ORIGINAL ARTICLE

Effects of Topical Diclofenac Plus Heparin (Dhep+H Plaster) on Somatic Pain Sensitivity in Healthy Subjects With a Latent Algogenic Condition of the Lower Limb

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■ **Abstract**

Objective: To evaluate whether a diclofenac epolamine + heparin topical (plaster) is more effective than diclofenac plaster alone in reducing deep somatic hyperalgesia in subjects without spontaneous pain and whether the effect is linked to or independent of the anti-edematous action of heparin.

Design: Prospective, double-blind, randomized and controlled, four-arm parallel design trial.

Subjects: One hundred and four patients (84 women, 20 men, mean age 42.2 ± 13.3 years), with deep somatic hyperalgesia in one thigh, randomly assigned to one of 4 groups of 26 each.

Intervention: Each group underwent one of the following plaster treatments on one thigh: diclofenac+heparin; diclofenac; heparin; placebo, for 7 days, renewing the plaster every 24 hours.

Outcome Measures: Before treatment (day 1), at day 4 and day 8, assessment of (a) pressure and electrical pain thresholds of vastus lateralis and overlying subcutis and skin; and (b) structure/thickness of subcutis and muscle with ultrasounds at the same level.

Results: During treatment, in placebo and heparin, no significant threshold changes, except subcutis thresholds which increased slightly ($P < 0.02$); in diclofenac and diclofenac+heparin, significant increase in all thresholds ($0.0001 < P < 0.04$). Electrical muscle pain thresholds increased significantly more in diclofenac+heparin than in diclofenac, heparin, and placebo ($0.0001 < P < 0.04$). In all groups: no edema and thickness changes at ultrasounds in muscle and subcutis.

Conclusions: Topical diclofenac+heparin is significantly more effective than diclofenac alone in reducing muscle hyperalgesia in subjects without spontaneous pain, independently of the anti-edematous action of heparin. The results provide a rationale for the use of diclofenac+heparin also in

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algogenic conditions without evident signs of injury/edema/hematoma. ■

Key Words: plaster, diclofenac plus heparin, deep somatic hyperalgesia, pain thresholds, ultrasound, topical, RCT

INTRODUCTION

Topical formulations of analgesics/anti-inflammatory agents are being increasingly used clinically for the treatment of localized pain conditions of soft tissues, as they bear a number of positive aspects with respect to systemic drug administration.[1–5] Firstly, thanks to the minimal systemic absorption of the compounds, the incidence of side effects is greatly reduced, and this is particularly important in the case of nonsteroidal anti-inflammatory drugs (NSAIDs) which can cause serious gastrointestinal bleeding or impairment of renal function.[3,6–9] Secondly, patients' compliance to treatment is enhanced, due to both the absence of any trauma on application— differently from what happens with intramuscular or intravenous therapy—and the possibility of self-administration.[10–12] Topical application of diclofenac hydroxyethylpyrrolidine (diclofenac epolamine/DHEP plaster) has proven successful in the treatment of a number of somatic pain conditions of mild-to-moderate intensity, both acute—such as sprains or tears—and chronic, such as painful osteoarthritis, providing significant relief with minimal side effects.[2,4,6,13–18] Furthermore, DHEP plaster has been shown to produce local antinociceptive effects also in subjects without spontaneous pain: its application for 24 hours, in fact, significantly reduced pain sensitivity, selectively in deep somatic tissues, as testified by increased pain thresholds to electrical stimulation, and this effect was more pronounced in the case of tissue hyperalgesia.[19]

The combination of diclofenac epolamine and heparin in the same patch formulation (DHEP+H), applied for several days ($n = 7$) to patients with an acute ankle sprain, has proven more effective than DHEP alone in reducing pain symptoms, an effect attributed mainly to the reduction in the local edema due to heparin.[20] Based on these data, the aim of this study was to verify whether the DHEP+H combination, applied for 7 days is more effective than DHEP alone in desensitizing deep somatic tissues in subjects who present hyperalgesia at this level (subcutis and muscle) but who do not complain of spontaneous pain, and in the case of a positive response, whether this effect is linked to or independent of an action onto the thickness/consistency of the examined tissues. To this aim, we assessed the possible changes, due to therapy, in pain thresholds to electrical and pressure stimulation of the somatic tissues in a body area presenting deep hyperalgesia in basal conditions and in tissue structure/thickness at ultrasounds. As a comparison, we also included 2 other group treatments, respectively, with placebo plaster and heparin plaster.

METHODS

Subjects

Healthy subjects with a latent algogenic condition (hyperalgesia without spontaneous pain) of the deep tissues (subcutis and muscle) of the lower limbs were selected on the basis of the inclusion criteria defined below. All of them were recruited from students attending the Medical Faculty and from the Health care and Nurse personnel of the Department of Medicine and Science of Aging at the "G. D'Annunzio" University of Chieti, Italy. The time frame of subjects' recruitment was 12 months. The study adhered to the guidelines established by the Helsinki declaration and was approved by the Ethic Committee of the "G. D'Annunzio" University of Chieti (no. 1474/07). The trial was registered with the EU Clinical Trials Register, EudraCT no. 2007-003848-30.

Inclusion criteria were:

- Age between 18 and 65 years.
- Men and nonpregnant, nonlactating women. Sexually active women had to be postmenopausal, surgically sterile, or practicing an effective method of birth control according to the definition of Note 3 of ICH M3(R2) Guideline [Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; June 2009] (eg, prescription of oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization, abstinence) before entry and throughout the trial. Female subjects had to present a negative pregnancy test at screening.
- No spontaneous somatic pain since at least 1 month before enrollment.

- Hyperalgesia in deep somatic structures of at least one thigh (latent algogenic condition, eg, from previous knee microtraumatic events, latent myofascial trigger points [TrPs]) with (1) abnormally low pain threshold of vastus lateralis muscle to electrical stimulation (< 4 mA); (2) abnormally low pain threshold of vastus lateralis muscle to local pressure (< 4 kg-f); and (3) abnormally low pain threshold to electrical stimulation of subcutis (< 2 mA).
- Absence of any organic lesion in subcutis and muscle, evaluated by ultrasound examination, at the site of hyperalgesia.
- A 15-day washout from any treatment with drugs potentially interacting with the tested drugs (lithium, digoxin, oral anticoagulants, parenteral heparin or low molecular weight heparins, antidiabetic agents, cyclosporine, methotrexate, quinolone antimicrobials, and diuretics) and potentially interfering with the evaluation of the study parameters (eg, NSAIDs, central analgesics, corticosteroids).
- Subjects cooperative and able to respect the scheduled procedures.
- A negative history of alcohol and/or drug abuse in the last 2 years.
- A negative history of any clinically significant disease that in the investigator's opinion could affect the efficacy or safety assessments (eg, neurological or cerebrovascular disease, as well as pulmonary, infectious, GI, endocrine, psychiatric diseases, or metabolic disturbances, disorders of coagulation and hemostasis, etc.).
- A negative history of hypersensitivity, allergy, or contraindications to the experimental drugs or any excipient of the test plasters, or to any other NSAID drug (including aspirin or paracetamol).
- A negative history of GI disturbances or disease that in the opinion of the investigator could be worsened by the administration of a NSAID.
- A negative history of diseases known to interfere with the evaluation of the pain thresholds (eg, hypertension, diabetes).
- Absence of any medical or surgical condition that might interfere with absorption, metabolism, or excretion of the tested compounds (diclofenac and heparin), for example skin lesions or dermatological diseases at the plaster application site.
- Informed, written consent to participate in the study.

Treatments

Four topical preparations with identical formulation and list of excipients were used:

- DHEP heparin plaster containing diclofenac epolamine 180 mg and heparin sodium 5.600 IU [DHEP+H].
- DHEP plaster containing diclofenac epolamine 180 mg (corresponding to 140 mg of diclofenac sodium) [DHEP].
- Heparin plaster containing heparin sodium 5.600 IU [H].
- Placebo plaster deprived of both diclofenac epolamine and heparin sodium.

Each plaster was a rectangle of 10 × 14 cm of nonwoven polyester equipped with a gel pad.

Study Design

The study was a prospective, double-blind, randomized, and controlled, four-arm parallel design trial.

A total of 104 subjects meeting the inclusion criteria (84 women and 20 men) were selected out of 150 examined. They were randomly assigned and equally distributed to one of the 4 treatments specified above. Twenty-six subjects (25% of total population) therefore constituted each of the following groups: (1) DHEP+H group; (2) DHEP group; (3) H group; and (4) P group (see Table 1 for demographic characteristics).

The primary objective of the study was to evaluate the effect of the addition of heparin to DHEP in the medicated plaster on raising the pain threshold to electrical stimulation (skin, subcutis, and muscle) at the level of the vastus lateralis muscle. Secondary objectives were as follows:

- To evaluate whether DHEP+H is more effective than DHEP alone in raising the pain threshold to mechanical stimulation at the level of the vastus lateralis muscle.
- To evaluate whether DHEP+H has more effect on trophic changes of subcutis and muscle than DHEP alone.
- To compare the effects of the DHEP+H, DHEP, and H plasters with those of placebo.
- To evaluate the safety of the tested plasters in terms of local and general tolerability.

The global period of treatment for each group of patients was 7 days, renewing the plaster every

Table 1. Baseline Demographics of the Experimental Groups

Treatment	DHEP + Heparin (n = 26)	DHEP (n = 26)	Heparin (n = 26)	Placebo (n = 26)
Age (years), mean (SD)	42.2 (13.3)	40.4 (11.3)	38.4 (11.0)	43.6 (10.4)
Gender, *n* (%)				
Male	8 (30.8)	8 (30.8)	3 (11.5)	1 (3.8)
Female	18 (69.2)	18 (69.2)	23 (88.5)	25 (96.2)
Height (cm), mean (SD)	167.9 (8.6)	168.1 (8.3)	164.5 (8.7)	165.0 (7.9)
Weight (kg), mean (SD)	71.9 (14.6)	70.6 (13.9)	65.42 (14.51)	66.8 (13.3)
BMI (kg/m^2), mean (SD)	25.5 (4.9)	24.8 (3.1)	24.08 (4.27)	24.5 (3.9)

BMI, body mass index; DHEP, diclofenac epolamine; SD, standard deviation.

24 hours. The study plan included 3 visits at the clinics, which took place at screening/randomization (Visit T1, day 1), after 3 days (Visit T4, day 4) and 7 days of plaster application (Visit T8, day 8, final visit).

Scheduled Visits

Baseline (T1). All subjects underwent clinical and instrumental examination to verify the inclusion criteria. Pain thresholds to pressure and electrical stimulation of somatic tissues at thigh level (vastus lateralis muscle and overlying subcutis and skin) were measured to identify the presence of deep hyperalgesia.[21,22] At the same level, ultrasound examination was carried out to exclude the presence of any organic lesion, and to measure subcutis and muscle thickness.[23] Subjects were then randomly allocated to 1 of 4 treatment groups, according to a double-blind design.

In each enrolled subject, the operator applied the selected plaster at the level of the lowest third of the vastus lateralis muscle of one side (the one showing the higher degree of hyperalgesia—lower values of thresholds to electrical stimulation). The longer side of the plaster was placed parallel to the direction of the muscle fibers. All subjects were then instructed to replace the plaster every 24 hours for 7 days (with only a daily short interval for personal hygiene [15 to 20 min]), with the exception of the day of the first control visit (T4) when they were asked to come to the clinic without replacing the plaster, to undergo ultrasound evaluation and threshold measurement. On this occasion, a new plaster was applied by the operator soon after completion of the instrumental evaluation.

First Control Visit (T4). After 3 days of treatment (on day 4) all subjects underwent the first control visit, during which the experimenter physician reassessed the presence of the inclusion criteria and evaluated any general or local side effects. Furthermore, the used plasters were counted. The thickness of muscle and subcutaneous tissue was then evaluated via ultrasound to verify the possible influence of treatment on the somatic structures. Pain thresholds to electrical and pressure stimulation were subsequently measured at the level of the treated vastus lateralis muscle and overlying skin and subcutis. At the end of the visit, the physician applied a new plaster.

Second Control Visit (T8). At the end of 7 days of treatment (on day 8), all subjects underwent the last control visit, during which the experimenter physician reassessed the presence of the inclusion criteria and occurrence of any general or local side effects. The used plasters were again counted. Muscle and subcutaneous tissue thicknesses, as well as pain threshold to electrical and pressure stimulation at the treated site, were remeasured.

Experimental Procedure

During the instrumental evaluation, the subject was lying comfortably on an examination bed in a quiet room. Ultrasound evaluation was carried out first, followed by the sensory testing. The evaluations were always performed in the morning (09:00 to 10:00 am); in women of reproductive age, the first evaluation was performed in the same relative phase of the menstrual cycle (follicular phase).

Ultrasound Evaluation of Tissue Thickness

The thickness of the whole muscle wall and of the overlying subcutaneous tissue was measured (in millimeters) at the level of the lowest third of the thigh, by means of ultrasounds. An Esaote MyLab70 Xvision (Esaote, Florence, Italy) echograph was employed with an LA435 linear probe (18 to 16 MHz).[23]

Evaluation of Somatic Pain Sensitivity

Pressure pain thresholds and electrical pain thresholds were measured at the level of the vastus lateralis muscle and overlying skin and subcutis. Pressure thresholds were measured first; electrical thresholds were subsequently measured first in the skin and then in the subcutis and muscle.

Measurement of Pressure Pain Thresholds

Pressure pain thresholds were measured with a Fischer's algometer (a pressure dynamometer with a rounded probe 1 cm in diameter; Pain Diagnostics & Treatment Inc., Great Neck, New York, U.S.A.). The algometer was placed perpendicularly on the evaluation site, and the pressure was increased gradually (0.1 kgf/second) until the patient reported discomfort. The corresponding value was recorded as the threshold for the tested point. For each subject, the measurement was performed in 1 site in the middle of the area selected for plaster application.[19,21,22]

Measurement of Electrical Pain Thresholds

A computerized, constant-current, electrical stimulator (R.S.D. Stimulator, prototype, Florence, Italy) was used to deliver 18-ms trains of 0.5-ms monophasic, square-wave pulses (frequency, 310 Hz), which were repeated automatically every 2 seconds. To stimulate the skin, the current was passed through surface electrodes, with the interposition of conductor paste, consisting of 2 circular plates in Ag/AgCl, 10 mm in diameter, placed 1 cm apart (one reference electrode, one stimulating electrode). Two monopolar needle electrodes were used to stimulate the subcutis and muscle. The electrodes were 0.3 mm in diameter, 25 mm in length, and isolated with polytetrafluoroethylene except for 2 mm at the tip. Insertion of these thin needles does not normally provoke any painful reaction in the tested subjects. However, after insertion, the subjects were systematically asked by the investigator whether the procedure had provoked any particular discomfort: none of them reported any pain. To measure the subcutis, the 2 needles were inserted vertically below the skin surface, 1.5 cm apart. These same needle electrodes were used to measure muscle; the tips of the needles were placed deep under the fascia (the intramuscular position was verified by observation of the movement of the electrodes under voluntary contraction and/or low-intensity electrical stimulation of the muscle).

Stimulation was started at a very low current (0.1 mA), and the device automatically increased the intensity of the current in increments of 0.1 mA until the subjects reported a clearly painful sensation. With the stimulation parameters and electrodes that were used in this study, the sensation had distinct characteristics in the 3 tissues: pricking pain in the skin; linearly radiating prickling pain in the subcutis; and cramp-like pain in muscle. Pain thresholds were always measured using the method of the limits. The value when pain was first perceived was stored in the computer. The stimulus was then decreased, always at the same rate (0.1 mA), until the pain disappeared and that value was stored in the computer. The stimulus was increased again until pain reappeared, and the corresponding value was stored. The mean of the 3 readings was calculated automatically by the stimulator's computer and displayed as the final pain threshold for each tissue. The subjects were instructed to signal the appearance and disappearance of the sensation by pressing a button connected to the stimulator's computer. They were informed that the assessments were not tests of pain endurance, that no suprathreshold stimuli were supposed to be given, and that they should not try to bear any pain before reporting it.[19,21,22]

Statistical Analysis

Statistical analysis of the data was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

Sample Size. The sample size was based on an *a priori* calculation, using the nQuery Advisor 6.0 (Statistical Solutions Ltd., Cork, Ireland) software on assumptions derived from the results observed in previous clinical investigations for the primary efficacy variable "pain threshold measured following electrical stimulation".

Assuming a difference between the DHEP heparin group and the DHEP group of 20% at day 4 on pain threshold improvement from baseline with a standard deviation of 25% for each group, a minimum of 25 subjects per group had to be analyzed using the two-tailed Student's *t*-test for independent data, with $a = 0.05$ and $b = 0.20$ (ie, a power of 80%).

Analysis of the Study Results

Mean ± SD values were calculated for each parameter (pressure and electrical pain thresholds in skin, subcutis

and muscle, thickness of muscle and subcutaneous tissue) for each group of subjects at every evaluation time.

The baseline values of the experimental parameters for the 4 groups of subjects were compared using one-way analysis of variance (ANOVA) followed by the Tukey's test for internal comparisons. For each group, repeated-measures ANOVA was used to assess the effect of treatment on each of the evaluated parameters, with *post hoc* tests for internal comparisons when appropriate. The change (increase or decrease) in every parameter was calculated at days 4 and 8 relative to baseline. The comparison between groups on mean changes from baseline after 3 and 7 days of treatment for all parameters was performed by means of an ANOVA model with baseline values as a covariate. The level of significance was established at $P < 0.05$.

RESULTS

Patient Disposition

At baseline (T1), the 4 groups of subjects did not show significant differences in age and other demographic characteristics, except for gender ($P < 0.03$) (Table 1). A total of 104 patients were randomized into the 4 groups (26 in each group). The disposition and flow of subjects through the study is summarized in Figure 1. All patients received at least one dose of the study drugs and therefore were included in the intention-to-treat (ITT) and safety populations. There were 3 major protocol violations, in 2 patients in the heparin group and one patient in the placebo group, all consisting of withdrawal of the study due to adverse reactions. These patients were excluded from the per-protocol population. Three minor protocol violations relating to assignment of random numbers in the wrong sequence did not impose any consequences on the integrity of randomization blocks or cause imbalance in the treatment arms, and these patients were included in the ITT and safety populations.

The 4 groups did not differ significantly regarding all thresholds and muscle tissue thickness. Subcutis thickness showed a significant trend for variation among groups ($P < 0.05$), reflecting the large variability, in the normal population, of adipose distribution at this level. Qualitative ultrasound examination, however, excluded any evidence of lesion/edema/hematoma at subcutis level, as well as at muscle level in all groups.

Effects of Treatment in Each Group

Placebo group – No significant changes were found in all the experimental parameters at all evaluation times, except for subcutis pain threshold, which showed a significant trend for increase (ANOVA: $P < 0.02$) (Figure 2).

DHEP group – There was a significant trend for increase in both pressure and electrical pain thresholds (ANOVA: $0.002 < P < 0.04$); no differences were found in thickness of muscle and subcutis (Figure 3).

H group – The experimental parameters measured did not change significantly, with the exception of the electrical pain threshold of subcutis, which showed a significant trend for increase (ANOVA $P < 0.02$); no differences were seen in muscle and subcutis thickness (Figure 4).

DHEP+H group – All pain thresholds showed a significant trend for increase (ANOVA: $0.0001 < P < 0.007$), particularly thresholds in deep tissues (electrical subcutis threshold, pressure and electrical muscle thresholds); no differences were found in thickness of muscle and subcutis (Figure 5).

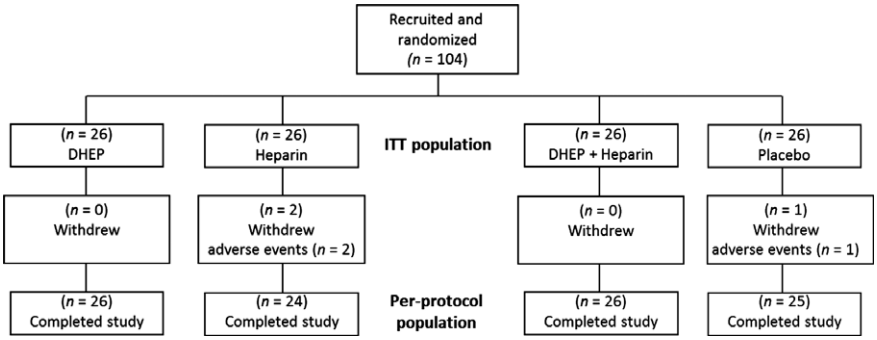

Figure 1. Summary of subject disposition and flow through the study.

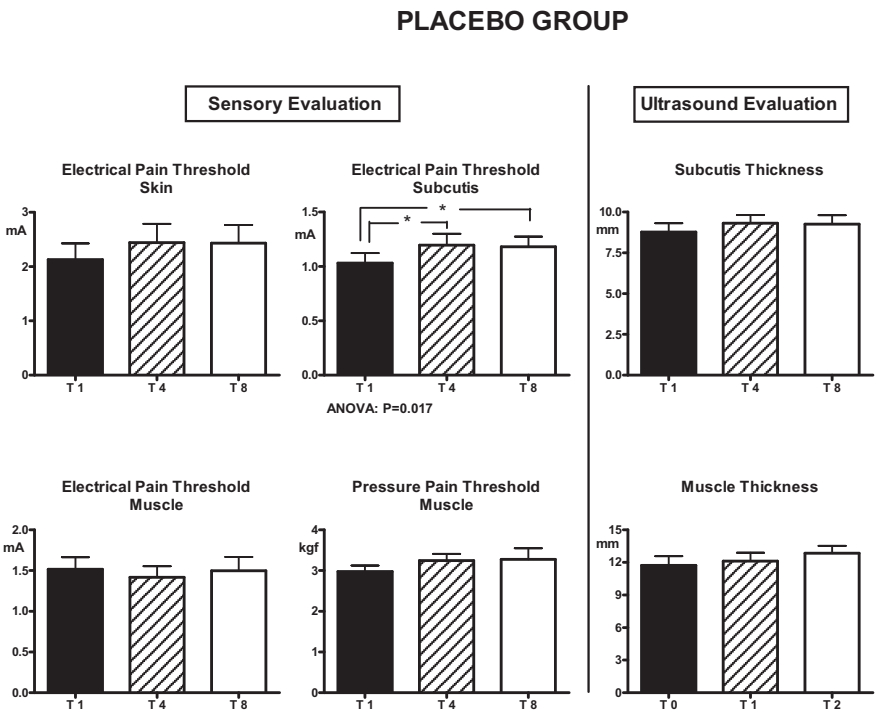

Figure 2. Pain thresholds to electrical and pressure stimulation (sensory evaluation) and tissue thickness (ultrasound evaluation) in somatic tissues at the level of the lowest third of one thigh in subjects treated with placebo plaster for 7 days (n. 25, Mean ± SEM). T1, basal visit at day 0; T4, visit at day 4; T8, visit at day 8. *$P < 0.05$.

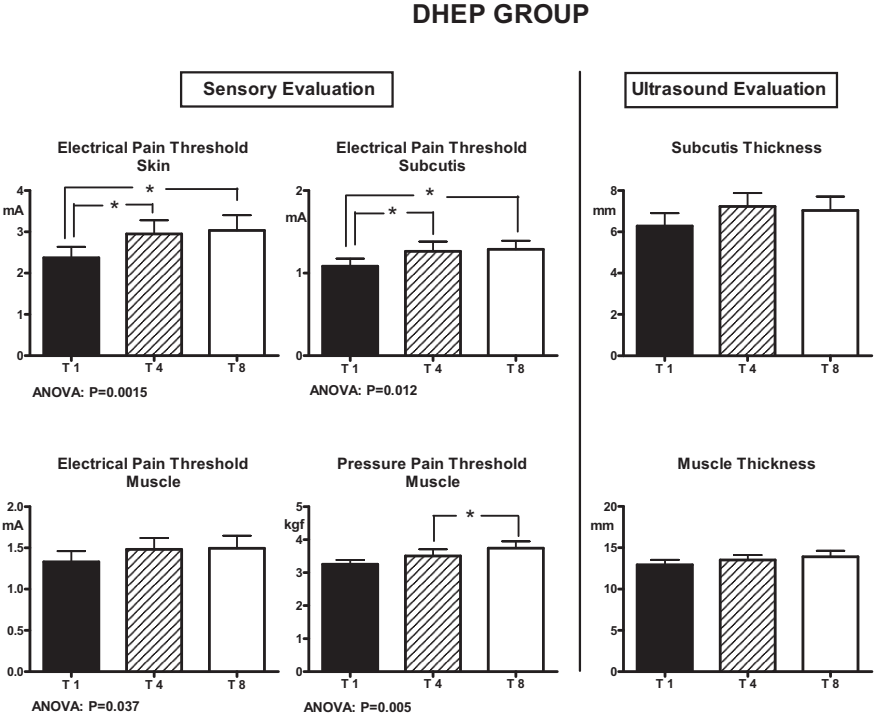

Figure 3. Pain thresholds to electrical and pressure stimulation (sensory evaluation) and tissue thickness (ultrasound evaluation) in somatic tissues at the level of the lowest third of one thigh in subjects treated with DHEP plaster for 7 days (n. 25, Mean ± SEM). T1, basal visit at day 0; T4, visit at day 4; T8, visit at day 8. *$P < 0.05$.

Comparison of Group Treatments

The increase in electrical muscle pain threshold was significantly higher in the DHEP+H group than in the other active groups ($P < 0.04$ vs. DHEP; $P < 0.003$ vs. H) and placebo group ($P < 0.0001$). The increase in pressure muscle pain threshold and skin and subcutis electrical pain thresholds did not differ between groups.

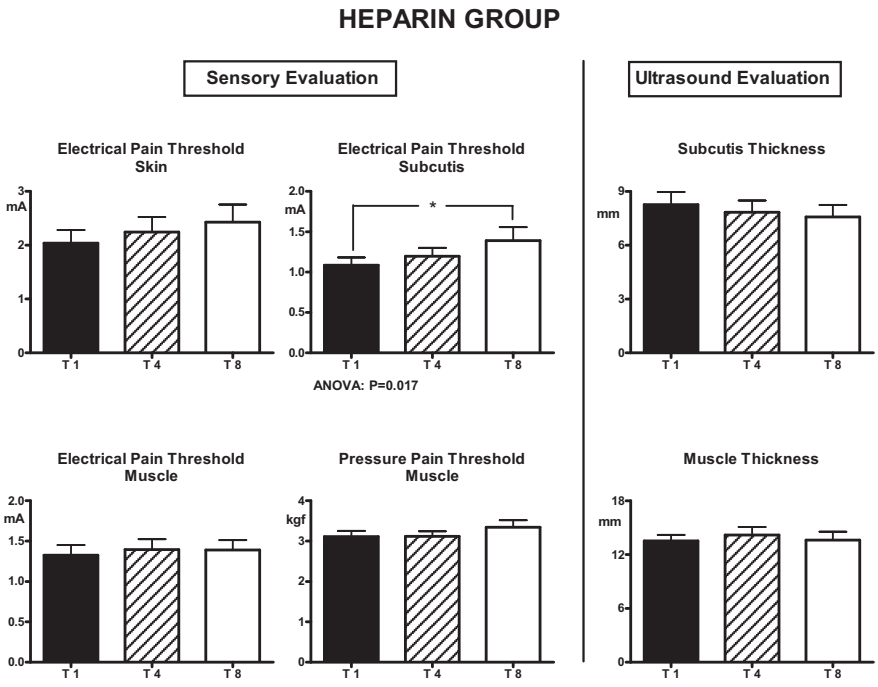

Figure 4. Pain thresholds to electrical and pressure stimulation (sensory evaluation) and tissue thickness (ultrasound evaluation) in somatic tissues at the level of the lowest third of one thigh in subjects treated with heparin plaster for 7 days (n. 25, Mean ± SEM). T1, basal visit at day 0; T4, visit at day 4; T8, visit at day 8. *$P < 0.05$.

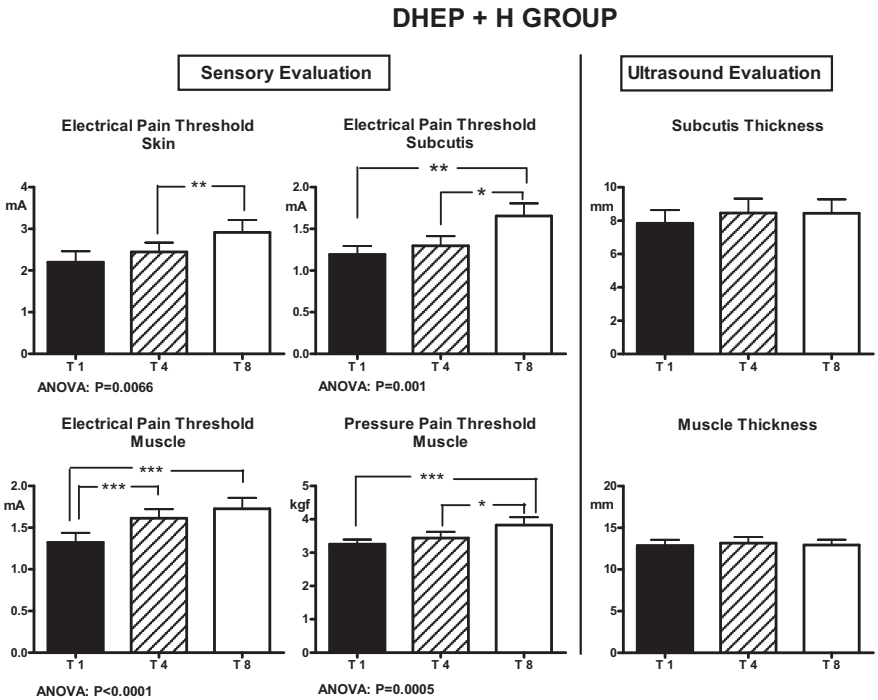

Figure 5. Pain thresholds to electrical and pressure stimulation (sensory evaluation) and tissue thickness (ultrasound evaluation) in somatic tissues at the level of the lowest third of one thigh in subjects treated with DHEP+H plaster for 7 days (n. 25, Mean ± SEM). T1, basal visit at day 0; T4, visit at day 4; T8, visit at day 8. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Side Effects. Three subjects (1 in P group and 2 in H group) experienced mild/moderate adverse events at the site of application of the plaster. These consisted of erythema alone (1 in H group), erythema with pruritus (1 in H group), and erythema combined with a burning sensation (P group). All events spontaneously resolved after removal of the plaster. No systemic or serious adverse events were observed in any group. There was no significant difference in the incidence of adverse events between groups ($P = 0.2867$).

DISCUSSION

Diclofenac epolamine plaster and diclofenac epolamine+heparin plaster, administered continuously for 7 days to subjects with no spontaneous pain, were both significantly more effective than placebo plaster and heparin plaster in reducing deep tissue hyperalgesia (subcutis/muscle), as shown by the increase in pain thresholds to more than one stimulus modality (pressure, electrical tests). The effect of the DHEP+H combination plaster, however, was significantly higher than that of DHEP alone at muscle level.

This effect was not paralleled by any tissue change at ultrasound evaluation of the treated area, as revealed by a lack of any significant variation in the subcutis and muscle thickness after treatment with respect to basal conditions. Given also the absence of any ultrasound sign of tissue lesion/edema/hemorrhage neither in basal conditions nor at the subsequent evaluations, the superiority of the DHEP+H formulation with respect to the DHEP formulation only is therefore to be explained by a mechanism different from that of an anti-edematous action due to heparin.[24–27] On the other hand, the heparin plaster had only limited effects, not significantly different from those of the placebo plaster, on pain thresholds in the evaluated subjects (mild increase in subcutis electrical thresholds only): this would thus exclude a major direct action of this ingredient on pain sensitivity. Therefore, the superior effect of the combination DHEP+H plaster has, with a high probability, to be attributed to a facilitating action of heparin toward the effects of diclofenac. The presence of heparin could promote either a greater release of diclofenac from the plaster or its better diffusion in the affected tissues and finally enhance the action of this NSAID onto pain receptors locally, promoting their desensitization.[24–27]

The positive action of DHEP+H was furthermore achieved without systemic or local side effects.

CONCLUSION

The results of this study provide a rationale for the use of the combination plaster diclofenac-heparin not only in pain conditions with evident injury/edema/hematoma, but also in algogenic conditions (even latent) deprived of these objective signs, which are in percentage much more numerous than those related to a frank injury, such as sprains or tears. A paradigmatic example is represented by myofascial pain syndromes (MPS) from TrPs, which affect over 80% of the individuals at some time during their life, where the spontaneous muscle pain, or the local deep tissue hyperalgesia in the case of latent TrPs—is not accompanied by any evidence of local edema/hematoma.[21,22,28,29] Future studies will be needed in patients with somatic pain conditions not accompanied by local injury, such as MPS, to confirm the antalgic superiority of DHEP+H vs. DHEP.

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