

ORIGINAL RESEARCH ARTICLE – CLINICAL SCIENCE

Pain and quality of life for patients with venous leg ulcers: proof of concept of the efficacy of Biatain[®]-Ibu, a new pain reducing wound dressing

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ABSTRACT

Wound pain is a serious problem for elderly patients suffering from chronic leg ulcers, and it may lead to reduced wound healing rates and reduced quality of life. Biatain[®]-Ibu Non-adhesive (Coloplast A/S), a new pain-reducing moist wound healing dressing containing ibuprofen was tested for pain reduction, safety, and efficacy on 10+2 patients in a single-blinded crossover study against Biatain Non-adhesive (Coloplast A/S). Pain was measured with a Numeric Box Scale before, during, and after dressing change. Quality of life was measured using the World Health Organization-5 Well-Being Index. Dressing moist wound healing properties such as absorption capacity and leakage were tested together with assessment of wound exudate and blood plasma content of ibuprofen. Use of the Biatain[®]-Ibu foam dressing correlated with a decrease in pain intensity scores from 7 in the run-in period to approximately 2.5 in the Biatain[®]-Ibu treatment phase. Quality of life measures were improved which together with the reduced pain could contribute to faster wound healing. The moist wound healing properties of Biatain[®]-Ibu were similar to that of the Biatain Non-adhesive and ulcer size was reduced by 24% during the treatment period. Neither side effects nor systemic plasma concentrations of ibuprofen were observed. These data indicate that Biatain[®]-Ibu could reduce persistent and temporary wound pain, increase Quality of life, was found safe to use, and had excellent moist wound healing properties.

People 65 years of age and older constitute one of the fastest growing segments of the population in the USA and Europe.^{1,2} Chronic leg ulceration is a serious problem among elderly people mostly caused by venous insufficiency.³ Many patients with venous leg ulcers suffer persistent pain during the day, and part of these patients experience exacerbated pain at dressing change.⁴ Therefore, more and more patients are having problems with painful venous ulcers. Hamer⁵ found that 37.5% of patients with leg ulcers indicated that the worst complication was the associated pain. These patients can undertake light or very light activity only, are depressed or irritated, and have reduced social activities.⁴ Furthermore, persistent pain disturbs sleep of 73% of the patients in a qualitative study by Noonan and Burge⁴ and 50% had their mood affected. Thus, a rational wound management regime should reduce wound pain to alleviate its negative influence on patient's everyday life.

Compression bandaging of the lower leg is the cornerstone of chronic leg ulcer treatment in the absence of any significant arterial disease.⁶ Leakage of exudate from ulcers has been shown to be a major problem causing distress to the patient⁷ and affecting the general quality of life (QoL) for the patient as well. In addition, poor exudate handling is recognized as a barrier to granulation and

epithelialization.⁸ Consequently, optimal management of chronic painful leg ulcers includes selection of an appropriate treatment that addresses pain⁹ minimizes venous stasis and promotes an optimal moist wound bed environment to facilitate healing.¹⁰

Two types of pain are associated with venous leg ulcers: neuropathic and nociceptive pain. Neuropathic pain arises from damaged nerve tissue, whereas nociceptive pain results from actual tissue damage,¹¹ both types being a major factor in the development of chronic pain. Persistent pain may result in increased sensitivity to nonpainful stimuli. For a patient with an ulcer due to venous insufficiency, a gentle touch of the skin therefore can cause pain and an uncomfortable sensation.¹² Reducing nociceptive and neuropathic pain requires two different treatment regimes. Treating nociceptive pain may not necessarily reduce pain of neuropathic origin and vice versa. Therefore, pain assessment and treatment is a multifaceted holistic process

NBS	Numeric box scale
NSAID	Nonsteroidal anti-inflammatory drug
QoL	Quality of life
WHO	World Health Organization

including description, location, duration, occurrence, trigger of, and historic treatment of pain.¹³ From a health care professional's perspective, wound pain can be categorized as persistent (chronic) or temporary (cyclic or noncyclic) pain.¹⁴ Persistent pain includes pain at rest and activity, whereas temporary pain is at cleansing, debridement, and dressing change.¹⁵ Early pain control may improve the patient's psychological state and is thought to have an impact on wound healing.¹⁶

According to the World Health Organization (WHO) pain relief ladder, persistent and temporary pain should be treated starting with nonpharmacological methods, oral nonsteroidal anti-inflammatory agents (NSAIDs), mild oral opiates, and as a last option using potent opioid analgesics.¹⁷ Practitioners are encouraged to treat pain in steps from the lowest level and upward. If one pain relief method is nonfunctional they should add the next level. Pain related to venous leg ulcers is often insufficiently-treated as the patients often are fragile, do not respond well to systemic analgesics, or are reluctant to take more medicine.¹⁸ To expand the leg ulcer pain treatment options, additional treatment options at the lowest level of the WHO pain relief ladder are urgently needed.

Reducing barriers to wound healing such as maceration, infection, pain, and low QoL should all be part of a holistic wound management approach for faster wound healing. Local topical treatment of pain associated with ulcers is underresearched¹⁹ and the purpose of this study has been to investigate pain reduction efficacy, impact on QoL, and safety aspects of a new innovative local dressing for patients suffering from painful ulceration. The dressing used in this study is a combination of an advanced foam and the NSAID drug, ibuprofen, that will provide local treatment of nociceptive pain, i.e., pain associated with tissue damage. The new dressing option combines the beneficial effect of moist wound healing and reduction of pain.

MATERIALS AND METHODS

In a recognized wound-healing center, patients with venous leg ulceration were included for treatment.²⁰ The study was a single-blinded crossover study on 10 patients with painful venous leg ulceration. The study included a pretreatment period with two placebo foam dressings (Biatain-pre), a test-treatment period of five active foam dressings containing ibuprofen (Biatain[®]-Ibu, Coloplast A/S, Humlebæk, Denmark) and a washout period with two placebo foam dressings (Biatain-post). The patients were treated for about 3 weeks. In addition, two patients also with painful venous leg ulcers were followed closely with additional blood sampling while wearing one placebo dressing initially followed by two active foam dressings with ibuprofen and one placebo dressing in the end of the treatment period. The observation period for these two patients was 8 days. Wear time of the dressings was 2–3 days. Short stretch compression therapy according to the clinical practice of the wound healing center was mandatory throughout the study period and could not be changed during the study period.

Inclusion criteria were patients more than 18 years of age with painful chronic venous leg ulcer more than 8 weeks old, and receiving compression therapy for at least 4 weeks before inclusion. The ulcer dimensions at inclusion were a

minimum of 6 cm² and a maximum corresponding to 2 cm from the edge of the 15 × 15 cm dressing. Leg ulcer pain scores were 6 or more at inclusion in the numeric box scale (NBS)⁹ where 0 is "No Pain" and 10 is the "Worst Imaginable Pain."

Exclusion criteria were: presence of clinical infection including erysipelas and cellulitis of per ulcer skin and diseases that may interfere with ulcer healing such as: vasculitis, rheumatoid arthritis, severe kidney insufficiency, heart disease, gastrointestinal bleeding, serious heart/liver insufficiency, serious hypertension, serious thrombocytopenia, asthma bronchiale, or other allergic symptoms caused by salicylic acid or other NSAIDs. They were allowed to take concomitant pain medication during the study, but should keep the medication constant during the study. Any changes were recorded.

The Biatain[®]-Ibu Non-adhesive foam dressing (Coloplast A/S) consists of a soft hydrophilic polyurethane foam containing ibuprofen (ibuprofen concentration: 0.5 mg/cm²) as an integral part of the matrix. The foam is bonded to a semi-permeable polyurethane film. Ibuprofen is released to the wound in the presence of fluid or wound exudate. In vitro studies have shown that ibuprofen is released throughout the dressing wear time. Biatain[®] Non-adhesive foam (Coloplast A/S), similar to Biatain[®]-Ibu but without ibuprofen, was used for pre- and posttreatments.

Assessments

The patients were evaluated every 2–3 days throughout the 3-week study period. The dressing was evaluated with respect to efficacy and safety. Pain intensity was recorded by the patients in a patient diary and by the nurses at dressing change visits. At the dressing change sessions, the nurses asked the patients to score their pain just before dressing change, during dressing change and 15 minutes after dressing change using the NBS. QoL scores were assessed with the WHO-5 Well-Being Index.²¹ Table 1 indicates the specific wording of the QoL questions modified from Price and Harding.²² Wound size was traced using transparent wound tracing sheets and measured using Image Pro Plus S.O software (Image House, Copenhagen, Denmark).

Table 1. Questions asked and verbal rating scale in the five-point QoL assessment

In the last week I have been:	
	Happy and in a good mood
	Calm and relaxed
	Active and energetic
	Awoken fresh and well rested
	Doing things that had my interest
Response categories	
	Always
	Mostly
	More than half
	Less than half
	Never

QoL=quality of life.

The safety aspects included measuring the impact of the dressing on the local wound environment, wound exudate leakage, absorption capacity, ibuprofen concentration in blood plasma, and wound bed exudate. The impact of the dressing on the local wound environment was measured by assessing whether the dressing stuck to the ulcers at removal, whether removal was “easy,” and whether there were dressing residues in the ulcer.

Ibuprofen analysis

Blood was sampled at the end of the Biatain-pre treatment period, at the end of the Biatain[®]-Ibu treatment period and at both of the two Biatain-post treatment dressing changes. Blood samples of approximately 5 mL were taken and cooled down to subzero temperature before centrifugal treatment (1,500×g for 10 minutes). Plasma was then frozen for later quantitative HPLC analysis with a detection limit of 0.5 µg/mL. Two stock solutions of 1 mg/mL Ibuprofen were used—one for standards and one for control samples. In the standard series, control samples and plasma samples Ketoprofen were used as internal standard.²³

Ibuprofen concentration in wound exudate was measured at each dressing change by letting five dots (each 10 mm diameter) of sterile filter paper absorb wound exudate after removing the old dressing. To minimize any problem with degradation of ibuprofen in the exudate or fluid evaporation, the filter paper saturated with exudate was placed in a preweighed tube with screw cap and frozen immediately. The extraction was carried out in the thawed tubes. Ibuprofen was extracted with methanol and analyzed quantitatively using the same method as for the blood plasma samples. The method was validated by producing solutions with known amount of ibuprofen in 10% calf serum. Samples (one sample = five pieces of filter paper) were saturated with the solution and the amount of absorbed solution was determined by placing the filter paper in a preweighed tube with screw cap and weighed again. Extraction media and internal standards were added to the samples and the amount of ibuprofen determined by high-performance liquid chromatography and compared with the amount in the known solution.

The nurse evaluated dressing leakage and absorption capacity at the dressing change session. Leakage of wound exudate outside the dressing was evaluated at dressing change using the scale (no, little, moderate, much). Dressing absorption capacity was quantified on a scale ranging from: poor, moderate, good, to very good absorption capacity. On dressing removal the study personnel evaluated odor and maceration of the periwound area using the scale (no, little, moderate, much).

Ethical assurances

The study was conducted in accordance with the Declaration of Helsinki II 1964, as amended in Scotland, October 2000, and in accordance with Council Directive 93/42/EEC of June 14, 1993, concerning medical devices (commonly known as the Medical Device Directive), the Council Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the International ISO standard ISO/DIS 14155—1:2000 Clinical investigation of medical devices on humans. All approvals were obtained

prior to inclusion of patients. Written informed consent was obtained from all patients after written and verbal information about the study, procedures, potential risks or inconveniences, and/or expected benefits.

Statistical analysis

Double entry and data management were performed in a data management system. The assessed pain (the response variable) was analyzed using dressing standard analysis of variance in a general linear model with patients 1–10 and treatment (Biatain-pre, Biatain[®]-Ibu, and Biatain-post) as explanatory group variables. Furthermore, a Pearson's correlation analysis was performed on the three assessed pain intensity variables; “before dressing change,” “during rinsing and dressing change,” and “15 minutes after change.” QoL scores were recorded in the end of the Biatain-pre phase and the end of the Biatain[®]-Ibu treatment phase, and the responses were rated on a scale from 0 to 5. To analyze treatment differences the five individual QoL responses (Mood, Calm, Active, Refreshed, Interesting) were modeled using a proportional odds model with patients (1..10) and treatment (Biatain-pre and Biatain[®]-Ibu) as explanatory group variables. In Figure 2, the QoL scores were converted to an average percentage scale where the maximum score for a particular question was rated 100% and zero to the lowest. The response variables for side effects (odor, itching, inflammation, stinging, bleeding, peri-ulcer reactions, and leakage) were dichotomized to a yes/no variable. The side effects of the dressing were then modeled with a logistic regression model as a function of dressing treatment (Biatain-pre, Biatain[®]-Ibu, and Biatain-post). All reported significant differences were based on 5% significance levels.

RESULTS

The patients were aged between 58 and 89 years (mean=82.9), 66% females, all had venous ulcers with measurable leg pulse and 60% had earlier ulcers. Most of them have had ulcers before, all had ABPI above 0.8 at inclusion (mean=0.9), with wound sizes varying between 9.31 and 53.3 cm² (mean=21.9 cm²). Three patients changed medication during the study. Two patients increased their medication with 1 g paracetamol because of unbearable night pain after returning to the Biatain-post nonactive treatment. One patient took medication due to unbearable pain at night concomitant with depot tablets of morphine (unspecified dose) while wearing the fourth Biatain[®]-Ibu dressing. This last patient did not experience pain reduction with Biatain[®]-Ibu at all (data not shown).

Pain reduction and moist wound-healing effect of Biatain[®]-Ibu

Pain was not relieved equally between patients ($p \leq 0.0001$) and there was an effect of wearing the active dressing compared with wearing a nonactive dressing ($p \leq 0.0001$). The measured pain levels of the Biatain-pre treatment were significantly higher than the Biatain[®]-Ibu treatment ($p \leq 0.0001$) and the Biatain-post treatment levels ($p \leq 0.0001$). The pain levels of the Biatain-post treatment were higher than the levels of the Biatain[®]-Ibu treatment ($p \leq 0.005$).

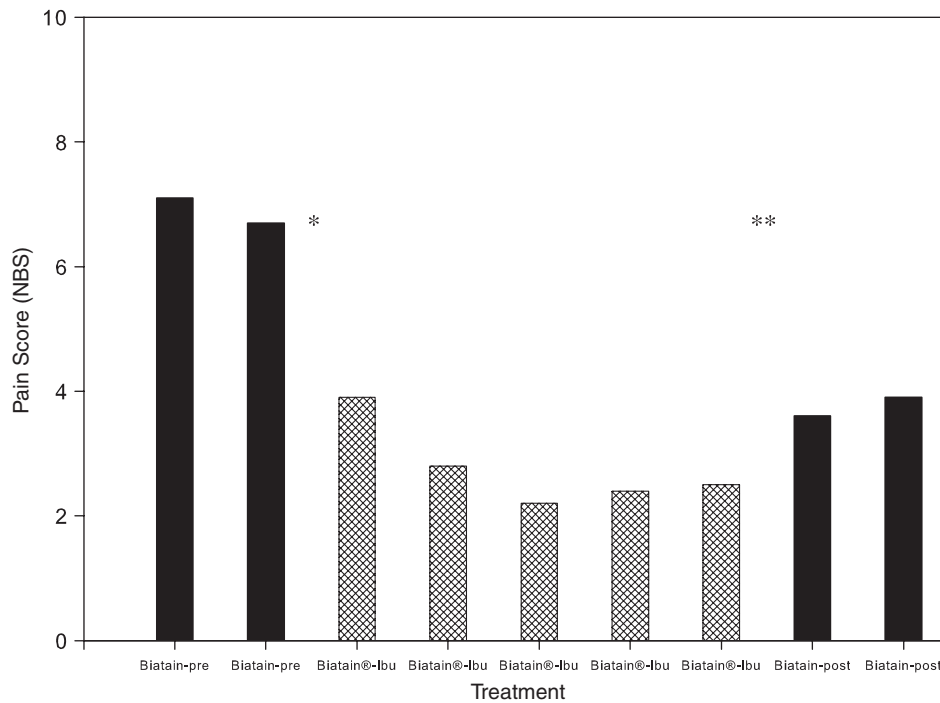


Figure 1. Pain intensity measurements determined just before dressing change sessions. The pain was measured just before dressing change using the NBS scale. * Biatain®-Ibu group was significantly different from the Biatain-pre group; and ** Biatain®-Ibu was different from the Biatain-post group.

Consequently, the Biatain®-Ibu treatment correlated with a decrease in pain intensity scores from 7 in the pretreatment period to approximately 2.5 in the Biatain®-Ibu treatment phase (Figure 1). The posttreatment pain levels were significantly higher than observed during active treatment and the average pain intensity score increased to 4.

The assessed pain levels during dressing change were correlated with the assessed levels before dressing change

($|r|=0.62, p \leq 0.0001$) and correlated with the assessed pain levels 15 minutes after dressing change ($|r|=0.83, p \leq 0.0001$). Thus, wearing a Biatain®-Ibu before dressing change, reduced pain during dressing change as well as after a new dressing was applied. The relative reduction in ulcer size was measured to be $24.5 \pm 28.5\%$ (median 14.8) during the 10 days the patient was wearing a Biatain®-Ibu dressing.

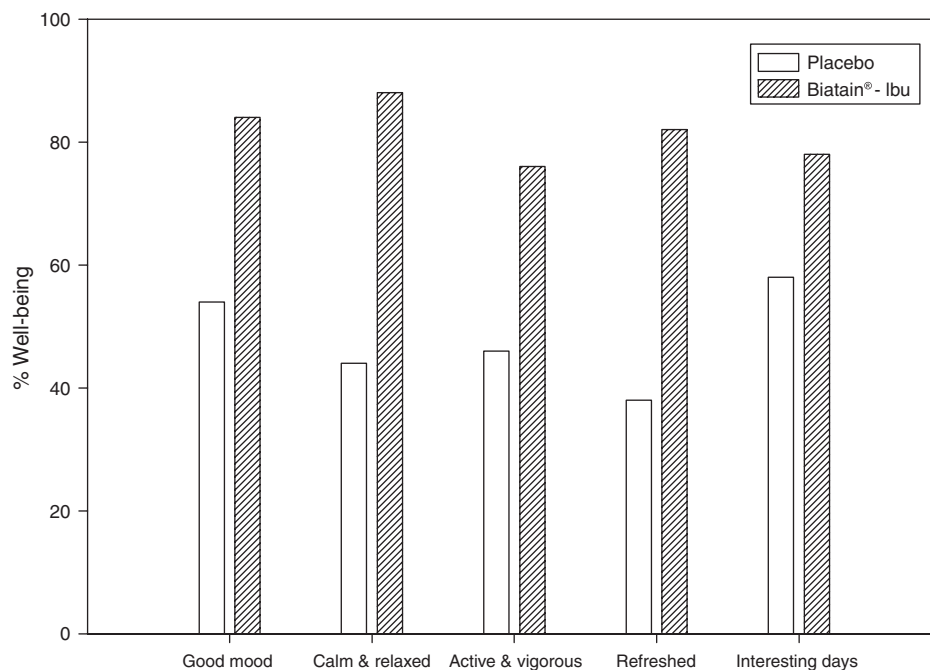


Figure 2. QoL values based on the WHO-5 measures rated on a scale from 1 to 6 before and after treatment. This scale was converted to a percentage score with 100% as the maximum score of 6 and 0% for the lowest score.

Effect of Biatain[®]-Ibu on QoL and safety

All five questions in the WHO-5 Well-Being Index (good mood, calm and relaxed, active and vigorous, refreshed, interesting days) were statistically improved ($p \leq 0.0001$) during the Biatain[®]-Ibu treatment (Figure 2).

Ibuprofen was not found in the blood serum samples except for two patients who ingested oral ibuprofen as concomitant medication during the study (Table 2). The average ibuprofen concentration in wound exudate was $61.4 \pm 40.4 \mu\text{g/mL}$ (Table 2) during the treatment with Biatain[®]-Ibu, with $171.8 \mu\text{g/mL}$ as the highest concentration measured. In the first Biatain-post treatment, the average ibuprofen content in the wound exudate was reduced to $15.6 \mu\text{g/mL}$, and in the second postdressing reduced to $5.0 \mu\text{g/mL}$. Wound exudate leakage was not significantly different between Biatain[®]-Ibu and Biatain pre- and post-foam (Table 3). The absorption capacity of all the dressings was rated as good or very good. There was no difference in Biatain-pre, Biatain[®]-Ibu, and Biatain-post treatment in associated odor, itching, inflammation, and peri-ulcer skin problems (Table 3). However, stinging was significantly less severe with Biatain[®]-Ibu and there was a tendency to reduced bleeding with Biatain[®]-Ibu at dressing changes (Table 3).

DISCUSSION

In this study, the decrease in pain intensity was directly correlated with the use in the Biatain[®]-Ibu dressing as pain was significantly reduced when changing to the first active dressing (Figure 1). This indicates that Biatain[®]-Ibu has a fast onset of action as pain was significantly reduced just before removal of the dressing. This also suggests a pain-reducing effect during the wear time of the dressing. Temporary pain experienced at wound dressing change was reduced with Biatain[®]-Ibu as ibuprofen from the previous dressing reduced pain during dressing change. The pain was further reduced 15 minutes after application of the new Biatain[®]-Ibu.

The patients treated with Biatain[®]-Ibu all had painful venous leg ulcers. In such wounds the combination of neuropathic and nociceptive pain is probably the most common presentation.^{4,9,11,12} Appropriate treatment of neuropathic pain alone requires tricyclic antidepressants, and anticonvulsants, thus ibuprofen would probably not be an effective treatment for neuropathic pain.²⁴ However, most patients suffer from nociceptive pain or a combination of nociceptive and neuropathic pain, and on these patients the observed decrease in pain was expected.

A reduction in pain levels may promote faster wound healing as pain stimulates catecholamine secretion (norepinephrine, epinephrine, and dopamine), probably resulting in local, peripheral capillary contraction, reducing amounts of available oxygen^{25,26} in the wounds. Reduced oxygen in wounds may result in prolonged wound healing, also by reducing resistance to infection.^{27–29} Wound pain can have a negative influence on well-being, mobility and function, and sleeping pattern.^{30,31} High pain intensity can cause appetite impairment,³² which may reduce the healing potential due to lack of nutrients.¹⁹ In a study 36 patients with venous leg ulcers, pain, and wound healing were studied. It was found that those not experiencing pain at the beginning of treatment had higher wound-healing rates than those experiencing pain.³³ Moffatt et al.¹⁶ found similar results, both studies concluding that faster wound healing is promoted through early pain relief. Collier and Hollinworth³⁴ found that pain and trauma at dressing change delay wound healing, as there is a direct link between psychological stress and wound healing. Stress increases glucocorticoids levels reducing inflammatory response, etc., resulting in delayed wound healing.³⁵

Wound healing can be affected by emotional factors, i.e., QoL and relief of subjective distress may therefore support wound healing itself.³⁶ Addressing the wound pain improved the QoL for the study patients. When wearing a Biatain[®]-Ibu dressing they had improved mood, were more calm and relaxed, were more active and vigorous, felt more refreshed and did more interesting things during the day, than compared to wearing a Biatain[®] dressing. Pieper et al.³⁷ found a correlation between QoL and wound pain and Mitchell reported that persistent pain in elderly people had a greater impact on their sense of well-being (QoL) than in younger patients.³⁸ Also wound pain increases at night which causes substantial sleep disturbance. The pain made the patients change their lives significantly, made them more frustrated, caused immobility, which made them stay at home, thus made them feel more socially isolated.^{7,34} In a descriptive study on patients with leg ulcers among others the following was stated "Pain seemed difficult to control. Prescribed pain killers were often ineffective, and the only other coping mechanism described was one of trying to avoid situations which triggered more pain, such as going out."³⁹ Douglas⁴⁰ interviewed patients about the effect of chronic leg ulcers on QoL and how it was experienced. He found pain to be an important feature, which affected sleep and thus could affect healing.

This study showed that Biatain[®]-Ibu did not cause detectable levels of ibuprofen in the blood sampled at the treated patients. This is advantageous as systemic NSAID

Table 2. Ibuprofen concentration in blood plasma and wound exudate during the different phases of the study

Parameter	Biatain-pre	Biatain [®] -Ibu	Biatain-post1	Biatain-post2
Ibuprofen concentration in blood plasma ($\mu\text{g/mL}$)	< 0.5*	< 0.5 [†]	< 0.5 [‡]	< 0.5 [‡]
Ibuprofen concentration in wound exudate ($\mu\text{g/mL}$)	—	61.4 ± 40.4	15.6 ± 29.1	5.0 ± 6.6

*Patient 12 with 10 ppm ibuprofen (concomitant intake of ibuprofen).

[†]Patient 12 with 49 ppm ibuprofen.

[‡]Patient 12 with 10 and 4 ppm ibuprofen observed in the last two blood samples. Patient 5 with 13 ppm in the last blood sample.

Table 3. Local effects of dressings with Biatain[®]-Ibu

Local effect*	Biatain-pre	Biatain [®] -Ibu	Biatain-post	p-value
Leakage from dressing	10 [†]	17	20	0.67
Odor from dressing	20	38	45	0.22
Itching in wound	55	42	35	0.43
Wound inflammation	53	45	45	0.83
Wound stinging	95	60	85	0.0047
Dressing change bleeding	20	4	20	0.061
No peri-ulcer skin problems	39	26	21	0.44

*Assessed by the nurse at dressing change. Problems included skin scratches, thin skin, redness, blisters, and dry-shiny skin.

[†]Numbers indicate observed percentages of patients with side effects scored "little," "moderate," and "much." The presented scores represent the incidences where adverse side effects such as smell, itching, inflammation, stinging, bleeding, and peri-ulcer problems were observed at dressing change.

treatment can lead to gastric problems for elderly users potentially treated with multiple drugs.⁴¹ Therefore, many doctors may be reluctant to treat elderly patients with appropriate amounts of analgesic. Barat et al.⁴² studied the drug intake of 492 patients, 75 years of age, and found that almost all took drugs with potential poly-pharmacy drug-related risks. As ibuprofen was not found in the blood plasma during treatment with Biatain[®]-Ibu, it was a safe solution for patients with risk of developing side effects of systemic analgesia, fear of taking additional medication, or suffering from poly-pharmacy-related gastric problems.

The highest measured wound exudate concentration of ibuprofen was 172 µg/mL and the mean value was 61.4 µg/mL. Concentrations of ibuprofen up to 520 µg/mL have been shown to be noncytotoxic for keratinocytes and fibroblaster.^{43,44} This indicates that Biatain[®]-Ibu is noncytotoxic with an average safety margin of nine, and a safety margin of three in extreme cases. Furthermore, the data showed that ibuprofen concentration was stable in the wound, which meant that there was no build up of active substances. Also, ibuprofen was rapidly washed out of the wounds as decreasing (15.6 and 5 µg/mL) amounts of ibuprofen were found in the wound exudate measured after Biatain-post1 and Biatain-post2 dressings.

This study shows that there are no local effects of using Biatain[®]-Ibu, as odor, itching, inflammation, bleeding, peri-ulcer reactions, and leakage are similar for the Biatain-pre, Biatain[®]-Ibu, and Biatain-post treatments. The reduction in stinging and bleeding for the Biatain[®]-Ibu dressing could be related to an ibuprofen-mediated reduction of wound erythema, heat, and edema.⁴²

The relative reduction in ulcer size was comparable to results from an earlier study where reduction in ulcer size was reported for different non-active foam dressings.¹⁰ This indicated that dressings containing ibuprofen have the same positive healing properties as other foams,

despite the concept that painful wounds are probably more difficult to heal than other, nonpainful wounds.¹⁶

We conclude that persistent and temporary wound pain was significantly reduced in the period patients were wearing the Biatain[®]-Ibu dressings and at dressing change. Biatain[®]-Ibu improved patients' QoL and while treated they were more happy, relaxed, felt more rested, and did more interesting things in their everyday life. Biatain[®]-Ibu has similar moist wound-healing properties as that of the Biatain[®] Non-adhesive dressing. Biatain[®]-Ibu reduced ulcer size with 24% during the treatment period. Biatain[®]-Ibu decreased wound smell, itching, inflammation, stinging, bleeding, and peri-ulcer problems. Ibuprofen was not detected in the blood serum while treating with Biatain[®]-Ibu. This meant that there was no systemic effect of ibuprofen, which is advantageous and may lead to improved compliance in elderly, intensively medicated patients. This study has shown that Biatain[®]-Ibu may be effective in decreasing persistent and temporary wound pain, improved QoL, and was safe to use.

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