A comparison of the efficacy of the topical NSAID felbinac and ultrasound in the treatment of acute ankle injuries

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Summary

In this multicentre, prospective, randomised, double blind study 220 out-patients were treated at hospital Accident and Emergency departments, in the UK, for acute injuries of the lateral ankle ligaments. Patients received seven days treatment with either felbinac (Traxam*) gel plus placebo ultrasound (72 patients), or ultrasound plus placebo gel (73 patients), or felbinac gel plus ultrasound (75 patients).

All three treatments were highly effective and a moderate or better improvement in the investigators' global assessment of the injury was seen for approximately 85% of all patients. Greater improvement in the mean change in pain on movement (the primary efficacy variable) was seen for the combined (felbinac plus ultrasound) group, although this did not reach statistical significance compared with the other groups.

The treatments were well tolerated and no serious adverse events were reported.

The results of this study demonstrate that the topical NSAID felbinac is an effective treatment of acute injuries to the lateral ligaments of the ankle, and its efficacy is similar to that of ultrasound. The data also suggest that the combination of felbinac and ultrasound may provide additional benefit to the patient.

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Introduction

Acute soft tissue injuries of the ankle are extremely common and many patients attend Accident and Emergency departments for treatment. Standard treatment comprises rest, ice, compression and elevation (RICE), but additional therapy such as ultrasound and oral non steroidal anti-inflammatory drugs (NSAIDs) are frequently required.

Oral NSAIDs provide effective symptomatic relief but are associated with a number of systemic side effects. The gastrointestinal system is most commonly affected, with side effects ranging from mild discomfort to peptic ulceration [1-3].

Ultrasound has been used as a physical therapy in the treatment of soft tissue injuries for more than 40 years. The resultant agitation of tissues is thought to increase blood flow to the injured area and stimulate cellular activity, accelerating the tissue repair process [4]. Treatment with ultrasound is, however, inconvenient for the patient and is costly in terms of the equipment required and the physiotherapist's time. It is also not always freely available to all patients.

Ultrasound is not effectively transmitted through air so a coupling agent is required between the ultrasound emitter and the treatment site. Degassed water, oils, emulsions and aqueous gels have been used but more recently topical NSAIDs have been investigated as coupling agents [5,6].

The topical NSAID Traxam® contains 3% (w/w) felbinac, and is available as a gel and a foam formulation in the UK. Felbinac has been shown to be highly effective in the treatment of soft tissue injuries [7-9]. A major advantage of felbinac gel compared with oral NSAIDs is that therapeutic levels of felbinac are achieved in the soft tissues underlying the application site with only low plasma levels [10], minimising the incidence of systemic side effects.

The aim of this study was to compare the efficacy and tolerability of felbinac gel and ultrasound, alone and in combination, in the treatment of acute injuries of the lateral ankle ligaments.

Patients and methods

The study was a randomised, double blind, parallel group, placebo-controlled trial. A total of 220 patients were entered and treated for acute injuries of the lateral ankle ligaments in the Accident and Emergency departments of eight UK hospitals. The protocol was approved by the Ethics Committee of each hospital prior to the start of the study.

- ***Inclusion and exclusion criteria***

All patients had an injury of the lateral ankle ligaments of one ankle, of at least mild severity, and of less than 48 hours duration since the time of injury.

Patients with a known hypersensitivity to NSAIDs, abraded skin at the treatment site,

a history of asthma, systemic connective tissue disorders, metabolic joint disease or rheumatic conditions, fractures, internal derangement or chronic injury of the joint to be treated, severe renal, hepatic, cardiovascular, metabolic, haematological or dermatological disease were excluded from the study.

Patients who required concomitant analgesics or other anti-inflammatory medication during the study, were pregnant and/or lactating, had previously participated in the trial or were participating in another clinical trial were also excluded.

- ***Baseline visit***

At the baseline visit (Day 1) demographic data and details of any concomitant medication and concurrent conditions not being treated were recorded.

Patients assessed their pain from voluntary movement (the primary efficacy variable) and pain at rest using 100 mm visual analogue scales (VAS), ranging from "none" to "as severe as possible".

The investigators assessed the injury with respect to swelling, pain and global severity using a scale of "none", "mild", "moderate", or "severe". Swelling was also assessed by measurement of both ankles at three specified points. The measurements were added together and the difference between the injured and uninjured ankles used as the amount of swelling. Range of movement was measured using a goniometer, and the ability to bear weight categorised as either unable to bear weight, able to place foot on ground but unable to bear weight, able to bear partial weight, or able to bear full weight.

Patients were randomly allocated to receive either felbinac gel plus placebo ultrasound, ultrasound plus placebo gel, or felbinac gel plus ultrasound. The randomisation schedule was generated by a computer in blocks of six. The gel (1 – 2 g) was applied to the affected area and gently massaged in, two to three times each day. Ultrasound treatment was administered at this baseline visit and the follow-up visits as 2 – 3 minutes pulsed therapy using a 3 MHz head, an intensity of 0.25 – 0.5 w/cm ^{2} and the appropriate gel, either active or placebo, as the coupling agent. Placebo ultrasound was applied in an identical manner but without the emitter switched on.

- ***Follow-up visits***

Patients were assessed at three follow-up visits on Days 3 ("Visit 2"), 5 ("Visit 3") and 7 ("Visit 4"). The assessments and measurements made at the baseline visit were repeated. The investigators assessed swelling, pain and global severity as worse, no change, slight improvement, moderate improvement or marked improvement compared with the baseline. Details of any adverse events, changes in concomitant illnesses/medications and compliance were also recorded.

Ultrasound was performed at each visit, except the final visit.

The outcome of all patients was recorded and reasons for withdrawal were given if the patient withdrew from the study prior to Visit 4.

• *Data analysis*

The primary efficacy analysis was performed on all patients who received treatment and had follow-up data (intention to treat). The data from patients who were eligible based on the inclusion and exclusion criteria, and evaluable because they had conformed to the study protocol were used in a secondary efficacy analysis.

Continuous variables, such as age and VAS data, were compared between the three treatment groups, based on a normal distribution, using analysis of variance. When normality was not justified the Kruskal-Wallis analysis of ranks was applied. Categorical data, such as sex and ability to bear weight, were analysed using a Chi-squared test. When numbers in a group were particularly low Fisher's exact test was used.

Follow-up data were analysed with respect to the amount of change from baseline. The same statistical methods were used for comparing the treatment groups.

The statistical analysis was conducted by Dr D Hewitt, Senior Statistician, BIOS Limited, Bagshot, Surrey, UK.

Results

• *Study population*

Baseline

A total of 220 patients were enrolled and received treatment. Seventy-two received felbinac gel plus placebo ultrasound (felbinac group), 73 received ultrasound plus placebo gel (ultrasound group) and 75 received felbinac gel plus ultrasound (combined group). At the baseline visit three felbinac group patients who had required concomitant analgesics were excluded from the secondary efficacy population.

There were no significant differences between the treatment groups with respect to age, weight and the proportion of males and females (see Table 1). The mean duration of the injury was 24.6 h, 22.1 h and 23.1 h for the felbinac, ultrasound and combined groups respectively (duration of injury was not recorded for one combined group patient).

The assessments and measurements showed no significant differences in the severity of the injuries between the treatment groups at the baseline. The majority of patients – 47 (65%) felbinac group, 58 (79%) ultrasound group and 53 (71%) combined group – had an injury of moderate severity. Similar numbers of patients in each treatment group had been using concomitant medications (for other indications) or had concurrent illnesses.

Follow-up visits

Fifty-two patients withdrew during the study. Of these patients, 41 (12 felbinac group, 17 ultrasound group, 12 combined group) did not attend for a follow-up visit (reasons unknown), nine (three in each group) required no further treatment, one ultrasound group patient withdrew because of an adverse event, one felbinac group patient withdrew as their condition worsened and two felbinac group patients withdrew for other reasons. Two patients in the ultrasound group had two reasons for withdrawal.

TABLE 1. *Demographic data recorded for patients who received treatment.*

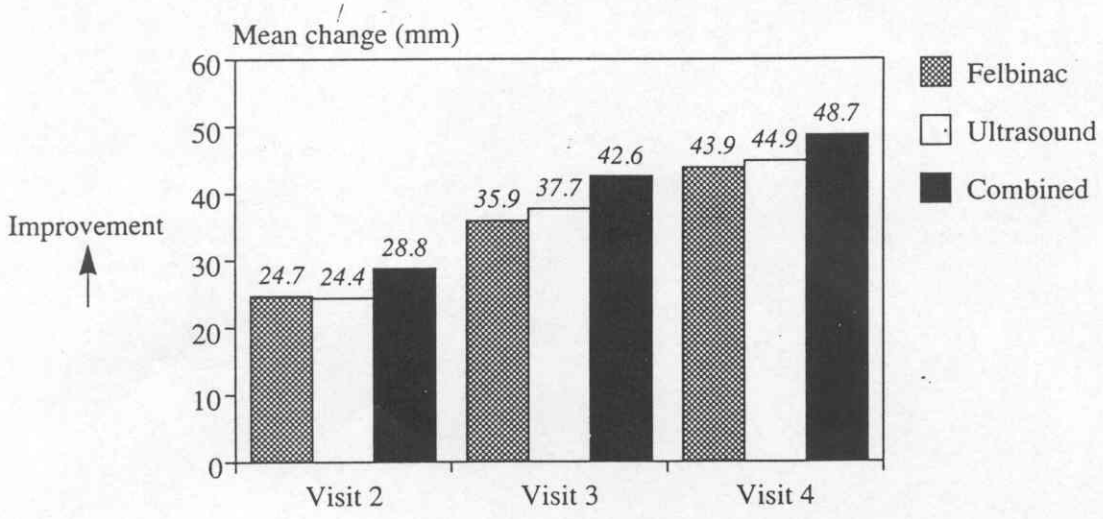
Characteristic		Felbinac plus placebo ultrasound (felbinac)	Ultrasound plus placebo gel (ultrasound)	Felbinac plus ultrasound (combined)
No. of patients		72	73	75
Sex (no.):	male	50	48	46
	female	22	25	29
Age (years):	mean (± sd)	27.0 ± 8.4	28.1 ± 10.3	28.2 ± 10.1
	range	17 – 53	17 – 57	16 – 54
Weight (kg):	mean (± sd)	73.8 ± 12.3	77.2 ± 13.5	72.8 ± 13.2
	range	50.0 – 100.2	60.0 – 120.9	48.0 - 122.3

Age was not recorded for one combined patient and weight for 19 patients (4 felbinac group, 10 ultrasound group, 5 combined group).

The data from all 220 patients were used for the primary analysis of efficacy at the follow-up visits. If a patient withdrew or did not attend for a visit the last available value was carried forward for this analysis. A total of 190, 161 and 139 patients were used for the secondary efficacy analysis at Visits 2, 3 and 4 respectively.

Overall the results showed that there was improvement in symptoms and there were few significant differences between the treatments. The primary efficacy variable, pain on movement, reflected this but improvement favoured the combined treatment group (see Figure 1).

FIGURE 1. *Mean change in pain on movement at each follow-up visit as measured from the baseline (VAS, mm). All values represent a decrease in pain on movement. Data were missing for one felbinac group patient at Visit 2, three at Visit 3 and four at Visit 4, and one ultrasound patient at each visit.*



The changes in the other assessments of pain were similar for each treatment group. At Visit 4 mean changes in pain at rest were reductions of 21.5 mm, 19.4 mm and 16.5 mm for the felbinac, ultrasound, and combined treatment groups respectively (pain at rest was not assessed for two felbinac patients at Visit 4). A moderate or better response in the investigators' assessment of pain was seen for 57 (79%) felbinac, 61 (85%) ultrasound and 67 (90%) combined group patients by Visit 4 (pain was not assessed for one ultrasound patient at Visit 4). By the end of treatment 53 (74%) felbinac, 56 (77%) ultrasound, and 60 (80%) combined group patients could bear their full weight compared with 15 (21%) felbinac, 14 (19%) ultrasound, 19 (25%) combined group patients at the baseline visit.

Improvement in global severity at the end of the treatment period was moderate or better for approximately 85% of the patients in each treatment group (see Figure 2). Patients in the felbinac and combined treatment groups possibly improved quicker as at Visit 2 the difference in results approached statistical significance in favour of these treatment groups ($p = 0.065$, Chi-squared test).

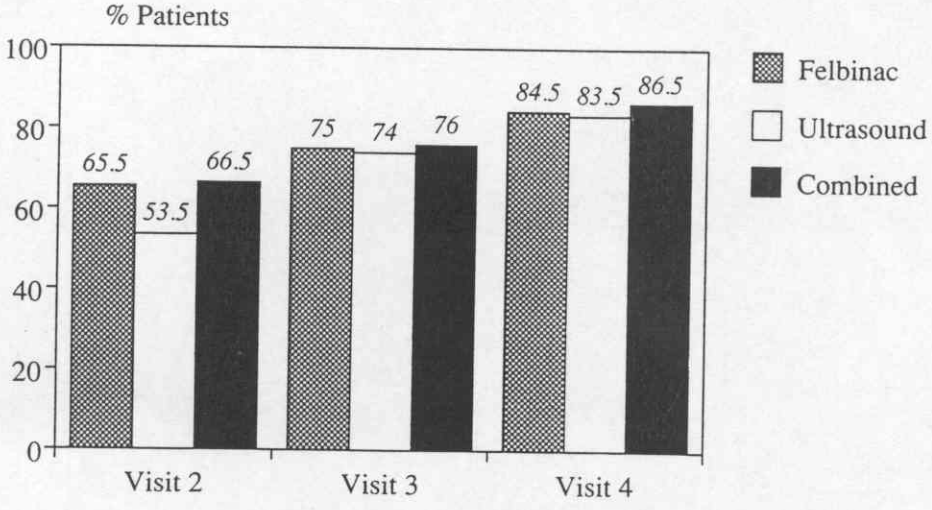
The mean change in measured swelling favoured ultrasound treatment at all visits and this was significant at Visit 4 ($p = 0.029$, Kruskal-Wallis analysis of ranks). In contrast, change in swelling assessed using the four-point scale of worse to marked improvement was similar for all treatment groups except at Visit 3, where the combined treatment group showed significantly more improvement ($p = 0.004$, Chi-squared test).

Difficulties were encountered in the measurement of range of movement and as a result the data were not analysed.

- ***Adverse events***

No serious adverse events were reported during the study. Seventeen (7.7%) of the patients who received treatment reported a total of 20 non-serious adverse events. Of these, two felbinac group patients reported two adverse events, eight ultrasound group

FIGURE 2. *Percentage of patients in each treatment group showing a moderate or better improvement in the investigators' global assessment of severity. Data were missing for one ultrasound patient at each visit.*



patients reported 11 adverse events, and seven combined group patients reported seven adverse events.

Six patients reported skin reactions, an incidence rate of 2.7% (three (2.0%) felbinac gel and three (4.1%) placebo gel patients). The severity was recorded as mild in all cases. One ultrasound group patient was withdrawn from the study as a result of a skin reaction.

Three gastrointestinal events were reported by two patients, both in the ultrasound group. The most severe of these were diarrhoea and vomiting, reported by one patient, classified by the investigator, as moderately severe and remotely related to the study drug.

Discussion

This multicentre, randomised, double blind study demonstrates that felbinac gel has a similar clinical efficacy to ultrasound in the treatment of acute injuries of the lateral ankle ligaments.

The patients' assessment of pain on movement (the primary efficacy variable) favoured the combined (felbinac plus ultrasound) treatment group. This, and the improvement in global severity in favour of the felbinac and combined treatment groups at Visit 2 suggests that felbinac gel is at least as effective as ultrasound alone and may provide additional benefit when used in conjunction with ultrasound.

For ethical reasons (and to ensure high recruitment) the study did not include a true placebo group (placebo gel plus placebo ultrasound). However, patients in all three treatment groups responded well, with approximately 85% of patients achieving moderate or better improvement in global severity. This response rate compares well with previously reported double blind, placebo-controlled trials, where good or better overall efficacy was 73% and 81% for felbinac gel patients compared with only 41% and 28% for placebo gel patients [7,8]. Therefore, despite the absence of a true placebo group, reference to previous studies implies that all three treatments are more effective than placebo.

All three treatments were well tolerated and no serious adverse events were reported during the study. The overall incidence of skin reactions was low (2.7%) and all were of mild severity. This incidence compares well with the results from a recent post marketing surveillance study involving 23,590 patients, in which the incidence of skin reactions was 1.1% [11]. There were no gastrointestinal adverse events reported by patients treated with felbinac, which agrees with the very low incidence (0.1%) previously reported [11].

In conclusion, the results of this study demonstrate that felbinac gel is an effective treatment of acute injuries of the lateral ankle ligaments. The efficacy of felbinac is similar to that of ultrasound treatment and may therefore be a useful alternative, especially when ultrasound is not available. The data also suggest that the combination of felbinac and ultrasound treatment may provide additional benefit to the patient. This study has also shown that felbinac is extremely well tolerated and

therefore represents an alternative to the use of oral NSAIDs in the treatment of soft tissue trauma.

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References

1 Editorial. C S M Update.
Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions-2.
Br Med J 1986; **292**: 1190 – 1191.

2 Bradley C.
NSAIDs a review.
The Physician 1988; **1** (5): 326 – 328.

3 Jacyna M.
Serious gastrointestinal adverse events to NSAIDs: complications in the treatment of arthritis. *Br J Med Econ* 1992; **5**: 15 – 21.

4 Dyson M.
Role of ultrasound in wound healing. In: Kloth L C, editor. Wound healing: alternatives in management. Davis-Co, Philadelphia, USA, June 1990: 259 – 285.

5 White S.
Topical non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of inflammatory musculoskeletal disorders.
Prostaglandins, Leukotrienes & Essential Fatty Acids 1991; **43**: 209 – 222.

6 Benson H A E, McElnay J C.
Transmission of ultrasound energy through topical pharmaceutical products.
Physiotherapy 1988; **74** (11): 587 – 589.

7 McLatchie G R, McDonald M, Lawrence G F *et al.* Soft tissue trauma: a randomised controlled trial of the topical application of felbinac, a new NSAID.
Br J Clin Pract 1989; **43** (8): 277 – 280.

8 Sanguinetti C.
Treatment of soft tissue trauma with BPAA gel. Results of an Italian multicentre study vs. placebo. *La Clinica Terapeutica* 1989; **130** (5): 255 – 258.

9 Morris W D, Scott H V, Peters W A *et al.*
Felbinac topical gel for acute soft tissue sports injuries.
New Zealand Journal of Sports Medicine, Spring 1991; 45 – 47.

10 Sugawara Y, Ono H, Ueda R *et al.*
Percutaneous absorption and tissue distribution of L-141 topical agent.
J Med Pharmacol 1985; **13** (6): 2761 – 2775.

11 Newbery R, Shuttleworth P, Rapier C.
A multicentre post-marketing surveillance study to evaluate the safety and efficacy of felbinac 3% gel in the treatment of musculoskeletal disorders in general practice.
Eur J Clin Res 1992; **3**: 139 – 150.