A randomised controlled trial on the efficacy of hydroelectrophoresis in acute recurrences in chronic low back pain patients

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Aim. **Physical therapy efficacy in the treatment of low back pain (LBP) has been widely debated and is far from achieving high levels of evidence. Hydroelectrophoresis (Hydrofor) is a novel method of driving drugs through the dermal tissue, which has been proposed for muscle pain treatment. Aim of this randomised placebo-controlled study was to ascertain the efficacy of Hydrofor treatment on acute relapsing episodes of pain in chronic LBP subjects.**

Methods. **Eighteen under-50 adults (M/F: 7/11; age 35±8 years) suffering from chronic LBP were enrolled within 3 to 4 days of back pain relapse. After a complete clinical and functional assessment patients were randomly divided into 2 equal groups. Group A received 3 Hydrofor applications of a mixture containing both NSAIDs and muscle relaxants, whereas Group B received 3 Hydrofor applications of a drug-free solution. Afterwards, both groups performed the same rehabilitation treatment consisting of 7 group sessions of standard physiotherapy, including stretching, range of motion and extension exercises. The Oswestry disability index (ODI), the Million instrument scale and a visual analogue scale (VAS) were chosen as outcome measures and applied at baseline, after Hydrofor/placebo applications, after completion of rehabilitation sessions and, at last, 2 months later. The two-way Friedman test was used to analyse within-group (time effect) and between-group (time x group effect) differences.**

Results. **All subjects declared a significant pain reduction since the first Hydrofor application. Pain evolution overlapped in the 2 groups until the 3rd session, after which Group A significantly diverged from Group B, as they affirmed a greater symptom reduction than controls (time x group effect: VAS: F = 7.4, p <0.01). Such difference disappeared after the physiotherapy sessions as well as 2 months later (time x group effect: VAS: F = 2.1, p =0.08). Pain-related disability showed a greater reduction in Group A than B immediately after Hydrofor application (time x group effect: ODI: F=3.9 p <0.05; Million: F=4.1 p<0.05), but the mean scores almost overlapped at the 2 month follow-up (time x group effect: ODI: F=2.3 p =0.08; Million: F=1.3 p=0.26).**

Conclusion. **Hydrofor treatment relieves relapsing LBP and could be recommended to active adults as a safe technique shortening the time needed to achieve functional restoration.**

Key words: **Low back pain, therapy - Hydroelectrophoresis - Recurrence.**

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Low back pain (LBP) is a very common condition. In developed countries acute episodes affect up to 75-80% subjects at least once in the lifetime, whereas chronic pain syndromes represent the most common cause of disability in people under 45 years.[1] Data on health care resources allowed to calculate that LBP costs 100 billion dollars per year in the USA. This amount of money is explained by both direct and indirect costs, these latter being related to absences from work that equal 25% of the total lost working days.[2]

In this view, LBP, affecting people in the period of their best social and individual fulfilment, deserves focused attention as well as an effective care.[3] Rehabilitation techniques aimed at reducing acute pain are not evidence-based, according to many reviews assessing the efficacy of bed rest,[4, 5] trunk orthoses,[6] massage,[7] manipulation,[8] transcutaneous electrical nerve stimulation (TENS) [9] or exercise.[10]

On these premises, international guidelines on LBP management do not recommend rehabilitation treatment for relieving acute pain episodes.[11] On the other hand, recent reviews on the efficacy of any rehabilitation approach in chronic pain syndromes deny indications to either massage,[7] manipulation [8] or lumbar supports [6] and suggest the possible superiority of exercise on placebo effect,[10] whereas others affirm, based on Level I studies, that strength exercises do not prevail on modalities in achieving clinical benefits.[12, 13]

Several researchers complain how the lack of standard therapy protocols, reduced follow-up length and the big influence of placebo effect prevented most clinical trials on acute and chronic pain treatment from succeeding in the demonstration of rehabilitation efficacy.[10]

In this scenario, there is still large request for randomised controlled trials attempting either to demonstrate or rule out the effectiveness of the current approaches to the management of LBP. Meanwhile, analgesic or anti-inflammatory drugs keep being the mainstay of pain treatment,[14-16] arising concerns about the cost/benefit of a long term assumption. Local application of drugs *via* ionophoresis has never been demonstrated effective,[17] although it is still widely applied to pain care in the current practice in Italy.

We designed a randomised placebo-controlled study aimed at ascertaining the possible role of locally applying anti-inflammatory and muscle relaxant drugs *via* a novel technique called hydroelectrophoresis, in a sample of chronic LBP subjects complaining of acute pain relapses.

Materials and methods

Study design

A randomised placebo-controlled trial of hydroelectrophoresis in chronic LBP outpatients complaining of pain relapse is presented.

Subjects

Patients referred to the local rehabilitation centre for the treatment of relapsing LBP were found eligible to the study if they met the following criteria:

a) symptom onset within the last 10 days;

b) history of chronic LBP, with recurrent pain relapses;

c) mild or none disability prior to symptom onset (as indicated by an Oswestry LBP disability score < 20%, and a Million instrument score < 30/150);

d) age range between 18 and 50 years;

e) informed consent to the investigation.

Exclusion criteria were:

a) signs or symptoms of either central or peripheral nervous system involvement;

b) secondary LBP (following cancer, bone fractures, infections);

c) coexistent morbidity eventually affecting patient functional abilities within the period of investigation;

d) previous exposition to hydroelectrophoresis;

e) contraindications to the technique (pregnancy, allergy to study drugs, epilepsy, metal prosthesis, pacemaker or other mechanical and/or electric devices).

The screening of 51 consecutive subjects over 9 months (June 1, 2003-February 28, 2004) led to the inclusion of 18 patients (7 male and 11 female, age: 35±8 years, range: 20-50 years) who presented with acute relapse of chronic back pain (time elapsed from onset: 4.0±1.2 days, range: 3-7 days). The remaining 33 were excluded because they failed either the time (pain onset earlier than 10 days before) or the age criteria.

After a complete clinical and functional assessment, subjects were randomised to receiving:

A (n=9): 3 local applications of anti-inflammatory and muscle relaxant drugs (Sodium Diclofenac 75 mg/3 ml, 2 ampoules + Mesilate Pridinole 1 ml, 2 ampoules) added with Prometazine (50 mg, 1 ampoule) *via* hydroelectrophoresis (Hydrofor device by Bioelectra), on alternate days, followed by 7 group physiotherapy sessions (3 times per week).

B (n=9): 3 local applications of a drug-free water solution *via* hydroelectrophoresis, followed by group physiotherapy sessions according to the same schedule as for Group A.

Randomisation was performed by coupling consecutively eligible subjects to a list of random numbers,

TABLE I.—*Study protocol.*

Time	Scheduled activities	Assessment	Measure
1st day	Eligibility screening Group allocation	T_0	VAS, ODI, Million
	1st Hydrofor/placebo application	T_{1post}	VAS
3rd day	2nd Hydrofor/placebo application	T_{2pre}	VAS
		T_{2post}	VAS
5th day	3rd (last) Hydrofor/placebo application	T_{3pre}	VAS
		T_{3post}	VAS
8th day	1st physiotherapy session	T_{prePT}	VAS, ODI, Million
22nd day	7th (last) physiotherapy session	T_{postPT}	VAS, ODI, Million
60th day	Follow-up	T_{2m}	VAS, ODI, Million

corresponding to numbered sealed envelopes concealing group allocation. The investigator who declared patients eligible (P.G.) was not involved in the envelope preparation, that was under the responsibility of the main investigator (M.G.C.). Furthermore, both the physiatrists (A.G. and P.G.) who examined all the subjects and the physiotherapist (S.S.) who treated them were blind to treatment allocation. The hydroelectrophoresis solution was prepared by A.B.

Treatment protocols

Hydroelectrophoresis sessions lasted 20 min during which the physiotherapist spread the drug/placebo solution over the painful lumbar region and applied pulse currents of intensities ranging from 10 mA to 30 mA in order to drive the drug molecules through the tissues.

Physiotherapy started 3 days after the last hydroelectrophoresis application and consisted of seven 45 min sessions, during which groups of 3-4 subjects performed flexibility and extension exercises, abdominal muscle strength and respiratory exercises, 3 times/week.

To complete this protocol, an educational booklet was given to the patients, advising them to practice correct postures and the exercise schedule at home.

Outcome measures

Given our interest into the efficacy of hydroelectrophoresis in relieving LBP and attending disability, we chose to measure outcome through a visual analogue scale (VAS) of pain intensity (score range from 0 = no pain to 10 = worst ever suffered pain) [18, 19] and 2 LBP-related disability scales: the Oswestry disability index (ODI) (rating disability from 0= no disability to 100 = pain interference with all meaningful activities) [20] and the Million instrument (rating disability from 0= no disability to 150 = pain interference with all meaningful activities).[21]

Patients were asked to rate pain severity at baseline (T_0), immediately before (T_{1pre}, T_{2pre}, T_{3pre}), and after each hydroelectrophoresis session (T_{1post}, T_{2post}, T_{3post}), before starting (T_{prePT}) and after completing (T_{postPT}) the physiotherapy cycle, and, lastly, 2 months later (T_{2m}).

Disability questionnaires were filled up by the patients at baseline (T_0), before (T_{prePT}) and after physiotherapy sessions (T_{postPT}) and at the follow-up visit (T_{2m}). In these phases they were requested to rate to what extent pain had hindered meaningful activities over the previous 3 days (Table I).

Finally, in order to achieve individual reference scores for the ODI and Million scales, patients were also asked to recall their overall state during the 3 months preceding symptom onset. The quoted search revealed that median ODI scores were 7 (range 0-20) in Group A and 5 (range 0-19) in Group B, whereas median Million scores were 18 (range 2-26) in Group A and 15 (range: 3-24) in Group B, before the acute relapse leading to patient enrolment.

Data analysis

All outcome measures were treated as non parametric continuous data and described in terms of median and range. Baseline between-group comparisons were approached through the U-Mann-Whitney test, whereas differences in the evolution of outcome measures in the 2 groups were sought by means of the two-way Friedman test. This test allows to analyse within- and between-group differences simultaneously, quantifying both the time and the time x group effects.

TABLE II.—*Evolution of pain intensity and pain-related disability scores (median, range) in the 2 groups. The main findings from comparative statistics are also presented.*

	T_0	T_{3postH}	$T_{pre\ PT}$	Two-way Friedman test	$T_{post\ PT}$	T_{2m}	Two-way Friedman test
VAS				Time effect			Time effect
Group A	6 (3-8)	0 (0-4)	1.5 (0-4)	F=31.	0 (0-3)	0.5 (0-3)	F=41.1
Group B	5 (3-7)	1 (3-7)	3 (0-8)	p<0.0001	2 (0-6)	2 (0-3)	p<0.0001
				Time x group effect			Time x group effect
				F=7.4. p<0.01			F=2.1 p=0.08
ODI				Time effect			Time effect
Group A	23 (8-78)	—	7.5 (2-58)	F=9.8	4 (0-66)	5 (0-32)	F=12.9
Group B	22 (4-34)	—	14 (2-26)	p<0.007	8 (0-22)	6 (0-18)	p<0.0001
				Time x group effect			Time x group effect
				F=3.9 p<0.05			F=2.3 p=0.08
Million Ins.				Time effect			Time effect
Group A	69 (41-110)	—	36 (20-98)	F=8.4	26 (11-125)	21 (1-52)	F=19.8
Group B	60 (20-83)	—	59 (16-77)	p<0.01	32 (10-56)	16 (5-42)	p<0.0001
				Time x group effect			Time x group effect
				F=4.1 p<0.05			F=1.3 p=0.26

Results

Groups did not differ with respect to the main personal and clinical factors. All subjects were satisfactorily employed and complained of mild LBP-related disability since variable time.

At baseline they were all on sick leave: pain intensity was moderate to severe in both groups, median VAS scores being 6 (range 3-8) in Group A and 5 (range 3-7) in Group B.

Pain-related disability was moderate, as described by median ODI scores of 23 (range 8-78) in Group A and 22 (range 4-34) in Group B, and median Million scores of 69 (range:41-110) in Group A and 60 (range 20-83) in Group B.

All patients completed the treatment and assessment protocols with a 100% compliance. They returned to work within 7.4±2.1 days, without group differences. Neither local nor systemic side effects from Hydrofor application were observed.

Table II describes the evolution of the outcome measures taken during the study.

Pain intensity

Both groups declared a significant pain reduction immediately after each Hydrofor/placebo application, but rated VAS intensity as high as at baseline before starting each new session, until the third application. In fact, median VAS scores decreased from 6 (range 3-8) (T_0) to 0 (range 0-4) (T_{3post}) in Group A and from 5 (range 3-7) (T_0) to 1 (range 0-3) (T_{3post}) in Group B, with a highly significant time effect (F=26.4 p <0.0001), without group differences. However, measures taken one week later, immediately before starting physiotherapy (T_{prePT}) described a significant divergence in VAS trends in the 2 groups, given a substantial stability of pain reduction in Group A (median VAS score: 1.5) against the symptom worsening in Group B (median VAS score: 3) (time effect: F=31.2 p<0.0001, time x group effect: F = 7.4, p<0.01). Further assessments performed after physiotherapy cycle confirmed the persistence of a lower (though not significantly) pain intensity in Group A (median VAS: 0) than B (median VAS: 2) whereas no differences could be appreciated at the 2 month follow-up (time x group effect: 2.1 p = 0.08) (Figure 1).

Pain-related disability

The analysis of the pain-related disability evolution by means of the ODI and Million instrument scales gave similar results. Group A showed a significantly higher disability reduction than Group B at

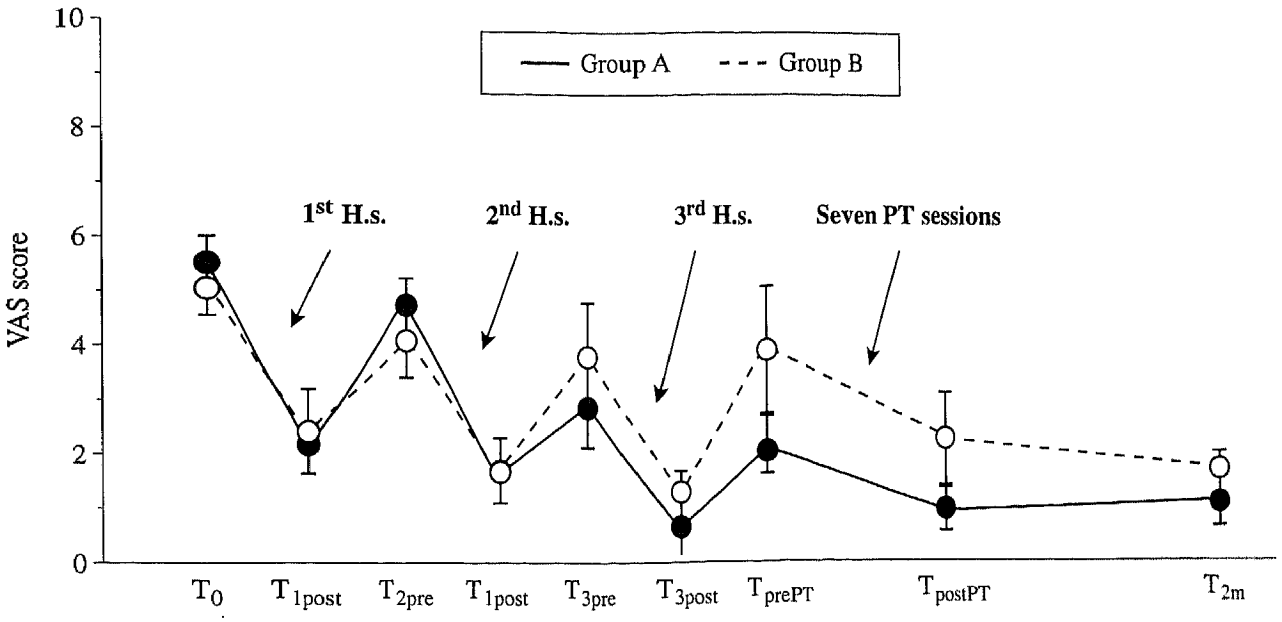

Figure 1.—Pain severity trends in the 2 groups. Assessments were performed before and after each Hydrofor/placebo application and PT cycle, as well as 2 months later. H.s.=Hydroelectrophoresis session; PT=physiotherapy.

the evaluation performed after completing hydroelectrophoresis applications. Median ODI scores decreased from 23 (range 8-78) (T_0) to 7.5 (range 2-58) (T_{prePT}) in Group A and from 22 (range 4-34) to 14 (range 2-26) in Group B (time x group effect: $F = 3.9$ $p < 0.05$), whereas median Million scores decreased from 69 (range 41-110) (T0) to 36 (range 20-98) (T_{prePT}) in Group A and from 60 (range 20-83) to 59 (range 16-77) in Group B (time x group effect: $F = 4.1$ $p < 0.05$).

After completing rehabilitation cycle, the 2 groups exhibited overlapping scores in both disability measures and did not show further differences at the 2 month follow-up (Table II).

Discussion and conclusions

Western countries are paying big attention to physical and mental health. Recent studies have shown that anxiety and depression are strictly linked to pain and consequent disability, underlining the variable cause-effect relationship between these 2 dimensions.[22-24]

Marks *et al.*[25] have clearly expressed the harmful consequences of the vicious circle inaugurated by muscle-skeletal pain pointing out the need for an early cure halting its progression towards refractory chronic pain syndromes.

A fast recovery from LBP would not only allow to shorten patient distress but also lower both direct and indirect costs. Analgesic medication and non steroidal anti-inflammatory drugs (NSAIDs) are the most common methods for reducing acute pain.[14-16] However their systemic use is loaded with concerns about side effects, especially in cases needing a long-term assumption.[11,12]

In the view of seeking a more cost-effective pain treatment, local drug application has been proposed *via* several techniques including trans dermal plaster, ionophoresis, criophoresis, always with scarce efficacy due to the low penetration of the medicament through the skin.[17]

Hydroelectrophoresis (i.e. electric transport – electrophoresis - of a water solution -hydro) is a novel method for drug transportation applying the principles of electrophoresis which permit to convey drugs through skin layers by applying pulse currents and get to the lesion site to the desired depth, by creating a directional flow of ionised molecules (instead of ions, as in ionophoresis). The wave shape together with the gel formulation allow medicaments to penetrate into

the tissues within a range going from 0.1 to roughly 10 cm thus reaching high concentrations in spite of a low starting quantity.[26,27]

In the present study on relapsing LBP, a treatment protocol based on 3 Hydrofor applications of a water solution containing Sodium Diclofenac + Mesilate Pridinole (added with Prometazine in order to enhance drug molecule transport) induced a significant higher benefit than placebo, as measured by persistent VAS and pain-disability score reductions.

The demonstration of efficacy of any pain treatment may be hindered by bias related to the subjective domain of the symptom, making VAS very soft and poor reliable outcome measures.[28,29] In our study, all subjects tended to judge pain intensity significantly lower at the end of Hydrofor/placebo application, since the first session. This finding may be regarded as the obvious consequence of a placebo effect, and outline the arguable appropriateness of VAS as efficacy index. The application of pain-related disability questionnaires allows to translate subjective distress feelings into objective lifestyle changes. In our study, both the ODI and the Million instrument scales showed the functional improvement occurring in the 2 groups at 1 week, after completing the Hydrofor/placebo sessions. The benefit was significantly greater in the group receiving active drugs, than in controls whose disability scores showed only a mild decrease. Such difference was not present any further in the subsequent assessments, when both groups showed overlapping disability scores, resembling those complained before pain relapse.

The favourable functional evolution observed after the physiotherapy approach could be viewed as a rehabilitation effect; however, the lack of a control group not undergoing any treatment should induce caution in drawing such conclusions.

In order to enhance the clinical and economical consequences of the study findings and reduce the number of independent variables we decided to investigate the potential benefits of the treatment in under-50 adults excluding subjects with a history of moderate to severe pain-related disability. These criteria depict a subgroup of chronic LBP subjects who are still able to fulfil most professional and social requirements but recurrently complain of pain relapses preventing them from realizing meaningful activities. These subjects are supposed to derive maximum advantage from a pharmacological approach that accelerates functional recovery.

In conclusion hydroelectrophoresis can be considered a useful, low-cost and easily available alternative to systemic drug assumption, whenever drugs should be driven to selected targets located at up to 10 cm depth. Hydrofor treatment relieves relapsing LBP and could be recommended to active adults as a safe cost-effective technique shortening the time needed to achieve functional restoration.

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