

Less pain with Biatain–Ibu: initial findings from a randomised, controlled, double-blind clinical investigation on painful venous leg ulcers

Finn Gottrup, Bo Jørgensen, Tonny Karlsmark, R Gary Sibbald, Rytis Rimdeika, Keith Harding, Patricia Price, Vanessa Venning, Peter Vowden, Michael Jünger, Stephan Wortmann, Rita Sulcaite, Gintaris Vilkevicius, Terttu-Liisa Ahokas, Karel Ettler, Monika Arenbergerova

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ABSTRACT

Six out of 10 patients with chronic wounds suffer from persistent wound pain. A multinational and multicentre, randomised, double-blind clinical investigation of 122 patients compared two moist wound-healing dressings, a non adhesive foam dressing with ibuprofen (62 patients randomised to Biatain-Ibu non adhesive, Coloplast A/S) with a non adhesive foam without ibuprofen (60 to Biatain non adhesive). The ibuprofen-foam was regarded successful, if the pain relief on a 5-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 and days 43–47. The primary response variable, persistent pain relief, was significantly higher in the ibuprofen-foam group compared with the comparator on days 1–5, with a quick onset of action ($P < 0.05$). The patients in the ibuprofen-foam group had a significant ($P < 0.05$) higher reduction in the persistent wound pain from baseline (40%) as the comparator (30%).

Authors: F Gottrup, MD DMSc, University Centre for Wound Healing, Odense University Hospital, Odense, Denmark, and Copenhagen Wound Healing Centre, H:S Bispebjerg University Hospital, Copenhagen, Denmark; B Jørgensen, MD, Copenhagen Wound Healing Centre, H:S Bispebjerg University Hospital, Copenhagen, Denmark; T Karlsmark, MD, Copenhagen Wound Healing Centre, H:S Bispebjerg University Hospital, Copenhagen, Denmark; RG Sibbald, MD, Wound Healing Clinic, Women's College Hospital, University of Toronto, Toronto, Ontario, Canada; R Rimdeika, MD, Department of Plastic and Reconstructive Surgery, Kaunas University of Medicine, Kaunas, Lithuania; K Harding, MB MRCGP FRCS, Wound Healing Research Unit, Cardiff University, Heath Park, Cardiff, UK; P Price, PhD, Wound Healing Research Unit, Cardiff University, Heath Park, Cardiff, UK; V Venning, DM FRCP, Department of Dermatology, The Churchill Hospital, Oxford, UK; P Vowden, MD, Department of Vascular Surgery, Penthouse, Bradford Royal Infirmary, Bradford, UK; M Jünger, MD, Klinik und Poliklinik für Hautkrankheiten, Ernst-Moritz-Arndt University of Greifswald, Greifswald, Germany; S Wortmann, Dr Med, Facharzt für Dermatologie, Gesundheitszentrum, Blaubeuren, Germany; R Sulcaite, MD PhD, Institute of Endocrinology, Kaunas University of Medicine, Kaunas, Lithuania; G Vilkevicius, MD PhD, Department of Vasculology, Vilnius University Antakalnio Hospital, Antakalnio Vilnius Lt-10200, Lithuania; T-L Ahokas, MD, HUS, Iho-ja allergiasairaala, Ihotautien klinikka, Meilahdentie 2, PL 160, 00029 HUS, Finland; K Ettler, MD PhD, Department of Dermatology, Sokolska 581, Building 22, Hradec Kralove, Czech Republic; M Arenbergerova, MD PhD, Department of Dermatology, Charles University 3rd School of Medicine, Srobarova 50, Prague, Czech Republic

Address for correspondence: Dr F Gottrup, University Centre for Wound Healing, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark; and Copenhagen Wound Healing Centre, H:S Bispebjerg University Hospital, Bispebjerg Bakke 23 DK-2400 Copenhagen, Denmark

E-mail: fgottrup@post4.tele.dk

Women reported less pain intensity than men, and pain intensity decreased with increasing age. In addition, pain intensity increased with increasing initial pain intensity and increasing wound size. Wound healing was similar in the ibuprofen-foam group to that of the comparator group. No difference in adverse events between placebo and local sustained release of low-dose ibuprofen was observed in this study. This study has demonstrated that the ibuprofen-foam dressing provided pain relief and reduced pain intensity without compromising healing or other safety parameters. The full report of this study will be published in *Wound Repair and Regeneration*.

Key words: Fast wound healing • Topical treatment • Wound pain relief • Wound pain intensity reduction

Key Points

- 6 out of 10 people with chronic wounds suffer from persistent pain
- the aim of this clinical investigation was to find out whether the ibuprofen-foam dressing relieves venous ulcer pain without compromising the beneficial properties of moist wound healing, with an acceptable safety profile

INTRODUCTION

Despite the fact that six out of ten people with chronic wounds suffer from persistent wound pain (1–3), little is known about the effectiveness of local treatment interventions (4) for persistent pain between dressing changes. Persistent pain associated with non healing wounds is caused by tissue (nociceptive) or nerve (neuropathic) damage and is influenced by dressing changes and chronic inflammation. Chronic wounds take long time to heal, and patients can suffer from chronic wounds for many years (5). Chronic wound healing may be compromised by coexisting underlying conditions, such as peripheral vascular disease, uncontrolled oedema and diabetes mellitus.

The pain from chronic wounds can be extremely severe, causing both physical and mental debilitation. Patients can become immobile, which in turn can lead to social isolation, depression and feelings of hopelessness (5). The pain experienced by persons with chronic wounds has been described as a red raw (feeling), burning and like having acid thrown onto the skin (5).

The application of compression bandaging is generally accepted to improve venous ulcer healing; however, in many cases, patients with chronic venous ulceration find it difficult to tolerate high-compression bandaging (44%) because of associated pain (6), and this will adversely affect ulcer healing. In general, wound pain is reported to reduce appetite

(7), reduce mobility, induce loneliness (8) and disturb sleeping (9). All these factors lead to a general decrease in health, which is a barrier to wound healing.

This investigation compares the performance and safety of a non adhesive foam dressing with ibuprofen (ibuprofen-foam) with a foam non adhesive dressing alone (comparator). The aim of this clinical investigation was to investigate whether the ibuprofen-foam dressing relieves venous ulcer pain without compromising the beneficial properties of moist wound healing, with an acceptable safety profile.

MATERIALS AND METHODS

Design

This randomised, controlled, double-blind, parallel group, multicentre, and multinational clinical investigation was conducted according to the international standards of good clinical practice. The primary outcome was to investigate the pain-relieving effect of the ibuprofen-foam, together with monitoring safety. The study compared three investigation periods, days 1–5, days 6–42 and days 43–47 (Figure 1). On days 1–5 and days 6–42, the patients were randomised 1:1 to either the ibuprofen-foam group or the comparator group using pre-made, treatment-coded envelopes. On days 43–47, the treatment was blinded only to the patients, and all patients were crossed over

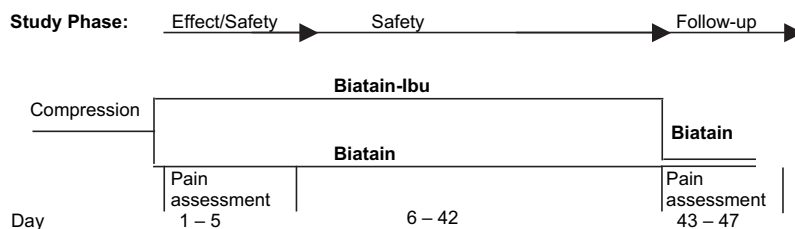


Figure 1. The patients were in two groups. On days 1–5 and on days 43–47, pain intensity was assessed on a numeric box scale and pain relief on a verbal rating scale.

Key Points

- all adverse events in this study were reported spontaneously either by the patients or by the study personnel
- 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 is bound to a semi-permeable polyurethane film and in the presence of exudate, there is a continuous release of a safe low dose of ibuprofen into the wound bed

and treated with the comparator dressing. The dressings were changed on a regular 48-hour interval to ensure a uniform dressing environment (absorption, retention, release).

Patient characteristics

Independent ethic boards for each study site have approved this study according to internationally approved standards. The recruited patients had received both oral and written information about the study, and signed consent. The study subjects were older than 18 years of age with painful chronic venous leg ulcer of more than 8-week duration, and they were required to receive compression therapy for at least 2 weeks before inclusion, and throughout the study period. 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 at inclusion was moderate on a 5-point verbal rating scale (VRS) (none, slight, moderate, lots, complete). Exclusion criteria included painful ulcers that had been resistant to analgesic treatment over the past 6 months or more, pregnant or lactating women, clinical infection (erysipelas and cellulitis) or critical colonisation (local infection) within or surrounding the study ulcer, vasculitis, allergy or other contraindication to ibuprofen or other related analgesics (including known hypersensitivity to acetylsalicylic acid or related non steroidal anti-inflammatory agents especially associated with a history of asthma, rhinitis or urticaria), diabetes, the use of unscheduled additional pain medication for 3 days prior to study admission (regular concomitant pain medication was acceptable for inclusion), concomitant treatment with systemic antibiotics other than nitrofurantoin, concomitant treatment with systemic corticosteroids (more than 10 mg/day of prednisolone or equivalent), treatment with other immunosuppressant or cancer chemotherapeutic agents within 1 month prior to inclusion, concomitant participation in other studies and previous participation in this study.

The study participants were allowed to take concomitant pain medication during the study, but the medication had to be constant at days 1–5 and at days 43–47 when pain was assessed.

Assessments

Persistent (chronic) and temporary pain (dressing change related) was assessed on days 1–5

and on days 43–47 (Figure 1). The persistent pain was rated in the morning and evening by the patients between dressing changes, using a diary. The persistent pain was rated on a pain relief 5-point VRS (0 = no relief, 1 = slight relief, 2 = moderate relief, 3 = lots of relief, 4 = complete relief). Pain relief was regarded as a retrospective view of the treatment efficiency, and the high score was associated with high treatment efficacy (10,11). In addition, 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. A low pain intensity score was regarded a preferred score (10,11). Pain at dressing change was rated (NBS) by the patients at the visits on days 2 and 5 and on days 45 and 47, immediately after removal of the dressing and cleansing of the wound. Patients were asked to score their pain intensity on the 0–10 NBS.

The ulcer area was assessed at baseline, on days 15, 29 and on day 42 with wound tracings of the ulcer margins. Infection was assessed by coexistence of the classical signs of clinical infection: pain, erythema, oedema, heat and purulence. Delayed or stalled wound healing and one of the following three characteristics identified bacterial imbalance: increased level of exudate, granulation tissue, discoloration or odour; the combination led to study exclusion. Safety was monitored according to the European standards for testing medical devices on human subjects (12,13). 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 spontaneously either 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) consists of a soft hydrophilic polyurethane foam containing ibuprofen (ibuprofen concentration: 0.5 mg/cm²) homogeneously dispersed throughout the foam. The foam is bound to a semipermeable polyurethane film. In the presence of exudate, there is a continuous release of a safe low-dose ibuprofen into the wound bed (14). One dressing (15 × 15 cm)

contains 112.5 mg of ibuprofen to be released between 1 and 7 days, compared to a maximum daily oral dose of 1200 mg and in special cases 3200 mg (15). A proof of concept study suggested an anti-inflammatory and pain-reducing effect of the dressing (16). 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 backing film and the packaging of the two compared dressings were similar to ensure the double blinding.

Clinical endpoints

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

Data analysis and statistics

Sample size was determined by evaluating a previous study (16) on pain relief observed on a 5-point scale during morning and evening where an overall mean pain relief of 3.8 for the ibuprofen-foam and 3.3 for the comparator was observed. The common standard deviation was 0.79. With a 90% power, this yields a sample size of 54 per group (data on file). Empirically a drop-out rate of 10% is observed in similar clinical studies, hence resulting in a sample size of 60 per group. Before the statistical analysis was performed, the data were entered twice and discrepancies resolved. All data analysis was performed on the intention-to-treat (ITT) population. The primary response variable was persistent pain relief on days 1–5. The secondary outcome variables were persistent pain intensity, ulcer size, pain at dressing change, activities of daily living and adverse events. The results were analysed according to the statistical analysis

plan designed prior to study commencement (17). Alpha was set at 0.05. The persistent pain relief for days 1–5 was for each patient assessed during morning and evening on a 5-point VRS (none, slight, moderate, lots, completely). After dichotomising data (relief, no relief), differences were analysed with an analysis of variance. Persistent pain intensity for each patient was assessed during morning and evening on an 11-point NBS and analysed with an analysis of variance, and statistically significant ($P < 0.05$) parameters were reported together with adjusted treatment means. Pain at dressing change (temporary pain) was evaluated after each dressing change between day 1–5 and days 43–47. An analysis of variance was used to test differences between groups. For the follow-up period, the visit on day 43 was used as the baseline for the dressing pain intensity. Adverse events were divided into the following categories: non device-related adverse events, non device-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 chi-square 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. Wound healing was also tested using a linear healing parameter, as described by Gilman (18). This quantifies wound healing as the linear movement of the wound edge towards the centre of the wound.

RESULTS

Baseline data

The study population consisted of 122 patients (62 in the ibuprofen-foam group and 60 in the comparator group) with chronic, painful venous leg ulcers on the lower limb. Patients were recruited from 13 different centres: three in Great Britain, three in Lithuania, two in Denmark, two in Germany, two in the Czech Republic and one in Finland. The first patient was included on 19 September 2005, and last patient out was on 21 April 2006, with a clinical report approved by investigators on July 2006. Table 1 summarises the demographic profile of the study group. Table 2 summarises the medical history of the patients. In the ibuprofen-foam group, 11% (7/62) of the patients

Key Points

- the comparator foam consisted of the same materials and had a similar structure but ibuprofen was not incorporated
- the study population consisted of 122 patients (62 in the ibuprofen foam group and 60 in the comparator group) with chronic, painful venous leg ulcers on the lower limb
- all patients were asked to keep their concomitant medication constant between days 1-5 and days 43-4

Key Points

- wound pain was significantly reduced with the ibuprofen foam during days 1-5
- dressing change related pain intensity increased in the ibuprofen-foam group when the non adhesive comparator was introduced between days 43-47
- the decrease in ulcer area between the 2 groups was comparable with no statistical difference in healing time

Table 1 Demographics of patients in the two treatment groups

Assessment		ibuprofen-foam	Comparator
Age (years)	Mean	66.0	70.0
	Standard deviation	14.8	11.7
Gender	Female, <i>n</i> (%)	43 (69)	37 (62)
Height (cm)	Mean	168	168
	Standard deviation	1.3	1.2
Weight (kg)	Mean	83.0	79.4
	Standard deviation	2.6	2.1

dropped out of the study prematurely, and 5% (3/60) did not complete the study in the comparator group. The dropouts were related to withdrawal of consent (4), protocol violation (3), pain in the study ulcer (1), serious non related adverse event (1) and suspected allergic reaction (1). In this trial, all patients were asked to keep their concomitant medication constant between days 1–5 and days 43–47, and no patient was excluded due to change in pain medication.

Pain**Persistent pain relief on days 1–5**

In the ibuprofen-foam group, patients experienced significantly ($P = 0.0003$) more pain relief in the wound throughout the first 1–5 days of wear time compared with the comparator. In the first evening, 74% (46/62) of the patients in ibuprofen-foam group had pain relief, compared with 58% (35/60) in the comparator group (Figure 2). Twenty-eight percent ($74 - 58/58 \times 100$) more patients experienced pain relief the first evening in the ibuprofen-foam group than in the comparator.

Persistent pain intensity on days 1–5

Wound pain was significantly reduced with the ibuprofen-foam during days 1–5 ($P <$

0.0003). 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. Women reported less pain intensity than men, and pain intensity decreased with increasing age. Furthermore, pain intensity increased with increasing baseline pain intensity and increasing wound size (Table 3).

Pain at dressing change

Dressing change-related pain intensity increased in the former ibuprofen-foam group when the non adhesive comparator was introduced between days 43 and 47. A significant difference ($P < 0.05$) in pain intensity was detected at dressing removal (Figure 3). The pain intensity increased significantly for the previous ibuprofen-foam group from baseline NBS value of 0.3 to 0.9 ($0.9/0.3 \times 100 = 300\%$) in contrast to constant levels in the comparator group with an average 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

The ulcers decreased on average from 11.2 to 7.9 cm² in the ibuprofen-foam group and from 7.2 to 3.8 cm² in the comparator group (Figure 4). The decrease in ulcer area between

Table 2 Important baseline values of patients in the two treatment groups

Assessment		ibuprofen-foam	Comparator	<i>P</i> value
Pain intensity at inclusion (numeric box scale)	Mean	6.82	6.58	NS
	Standard deviation	1.8	1.6	
Exudate level of ulcer	Moderate, <i>n</i> (%)	41 (66)	51 (85)	—
	High, <i>n</i> (%)	21 (34)	9 (15)	
Absolute ulcer area (cm ²)	Mean	11.0	7.3	<0.05
	Standard deviation	9.6	5.7	
Absolute ulcer circumference (cm ²)	Mean	15.5	12.5	NS
	Standard deviation	9.1	6.9	

—, not tested; NS, not significant.

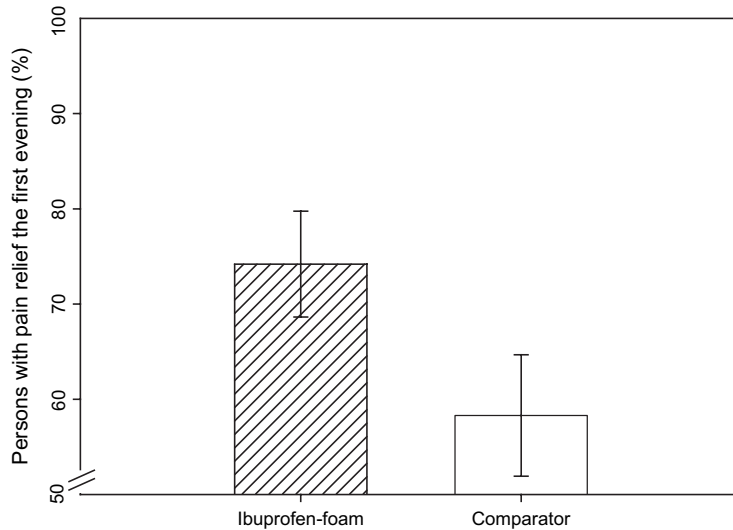


Figure 2. Percentage of patients with pain relief the first evening including standard deviations. The first evening there were 28% more persons with pain relief in the ibuprofen – foam (74%) group, than the comparator group (58%).

Key Points

- in the ibuprofen-foam group 12 patients experienced 21 adverse events
- in the comparator group 7 patients experienced 10 adverse events
- most of these adverse events had no relation to either the ulcer or the dressing

the two groups was comparable, with no statistical 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 Gilman (18) method. Both study group wound perimeters moved towards the centre of the

wounds with comparable speed. Ten ulcers in the comparator group and nine ulcers in the ibuprofen-foam group healed during the trial, and there was no statistical difference in healing time.

Adverse events

In total, 31 adverse events on 19 persons were reported (Table 4). In the ibuprofen-foam group, 12 patients experienced 21 adverse events, and in the comparator group, seven patients experienced ten adverse events. One patient was hospitalised (serious adverse event) because of a non device-related pulmonary oedema and was excluded from the study. In the ibuprofen-foam group, 19% (12/62) adverse events were reported compared with 12% in the comparator group (7/60). The relation to the device is reported in Table 4. 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 categorised into four groups: study ulcer pain, infection in study ulcer, local skin reactions and other. Skin reactions were, in the ibuprofen-foam group, observed with four patients; one had urticaria and later eczema, one had eczema alone, and two 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

Table 3 Patients’ pain intensity depended on the following statistically significant variables from the analysis of variance (d.f. = 914) on morning and evening pain intensity values from day 1 to 5

Effect	P value	Interpretation
Treatment (ibuprofen-foam versus comparator alone)	0.0003	Ibuprofen-foam reduces pain intensity
Time (between assessments)	<0.0001	Pain intensity for all patients decreases over time
Gender (women)	0.01	Women have less pain
Age	<0.0001	Older people have less pain
Baseline pain intensity	<0.0001	High baseline pain level, associated with high levels of pain at any time or with any treatment or other included variables
Baseline ulcer size	<0.0001	Larger ulcers, associated with higher pain levels

Key Points

- this study confirmed the benefit of foam dressing with low-dose ibuprofen for the treatment of chronic wound pain

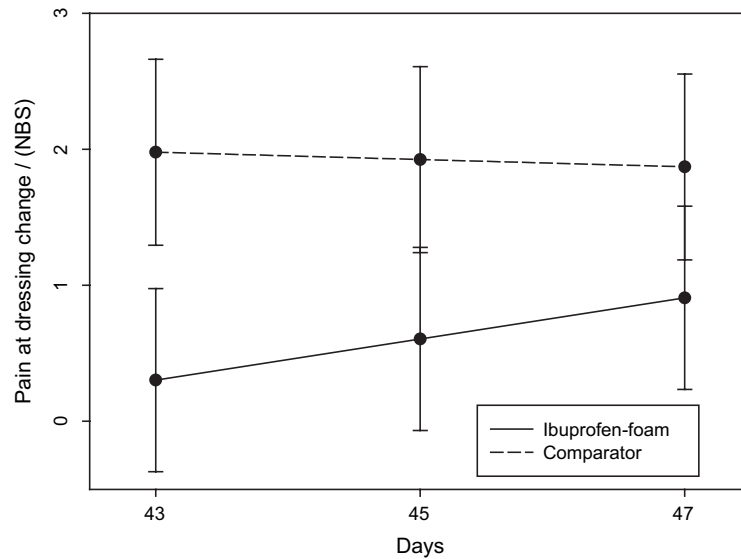


Figure 3. Pain at dressing change on days 43–47 increased in the former ibuprofen–foam group ($P = 0.05$). NBS, numeric box scale.

patch test was applied on the patient’s normal skin. The patch test showed a weak, potentially allergic reaction to the complete product, but not to ibuprofen-standardised patch test (petrolatum base), or to the comparator product. The negative patch tests to the components of the dressing controverts a contact irritant dermatitis, although there is a slight chance that the patient is allergic to a metabolite of ibuprofen.

DISCUSSION

This study has confirmed the benefit of foam dressing with low-dose ibuprofen for the

treatment of persistent chronic wound pain. In proof-of-concept studies, Jørgensen *et al.* (16), Sibbald *et al.* (19) and Flanagan *et al.* (5) have demonstrated that the ibuprofen–foam combines effective moist wound healing and ibuprofen release. This combined action reduced persistent pain, reduced pain at dressing change and increased quality of life, without being able to detect ibuprofen in the blood plasma (16). This randomised, controlled, double-blind study was designed for a 42-day treatment period plus an additional follow-up period of 5 days, where all patients were treated with the comparator foam dressing alone without ibuprofen. Based on results from preclinical and human pilot studies (5,16,19,20), a treatment period of 42 days should be sufficient time for evaluating adverse events and following the change in wound healing (e.g. ulcer area). Biatain Non adhesive foam dressing was considered the appropriate comparator product, as the presence of ibuprofen was the only difference between the two dressings. The addition of the follow-up period days 43–47 was to test whether patients from the ibuprofen-foam group would experience increase in pain during the last 5 days due to the withdrawal of the local low-dose release of ibuprofen.

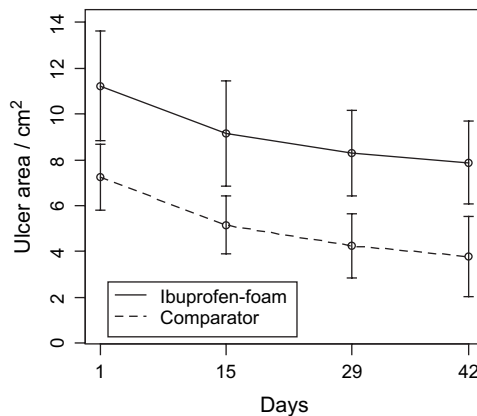


Figure 4. Absolute change in ulcer area (cm²) on the intention-to-treat population. There was no statistical significant difference on ulcer area reduction ($P = 0.26$) between the treatment groups.

Patient population

The patients in previous studies that compared the analgesic effect of topical ibuprofen on

Table 4 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†				P value
	Unrelated	Possible related	Related	Total	Unrelated	Possible related	Related	Total	
Total N (%)	3 (14)	5 (24)	13 (62)	21 (100)	1 (10)	3 (30)	6 (60)	10 (100)	NS‡

*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).‡NS, not significant.

intact skin with systemic use of ibuprofen were rarely above 50 years of age (21–23). In the ibuprofen-foam group of this study, the patients were on average 66 years of age, and 70 years of age in the comparator group (Table 1). The ideal patient in a pain trial may be often younger and male because pain-relieving medication is more likely to result in improved pain scores (24). For this reason, there are few previous reports of topical pain trials in an older, often female-predominant polymedicated population. Therefore, this investigation, together with the few clinical trials on interventions on the elderly population, showing statistical differences has high societal value.

Pain

Patients' perception of pain is known to change over time (11). Therefore, to get comparable results, pain interventions must be evaluated over relatively short periods (10).

Persistent pain relief on days 1–5

The primary endpoint of this study was pain relief. This study demonstrated that patients treated with the ibuprofen-foam had more pain relief than the comparator group ($P < 0.05$). This significant result is in line with a pilot cross-over study that demonstrated a reduction in pain intensity when changing from a comparator to the ibuprofen-foam (16). More patients (28%) in the ibuprofen-foam group had pain relief in the first evening (Figure 2), indicating that the observed pain relief has a quick onset of action. In a meta-analysis of topical non steroidal anti-inflammatory drug gels by Mason *et al.* (25), comparable results were shown, where the active treatment had an effect on 48% of patients, compared with 26% from placebo. In this case, we observed pain relief in 74% of patients in the active group compared with 58% in the

comparator group. Ibuprofen is mainly reported to have an effect on pain that is of a nociceptive origin (22). Therefore, it is not expected that the ibuprofen-foam would be effective in all patients. There is evidence in the literature (26) that moist wound healing provides pain relief. This study shows that by adding ibuprofen to a moist wound healing foam, an even stronger pain relieving effect is experienced by patients.

Persistent pain intensity on days 1–5

In this study, the data demonstrated that the pain intensity levels were reduced with the ibuprofen-foam, 40% from baseline compared with a 30% reduction for the comparator. Farrar *et al.* (27) found in a meta-analysis of pain trials, where the 11-point NBS scale was used, that a 30% reduction in pain intensity was clinically relevant. 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.

Pain at dressing change

Pain at dressing change or removal has been identified as a key patient concern (28,29). The ibuprofen-foam seemed to be associated with decreased pain at dressing change. On days 43–47, the former ibuprofen-foam group experienced an increment 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.* (16) and Sibbald *et al.* (19) similar results were observed, where the ibuprofen-foam reduced pain at dressing change. Pain at dressing change was not significantly different between the two comparative groups on days 1–5. Pain perception can be influenced by the effect of care (30);

Key Points

- more patients in the ibuprofen-foam group had pain relief in the first evening indicating the quick onset of relief from the ibuprofen-foam

Key Points

- the ibuprofen-foam showed clinically relevant pain reductions in the intensity of the wound
- the pain intensity levels were also influenced by gender, age, initial pain level and wound size

thus, measuring pain when crossing all patients over to the comparator foam is interpreted as a new baseline for the moist wound-healing parameters of the foam dressing alone. On day 43, the patients were accustomed to the best standard care. Therefore, differences observed during days 43–47 could be interpreted as free of the effect of care. Indirectly, it was, therefore, shown that the patients in the former ibuprofen-foam group versus the comparator had experienced less pain at dressing change.

Ulcer area

The ibuprofen-foam dressing was regarded as successful if the healing properties were similar to or better than those of the comparator foam. In this study, the patients in the ibuprofen-foam study had larger ulcers at baseline compared with the comparator group ($P < 0.05$). Area-based comparisons of the ulcer, therefore, gave biased results (18). In such 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.

Ibuprofen has an anti-inflammatory effect, and some literature discusses the effect of ibuprofen on wound healing (31–34). Theoretically, ibuprofen could inhibit the normal inflammatory wound-healing stage by reducing the amounts of prostaglandin. Most of the reported research has been performed on acute wounds, or with extremely high doses of ibuprofen in preclinical studies on animals, with variable outcomes (35). Often, patients with a chronic wound suffers from chronic medical disorders and the wounds may be stuck in the inflammatory phase (36). Therefore, low-dose ibuprofen use in chronic wounds is less likely to significantly influence healing of chronic wounds (16). Both methods used in this study to quantify wound healing showed that there was no difference in the chronic wound-healing rate between comparative groups, and the healing rate was comparable with earlier randomised controlled trials on the comparator foam (37).

Healing venous leg ulcers requires compression bandaging (6). In this study, patients were required to receive compression bandaging

before inclusion and throughout the study period. However, patients often discontinue compression treatment because of the associated pain. In a study by Briggs and Closs (6) on 96 venous leg ulcer patients, 44% of 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 patient's compression bandage adherence. In addition, for the 30% of patients who are unlikely to heal within 5 years (38), pain control should be considered as important to patients as healing.

Adverse events

The usual adverse events reported for ibuprofen are related to relatively high dose with oral intake (15). None of the most frequently reported oral ibuprofen adverse events (15) were observed in this study. The 15 × 15 cm ibuprofen-foam chosen in this investigation contains 112.5 mg of ibuprofen to be released into the wound over 7 days, depending on the exudate level (14). This is much lower than the recommended daily dose of 1200 mg, and in special cases 3200 mg (39). It has been shown in another study that the ibuprofen could not be detected systemically when the ibuprofen-foam was used (16).

The data from this study and other clinical studies on the ibuprofen-foam including more than 373 patients (5,15,19,20,39) 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 including studies from 1500 patients has demonstrated no difference in adverse reactions (including allergies) between placebo and topical use of ibuprofen gels (25). Based on the results from this study and the literature, the likelihood of adverse events with the ibuprofen-foam would be considered low. The likelihood of adverse events following long-term use of the ibuprofen-foam is unknown.

CONCLUSION

This is a report of a multinational and multi-centre, randomised, double-blind, clinical investigation on ibuprofen-foam. The study compared two moist wound-healing dressings and included 122 patients, with 62 randomised to the ibuprofen-foam and 60 to the

comparator. The primary outcome, the persistent wound pain relief during the first 1–5 days, was significantly higher in the ibuprofen-foam group. There was a quick onset of action, with a significant pain relief in the first evening. Women reported less pain intensity than men, and pain intensity decreased with increasing age. In addition, pain intensity increased with increasing initial pain intensity and increasing wound size. Wound healing was similar in the ibuprofen-foam group to that of the group that used comparator foam alone. No difference in adverse events between comparator and local sustained release of low-dose ibuprofen was observed in this study. There was no difference between dressing absorption capacity between the two compared dressings. This study has demonstrated that the ibuprofen-foam dressing is beneficial for persistent pain relief and reducing persistent and temporary wound pain intensity without compromising healing or safety.

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CONFLICTS OF INTEREST

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Key Points

- this study has demonstrated that ibuprofen-foam dressing is beneficial for persistent pain relief and reducing persistent and temporary wound pain intensity without compromising healing or safety

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