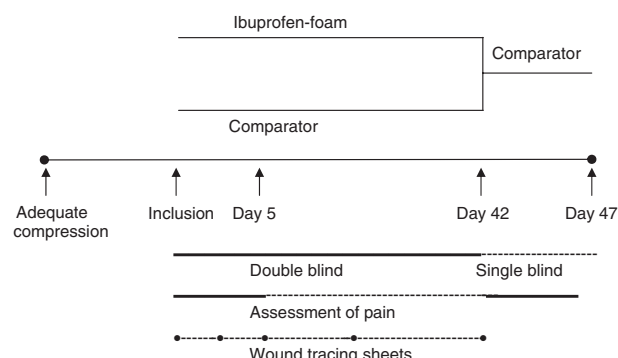


Figure 1. Study design. Patients were allocated in two groups. The study was double blind from day 1–42, and single-blind from day 43–47. On day 1–5 pain relief was assessed on a verbal rating scale and pain intensity was assessed on a NBS. On day 43–47 pain intensity was assessed on a NBS. NBS, Numeric Box Scale.

verbal rating scale (VRS) (0=no relief, 1=slight relief, 2=moderate relief, 3=lots of relief, 4=complete relief).¹¹ Pain relief was regarded as a retrospective view of the treatment efficiency and a high score was associated with high treatment efficacy.^{12,13} Pain intensity was measured on a validated 11-point Numeric Box Scale (NBS) from 0 to 10 with “0” as no pain and “10” as the worst imaginable pain.¹¹ Patients rated pain at dressing change (NBS) immediately after removal of the dressing and cleansing of the wound at the visits on days 2 and 5 and on days 45 and 47. The effect of compression was assessed throughout the study by measuring the circumference at three different places on the lower limb.

The ulcer area was assessed with wound tracings of the ulcer margins at baseline, at days 15, 29, and at day 42. Wound healing was also tested using a linear healing parameter, as described by Gilman.¹⁴ This quantifies wound healing as the linear movement of the wound edge toward the center of the wound, and this method has been shown to be independent of initial wound size. Infection was assessed by coexistent presence of the classical signs of clinical infection: pain, erythema, edema, heat, and purulence. Delayed or stalled wound healing and one of the following characteristics identified bacterial imbalance: increased level of exudate, fragile granulation tissue, or discoloration or odor. Safety was monitored according to the European standards for testing medical devices on human subjects.^{15,16} The causality of the adverse event was defined as related, possibly related, and not related to the dressing. All adverse events in this study were reported either spontaneously by the patients or by the study personnel.

Materials

The two moist wound-healing foam dressings used in this study absorb exudate and provide a physical barrier between the wounds and the environment. The ibuprofen foam (Biatain—Ibu Non-Adhesive foam dressing, Coloplast A/S, Denmark) consists of a soft hydrophilic polyurethane foam containing ibuprofen (ibuprofen concentration: 0.5 mg/cm²) dispersed homogeneously throughout the foam. The foam is bound to a semipermeable polyurethane

film. In the presence of exudate, there is a continuous release of safe low-dose ibuprofen into the wound bed.¹⁷ One dressing (15×15 cm) contains 112.5 mg of ibuprofen to be released in a period of up to 7 days, compared with a maximum daily oral dose of 1,200 mg and in special cases 3,200 mg.¹⁸ A proof-of-concept study suggested an anti-inflammatory and pain-reducing effect of the dressing.¹⁹ The comparator foam consisted of the same materials, and had a similar structure as the ibuprofen foam, but ibuprofen was not incorporated (Biatain Non-Adhesive, Coloplast A/S). The dressings were changed on a regular 48-hour interval to ensure a uniform dressing environment (absorption, retention, release).

Data analysis and statistics

Sample size was based on unpublished data on pain relief from a study where pain intensity has been reported previously.¹⁹ This study had a standard deviation of 0.79 and, with 90% power, yielded 54 patients in each group. A dropout rate of 10% was estimated adding each group up to 60 patients. Before the statistical analysis was performed, the data were entered twice in order to resolve discrepancies. All data analysis was performed according to the prespecified analysis plan on the intention-to-treat (ITT) population. α was set at 0.05. The persistent pain relief for days 1–5 was assessed morning and evening for each patient on a five-point VRS (none, slight, moderate, lots, completely). Pain relief was dichotomized into patients with relief (slight, moderate, lots, or completely) and patients with no relief. Differences in pain relief were analyzed with an analysis of variance with repeated measures, with treatment and time as fixed variables, and patients were treated as random variables to sort out distortion from the fixed effects. A statistical model with repeated measures was used to analyze pain intensity data on days 1–5, at days 43–47 and at dressing change, using patient-ID as a random variable to sort out distortion.

Differences in medical history were determined with a χ^2 -test, or Fishers Exact Test when the number of events was small. Differences in pain intensity at inclusion, duration of treatment before inclusion, and ulcer circumference were tested with the Wilcoxon–Mann–Whitney *U* test. Quality of life indicators such as appetite, sleep, mood/feeling, and well-being were assessed at day 5 and at day 43 with reference to the baseline values at day 1. Differences between groups were established using a χ^2 test. Adverse events were divided into the following categories: nondevice-related adverse events, nondevice-related serious adverse effects, device-related adverse events, and serious device-related adverse effects. Any difference in observed adverse events between study groups was tested using a χ^2 test.

Ulcer size was recorded at inclusion and after 15, 28, and 42 days of treatment. A *t*-test was used to test differences in means reported for the ITT population.

RESULTS

Baseline data

The study population consisted of 122 patients (62 in the ibuprofen-foam group and 60 in the comparator group)

Table 1. Demographics of patients in the two treatment groups

Assessment		Ibuprofen foam	Comparator
Age (years)	Mean $\pm$ SD	66.0 $\pm$ 14.8	70.0 $\pm$ 11.7
Gender	Female <i>n</i> (%)	43 (69)	37 (62)
Height (cm)	Mean $\pm$ SD	168 $\pm$ 1.3	168 $\pm$ 1.2
Weight (kg)	Mean $\pm$ SD	83.0 $\pm$ 2.6	79.4 $\pm$ 2.1

with chronic, painful venous leg ulcers on the lower limb. Patients were recruited from September 2005 to April 2006, from 13 different centers: three in Great Britain, three in Lithuania, two in Denmark, two in Germany, two in the Czech Republic, and one in Finland. Table 1 summarizes the demographic profile of the study group. Table 2 summarizes the medical history of the patients. Using deviations in two subsequent measurements in the circumference at the ankle to define change in compression, seven people changed compression: four in the ibuprofen-foam group and three in the comparator group. There were 29 dropouts: 16 in the ibuprofen-foam group and 13 in the comparator group (Figure 2). Healing occurred for 19 patients and six patients withdrew their consent.

Pain

Persistent pain

Pain relief differences were tested in a repeated measures model with treatment and time as fixed variables and patient ID as the random variable. In the ibuprofen-foam group, significantly more patients experienced pain relief in the wound starting the first evening and throughout the first 1–5 days of wear time as compared with the compar-

ator ($p < 0.05$). On the first evening, 74% of the ibuprofen-foam group had pain relief, compared with 58% in the comparator group (Figure 3). Twenty-eight percent more patients experienced pain relief the first evening in the ibuprofen-foam group than with the comparator.

Pain intensity at days 1–5 was tested in a repeated measures model with the fixed parameters treatment, time, age, gender, initial pain intensity, and initial wound size. Wound pain was significantly reduced in the ibuprofen foam group compared with the comparator group ($p < 0.003$) during days 1–5. The wound pain intensity levels were reduced from 6.8 at inclusion to 4.1, a reduction of 40% with the ibuprofen foam, and from 6.6 at inclusion to 4.6, a reduction of 30% with the comparator. The wound pain intensity decreased for all patients over time ($p < 0.001$). Women reported less wound pain intensity than men ($p < 0.01$), and wound pain intensity decreased with increasing age ($p < 0.0001$). Furthermore, wound pain intensity increased with increasing initial pain intensity ($p < 0.0001$) and increasing wound size ($p < 0.0001$). Wound pain intensity at days 43–47 was tested in a repeated measures model with time at treatments as fixed variables. Wound pain at days 43–47 increased significantly in the former ibuprofen-foam group from a baseline NBS value of 2.3 to a mean NBS value of 2.6 when the ibuprofen foam was changed to the comparator ($p < 0.05$). The wound pain intensity remained stable in the comparator foam group at a mean NBS value of 1.9 (Figure 4).

Pain at dressing change

A statistical model with repeated measures was used to analyze data. Pain intensity was analyzed with treatment and time as fixed variables. Dressing change-related pain intensity increased in the former ibuprofen-foam group when the nonadhesive comparator was introduced

Table 2. Patient medical history before entering the study in the two treatment groups

Assessment		Ibuprofen foam	Comparator	<i>p</i> -value
Present or previous peri-ulcer eczematous reactions (allergic and non-allergic)	No <i>n</i> / total (%)	37/62 (60)	45/60 (75)	0.071
Allergic contact dermatitis (Chloramphenicol, chromium)	Yes <i>n</i> (%)	4 (6)	0 (0)	0.12
Positive patch test for contact dermatitis	Yes <i>n</i> (%)	2 (3)	0 (0)	0.50
Pain intensity at inclusion (NBS)	Mean $\pm$ SD	6.82 $\pm$ 1.8	6.58 $\pm$ 1.6	0.42
Duration of treatment of the study ulcer at inclusion (months)	Mean $\pm$ SD	23.1 $\pm$ 42.9	19.8 $\pm$ 41.8	0.88
Exudate level of ulcer	Moderate, <i>n</i> (%)	41 (66)	51 (85)	0.02
	High, <i>n</i> (%)	21 (34)	9 (15)	
Absolute ulcer area (cm ²)	Mean $\pm$ SD	11.0 $\pm$ 9.6	7.3 $\pm$ 5.7	0.05
Absolute ulcer circumference (cm)	Mean $\pm$ SD	15.5 $\pm$ 9.1	12.5 $\pm$ 6.9	0.05
Compression				
Short stretch	(%)	56	58	0.61
Long stretch	(%)	41	35	
Other	(%)	3	6	

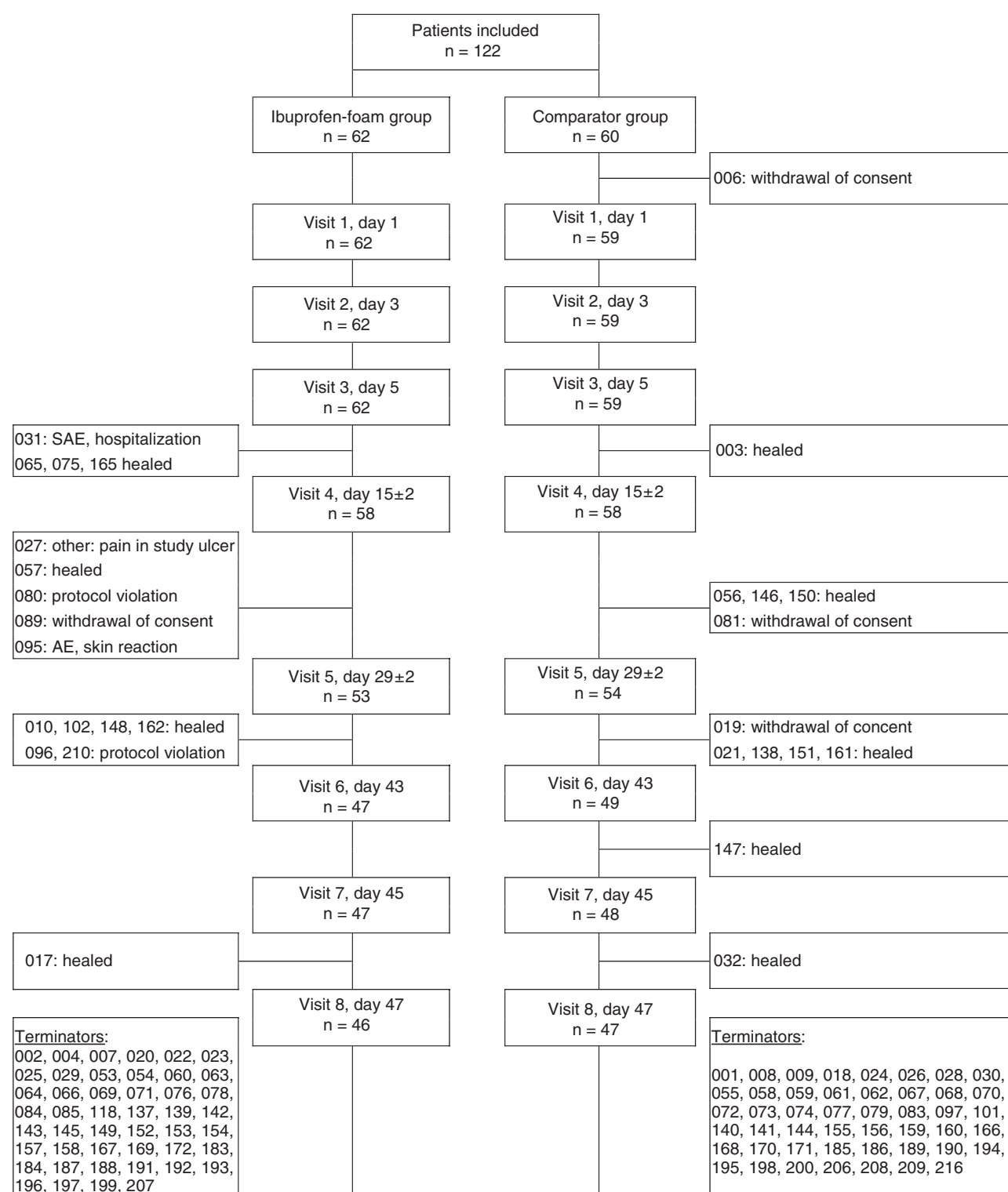


Figure 2. Patient flow chart. Patients are indicated with their unique patient ID numbers. Protocol violation consisted of: Too small study ulcers, unauthorized dressing changes, unable to come to visits.

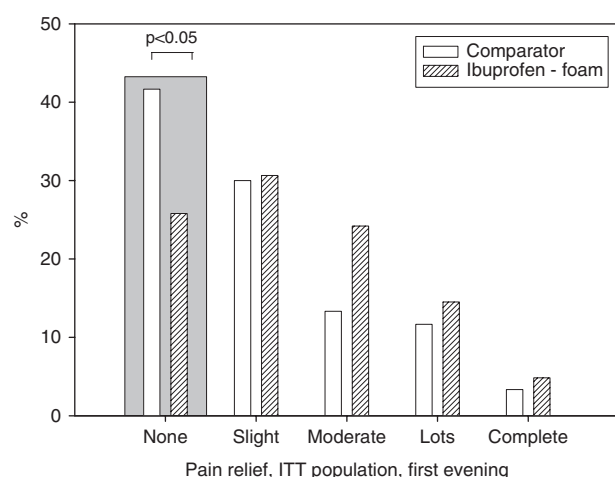


Figure 3. Pain relief measured the first evening according to the five-point verbal rating scale (VRS). The grey box indicates the first evening were 28% more persons had pain relief in the ibuprofen-foam group, than the comparator group ($p < 0.05$). In the ibuprofen-foam group 74% of the patients experienced pain relief and 58% in the comparator group.

between days 43 and 47. A significant difference ($p < 0.05$) in pain intensity was detected at dressing removal (Figure 5). The pain intensity increased significantly for the previous ibuprofen-foam group from the baseline NBS value of 0.3 to 0.9 in contrast to constant levels in the comparator group with a mean NBS value of 2.0 at baseline. At days 1–5 it was not possible to detect a difference in dressing change pain.

Ulcer area

Ten ulcers (16%) in the comparator group and nine ulcers (15%) in the ibuprofen-foam group healed during the trial and there was no statistical difference in healing time. On average, the ulcers decreased from 11.2 to 7.9 cm² in the ibuprofen-foam group and from 7.2 to 3.8 cm² in the com-

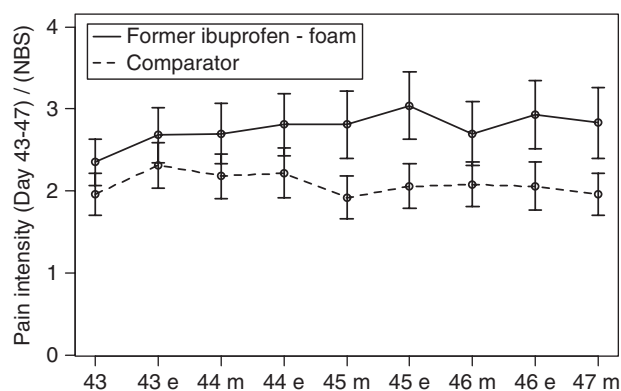


Figure 4. Pain intensity at day 43–47. All patients were changed to the comparator dressing. There was a statistical difference between the two groups including all assessments from the evening day 43 to 47 ($p < 0.05$) (e=evening, m=morning).

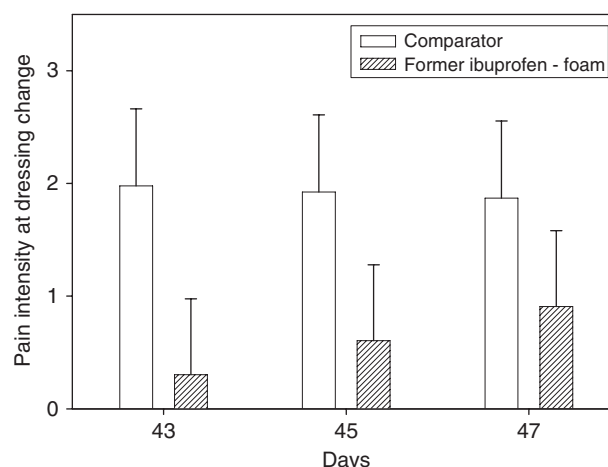


Figure 5. Pain at dressing change on day 43–47. A significant increase in pain intensity was observed in the former ibuprofen-foam group ($p=0.05$).

parator group (Figure 6). The decrease in ulcer area between the two groups was comparable, with no statistically significant difference. The wound area decrease between inclusion to day 43 divided by the average wound circumference was not significantly different between the groups using the Gilman¹⁴ method. Both study groups' wound perimeters moved toward the center of the wounds with comparable speed.

Adverse events

A total of 31 adverse events occurred in 19 persons (Table 3). In the ibuprofen-foam group, 12 patients experienced 21 adverse events and in the comparator group seven patients experienced 10 adverse events. One patient was hospitalized (serious adverse event) because of nondevice-related pulmonary edema, and was excluded from the study. In the ibuprofen-foam group, 19% (12/62 patients) adverse events were reported compared with 12% in the comparator group (7/60 patients). The relation to the device is reported in Table 3. Most of these adverse events had no relation to either the ulcer or the dressing. There were no serious device-related adverse events reported in the study. The device-related adverse events were categorized into four groups: study ulcer pain, infection in study ulcer, local skin reactions, and other. In the ibuprofen-foam group, skin reactions were observed in four patients: one had urticaria and later eczema, one had eczema alone, and two patients had blisters. In the comparator group, four patients had skin reactions: two had eczema and two had blisters. In the ibuprofen-foam group, allergic dermatitis was suspected in one patient. A patch test was applied on the patient's normal skin. The patch test showed a weak potential allergic reaction to the complete product, but not to the ibuprofen standardized patch test (petrolatum base), or to the comparator product. The negative patch tests to the components of the dressing are consistent with contact irritant dermatitis although there is a slight chance that the patient could have been allergic to a metabolite of ibuprofen.

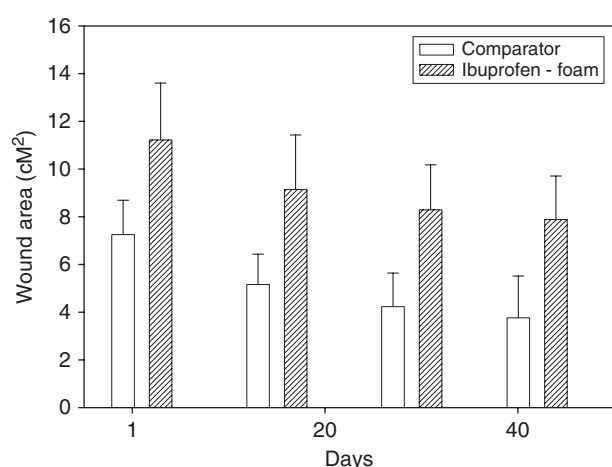


Figure 6. Absolute change in ulcer area (cm²) on the ITT population. There was no statistical significant difference on ulcer area reduction ($p=0.26$) between the treatment groups. ITT, intention to treat.

Quality of life

Both treatments had an effect on the patients' well-being and individual quality of life parameters as indicated in Table 4. The response to the general question on their sense of well-being during the last week was similar in both groups. Patients' rating of quality of life improved during the trial from day 5 to day 43 as compared with the time of trial entry. Other measured indicators demonstrated significant improvements from baseline in the ibuprofen-foam group: sleep 53%, general feeling/mood 45%, sense of well-being 39%, and appetite 24%. There were no statistically significant differences between the two study groups.

DISCUSSION

This double-blind randomized study evaluated the outcome of patients treated with an ibuprofen foam for 42 days. It demonstrated that more patients experienced pain relief with the ibuprofen foam and rated their pain relief higher than in the comparator group. In addition, it showed that pain

intensity was reduced with the ibuprofen foam. These results demonstrated the effectiveness of a foam dressing releasing a local low dose of ibuprofen while providing moist wound healing and maintaining a beneficial safety profile. This confirms results from studies that demonstrated that the ibuprofen foam reduced wound pain in combination with moist wound healing.^{5,19,20}

Normally, in pain trials comparing active against placebo, the placebo has no effect. In this study, the comparator group, because it is a moist wound healing dressing, will on its own have a pain-relieving effect independent of the ibuprofen.²¹ Consequently, any significant pain-relieving effect with the ibuprofen foam gives an indication of the real effect of the released ibuprofen. Pain perception changes over time¹³ and a strength of this study was that the intervention was evaluated over short periods at days 1–5 and days 43–47.

In this study, the study population was above 65 years. The most responsive patient in a pain trial may often be younger and male as they respond better to pain medication.²² For this reason, there are few previous reports of topical pain trials in an older often female-predominant polymedicated population. Therefore, an investigation such as the current one, comparing pain management interventions in an elderly population, showing statistical differences has a high social value.

The ibuprofen foam also demonstrated quick onset of action. In the present study, more patients (28%) in the ibuprofen-foam group had pain relief the first evening. This was also shown in topical NSAID gels by Mason,²³ where 48% of patients randomized to an active gel experienced fast relief, as compared with 26% from placebo. Ibuprofen is mainly reported to have an effect on pain that is of a nociceptive origin,²⁴ and it is not expected to be effective in all patients.

The wound pain intensity levels in this study were reduced with the ibuprofen foam 40% from baseline as compared with a 30% reduction for the comparator. In a meta-analysis of pain trials where the 11-point NBS scale was used, Farar²⁵ observed a 30% reduction. This means that both the ibuprofen foam and the comparator product had clinically relevant pain reductions, with the ibuprofen foam having a slight advantage. The pain intensity levels were also influenced by gender, age, initial pain level, and wound size.

Table 3. Adverse events separated into mild, moderate, and severe and relation to device for the ibuprofen foam and the comparator group

Type of adverse event	Ibuprofen foam*				Comparator**				<i>p</i> -value
	Unrelated	Possibly related	Related	Total	Unrelated	Possibly related	Related	Total	
Mild <i>N</i> (%)	1 (5)	3 (14)	4 (19)	8 (38)	0 (0)	1 (10)	2 (20)	3 (30)	
Moderate <i>N</i> (%)	2 (10)	1 (5)	7 (33)	10 (48)	1	2 (20)	4 (40)	7 (70)	
Severe <i>N</i> (%)	0 (0)	1 (5)	2 (10)	3 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
Total <i>N</i> (%)	3 (14)	5 (24)	13 (62)	21 (100)	1 (10)	3 (30)	6 (60)	10 (100)	1.00

*Infection in study ulcer three patients, eczema two patients, blisters two patients, urticaria one patient, study ulcer pain one patient, other 12 patients (13 incidences unrelated to the dressing)

**Infection in study ulcer two patients, bullae one patient, eczema two patients, blisters one patient, other four patients (six incidences unrelated to the dressing).

Table 4. Selected measures of well-being: appetite, sleep, feeling/mood

	Response		
	Improved (e.g., felt like eating more) N (%)	Stayed the same N (%)	Deteriorated (e.g., felt less like eating) N (%)
Has your appetite?			
Ibuprofen foam	12 (24)	36 (74)	1 (2)
Comparator	17 (32)	33 (63)	2 (4)
	Response		
	Improved (e.g., deeper, longer sleep) N (%)	Stayed the same N (%)	Deteriorated (e.g., restless, shorter sleep) N (%)
Has your pattern of sleep?			
Ibuprofen foam	26 (53)	21 (43)	2 (4)
Comparator	25 (49)	23 (44)	4 (8)
	Response		
	Brighter or more cheerful than usual N (%)	About the same as usual N (%)	A bit more down and lethargic than usual N (%)
Have you been feeling?			
Ibuprofen foam	22 (45)	27 (55)	0 (0)
Comparator	21 (41)	28 (54)	3 (6)
	Response		
	More content than usual N (%)	About the same as usual N (%)	Less content than usual N (%)
Have you noticed any change in your overall sense of well-being?			
Ibuprofen foam	19 (39)	30 (61)	0 (0)
Comparator	18 (35)	31 (60)	3 (6)

None of the parameters were significantly different.

The data demonstrated that the wound pain intensity significantly increased when patients allocated to the ibuprofen foam were switched to the comparator. In an earlier study by Jørgensen et al.,¹⁹ increased pain levels were also observed after returning to the comparator foam product. Pain perception changes over time, and a person in pain may develop a new baseline for their individual pain level,^{10,26} which may explain the same levels of pain observed in the two groups at day 43. The fact that an increase in pain intensity was observed in the ibuprofen-foam group indicates that the pain-reducing effect of ibuprofen is additive to the effect of moist wound healing alone.

Pain at dressing change or removal has been identified as a key patient concern.^{27,28} The ibuprofen foam seemed to decrease pain at dressing change. On days 43–47, the former ibuprofen-foam group experienced an increase in their dressing change pain. This increase was interpreted as a response to the removal of the analgesic effect. In other studies by Jørgensen et al.¹⁹ and Sibbald et al.,²⁰ similar results were observed where the ibuprofen foam reduced pain at dressing change. It was not possible to detect a difference in pain at dressing change in the first pain assessment period. This could be associated with a caring effect.²⁹

The ibuprofen-foam dressing was considered as successful if the healing properties were similar to or better than the comparator foam. In this study, the patients in the ibuprofen-foam study had larger ulcers at baseline as compared with the comparator group. Area-based comparisons of the ulcer therefore may give biased results.¹⁴ In this case a comparison of the linear healing parameter is more appropriate 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 shown in a 42-day treatment period. Kantor and Margolis³⁰ suggested that a period of 4 weeks would allow evaluation of chronic wound healing, and so the suggested 42 days should be a sufficient evaluation period for both wound healing and also for adverse event monitoring.

Ibuprofen has an anti-inflammatory effect and may exert this effect on wound healing^{31–34} by inhibiting the normal inflammatory wound healing phase. Most of the previously reported researches have been carried out on acute wounds and with high doses of ibuprofen in animal studies with variable outcomes.³⁵ Often patients with a chronic wound suffer from chronic medical disorders and the wounds may be halted in the inflammatory phase.³⁶

Therefore, low-dose ibuprofen used in chronic wounds is less likely to influence healing of chronic wounds.¹⁹ Both numbers of healed wounds and changes in wound area in this study showed that there was no difference in the healing rate between the comparative groups. In addition, the healing rate was comparable with earlier RCT trials on the comparator foam.³⁷

Healing of venous leg ulcers requires compression bandaging⁹ and all patients in this study were treated with compression for at least 2 weeks before inclusion. However, a study by Briggs et al. demonstrated that patients often discontinue compression treatment because of the associated pain. In a study by Briggs and Cross⁹ on 96 venous leg ulcer patients, 44 % of the patients could not adhere to their compression therapy because of persistent wound pain. Consequently, for chronic ulcer patients, pain is a serious barrier to wound healing. An ibuprofen foam may be a good solution for increasing patients adherence to compression.

Living with a painful venous leg ulcer is often a long-lasting condition, with a potential negative impact on quality of life.^{5,7} A study by Franks et al.³⁸ highlighted the negative effects of social isolation and decreased physical mobility in persons with venous leg ulceration as compared with the age/gender/social class norm. This study investigated the impact on the patients' activities of daily living within four domains, appetite, sleep, mood/feeling, and well-being, measured at day 42 as compared with the situation at inclusion. The number of patients with improved outcomes was comparable between the groups and no trends or differences could be detected between the groups. The improvement, therefore, may be due to the "caring effect," best clinical practice, and treatment of pain.

The usual adverse events reported for ibuprofen are related to the relatively high oral dose intake.³⁹ None of the most frequently reported adverse events associated with oral intake of ibuprofen were observed in this study.³⁹ The 15×15 cm ibuprofen foam chosen in this investigation contains 112.5 mg ibuprofen released into the wound over 7 days depending on the exudate level.¹⁷ This is considerably lower than the recommended systemic daily dose of 1,200 mg and, in special cases, 3,200 mg.³⁹ It has been shown in another study that the ibuprofen could not be detected systemically when the ibuprofen foam was used.¹⁹

The data from this study and other clinical studies on this ibuprofen foam including more than 370 patients^{5,19,20,40–42} have not detected any cases of allergic or contact dermatitis as adverse reactions to the ibuprofen foam. A meta-analysis on topical use of ibuprofen with 1,500 patients has demonstrated no difference in adverse reactions (including allergies) between placebo and topical use of ibuprofen gels.²³ The likelihood of adverse events with the ibuprofen foam may therefore be considered low. The likelihood of adverse events following long-term use of the ibuprofen foam is unknown.

To conclude, this multinational and multicenter randomized, double-blind clinical study of an ibuprofen foam comparing two moist wound healing dressings has shown a quick onset of action with significant pain relief in the ibuprofen-foam group. Wound healing was similar in the two groups, and no difference in adverse events was

observed. In summary, this study has demonstrated that patients with wound pain can experience wound pain relief with the ibuprofen foam and reduce their wound pain without compromising on healing or safety.

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