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Double-blind Study Comparing the Use of Voltaren Emulgel® versus Regular Gel During Ultrasonic Sessions in the Treatment of Localized Traumatic and Rheumatic Painful Conditions

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A total of 120 patients with moderate to severe pain due to localized rheumatic or traumatic conditions participated in a double-blind, randomized trial. Patients were randomly allocated to receive ultrasonic sessions three times weekly for 4 weeks, using either diclofenac in a gel base (Voltaren Emulgel®) or regular gel as a coupling medium. A statistically significant ($P < 0.01$) improvement was achieved in both treatment groups in most of the evaluation criteria by the end of the first week. Treatment was prematurely discontinued due to complete cure in 60% of patients using Voltaren Emulgel® compared with only 15% of those using regular gel ($P < 0.01$). Physician's assessment of complete relief of pain was also statistically significant ($P < 0.01$) in favour of Voltaren Emulgel® throughout the trial period and the physician's overall assessment of therapeutic efficacy revealed that a satisfactory result was achieved in 86% of Voltaren Emulgel®-treated patients compared with 76% of patients receiving regular gel ($P < 0.05$). Tolerability was good or excellent in over 95% of patients in both treatment groups. The results of the study strongly suggest that the use of Voltaren Emulgel® as a coupling medium during ultrasonic therapy is a preferable, effective alternative to the currently used regular gel.

KEY WORDS: Voltaren Emulgel®; diclofenac; ultrasonic therapy; coupling medium; rheumatic pain; traumatic pain.

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Voltaren® and Voltaren Emulgel® are registered tradenames of Ciba-Geigy Ltd, Switzerland.

INTRODUCTION

Painful diseases of the locomotor system include a wide range of rheumatic and traumatic conditions, and collectively are one of the largest disease groups requiring medical attention. Modern therapeutic approaches include physiotherapy, pharmacological agents and surgery, al-

though more recently the use of ultrasound waves in such conditions has proved effective. A review of the physiological reactions to ultrasound indicates that the potential therapeutic significance is primarily due to the temperature elevation resulting from the absorption of ultrasonic energy.[1,2] A few additional effects have been demonstrated, such as acceleration of the diffusion process across biological membranes, that are non-thermal in nature.[1-4]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the main pharmacological agents used in the management of acute painful conditions. Diclofenac (Voltaren®) is a well-established NSAID that has marked anti-inflammatory and analgesic effects, and a high therapeutic index. Systemic diclofenac, either alone or in combination with physiotherapy, has proved to be a potent and reliable agent, achieving complete or substantial pain relief and functional improvement within a relatively short period of time.[5-7] This is particularly important to athletes who need to return to training as soon as possible after injury.

Ultrasonic waves are poorly conducted by air and require a coupling medium (regular gel) to aid transmission from the transducer to the tissues. Current research has led to the development of Voltaren Emulgel®, a topical percutaneous formulation of diclofenac in a hydrophilic/lipophilic gel base. This can be used as a coupling medium during ultrasound therapy and ensures deep penetration of the active substance into the affected tissues, resulting in a more targeted treatment for localized painful conditions.

Pharmacokinetics and pharmacological and clinical studies have shown that Voltaren Emulgel® can produce therapeutic local concentrations of diclofenac in the area of inflammation without substantial systemic absorption.[8,9] Early open trials of Voltaren Emulgel® have also demonstrated that use of the gel during ultrasound physiotherapy can induce a satisfactory improvement in 93.4% of patients as well as a 50% reduction in the number of ultrasound sessions required.[10]

The present study was undertaken to validate these preliminary findings by employing a control emulsion and double-blind, randomized methodology to eliminate bias.

PATIENTS AND METHODS

Patients

A total of 120 ambulant patients, who were suffering from localized rheumatic or traumatic conditions, were included in the trial. All patients had moderate to severe pain on movement and most experienced pain at rest and tenderness on pressure. Patient characteristics are detailed in Table 1. Exclusion criteria were as follows: known or suspected hypersensitivity to NSAIDs, isopropanol, or propyleneglycol; presence of skin wounds or open injuries; and pregnancy.

Methodology

After a thorough clinical examination, patients fulfilling the inclusion/exclusion criteria were randomly allocated to receive ultrasonic sessions using either Voltaren Emulgel® or regular gel as a coupling medium.

It was emphasized to all patients that they were not allowed to administer other topical or systemic therapy throughout the trial period. If pain relief was considered inadequate by the patient, the physician could provide a rescue analgesic which had no anti-inflammatory characteristics (500 mg paracetamol, up to three times daily if pain persisted). All additional medication was recorded on the patient's case record form.

Treatment

Patients received three ultrasonic therapy sessions each week for a maximum of 4 weeks. At each session, 1 W/cm^2 was applied for 10 min using either Voltaren Emul-

Table 1
Characteristics of patients undergoing ultrasonic sessions using Voltaren Emulgel® or regular gel for the treatment of localized traumatic or rheumatic painful conditions

Characteristic	Voltaren Emulgel®	Regular gel	Total
No. of patients	60	60	120
Age (years)			
Mean (± SD)	46.0 ± 10.1	46.3 ± 10.2	46.0 ± 10.1
Range	24 63	26 63	24 63
Sex			
Male	21 (35%)	25 (42%)	46 (38%)
Female	39 (65%)	35 (58%)	74 (62%)
Weight (kg)			
Mean (± SD)	78.0 ± 8.2	80.2 ± 9.3	79.2 ± 8.8
Range	61 97	50 104	50 104
Diagnosis			
Rheumatic	48 (80%)	47 (78%)	95 (79%)
Traumatic	12 (20%)	13 (22%)	25 (21%)

gel® or regular gel as the coupling medium.

Evaluation of treatment

Patients were evaluated once after three consecutive ultrasonic sessions, i.e. each week, up to four times. The efficacy of the two gels was compared using the double-observer technique whereby the ultrasound sessions were conducted by physiotherapists and clinical evaluation was carried out by the investigating physician.

At initial and follow-up visits, the physician assessed tenderness on pressure and pain on passive movement, before and after ultrasonic treatment, using a four-point rating scale (0, no pain; 1, mild pain; 2, moderate pain; or 3, severe pain). In addition, patients' assessments of severity of pain at rest and during movement were noted before and after the ultrasonic sessions using a 100-mm visual analogue scale (VAS).

Patients who were declared cured before the completion of the 4-week treatment period, received no further ultrasonic sessions; hence, the number of sessions required for cure was used as a measure of efficacy. Any adverse effects spontaneously reported or observed by the physician were recorded with a description of their nature, severity, date of onset, duration and relation to the trial medication.

At the final consultation (or when the trial was prematurely discontinued), the physician made an overall assessment of both the efficacy and tolerability of the treatment. In addition, patients were asked whether they would be willing to receive the same therapy for similar conditions if ever required.

Statistical analysis

The Student's *t*-test with pooled estimate of variance and paired *t*-test were used for parametric data; however, the relative to identified distribution test[11] was carried out

for analysis of nominal data. In addition, the hypothesis test for the difference between two proportions was used. The level of statistical significance adopted for all comparisons was 5%.

RESULTS

All patients, except one in the Voltaran Emulgel® treatment group, completed the study; this patient, who discontinued treatment due to local irritation, was excluded from the efficacy analysis but included in tolerability evaluation. As a result, 119 patients were analysed for efficacy and 120 patients for tolerability.

Therapeutic effects

At the beginning of the study there were no statistically significant differences between the two groups for any of the baseline variables.

Physician's assessments. In all three parameters assessed by the physician Voltaren Emulgel® proved to be more effective than regular gel.

Tenderness on pressure showed a highly significant ($P < 0.001$) improvement over baseline values at all four visits, irrespective of the gel used. Analysis of the between-treatment differences after sessions 3, 6 and 9 (weeks 1 – 3), however, revealed that a significantly ($P < 0.05$) higher percentage of patients in the Voltaren Emulgel® treatment group showed a distinct improvement by at least two points on the rating scale (Fig. 1). Furthermore, Voltaren Emulgel® was strongly favoured in trend analysis of the number of patients within each treatment group experiencing complete freedom from tenderness compared to baseline values (Fig. 2).

Pain on passive movement markedly

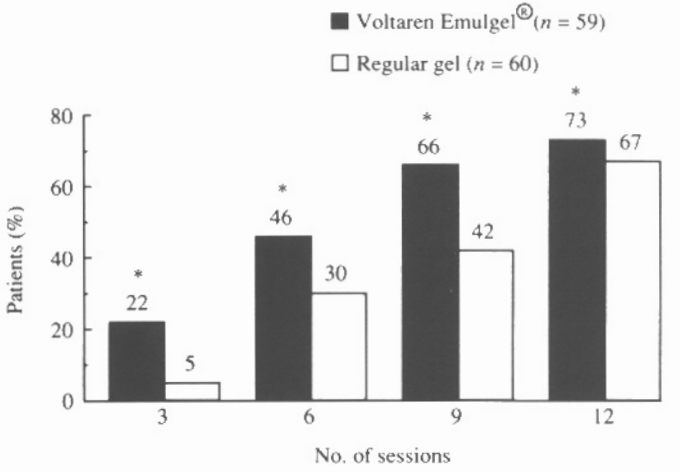

Fig. 1. Cumulative percentage of patients showing improvement in tenderness by at least two points on the four-point rating scale following ultrasonic sessions with Voltaren Emulgel® or regular gel as the coupling medium for the treatment of localized traumatic or rheumatic painful conditions; *$P < 0.05$ vs regular gel.

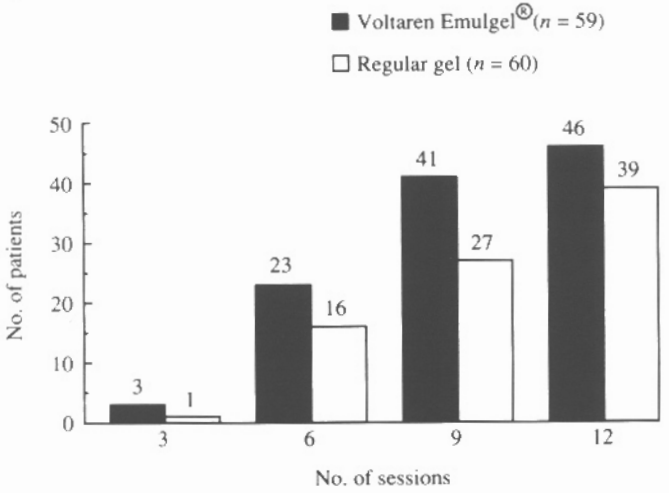

Fig. 2. Cumulative differences over baseline values in the number of patients experiencing complete freedom from tenderness following ultrasonic sessions using Voltaren Emulgel® or regular gel as the coupling medium for the treatment of localized traumatic or rheumatic painful conditions.

improved (by two points or more of severity on the rating scale) after session 12 (week 4) in approximately 56% of Voltaren Emulgel®-treated patients and in 54% of patients in the regular gel treatment group. Voltaren Emulgel® was also clearly favoured in an analysis of the complete relief of pain on passive movement compared to pretreatment values (Fig. 3).

Complete relief of pain was achieved by significantly ($P < 0.01$) more patients in the Voltaren Emulgel® treatment group than in the regular gel treatment group throughout the trial period (Table 2). This provides supportive evidence for the greater efficacy of Voltaren Emulgel® over the comparison gel.

Patients' assessment. Voltaren Emulgel® was superior to regular gel with respect to intensity of pain as assessed by the patients before and after each session using the visual analogue scale.

Pain at rest was reduced highly significantly ($P < 0.001$) in both treatment groups during the 4-week observation period; Voltaren Emulgel® was significantly more effective than regular gel after session 3 (week 1) and as the trial proceeded Voltaren Emulgel® continued to show better results than regular gel, although no statistically significant difference was detected at the end of the study. Pain on movement was significantly ($P < 0.01$) reduced in both treatment groups after 4 weeks, with Voltaren Emulgel® showing a definite superiority at each assessment (Fig. 4). The difference between the two treatment groups reached the level of significance ($P < 0.05$) after sessions 3 and 6 (weeks 1 and 2).

Premature discontinuation. Treatment was discontinued prematurely in 39 patients in

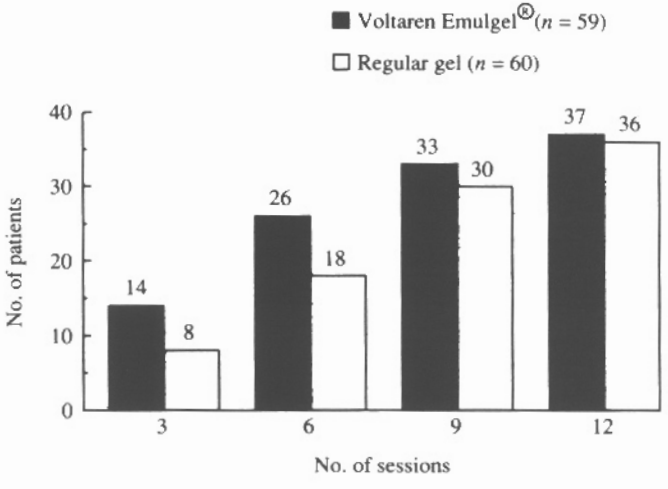

Fig. 3. Cumulative differences over baseline values in the number of patients experiencing complete relief from pain on passive movement following ultrasonic sessions using Voltaren Emulgel® or regular gel as the coupling medium for the treatment of localized traumatic or rheumatic painful conditions.

the Voltaren Emulgel® treatment group compared with 12 patients in the regular gel treatment group (Table 3). There was a statistically significant ($P < 0.01$) difference in the percentage of patients stopping therapy due to complete cure in the two treatment groups (60% and 15%, respectively).

Table 2
Number of patients experiencing complete pain relief following ultrasonic sessions using Voltaren Emulgel® or regular gel as the coupling medium for the treatment of localized traumatic or rheumatic painful conditions

No. of sessions completed	Voltaren Emulgel®	Regular gel
3	1 (1.7%)	0 (0%)
6	15 (25.0%)	7 (11.67%)
9	20 (34.0%)	12 (20.00%)
12	8 (13.5%)	11 (18.30%)
Total	44 (74.2%)[a]	30 (50.00%)

[a] $P < 0.01$ vs regular gel.

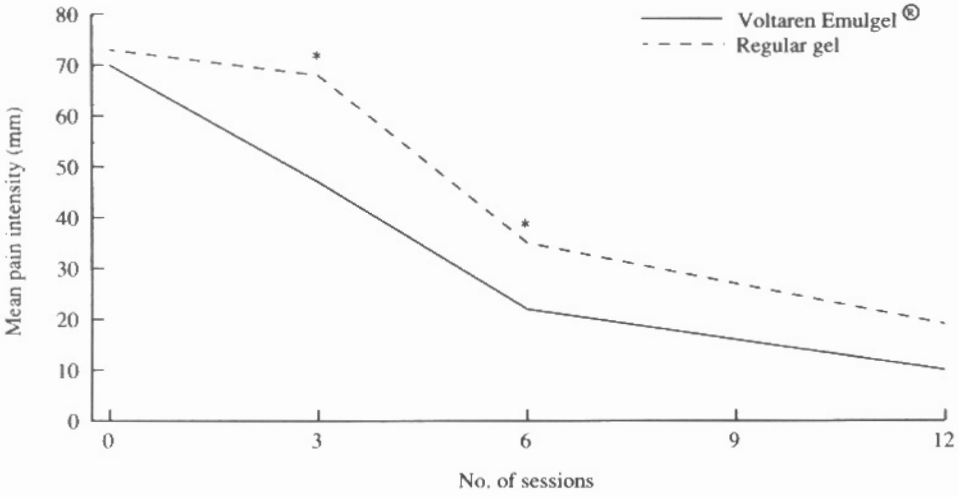

Fig. 4. Mean pain intensity measured on a visual analogue scale (mm) following ultrasonic sessions using Voltaren Emulgel® or regular gel as the coupling medium for the treatment of localized traumatic or rheumatic painful conditions; $P < 0.05$ vs regular gel.

Adverse events

Local signs of irritation were the only adverse events reported in the study; two patients in the Voltaren Emulgel® treatment group and one patient in the regular gel treatment group demonstrated unwanted local reactions, and one of the patients receiving Voltaren Emulgel® had to discontinue therapy as a result of local irritation.

Table 3

Causes of premature discontinuation of therapy with Voltaren Emulgel® or regular gel as the coupling medium in patients undergoing ultrasonic sessions for the treatment of localized traumatic or rheumatic painful conditions

Causes	Voltaren Emulgel®	Regular gel
Complete cure	36 (60.0%)	9 (15.0%)
Insufficient effect of therapy	1 (1.67%)	0 (0.00%)
Poor tolerability	1 (1.67%)	0 (0.00%)
Refusal of therapy	1 (1.67%)	2 (3.33%)
Other reasons	0 (0.00%)	1 (1.67%)
Total	39 (65.0%)[a]	12 (20.0%)

[a] $P < 0.01$ vs regular gel.

Overall evaluation

According to the physician's overall assessment of therapeutic effect, disappearance of symptoms or marked improvement occurred in 86% of the Voltaren Emulgel® treatment group and in 76% of the comparison treatment group ($P < 0.05$). The physician reported therapeutic failures in the two treatment groups of 3% and 10%, respectively.

An assessment of the percentage of patients willing to use the same therapy for similar conditions was 83% in the Voltaren Emulgel® treatment group and 78% in the regular gel treatment group. This supports the finding that tolerability of both formulations was reported as good or excellent (with one exception in the Voltaren Emulgel® treatment group) and was reflected in the physician's overall assessment, which was considered to have been good or excellent in over 95% of patients in both treatment groups.

DISCUSSION

The results of the present study show a statistically significant improvement over baseline ratings for most efficacy criteria in patients receiving either regular gel or Voltaren Emulgel® as a coupling medium for ultrasonic therapy. The improvement in tenderness on pressure, however, was significantly superior after sessions 3, 6 and 9 (weeks 1 – 3) in patients receiving Voltaren Emulgel®; and the improvement in pain on movement was significantly better after sessions 3 and 6 (weeks 1 and 2). In addition, complete pain relief showed a highly significant difference in favour of Voltaren Emulgel® throughout the trial.

The differences between the two treatments were more pronounced earlier in the course of therapy, i.e. after session 3 (week 1); however, as the study proceeded these differences became insignificant. This could be explained by the fact that both acute rheumatic and traumatic conditions are spontaneously self-limiting. The observed superiority of Voltaren Emulgel® may be attributed to the acceleration of diclofenac diffusion across biological membranes by ultrasound energy, leading to prompt anti-inflammatory and analgesic effects at the site of application.

Evaluation of premature discontinuation of therapy due to complete cure further confirmed that Voltaren Emulgel® was more effective than regular gel, with early cure being achieved in 60% of the Voltaren Emulgel® treatment group compared with only 15% of the regular gel treatment group. This is a valuable property as it enables a patient to resume normal activity after a shorter period of time and reduces the number of ultrasound sessions, hence allowing a higher turnover of patients and increased efficiency of the ultrasonic equipment.

It can be concluded that under the conditions of the trial the use of Voltaren Emulgel® during ultrasonic sessions provided a more effective and well-tolerated alternative to the currently employed gel. It can reduce the number of sessions of ultrasound therapy per patient, resulting in a shortening of the treatment period and, hence, earlier return to normal activity.

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