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Contents

4

Foreword

6

Treatment of proprioceptive balance disorders: comparison between kinesiotherapy and Hilterapia®.
Bodini G., Croce A.M.

10

Treatment of chronic low back pain: back school versus Hilterapia®.
Conte P.G., Santamato A., Fiore P., Lopresto A., Mazzaracchio M.

14

Effects of Hilterapia® vs. Viscosupplementation in knee osteoarthritis patients: a randomized controlled clinical trial.
Viliani T., Ricci E., Mangone G., Graziani C., Pasquetti P.

18

Hilterapia® efficiency in handling the post surgical pain after the release of the carpal tunnel.
Gleiser J.

22

Muscle lesions in athletes: case comparison between Hilterapia® and traditional therapy.
Valent A.

26

Effects of pulsed Nd:YAG laser at molecular and cellular level. A study on the basis of Hilterapia®.
Monici M., Cialdai F., Fusi F., Romano G., Pratesi R.

35

Abstract

36

Hilterapia® and chronic ankle pain syndromes.
Saggini R., Bellomo R.G., Cancelli F.

37

Clinical experience using Hilterapia® in “knee arthrosis”.
Sabbahi S.A.

38

Comparison of the clinical results of Hilterapia® and eswt in the lateral epicondylitis.
Kang H.J., Her M.S.

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Foreword

This special issue of Energy for Health is dedicated to the International Meeting on Hilterapia®, held in Venice, Italy, on November 29th, 2009.

The Meeting had a particular significance because it was the first time that a Meeting on Hilterapia had an international size. Moreover, it coincided with the 25th anniversary of ASA.

The city of Venice, with its incomparable beauty, and the “La Fenice” theatre, one of the most known temples of the music, were a wonderful frame for the event.

The scientific programme proposed very interesting communications and reports, presented by researchers with great expertise in physiatry, orthopaedics, sport medicine, biology, physics.

In this 3rd issue of Energy for Health there are papers related with the communications presented at the meeting. These describe the results of clinical studies on the application of Hilterapia in the treatment of muscle lesions in the athletes, knee osteoarthritis, back pain, post surgical pain after the release of the carpal

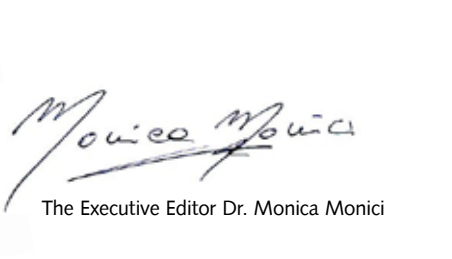
tunnel and also proprioceptive balance disorders. An overview on the findings of the research carried out in ASAcampus laboratories is reported. This research is aimed to highlight the molecular and cellular mechanisms of pulsed Nd:YAG laser effects. Finally, abstracts are reported on studies which will be completed in the next months and presented in the 4th issue of “Energy for health”.

We like to thank all the participants, who stimulated the meeting by presenting and discussing the results of their research and thereby contributing to the advancement of the knowledge in the field of laser application in medicine.

We hope you will enjoy the reading of this volume and you will find in it cues and inspiration for your future work.



The Editor in Chief Dr. Luigi Corti



The Executive Editor Dr. Monica Monici

FULL PAPER

Treatment of proprioceptive balance disorders: comparison between kinesitherapy and Hilterapia®.

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ABSTRACT

Proprioceptive vertigo disorders can be caused by several mechanisms, generally of muscle-tendon origin, able to induce an irritant stimulus on vestibular nuclei and on cervical sympathetic nervous system. Such disorders are often associated with pain and functional limitation of the cervical tract. Thirty subjects, subdivided in two groups, have been included in the study. One group was treated with kinesitherapy alone and the other group with kinesitherapy combined with Hilterapia®. Treatment has been administered on a daily basis for the first week and every other day for the following 2 weeks, for a total of 10 sessions. All subjects have undergone a clinical-anamnestic evaluation before treatment (T0), at the end of the first week (T1), at the end of the therapy (T2), and one month later (T3). A computerised stabilometric test, with elaboration of the cervical interference index has also been taken at T0, T2 and T3 time points. Data on semi quantitative scale have been analysed using the Mann-Whitney non parametric test. Data on cervical

interference have been analysed using the parametric Paired Samples T Test. With regards to the non parametric data, no significant variations between the two groups have emerged. However, both sets of data showed significant variations in the trend over time of the various parameters, within each group, with a more rapid improvement, in terms of pain and functional limitation, in those subjects undergoing a combined kinesitherapy and Hilterapia® treatment. With respect to the cervical interference index, a significant variation between T0 and T3 has been observed only in the combined treatment group. Hilterapia® has been found to be an effective help to produce faster subjective improvements with kinesitherapy and more importantly, it has been demonstrated to improve proprioceptive balance disorders.

INTRODUCTION

Some essential factors are required for a good balance control. Firstly, the knowledge of the environment static and dynamic conditions moment by moment;

secondly, the ability to rapidly and efficaciously adapt to every status change of the environment and one's body and finally, the ability to adjust biological functions to the different situations and the awareness of the situation itself. The balance control system is particularly complex and, to date, still partially unknown. A major role is played by the peripheral receptors sensitive to the environmental and somatic inputs (extero- and proprioceptive sensorial receptors), by the nerves designed to carry these afferences, by the central nervous system that is able to deal with peripheral inputs and to programme the right motor outputs, as well as muscles, tendons, and articulations designed to programmed motor adjustments. [1-2] Proprioceptive vertigo disorders have been linked for many years to the presence of hemodynamic regulation alterations in the vertebrobasilar district, secondary to regional perivascular sympathetic plexus stimulations by external irritating factors, predominantly of cervical tract arthrosic nature. Current knowledge tends to minimize the role of this pathology, mainly on the basis of the frequent presence of its symptomatology in young subjects without reduced cervical motility. The arthrosic factor is therefore no longer recognised as the only element able to induce an irritating stimulus, either intrinsic or extrinsic, on the cervical sympathetic and indirectly on the vestibular nuclei, although an association between arthrosis and balance disorders is often found. The latter can be linked to arthro-muscular alterations, to afferent fibres pathology, or to alterations of the central relays. It is currently believed that cervical pathologies can induce balance disorders by sending altered proprioceptive information to the central nervous system and/or not allowing a normal motor efferent program. Indeed,

proprioceptive efferent signals of muscle-tendon origin, via segmental reflexes or via their modulation at vestibular nuclei level of the cerebellum or of the vestibular cortical area, can affect the balance controlling system. [2] Balance impairment of such origin is rarely associated with the typical vertigo manifestation. They are more often subjective disorders characterised by unsteadiness and discomfort feeling, frequently associated with migraine, localised pain, stiffness, functional limitation, nausea and tinnitus. The rehabilitation therapy of vestibular balance disorders is aimed at the recovery of an altered function by reprogramming the function itself, promoting adaptive-compensatory activity and inducing the habit to disease. However, in the case of proprioceptive disorders the adjustment of arthromuscular dysfunction could lead to the elimination of the balance disorder cause itself. [2] The Nd:YAG high energy laser has an analgesic, antiedematous and bio-stimulating effect even on deep tissues, promoting healing processes and shortening recovery times. [3-4] Therefore, the aim of the present study was to evaluate if Hilterapia® treatment combined with kinesitherapy could be helpful in improving the symptoms of proprioceptive balance disorders.

MATERIALS AND METHODS

Patients. Thirty subjects suffering from proprioceptive balance disorders, 20 females and 10 males, aged between 25 and 65 (mean age 48.8 years) have been included in this study. Ten of the patients reported a previous cervical sprain trauma and 11 presented cervical spondiloarthrosis X-ray evidence. Nine patients had been reporting symptoms for less than 6 months; 14 between 6 and 12 months and 7 for more than 12 months.

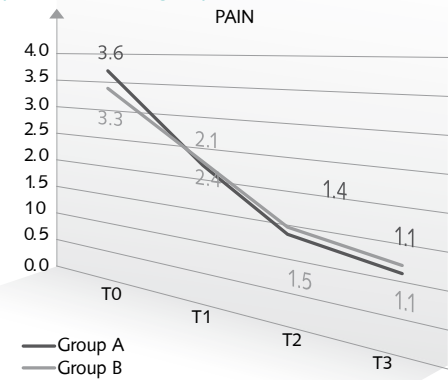
Patients have been randomly divided in two groups: group A was treated with kinesitherapy combined with Hilterapia® and group B with kinesitherapy alone. *Methodology.* Kinesitherapy protocol included active and passive mobilizing exercises of the cervical tract, stretching paravertebral exercises, postural rehabilitation and proprioceptive self-analysis. Hilterapia® treatment was carried out with a HIRO 3.0 (ASA S.r.l., Vicenza, Italy) pulsed Nd:YAG laser with peak power of 3 KW, pulse duration > 120 msec, mean power of 10 W, maximal fluence of 1780 mJ/cm², and standard handpiece with 5 mm spot. At each session, 3 manual scans on the cervical-scapular muscles have been performed bilaterally, using an increasing fluence (360 to 510 mJ/cm²) and a decreasing frequency (20 to 15 Hz), for a total of 1500 J. Whenever trigger points were present, an additional treatment with fixed handpiece was also performed on such points. Treatments were administered every day for the first week and every other day for the following 2 weeks, for a total of 10 sessions. All subjects have undergone a clinical-anamnestic evaluation before treatment (T0), at the end of the first week (T1), after therapy (T2) and a month later (T3). The following parameters were evaluated: pain by visual-analogical score (VAS 0-10), muscle contracture (0 absent, 1 mild, 2 severe), cervical tract global articular limitation with semi quantitative scale (1 < 25%, 2 between 25 and 50%, 3 > 50%), presence of subjective balance disorders and of functional subjective limitation (0 absent, 1 mild, 2 moderate, 3 severe) and, finally, the subjective improvement perception by visual-analogical score (0-10). Computerised stabilometric test with elaboration of the cervical interference index (ellipse area registered with closed eyes and head in upright position, and ellipse area

obtained with head in retroflex position ratio) was also taken at T0, T2 and T3 time points.[5-6] Stabilometric test was performed using a pressure platform (LorAn Engineering srl, Castel Maggiore (Bo), Italy) with resistive sensor, with a standard registration of 52 seconds. *Data analysis.* Data on semi quantitative scale have been analysed with the Mann-Whitney non parametric test, while data on cervical interference have been analysed with the parametric Paired Samples T Test.

RESULTS

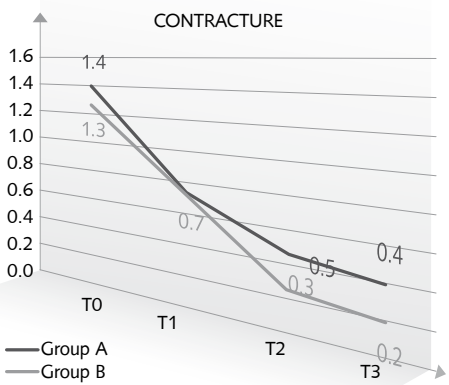
The two groups of patients did not differ significantly for age, sex, symptoms duration, presence of previous traumas at cervical rachis level and X-ray arthrosis evidence. As far as the parametric data are concerned, there are not significant differences between the two groups in the scores at different time points. We therefore analysed the variations in time for each clinical anamnestic parameter examined (pain, contracture, articular limitation etc.) within each group. In both groups, the pain reduction between T0 and T3 resulted significant. Also significant was the pain reduction between T0 and T1 in group A only, which included patients treated with Hilterapia® combined with kinesitherapy. In all other cases the variations observed were not significant (Figure 1).

Figure 1: Variation over time of mean value of pain in the two groups.



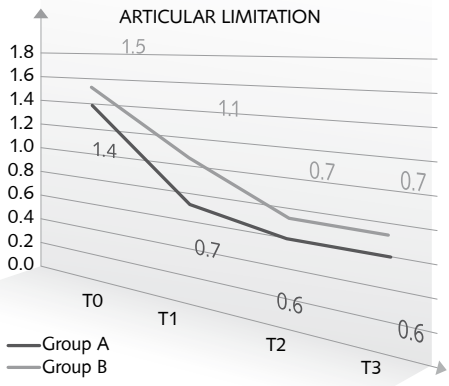
With respect to the contracture degree, there was a significant difference in both groups between T0 and T3, whereas no significant differences were found at intermediate times (Figure 2).

Figure 2: Variation over time of mean value of muscle contracture in the two groups.



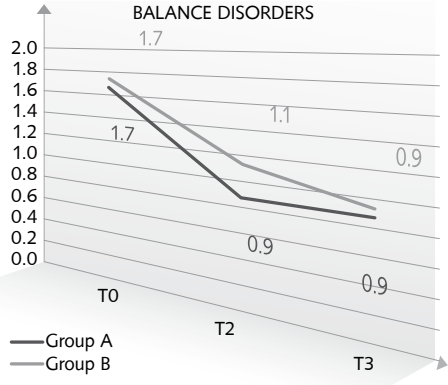
Cervical tract articular limitation has shown very mild variations on the whole. Statistical analysis has shown a significant variation only in group B between T0 and T3. No significant variation was reported for intermediate times (Figure 3).

Figure 3: Variation over time of mean value of articular limitation in the two groups.



As for the subjective balance disorders, variations between T0 - T2 were statistically significant for both groups. If total variations between T0 and T3 are taken into account, a significant difference is present only in group A (Figure 4).

Figure 4: Variation over time of mean value of balance disorders in the two groups.



Subjective improvement felt by patients has been measured by a visual analogical score at T2 and T3. The mean values of improvement have been quantified, on a 0 to 10 scale, at 5.9 and 6.1 for group A at T2 and T3, respectively. In group B, an improvement of 4.1 and 4.3 has been achieved at T2 and T3 respectively. These values remained virtually unchanged between the two control periods and the relative variation was not significant in either of the 2 groups (Figure 5). The subjective functional limitation, measured at T0, T2 and T3, shows a significant improvement only in group A in the first period (T0-T2), while considering the whole observation period (T0-T3) the functional limitation decreased significantly in both groups (Figure 6).

Figure 5: Variation over time of mean score of improvement reported in the two groups after therapy and one month later.

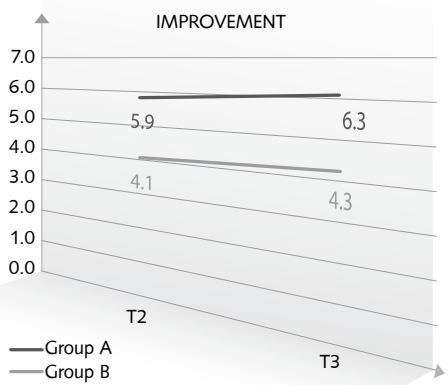
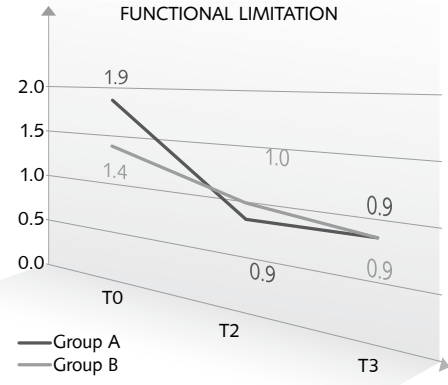
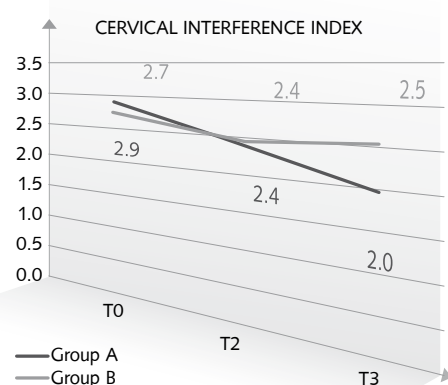


Figure 6: Variation over time of mean value of functional limitation in the two groups.



The cervical interference index has been calculated at T0, T2 and T3, and parametric test comparing the two groups could be applied. The variations observed resulted statistically significant only for group A in the T0-T3 period. In all other cases were not significant (Figure 7).

Figure 7: Variation over time of mean value of cervical interference index in the two groups.



DISCUSSION

The aim of this study was to evaluate the effect of Hilterapia® in proprioceptive balance disorders. For this scope we used a computerised stabilometric test to determine the cervical interference index. Unfortunately, no data is available in literature on this subject. Data obtained

from our study, although limited by the small sample size, showed that only in the group of patient treated with Hilterapia combined with kinesitherapy there was a significant variation of cervical interference between T0 and T3.

No significant variations were observed in the group treated with kinesitherapy alone. Even though, positive results were obtained in both groups with regard to pain reduction, in the Hilterapia® group a faster and statistically significant result, highlighted by the comparison between T0 and T1 data, was obtained. A similar trend was obtained for contracture and functional limitation variations, where is evident how a better and faster result is obtained combining the two therapies, even if at the end of the observation period, data do not differ significantly.

Positive results in both groups have been obtained for balance disorders measured with subjective evaluation scale, for the improvement reported by the patient and for the functional limitation. However, when single patients were analysed, in the Hilterapia® group some subjects reported a clear improvement, remarkably more appreciable than the mean improvement in the control group, even though other patients did not report significant variations. Another relevant observation was that parameters improving in the comparison before and after therapy, have always maintained such improvement or even increased it, like in the case of cervical interference in group A, even one month after therapy was ended.

This appears to confirm indirectly the initial hypothesis of efficacy on the pathogenic mechanism: balance disorders have a proprioceptive origin, and once this is removed, it would abolish symptoms as well.

CONCLUSIONS

We believe that our study could give interesting insights on a yet unexplored area. Although data need to be confirmed on larger sample groups and longer observation periods, we can assert that the combination of traditional kinesitherapy with pulsed Nd:YAG laser at high intensity (Hilterapia®) provides a more rapid clinical symptomatology and computerised stabilometric data improvement. Therefore, Hilterapia® demonstrated to be an effective aid in the treatment of cervical proprioceptive balance disorders.

ACKNOWLEDGEMENTS

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Treatment of chronic low back pain: back school versus Hilterapia®.

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ABSTRACT

Chronic low back pain can be treated with the use of back school, drugs, physical therapy with therapeutic medical equipment, psychological therapy, life style improvement and surgery. The aim of this study was to compare the efficacy of back school treatment with a combination of back school and treatment by pulsed Nd:YAG laser (Hilterapia®). Patients have been divided in two groups similar for age and sex: the first group was treated exclusively with back school exercises; conversely, the second group received a combined therapy of back school and Hilterapia®. Results obtained with the two therapy regimens have been evaluated measuring pain control and disability. Although an improvement has been observed in both groups, this was more evident in patients treated with the combined therapy.

INTRODUCTION

Chronic low back pain is a common pathology that can cause pain and disability. Therefore, the aim of treatment is pain resolution and best possible recovery of functional autonomy. According to the Kirkaldy-Willis degenerative cascade model [1] (see Table I), after a dysfunction phase

associated to disk and joint facets pathology, an instability phase follows. Finally, a stabilisation occurs, with fibrosis of annulus nucleus complex and posterior articulations and consequent loss of elasticity. Since 70% of the population has experienced low back pain in the past or is currently affected, and since 2 % of the adult population is constantly in therapy or off work for back pain problems [2], this pathology can be considered as disabling. Consequently, in order to evaluate therapy methods [3], in addition to pain evaluation criteria, quality of life and disability need to be accounted for [4]. Amongst the therapeutical methods commonly used, we have chosen to test those suggested by international literature as effective and free of side effects, such as therapeutical exercises [5,6,7,8,9] and analgesic laser therapy [10,11].

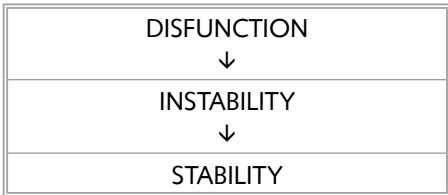


Table I - Kirkaldy-Willis degenerative cascade model

This choice is contrasting with the main national and international guidelines

[12,13], that do not consider these therapies as suitable. The former are recommended for postural exercises and postural education, while physiotherapy with therapeutic medical equipment is used for analgesic purposes within multimodal rehabilitation programs [12]. Some authors believe that there is no evidence of its efficacy while others would not use it even as second resort after patient self medication [13].

MATERIALS AND METHODS

Fifty six patients of both sexes, aged between 18 and 65, suffering from unspecific chronic low back pain (that had lasted for more than 4 weeks) and with enrolment VAS values of more than 30, have been examined. Exclusion criteria were as follows: basal VAS less than 30, pregnancy, severe traumatism, non spinal back pain, caudal syndrome, suspected or assessed neoplastic pathology, mild trauma in those patients suffering from osteoporosis, febrile infection in patients recently undergone surgery or therapy with intravenous injections, medical history of ankylosing spondylitis, fibromyalgia syndrome. The study has been designed according to a parallel randomised procedure where patients have been randomly assigned to the two therapy groups: Group a) back school with Hilterapia® Group b) back school without Hilterapia®

Table II describes the back school exercise program. Hilterapia was administered by using a pulsed Nd:YAG laser (ASA S.r.l., Vicenza, Italy) according to the protocol described in Table III.

1) UPPER LIMBS STRETCHING EXERCISES
2) Lower limbs stretching exercises
3) Klapp kneeling position
4) Costal and diaphragm ventilation
5) Muscle strengthening
6) Repeat stretching exercises
7) Exercises at the mirror to find neutral posture

Table II - Back school exercise program.

PHASE	SUBPHASE	FLUENCE MJ\CM²	FREQUENCY	MODE	TOTAL ENERGY
Initial	Step 1-500	660	Level 11	fast	1500
	Step 2-500	710	10	fast	
	Step 3-500	760	9	fast	
Intermediate	Four points 18-20 J	660	Level 7		
Final	Step 1-500	660	Level 11	Slow	1500
	Step 2-500	710	10	Slow	
	Step 3-500	760	9	Slow	

Table III - Hilterapia protocol

Evaluation at enrolling was performed by a first operator that referred the patients to the physiotherapist, who randomly divided them into the two therapeutical regimens. Results have been quantified blindly by another operator using VAS and modified Oswestry scales, the latter allowing to test the main elements of relation life as described in Table IV.

Data have been analysed using Student's T test and differences were considered significant for p<0.01.

RESULTS

Twenty eight patients, have been assigned to each group: study group (A) and control group (B). They showed similar functional tests with mean disability recorded at enrolment of 21.39 for group A and 19.60 for group B, a difference that is not statistically significant (Figure 1). Samples resulted homogeneous also for the perceived pain test, with a mean score of 60 in group A and 63.3 in group B, a difference not statistically significant (Figure 2).

Figure 1: Functional test (evaluated by Oswestry scale)

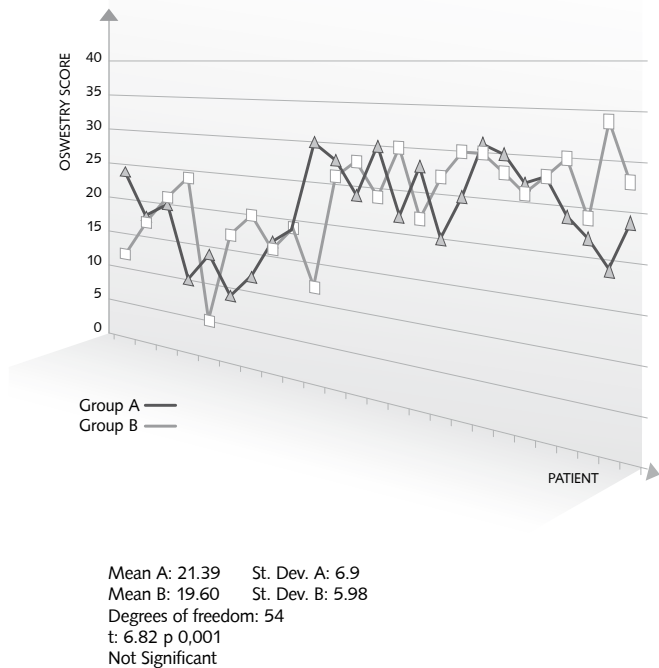
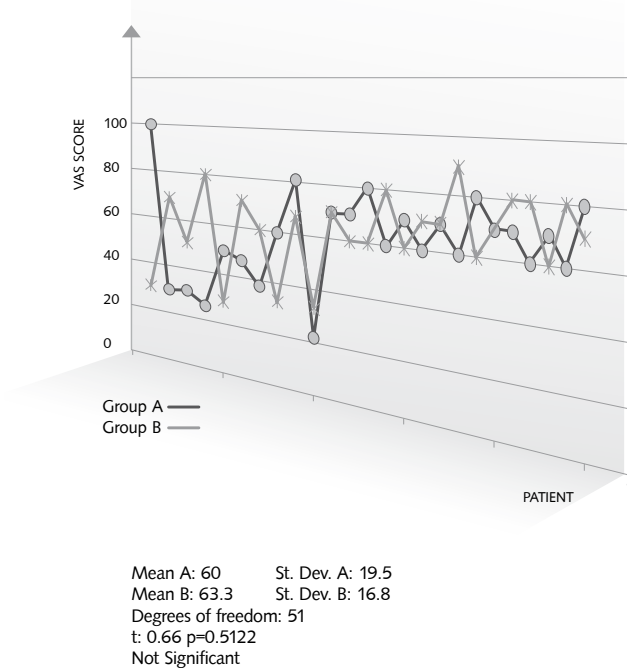


Figure 2: Percetive pain test (evaluated by VAS scale)



Results about disability and pain changes over time for group (A) and group (B) are shown in Figures 3,4,5,6. Comparison between results obtained in the two groups at the end of treatment is shown in Figures 5 and 6.

Figure 3

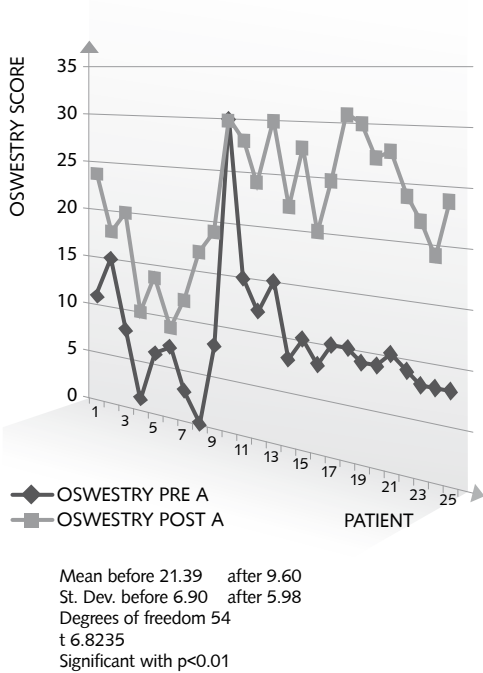


Figure 4

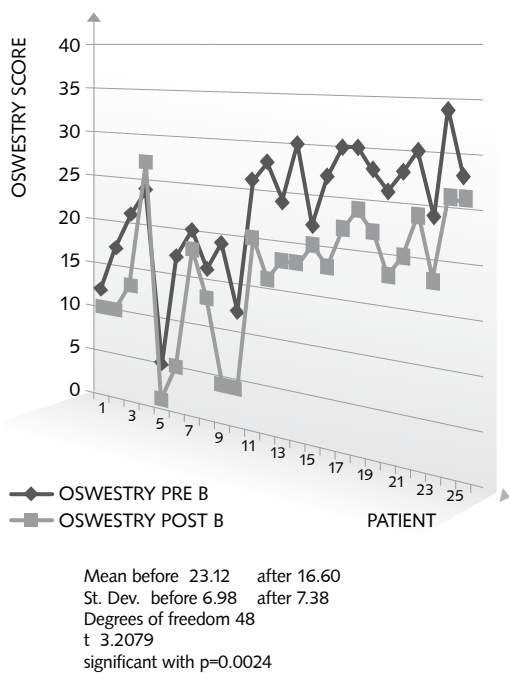


Figure 5

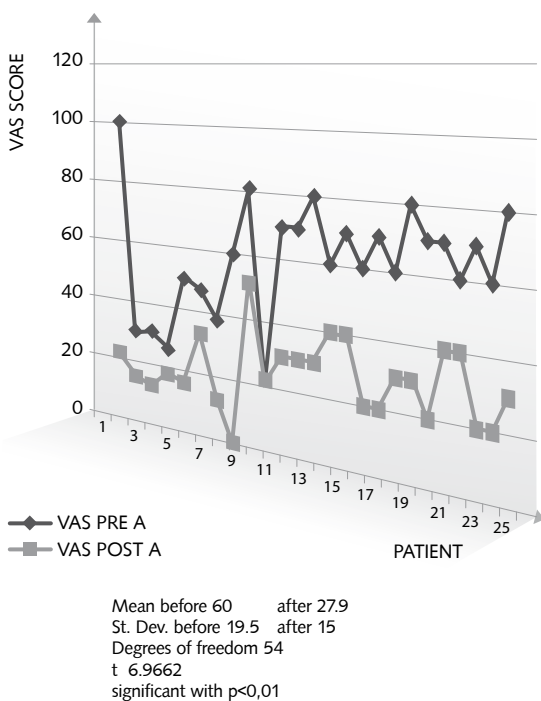


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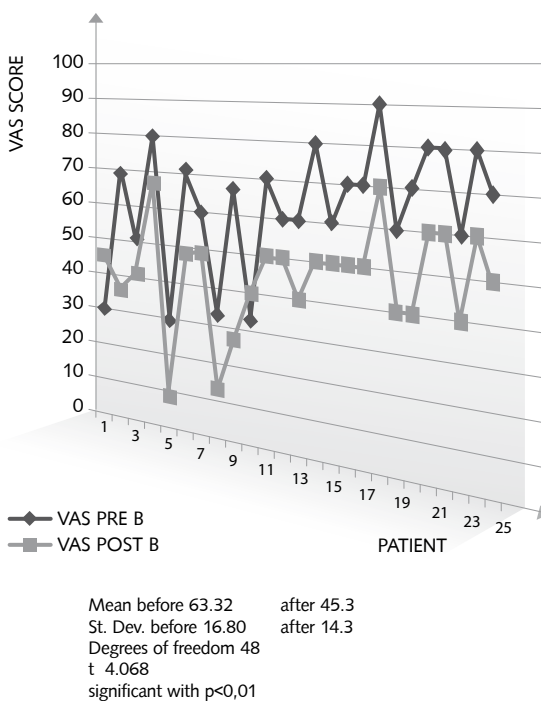


Figure 7: Differences in functional tests after therapy in group A compared to group B

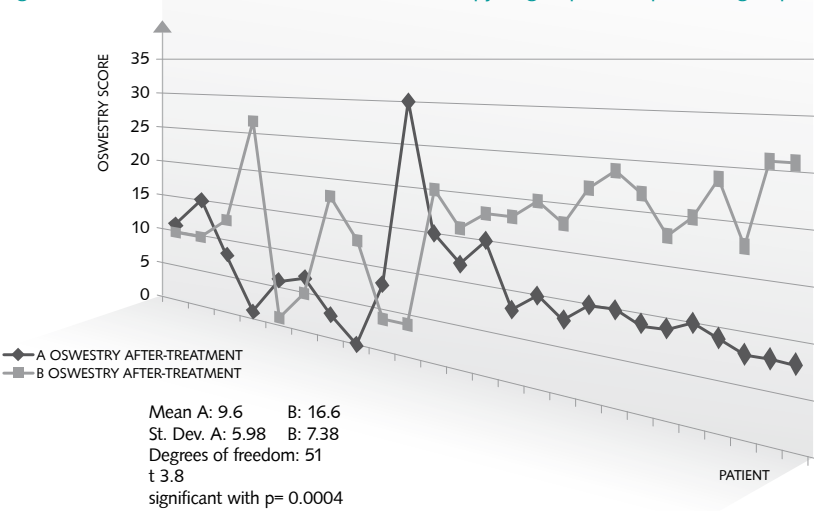
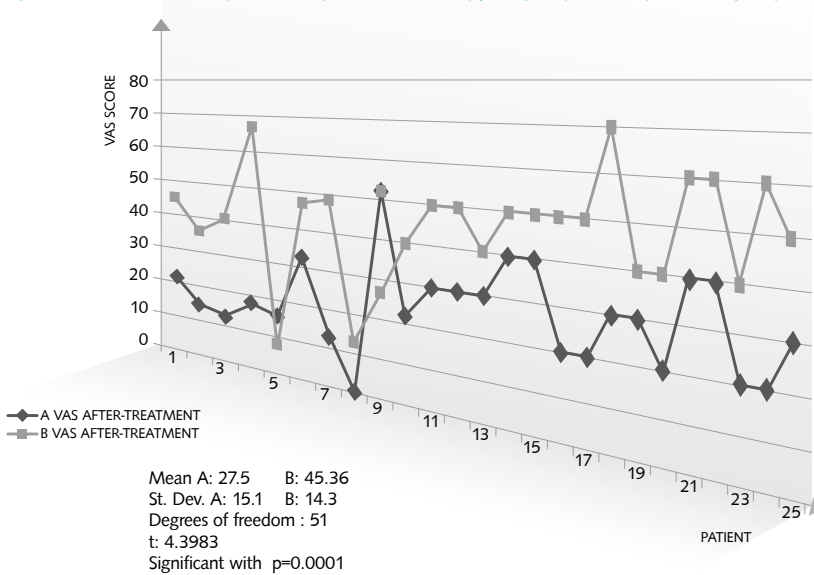


Figure 8: Differences in perceived pain after therapy in group A compared to group B



DISCUSSION AND CONCLUSIONS

As already discussed by other authors [9], results obtained in Physical and Rehabilitation Medicine fields, need to be submitted to selective criteria of statistical analysis to be validated. Moreover, it is paramount have large numbers of samples to validate the promising results obtained with physical means with high therapeutical potential such as pulsed Nd:YAG laser. The results from our study clearly show that both therapies used are effective in the management of chronic unspecific

back pain, especially when back school is combined with Hilterapia®. A rigorous statistical analysis applied to our samples had shown that these therapies are effective and they should therefore be considered suitable therapeutical choices, since:

1. They have a low biological impact, being virtually free of side effects as opposed to pharmacological therapies;
2. They are able to reduce considerably the pain and can also help to reduce the consequent disability associated with the pathology.

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Key words: Knee osteoarthritis, viscosupplementation, laser therapy, HILT, Hilterapia®

Effects of Hilterapia® vs. Viscosupplementation in knee osteoarthritis patients: a randomized controlled clinical trial.

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ABSTRACT
Therapeutic approach in Knee Osteoarthritis (KO), a long lasting disease with both epidemiological and social implications, may consider local interventions which are useful along the course of the pathology. Viscosupplementation has got efficacy with little side effects. Lasertherapy (Low Level Laser Therapy-LLLT-) is widely used but we don't still have sure demonstrations on its efficacy. High Intensity Laser Therapy (HILT, Hilterapia®) seems to be more effective than LLLT, due to its higher intensity and to the depth reached by the laser ray. The aim of this study was to compare the efficacy of Hilterapia® to viscosupplementation in patients with symptomatic KO. 41 out-patients with symptomatic KO (II-III Kellgren-Lawrence Scale stage) were enrolled and evaluated by WOMAC and Lequesne Scales, before treatment (t0), after treatment (t1) and after 4 months (t2). After randomization, the treatment consisted in viscosupplementation (4 Hyaluronic acid infiltrations 1/week) for Group A, or Hilterapia® (antalgic treatment, 10 sessions, three time a week) for Group B. Both the groups (A and B) showed a highly statistically significant improvement between t0 and t1 in WOMAC and Lequesne Scales.

The improvement was maintained at follow-up (t2) either by Group A or Group B. No side effect was found, neither in Group A nor in Group B. Hilterapia® showed analogous results to viscosupplementation. We conclude that Hilterapia® seems a good medical instrument for pain control and for improvement of patient's quality of life.

INTRODUCTION
Although underestimated, knee osteoarthritis (KO) is an important pathology, with both epidemiological and clinical implications [1, 2]. KO is a complex disease whose pathogenesis includes the contribution of biomechanical and metabolic factors [3, 4] which gradually lead to articular joint tissues destruction. As the disease progresses, clinical features include joint pain, limitation of movement, tenderness, and episodic inflammation. Especially among the elderly, chronic pain and disability can develop [5, 6]. Disability is directly correlated with pain level. Pain control, together with the control of the disease progression are the two main targets of the therapeutic approach. EULAR recommendations for the management of osteoarthritis include pharmacological and non-pharmacological

treatment modalities [7]. Considering the frequent side effects of long-term systemic pharmacotherapy [8], local treatments may be useful, such as instrumental physiotherapy or intra-articular injections. Viscosupplementation with hyaluronic acid (HA) represents one of the possible local treatments [9, 10, 11, 12]. Among physiotherapeutic treatments, Low Level Laser Therapy (LLLT) has been often proposed for pain and flogosis control in osteoarthritis, although no conclusions could be drawn on the optimal dose, the wavelength and the duration of treatment [13]. Some preliminary studies [14, 15, 16] indicate that High Intensity Laser Therapy (HILT, Hilterapia®), a more recent laser application modality, can be more effective than LLLT in pain and flogosis control, due to its more intense and deeper effects. The present study was a prospective, open-label, randomized clinical trial. The aim was to evaluate the clinical and functional efficacy of Hilterapia®, compared with viscosupplementation, in patients affected by symptomatic knee osteoarthritis.

MATERIALS AND METHODS
Patients. Patients suffering for symptomatic KO were recruited for this trial from outpatients of the Recovery and Rehabilitation Agency (AOU Careggi, Firenze). Forty-one patients with symptomatic KO, aged 50-85 years, were included. Informed consensus was obtained. Inclusion criteria required the presence of symptomatic KO (following ACR criteria [17]), I-II and IV stadi of Kellgren-Lawrence Scale [18] on the radiological evaluation. Exclusion criteria were: therapy with oral anticoagulants, non compliant patients (cognitive impairment or psychiatric disorder), neoplastic pathology, presence of deep vein thrombosis. The patients' evaluation included history and clinical examination. Initial assessment (t0), before treatment, included WOMAC Scale [19] and Lequesne Scale [20]. The patients were randomized for treatment in two groups, following the method of random number table. *Treatment.* After randomization the patients underwent two different treatment

protocols: Group A was treated with hyaluronic acid intraarticular infiltrations (4 infiltrations, 1 session/week, mw 500-1000 kD), whilst Group B was treated with Hilterapia® by pulsed Nd:YAG laser (HIRO 3 ASA S.r.l., Vicenza, Italy): ten sessions on alternate day, see Table I.

Hyaluronic acid infiltrations protocol (Group A): 4 sessions of Hyaluronic acid infiltrations, molecular weight 500 -1000 kD, once a week. Infiltration is performed by anterior access with supine patient and flexed knee.
Hilterapia® protocol (Group B): pulsed high power laser, Nd:YAG, λ1064nm, 10 sessions, on alternate days, analgesic program, in manual scansion. This program is articulated in three phases (initial, intermediate and final phase). Every phase is articulated in sub-phases in which increasing fluency (510-710 J/ cm 2) and decreasing frequency (15-10 Hz) are administered, total energy 2000-3000 J. The total session duration is 15-20 minutes.

Table I: Treatment protocol of the two groups

The patients were reassessed at the end of the treatment (t1) and after 4 months (t2). *Data analysis.* Data of patients were compared by Mann-Whitney and Wilcoxon tests.

RESULTS
Forty-one patients were included in the analysis. 22 and 19 patients respectively were randomized to hyaluronic acid treatment (Group A) and Hilterapia® (Group B). All the patient but one (Group A) finished the study. Baseline data of the two Groups are explained in table II. Although this was a randomized comparative study, the small number of patients did not guarantee against differences between treatment groups' baseline characteristics. The experimental groups resulted not exactly balanced for all the variables collected at baseline. Nevertheless the two groups resulted comparable and the resultant variables were not related to

	Pats. number	Median age	sex	WOMAC Scale	Lequesne Scale
GROUP A	22	74.4 yrs. (53-84)	2 M, 17 F	51.7 ±11	12.3 ± 4
GROUP B	19	70.2 yrs (54-81)	5 M, 17 F	46.3 ± 3	14.4 ± 3

Table II: Groups baseline characteristics

	WOMAC Scale t0	WOMAC Scale t1	WOMAC Scale t2
GROUP A	51.7 ± 11	35.5 ± 13 (p< 0.001)	31.4 ± 18
GROUP B	46.3 ± 3	26.7 ± 7 (p<0.001)	28.2 ± 13 (p:ns)

Table III: WOMAC Scales Values at t0, t1 and at the follow-up (t2) of the two Groups

	Lequesne Scale t0	Lequesne Scale t1	Lequesne t2
GROUP A	12.3 ± 4	9.1 ± 3 p< 0.001	9.7 ± 5 (p:ns)
GROUP B	14.4 ± 3	9.2 ± 4 p<0.002	9.6 ± 4 (p:ns)

Table IV: Lequesne Scales Values at t0, t1 and at the follow-up (t2) of the two Groups

the initial differences. Median age was 74.4 years (range:53-84) and 70.2 years (range:54-81) for Group A and Group B respectively, while the proportion of male (M) and female(F) patient was 2 M, 17 F and 5 M, 17 F respectively. WOMAC Scale values at t0 were 51.7 ±11 (Group A) and 46.3 ± 3 (Group B); Lequesne Scale values at t0 were 12.3 ± 4 (Group A) and 14.4 ± 3 (Group B), see Table II. At t1 the two groups showed improvement in the scale points: Group A changed WOMAC values from 51.7 ± 11 to 35.5 ± 13 (p< 0.001). WOMAC values of Group B varied from 46.3 ± 3 to 26.7 ± 7 (p<0.001), see Table III and Figure 1. t1 Lequesne values were 9.1 ± 3 (Group A) and 9.2 ± 4 (Group B), and these results were statistically significant versus t0: p< 0.001 and p<0.002 respectively, see Table IV and Figure 2. At follow-up (4 months) both the two groups maintained the improvement: t2 Lequesne values were 9.7 ± 5 for Group A, and 9.6 ± 4 for Group B. WOMAC scale also showed little variations at t2: 31.4 ± 18 for Group A and 28.2 ± 13 for Group B. At 4 months follow-up there

was a little tendency towards improvement in Group A, whilst a little worsening was seen in Group B, but WOMAC and Lequesne values at t2 showed little variations, reaching no statistical differences, neither in Group A nor in Group B versus t1 values. WOMAC sub item related with pain was analysed too, see Figure 3. This item showed the same tendency of total WOMAC scale scores (see Figure 3). No patient, in Group A neither in Group B, showed side effects.

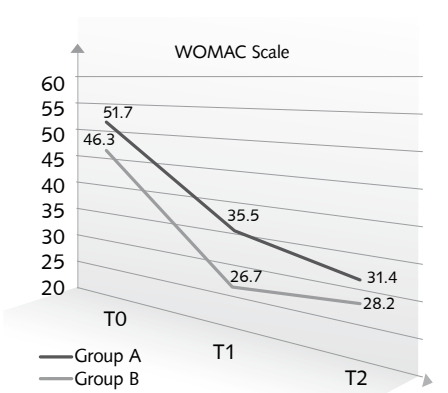


Figure 1: WOMAC Values before treatment (t0), at the end of treatment (t1) and after 4 months.

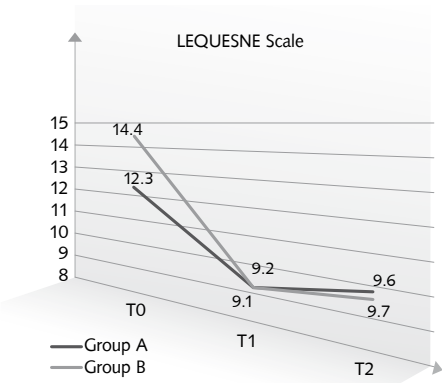


Figure 2: Lequesne Values before treatment (t0), at the end of treatment (t1) and after 4 months.

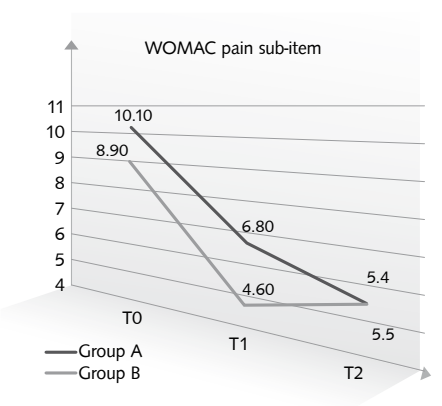


Figure 3: WOMAC pain sub-item values before treatment (t0), at the end of treatment (t1) and after 4 months.

DISCUSSION

WOMAC and Lequesne Scales are functional measurements, as they both investigate domains as pain, gait, and knee related ADL [19, 20, 21]. Scientific literature shows that knee pain and age are important determinants of functional impairment in elderly subjects [22, 23, 24]. Knee pain is central to daily living, and experiencing mobility limitations devalues self-worth [25, 26]. Pain control represents one of the principal tasks in KO, especially in order to get over acute phases. Viscosupplementation [27, 28] is a well known and accepted modality to improve

pain and perhaps the osteoarthritis evolution too. It has reached evidence based demonstrations, reported through recent reviews [13, 28]. Among instrumental physical therapy the effectiveness of low level lasertherapy has been often investigated with variable results. Despite a widespread use of this technique, a recent Cochrane review [13] didn't succeed in demonstrating a sure effect of lasertherapy, mainly due to methodological causes of the studies (differences in number of cases, doses and wavelength of laser, etc.). Traditional lasertherapy, which is a low level laser therapy, has got some limits, especially related both to a poor penetration and to a low intensity of the light radiation [29]. Experimental data [30] seem to enhance the hypothesis that high intensity laser therapy may overcome these difficulties, and the first clinical studies confirm its efficacy [14, 15, 16]. Our study aimed to investigate the clinical efficacy of Hilterapia® in KO, compared with viscosupplementation, which is nowadays a good reviewed medical treatment, and it is accepted following EBM criteria too. In relation to hyaluronic acid effects, our results agree with precedent literature findings, as the patients treated with intra-articular injections improved significantly, at the end of the treatment and at follow-up. The evolution of the improvement indicates a long-acting effect, as the results are maintained, and perhaps improved, at follow-up. In our study, Hilterapia® (antalgic program) showed a great efficacy too, comparable with viscosupplementation, achieving a rapid pain control and its maintenance till 4 months. Local clinical experiences strengthen the Hilterapia® efficacy, but, till today, sufficient proven data are very few. Our study gets into these first clinical researches, as a preliminary work. We don't still know which is the optimal sessions timing for the best results in KO patients. In our study we found a good clinical efficacy using a treatment protocol of 10 sessions on alternate days, but in this initial experience it seemed to us that patient's improvement begins rapidly during the first sessions, reaching a plateau.

To verify this hypothesis we are now using a shorter protocol, which provides the same laser program, 5 sessions on alternate days. The short term effects seem equally very good, but we don't still have the definitive and the follow-up data.

CONCLUSIONS

Viscosupplementation confirms its efficacy in KO, and Hilterapia® showed analogous results to hyaluronate acid treatment, at least in the medium term. From our data Hilterapia® appears to be a good medical instrument for pain control in KO, with consequent improvement in patient's quality of life. It has a rapid and long lasting effect, it is a non invasive technique and no side effects were reported. Our preliminary results suggest that Hilterapia® may be a useful resource in the management of knee osteoarthritis.

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Key words: Hilterapia®, carpal tunnel, pulsed Nd :YAG laser, high power laser

Hilterapia® efficiency in handling the post surgical pain after the release of the carpal tunnel.

DESCRIPTIVE OBSERVATIONAL STUDY.

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ABSTRACT
A descriptive observational study was made to evaluate the efficiency of a new option of treatment, the high power laser therapy (Hilterapia®) in handling a frequent pathology as the pain in the palm of the hand after the open release of the carpal tunnel (pillar pin). Pillar pain is a painful condition present in early stages in up to 41% of the patients after the transverse ligament release. This percentage diminishes with time, but has not yet had a therapeutic, efficient and non invasive treatment. Thirteen patients were evaluated after being operated by three different surgeons with a standard open carpal release technique. After six months of surgery, they still presented a persistent and incapacitating pain that could be attributed to a pillar pain. All patients were summated to eight sessions of Hilterapia® treatment with the HIRO 3 equipment (ASA S.r.l., Vicenza, Italy). The energy applied in the painful area of the hand was 600 Joules. Two different parameters were evaluated: pain scale and grip strength, both affected by the pathology of pillar pain. The study shows a tendency to diminish the pain and to improve the grip strength and the hand functioning. This can be

attributed to the use of Hilterapia®, which opens a therapeutic way to its use in this type of condition.

INTRODUCTION
Carpal tunnel syndrome is the most common entrapment neuropathy [1,2,3]. It is estimated to occur in 1% to 4% of the general population with a higher prevalence in women (3% to 5.6%) than men (0.6% to 2.8%) [2,3,4,5]. Although it is accepted that surgical decompression of the carpal canal is the treatment of choice in moderate to severe cases, or in those patients in whom non-operative treatment has failed to eliminate their symptoms, it is well known that this surgery sometimes fails to bring relief of symptoms to the patient [6,1,2,7,8]. Paresthesias and scar tenderness are common in the subacute recovery phase following carpal tunnel release [6,8,9]. An aggravation of symptoms is common in the period of two to six weeks after surgery. Several different situations may contribute, including the following: -Normal scar tenderness with anxiety and awareness after the surgery. -Normal scar adhesions to the perineural tissues. This may result in a sudden, brief electrical paresthesia. It may occur while reaching, gripping, or at rest. - Pillar

pain: tenderness adjacent to the actual ligament release, where the prominences of the trapezial ridge and the hook of the hamate are closest to the skin. The transverse retinacular ligament, divided during carpal tunnel release, attaches to these structures, and the inflammatory reaction of normal wound healing is most obvious at these points, often more than the central area of the actual release. -Reinnervation hypersensitivity: most often occurs if there was constant tingling, numbness or altered sensibility than before surgery. - Reflex sympathetic dystrophy. - Direct nerve irritation of one of the palmar cutaneous sensory branches to the palm or of the median nerve itself [6,1,2,3,7,8,10,11].

Pillar pain is a well known complication after carpal tunnel release. It is define as tenderness on the base of the palm superficial to the carpal tunnel, which is not a spontaneous pain, sometimes concurrent with swelling and without sensory disturbance. The etiology of postoperative "pillar pain" remains controversial. If its cause is because of alterations in the carpal arch or in the origin of the hypothenar and thenar musculature that occur after transection of the transverse carpal ligament, one would expect this manifestation, regardless of the size of the incision. An alternate theory is that violating the palmar skin, cutaneous nerves, and underlying palmar fascia is responsible for this phenomenon [10,11,12]. Povlsen and Tegnell found that 41% of patients experience pain at 1 month after surgery, 25% at 3 months, and 6% at 12 months [9]. Despite its prevalence, postoperative "pillar pain" remains a perplexing problem that has no reliable treatment other than the tincture of time, or the minimally invasive technique in some cases, with the infiltration of local anaesthetic for neuromodulation [1,10]. In this observational study, we evaluated the efficiency of a new option of treatment, the high power laser therapy (Hilterapia®), in handling the pain in the palm of the hand after the open release of the carpal tunnel.

METHODS AND MATERIALS
Patients. The patients included in the study had to have a minimum of six months of post surgical treatment, with a painful hand attributable to a diagnosis of pillar pain. They were all sent by the hand surgeons that proceeded with a conventional open technique. Patients with diabetic neuropathy, rheumatoid arthritis, gout, thyroidal dysfunction or previous fractures of the carpal area were excluded. The patients treated were distributed between the ages of 26 and 61 years old (average of 45). The gender distribution was of 30% male (4) and 70% female (9). The time average after surgery for the treated patients was 7.6 +/- 1.2 months; this time period is necessary because during the first months after surgery a spontaneous improvement of the pain can occur. Two main variables were evaluated before and after Hilterapia® : pain and grip strength. Pain was graded through graphics and punctuation by the patients in a visual analog scale (VAS). Grip strength was measured by density resistant balls (theraballs), asking the patient in his first visit to compress each ball during three seconds, starting with the least resistant (15% pink), continuing with an intermediate resistance (25% green), and ending with the one with highest resistance (35% black). After the last laser session (8 sessions), the patients were asked to do the same exercise, and then compare the results. "A" was graded if the patient could only compress the pink ball. "B" was graded if the patient could compress both the pink and the green, and "C" if the patient could compress all the pink, the green, and the black balls.

Instruments. The only treatment applied to the 13 patients was the Hilterapia® with the HIRO 3 equipment by (ASA S.r.l., Vicenza, Italy), which is a high intensity Nd: YAG pulsed laser, with the standard hand piece for the pain therapy.

Methodology. During each session the following parameters were used:

- Initial phase with fast scanning, applying a total energy of 300 Joules directed over the thenar and hypothenar

eminences of the hand (3 sub phases: phase 1 with a fluency of 360mJ/cm² and frequency of 30Hz, phase 2 with fluency of 510mJ/cm² and frequency of 25Hz, and phase 3 with a fluency of 610mJ/cm² and a frequency of 20Hz).

- In the intermediate phase the laser was applied over the painful points on the palmar area of the hand with a maximum of four applications with the following parameters: fluency 510mJ/cm² and frequency of 15Hz for a total of 8 Joules per point.
- The final phase was applied with a slow scan with the same chosen parameters from the initial phase.

Eight sessions were performed on each patient, one every day during the first five days. In the second week of the treatment, the last 3 sessions were applied in alternating days.

RESULTS
After treating all thirteen patients, with eight sessions of Hilterapia® each, and with the parameters explained above, the following results were found:
The average by which the patients graded the pain before and after the treatment were as follows: before the treatment 7.53 +/- 0.96, and after the treatment 2.33 +/- 1.07; the average variation was of 5.2 (Figure 1).

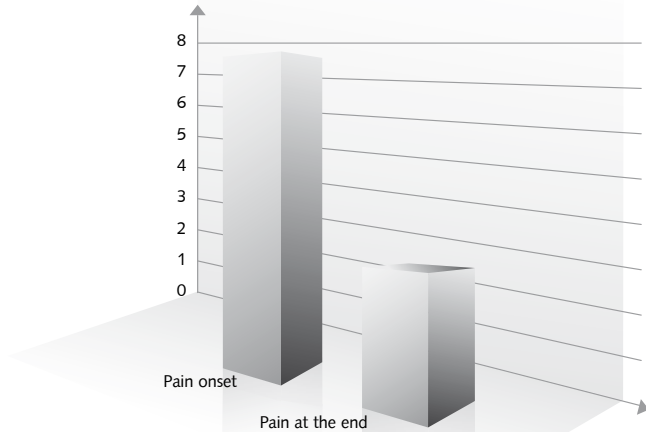


Figure 1: VAS score mean values before and after the treatment

The grip strength average before the treatment was of 1.3 +/- 0.48, increasing to 2.15 +/- 0.55 after the eighth session treatment, with an average variation of 0.85 (Figure 2).

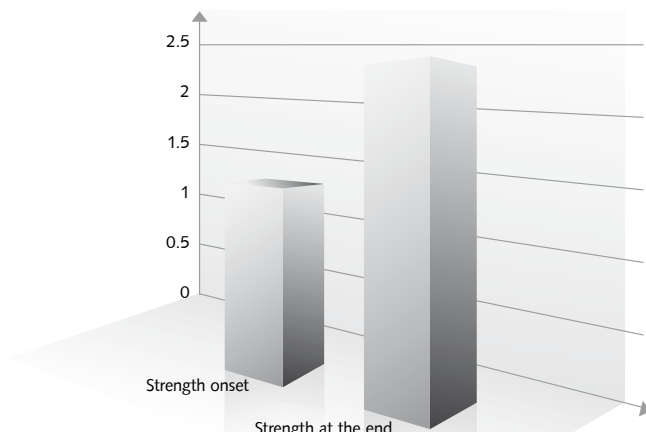


Figure 2: Grip strength average measured by density resistant balls (theraballs) before and after the treatment

The following pictures show the change in parameters of pain and grip strength respectively, in each patient, before and after the entire treatment with the Hilterapia® (Figure 3).

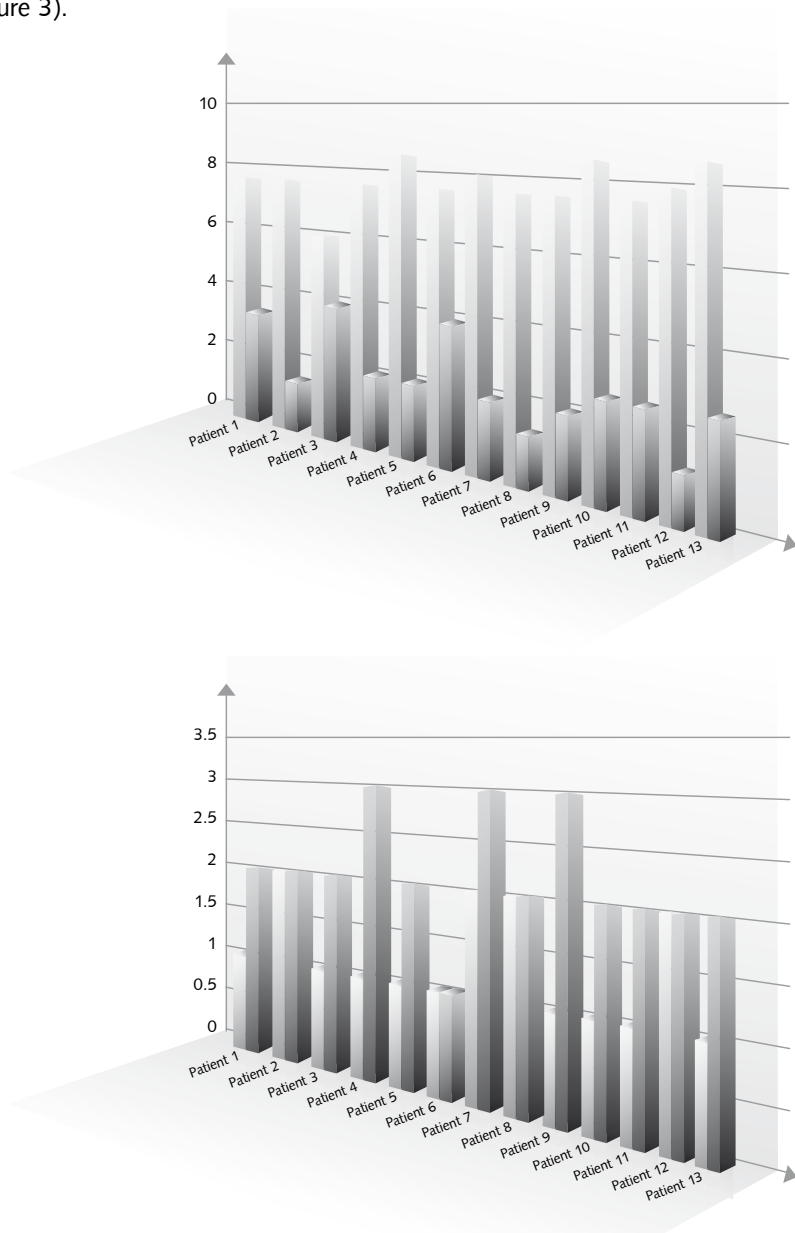


Figure 3: Pain and grip strength, in each patient, before and after the entire treatment with the Hilterapia®.

DISCUSSION

The release of the carpal tunnel is one of the most frequent surgical procedures. The open technique is the most used, due to its easiness and effectiveness. Nevertheless, a significant number of these patients remain with a hand pain, which incapacitate them from their diary activities. In the actuality, there is not an efficient treatment to this post surgical pain. That is why the efficiency of the Hilterapia® was evaluated, due to its known effects in the control of pain and inflammatory processes.[13,14].

The group of treated patients was exposed just to eight sessions of laser therapy with Hilterapia® in a period of two weeks. They were all irradiated with the same energy of 600 Joules over the painful palmar hand area. The results of this study lead us to believe that this treatment could help in the handling of this post surgical pain.

CONCLUSION

This study shows the preliminary results of the thirteen patients treated with Hilterapia® after undergoing the release of the carpal tunnel surgical procedure, and presented pillar pain. As can be seen in these series of cases, Hilterapia® improves both the post surgical pain after six months of proceeded and the grip strength in all patients. In conclusion, this study shows that it is worthwhile to perform future tests with a stronger epidemiological background to corroborate this new type of treatment.

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Key words: Muscle strain, sport, Hilterapia®, VAS (visual analog scale), ultrasound scan.

Muscle lesions in athletes: case comparison between Hilterapia® and traditional therapy.

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ABSTRACT

Muscle pathologies during sport activities are very frequent. The most serious event is the muscle strain that needs specific treatment based upon functional rehabilitation associated with physiotherapeutic medical equipments. This clinical study compared the results obtained in two groups of 15 patients, homogeneous for pathology (1st degree strain), sex and age, treated with either Hilterapia® or with traditional therapy (CO₂ laser therapy and ultrasound therapy). Results have been evaluated by using VAS pain score, ultrasound scan, number of therapy sessions, time before sport activity can be resumed and satisfaction index of patients. Based on this study, Hilterapia® proved to be effective in reducing pain and time before sport activity can be resumed, with statistically better results when compared to conventional therapy, according to all evaluation parameters.

INTRODUCTION

Muscle pathologies are very frequent events during sport activities, with variable incidences of between 10 % and 40 %, depending on the type of sport [1,2,3,4]. Muscular pathologies can be caused by direct or indirect traumas:

- Direct trauma: contusion and lacerated and contused injury
 - Indirect trauma: cramp, contracture, stretch, strain and Delayed onset muscle soreness (Doms) (delayed onset muscle soreness).
- Muscle strain, caused by indirect trauma is the most feared event. This is the rupture of a variable number of muscle fibres, always associated with haematic extravasation consistent with the severity and localisation of the lesion. Rupture can be partial or complete with the consequent separation of the two fragments. Following a specific technical movement, acute and serious pain occurs, preventing the athlete to continue his performance. Recovery to sport activity takes between 15 days to 2 months, depending on the muscle involved and on the lesion severity. The strain is classified in 3 degrees, depending on the amount of muscular tissue that has been torn:
- 1st degree: rupture of few muscle fibres but not of the entire bundle
 - 2nd degree: rupture of one or more muscle bundles that involves less than ¾ of the section of the muscle.
 - 3rd degree: rupture that involves more than ¾ of the section of the muscle in a particular area and can be divided in partial or total.

The most frequent muscle strain is the 1st degree one (~ 58%). Biarticular muscles, those with type 2 predominant fibres and those working eccentrically or in presence of muscle flexibility deficit, are prone to pathology. Diagnosis is based upon anamnestic and symptomatology criteria, supported by objective examination and ultrasound scan, performed at least 48 hours after the trauma in order to evaluate the possible presence of haematic extravasation. Muscle strain treatment is different depending on the clinical phase, classified as acute (lasting 3-7 days), sub-acute and recovery. During the first hours of the acute phase (24-72 hours) the RICE protocol is advised. This protocol suggests the use of a compressive bandage, the unload of the involved limb, cryotherapy and rest. Later, massotherapy, the use of physiotherapeutic medical equipment and stretching are gradually introduced. Only in the sub-acute phase (4-8 days after the trauma) thermotherapy is applied, as this could cause complications if introduced too early. The recovery phase is aimed to muscle strengthening and to cardio-pulmonary reconditioning, so that sport activity can rapidly be resumed. The most used physiotherapeutical tools in the treatment of muscle strain are laser therapy, ultrasound, endogenous thermotherapy and electrotherapy. Amongst physiotherapeutical tools, Hilterapia® [5, 6, 7, 8] has been demonstrated to be safe, practical and effective, thanks to the possibility of modulating its parameters, to its bio-stimulating effect and to the high energy driven in dept. Moreover, due to the variability in the parameters and methods of treatment, Hilterapia® can be used in all clinical stages, allowing a “cold” treatment in the acute phase and a “thermo” treatment in the following phases. The objective of the present study was the comparison of the efficacy of Hilterapia® versus traditional therapies (ultrasound and CO₂ laser therapy), in speeding up and optimizing recovery from 1st degree muscle strain.

MATERIALS AND METHODS

Patients. Thirty patients (26 males and 4 females, mean age 34.3 years, range 19-39 years) suffering from 1st degree muscle strain, randomly divided in two groups of 15 patients homogenous for age, sex and pathology, have been selected at the Riacef Private Outpatient Clinic of Modena [9]. Group H patients have been treated with Hilterapia®, while group C patients have been treated with ultrasound and CO₂ laser therapy, between September 2007 and October 2008. All patients have undergone a specific rehabilitation program aimed at resuming sport activity. After treatment, each patient has been evaluated by VAS pain score [10], ultrasound scan to establish the extent of the lesion, number of sessions (carried out during the acute and sub-acute phase respectively), and time before sport activity (partial or complete) could be resumed. VAS is a visual-analogical test that evaluates the subjective pain symptomatology. The score ranges between 0 (absence of pain) and 10 (maximal conceivable pain). Ultrasound scans have always been carried out by the same operator with a linear 10-5 MHz probe. VAS and ultrasound scan evaluation have been performed before therapy (T0), after 7 days (T1) and after 10 therapy sessions (T2). The number of sessions has been divided into total, acute phase, and sub-acute phase. The time before sport activity could be resumed has been expressed in days, and it has been subdivided in partial or complete, depending on whether the athlete was just training or also competing. Results have been expressed as mean values, according to the above discussed indexes of evaluation. The satisfaction index has also been evaluated at the end of therapy. Each patient has been asked if he was very satisfied, satisfied, a little satisfied or not satisfied of the therapy employed. **Methodology. Hilterapia® protocol** In the present study, each patient in group H has been treated with the Hiro 3.0 device (ASA S.r.l., Vicenza, Italy) (peak

power 3000 W) supplied with standard handpiece and parameters chosen according to the clinical phase [6, 7, 8]. During the acute phase, 3 scans at high speed with increasing fluence (360-610 mJ/cm²), decreasing frequencies (18-10 Hz) and total energy per session of 900-1200 J have been performed. During the sub-acute phase, 3 scans at low speed, with increasing fluence (810-1070 mJ/cm²), decreasing frequencies (30-20 Hz) and total energy per session of 1500 J have been performed. **Traditional therapy protocol** Each group C patient has been treated with CO₂ laser therapy followed by ultrasound therapy. CO₂ laser therapy parameters were 10 W of mean power in pulse mode, for a total of 10 minutes per session. Ultrasounds were set at 2 W/cm² of power, and 3 MHz of frequency for 10 minutes. **Data analysis.** Data obtained from the two groups have been compared using the t-test with p<0.05 considered as significative. Data have been analysed using Office 2007 Excel software.

RESULTS

The statistical analysis of the VAS score mean values (Figure 1) showed comparable scores at T0 (5.7±1.16 in group H vs. 5.72±0.98 in group C). T1 and T2 VAS scores resulted lower in group H when compared to group C, with statistically significant differences (P<0.001 and P<0.01 respectively). In particular, T1 scores were 1.52±0.48 for group H and 2.44±0.7 for group C; and T2 scores were 0.26±0.24 for group H and 0.5±0.48 for group C, respectively.

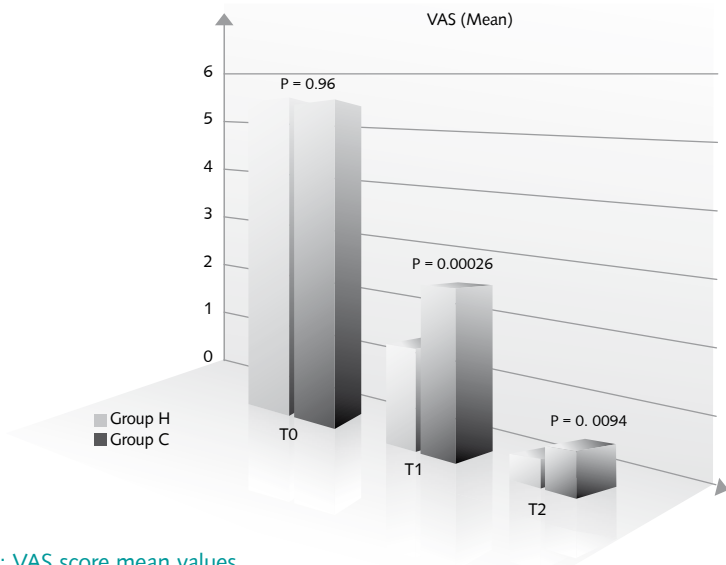


Figure 1: VAS score mean values

Ultrasound scan evaluation (Figure 2a and 2b) at time T1 shows 1 case of persistent lesion, 10 cases of edema and 4 cases of full recovery in group H. Four cases of persistent lesion, 10 cases of edema and only 1 case of full recovery was shown in group C. Analysis at time T2 has pointed out the presence of residual edema only in 1 case and full recovery in 14 cases in group H. In group C the presence of residual edema was shown in 6 cases and full recovery in 9.

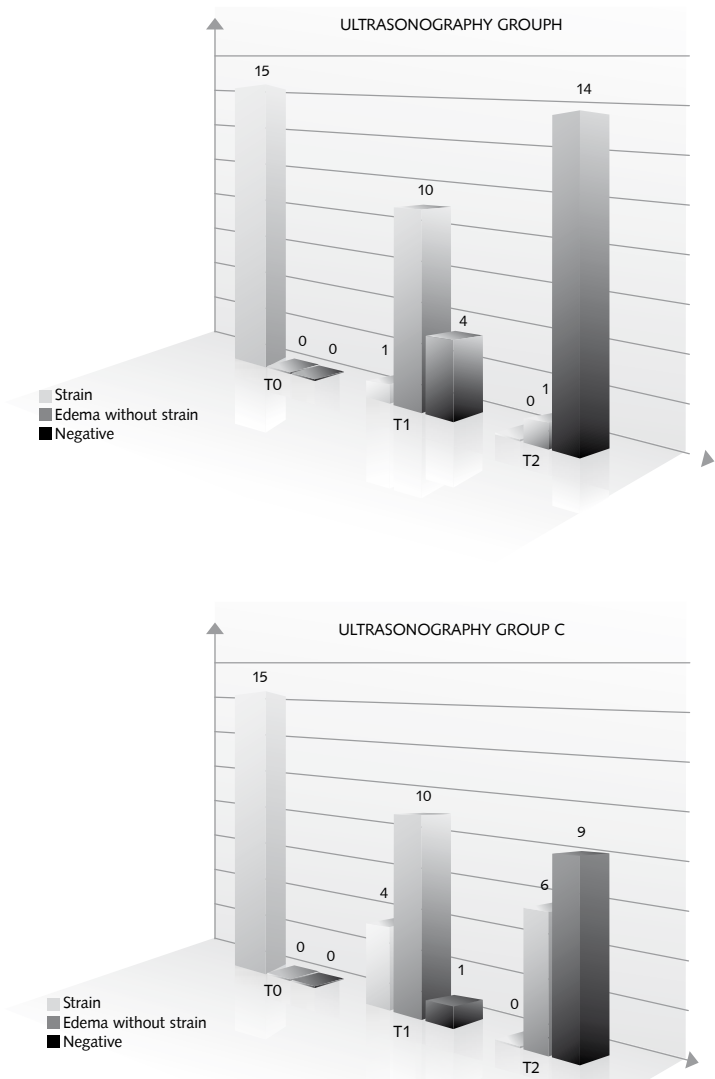


Figure 2a e 2b: Ultrasonography analysis

The statistical analysis of the mean scores of the total physiotherapy sessions, acute and sub-acute phases (Figure 3), has shown highly significant differences ($p < 0.001$) in favour of group H compared to group C. In particular, the mean number of total physiotherapy sessions was 12.2 ± 0.77 for group H and of 14.9 ± 0.74 for group C. The average time until sport activity could be resumed (Figure 4) has shown values of 13.7 ± 0.72 (partial) and 18.9 ± 0.99 (complete) days in group H and of 17 ± 0.65 (partial) and 22.9 ± 0.8 (complete) days in group C. These differences were highly significant ($P < 0.001$).

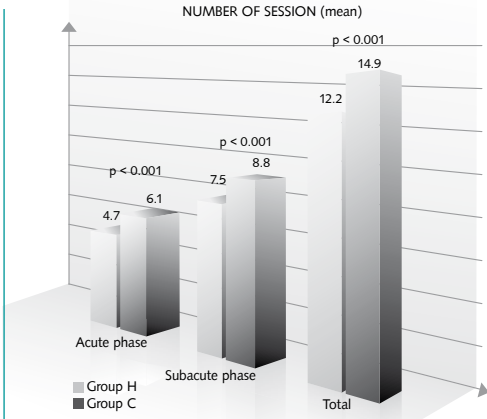


Figure 3: Average number of sessions sport activity.

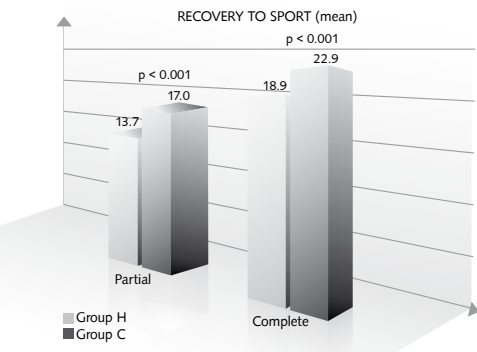


Figure 4: Average time (days) to recovery

Finally, the patients' satisfaction index is shown in Figure 5. Better results were achieved in group H, compared to group C also for this parameter. In group H, 9 patients were very satisfied (60%) and 6 satisfied (40%). In group C, 6 patients were very satisfied (40%), 7 satisfied (46%), 1 a little satisfied (7%) and 1 not satisfied (7%).

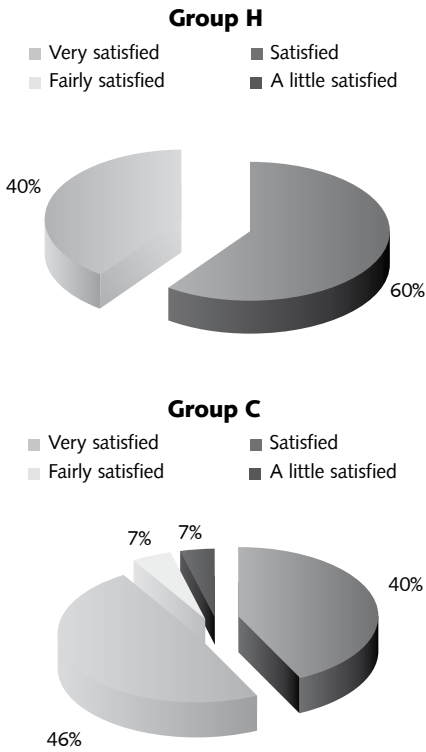


Figure 5: Satisfaction index at the end of treatment

DISCUSSION AND CONCLUSIONS

Modern sport, especially at professional level, requires the identification and treatment of sport-associated pathologies in an increasingly specific and effective way. In particular, there is a surging demand to reduce the recovery time, without compromising the patient safety. Physicians, health care providers and coaches have therefore the duty to allow the athlete to go back to competitive activity, whether professionally or not, in optimal conditions and without the risk of relapse. In this apparently difficult task, the physician can count on last generation physiotherapeutic medical equipments. In particular Hilterapia® has demonstrated to be effective in the treatment of several pathologies of the muscle-skeletal systems. In this clinical study we have focalised out attention on the treatment of 1st degree muscle strains, that are very common in sport activities, comparing a group of patients treated with Hilterapia® (group H) with a group of patients treated with well established and commonly used therapies, CO₂ laser and ultrasounds, (group C). Data obtained using the different evaluation parameters, showed that Hilterapia® was, without doubts, effective in speeding up recovery of 1st degree muscle strain but obtained also better scores compared to traditional therapy.

VAS score results have demonstrated a clear improvement from T0 to T1 and even better from T0 and T2 in both groups, with significative better results ($p < 0.001$ and $p < 0.01$ at T1 and T2 respectively) in group H compared to group C. Particularly, in group H, not only a greater reduction of pain in time, but also earlier analgesia has been shown. The clinical parameter of reduction of pain is widely justified by the ultrasound scan, which demonstrates the progressive disappearance of the lesion in time leading to full recovery, through a phase of persisting peri-lesion edema. Ultrasound scan evidence has demonstrated a quicker recovery of the lesion in patients of the Hilterapia® group compared to the group treated with traditional therapy (at the

end of treatment 14 out of 15 patients of group H made a complete recovery, versus 9 out of 15 in group C). Moreover, group H needed in average less therapy sessions (12.2 vs. 14.9), with shorter times before agonistic activity could be resumed compared to group C (18.9 vs. 22.9 days). In our opinion, the final crucially important parameter is the satisfaction index. Hilterapia® proved to be effective in satisfying the patients needs. In group H all patients declared to be satisfied, while in group C a patient declared to be a little satisfied and another not satisfied because of persistent pain, that required further physiotherapy sessions.

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Effects of pulsed Nd: YAG laser at molecular and cellular level. A study on the basis of Hilterapia®.

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ABSTRACT

Lasers have been widely applied in many different fields of medicine, proving their effectiveness in the treatment of a wide range of diseases. In spite of the great amount of literature, it is difficult to understand the molecular and cellular mechanisms at the basis of the systemic effects induced by laser irradiation because of different kinds of laser used, operative conditions, variety of biological targets and responses. The application of high power lasers in physiotherapy is quite recent. It is due to the development of instruments which allow the control of photothermal and photomechanical processes so as to obtain therapeutic effects without tissue damage. In particular, pulsed Nd:YAG laser has proved hisversatility and efficacy in the treatment of many different musculo-skeletal diseases and it is believed to have anti-inflammatory, anti-oedema, analgesic and also reparative effects. The aim of the studies here presented was to contribute in understanding the molecular mechanisms and cellular processes at the basis of the systemic effects produced by pulsed Nd:YAG laser irradiation. Owing to the lack of chromophores efficiently absorbing Nd:YAG radiation

(wavelength 1064 nm) in cells and tissues, we hypothesized that, rather than photochemical processes, aspecific mechanisms probably due to combined photothermal and photomechanical interactions could be responsible for the above mentioned effects of pulsed Nd:YAG laser. The finding suggeststhat cells "sense" pulsed ND:YAG laser irradiation and respond to it through mechanotransduction machinery. We hypothesize that the interaction between tissue and laser radiation alters the mechanics of cell microenvironment, thus acting on the cells as a mechanical stress.

INTRODUCTION

Phototherapy, that is the use of light for the treatment and prevention of diseases, has been widely used from ancient times till now. From the time of the Pharaohs until relatively recent times the source of light was the sun. The last century saw a rapid evolution in light sources, from inefficient arc lamps to lasers, which are the most advanced kind of light source. The great advantage of the laser, in comparison with other sources, is the very high intensity and monochromaticity of the emitted radiation and also the

possibility to be effectively focalized and coupled to optical fibres. Lasers have been widely applied in many different fields of medicine, proving their effectiveness in the treatment of a wide range of diseases [1, 2]. In spite of the great amount of literature, the molecular and cellular mechanisms at the basis of the systemic effects induced by laser irradiation are mostly unknown. The studies on this subject are very difficult because of the numerous effects and the variety of biological responses, the kind of laser used, the operative conditions, the biological targets (different areas of the body, different tissues, different cell populations, etc.....). However, they are very important because the increase in knowledge can lead to a higher therapeutic efficacy by improvement of laser sources and treatment protocols. Depending on interaction time and effective power density, three types of interactions between laser radiation and tissues can be distinguished: photochemical, photothermal and photomechanical[3]. The effects induced by low power lasers, the first to be applied in physiotherapy, are mostly due to photochemical processes. These occur when endogenous or exogenous chromophores introduced in the tissue absorb radiation of suitable wavelegh. A chromophore molecule which absorbs a photon is converted in an excited state and may subsequently participate in a chemical reaction that leads to the final biological effect [4]. High power lasers have been used at first for tissue ablation and surgery, because they are able to produce important photothermal and photomechanical effects (stress waves) [3]. Their application in fields different from surgery, such as physiotherapy, is quite recent and it has been possible thanks to the development of laser systems with emission modalities which allow the control of photothermal and photomechanical processes, so as to obtain therapeutic effects without tissue damage. In particular, pulsed Nd:YAG laser has proved his versatility and efficacy in the

treatment of many different musculo-skeletal diseases and it is believed to have anti-inflammatory, anti-oedema and analgesic effects [5]. In recent studies, even regenerative effects havebeenrevealed.Indeed,ithasbeenproved that treatment with pulsed Nd:YAG laser is effective in accelerating bone formation [6, 7], in inducing neo- chondrogenesis [8, 9] and in promoting cartilage matrix synthesis [10]. In tendon and ligament lesions, pulsed Nd:YAG irradiation has been demonstrated to improve the reparative process and to antagonize the possible fibrotic evolution [11]. In comparison with other laser sources, the advantages of the pulsed Nd:YAG laser consist in high power joined with a wavelength emission (1064 nm) which is weakly absorbed by cell and tissue chromophores, thus resulting in high penetrating capacity and ability to treat deep tissues and structures. Moreover, the photothermal effect can be controlled in terms of patient safety and comfort by modulating pulse intensity and frequency. Seeing the apparent lack of chromophores efficiently absorbing 1064 nm radiation in cells and tissues, it is quite difficult to ascribe the above reported effects of the pulsed Nd:YAG laser to photochemical processes. It is intriguing enough to hypothesize a less specific mechanism of action, probably due to combined photothermal and photomechanical interactions, producing mechanical stress at cellular level. Indeed, it is well known that loading/unloading and mechanical stress in general can deeply affect the behaviour of practically all the types of mammalian cells [12]. Endothelial, muscle, bone and cartilage cells, neurons and fibroblasts are very sensitive. These cell populations are involved in inflammation, pain, oedema and tissue repair. Therefore, a basic mechanism acting on them could explain the many different systemic effects produced by pulsed Nd:YAG laser. The aim of the studieshere described was to contribute in understanding the molecular mechanisms and cellular processes at the basis of the systemic effects produced by pulsed Nd:YAG laser irradiation.

MATERIALS AND METHODS

1) Cell Cultures

-Human fetal fibroblasts derived from fetuses 10-12 weeks old were maintained in primary culture in Coon's modified Ham's F12 medium containing 10% fetal calf serum, glutamine 2 mM, penicillin 100 U/ml and 100 µg/ml streptomycin. The cultures were incubated in humidified atmosphere at 37°C and 5% CO₂. For the experiments here described, cell populations between passages 9 and 13 were used. Cells were seeded in 24 well plates at a density of 7x10³ cells/well. -Human chondrocytes derived from adult hip joint cartilage(Promocell)were cultured in complete chondrocyte growth medium (Promocell), in humidified atmosphere at 37°C and 5% CO₂. Cell populations between passages 4 and 7 were seeded in 24 well plates at a density of 12x10³ cells/well and used for the experiments. -Human bone marrow cells were obtained fromtheiliaccrestofnormaldonorsmarrow aspirates as previously described [13]. Briefly, whole bone marrow was collected and small aliquots were centrifuged for 10 minutes at 900g; the buffy-coat of white blood cells was recovered and plated in 75 cm² flasks (1.6x10⁵ cells/cm²) in Dulbecco's Minimal Essential Medium (with L-glutamine and 25 mM Hepes) with 50 µg/ml gentamycin, 10% FBS. At the first passage, the morphologically homogeneous population of human mesenchymal stem cells (HMSc) was analyzed for the expression of cell surface molecules using flow cytometry procedures: HMSc, recovered from flasks by trypsin-EDTA treatment and washed in HBSS and 10% FBS, were resuspended in CellWASH buffer (0.1% sodium azide in PBS) with 2% FBS, then incubated with specific conjugated monoclonal antibodies. The ability of HMSc to differentiate along osteogenic, adipogenic and chondrogenic lineages was assayed, as described previously by Pittenger et al. [14]. Cell populations between passages 2 and 4 were used.

Cells were seeded in 24 well plates at a density of 5x10³ cells/well. -Microvascular endothelial cells (postcapillary venular endothelial cells, CVEc) were cultured in DMEM added with 100 µg/ml streptomycin, 100 U/ml penicillin, 2 mM glutamine and 10 % bovine calf serum (BCS, Hyclone, Logan). The cultures were maintained at 37°C and 5% CO₂. Cells between passages 15 and 25, seeded at density 7x10³ cells/well, were used in the experiments.

2) Laser Treatment

Subconfluent cells were plated on glass coverslips in 24 multiwell plates and incubated for 24 h in complete medium, 37°C, 5% CO₂, to allow adherence. In each multiwell plate only 6 wells contained cells. The surrounding wells were filled with black card to avoid light diffusion and reflection. Adherent cell monolayers were directly irradiated for 73 s by a pulsed Nd:YAG laser (ASA S.r.l., Vicenza, Italy), 1064 nm wavelength, 200 µs pulse duration, 10 Hz repetition rate, 458.65 mJ/cm² energy fluence. The treatment was repeated for three consecutive days in sterile conditions, under temperature control. Measurements carried out by a pyroelectric detector indicated that, relatively to the impinging laser energy, 80% was either not absorbed or reflected, 20% was released to the medium and substrate on which the cell monolayer adhered. We did not find any measurable laser absorption by the cell layer alone, as could be expected because generally the cells do not contain endogenous chromophores absorbing at 1064nm, the emission wavelength of Nd:YAG laser. Controls were prepared and kept in the same conditions used for the treated samples, except for laser irradiation.

3) Loading exposure

Cells were plated on glass coverslips and incubated for 24 h in complete medium, at 37°C and 5% CO₂, to allow adherence. 50 ml centrifuge tubes were partially filled with agarose gel (Merck),

on which the coverslips were placed with the surface perpendicular to the tube axis. To avoid shear stress, the tubes were then completely filled with culture medium. The exposure to loading was accomplished by hypergravitational stress in a thermostated centrifuge (3-18K, Sigma Zentrifugen). The treatment consisted of 5 periods of 10 min exposure to 10xg (227 rpm) spaced with 10 min recovery periods at 1xg, at 37°C. Controls were prepared as well, except for loading stimulation.

4) Immunofluorescence Microscopy

At the end of the experiments, the cells were fixed for 5 min in cold acetone, then washed in PBS. After blocking unspecific binding with PBS containing 3% BSA, the cells were incubated overnight at 4°C with the specific anti-human monoclonal antibodies α -tubulin, α and β actin, vimentin, $\alpha 5 \beta 1$, $\alpha v \beta 3$ integrin, fibronectin, collagen type I and II, aggrecan, Sox 9, Runx 2, PPAR γ (Chemicon). The cells were then incubated with anti-mouse IgG conjugated with fluorescein isothiocyanate (IgG-FITC) (Chemicon). Negative controls were obtained by omitting the primary antibodies. Samples were evaluated by an epifluorescence microscope (Nikon) at 100x magnification and imaged by a HiRes IV digital CCD camera (DTA). Image analysis was performed by extracting, for each cell image, the region of interest (ROI) by appropriate software (Image Pro Plus). Then, the mean pixel value (16 bit, gray level) related to the mean fluorescence intensity and therefore to the target expression was calculated.

5) Gene profile analysis

Gene expression profiling was analysed by recovering total RNA from cell cultures: the cells were resuspended in 2X lysis buffer (Applied Biosystems) and then immediately frozen. Total RNA was extracted by using the ABI PRISM® 6100 platform and reverse transcribed using a high-capacity cDNA Archive Kit (Applied Biosystems), random hexamer primers, and the following thermal profile: 25°C

for 10 min, 42°C for 1h and 95°C for 5 min. The cDNA was probed with TaqMan assays; results were subsequently analysed within the Panther database platform (www.pantherdb.org).

6) Data analysis

All the experiments were carried out in triplicate. For immunofluorescence analysis, at least 30 cells per slide were scored in 10 random fields/slide, and the data were expressed as mean $\pm$ SD. Statistical significance was determined using a Student's test. A p value lower than 0.05 was considered statistically significant. For gene expression, 1-way ANOVA and Duncan test ($p < 0.001$) were applied.

RESULTS

1) Cytoskeleton

It is well known that cytoskeleton has a key role in the process of mechanotransduction at cellular level [15]. This means that cytoskeleton, together with other cell structures, is responsible for cell "sensitiveness" and, through the reorganization of its network, triggers cell "response" to external forces. Therefore, in order to evaluate whether the effect of pulsed Nd:YAG laser on cells could be attributed, at least in part, to mechanical stress, the expression of the major cytoskeleton proteins, i.e. tubulin, actin and vimentin, has been assessed both in endothelial and connective tissue cells. These proteins are responsible for the assembling of the three structural components of cytoskeleton: microtubules, microfilaments and intermediate filaments, respectively. After the treatment, significant changes in cytoskeleton network have been observed. In general, all the cell populations studied showed a decrease in tubulin and vimentin expression ranging from 25 % to 35% ($p < 0.05$). In addition to the quantitative differences, interesting morphological alterations appeared (Figure 1 and 2). In comparison with controls (Figure 1A), the microtubules decreased significantly

in the peripheral area of the cells (Figures 1B and 1C), while in the perinuclear area the network often became even closer (Figure 1C). Sometimes, in endothelial cells, numerous microtubule organizing centres were found (Figure 1D).

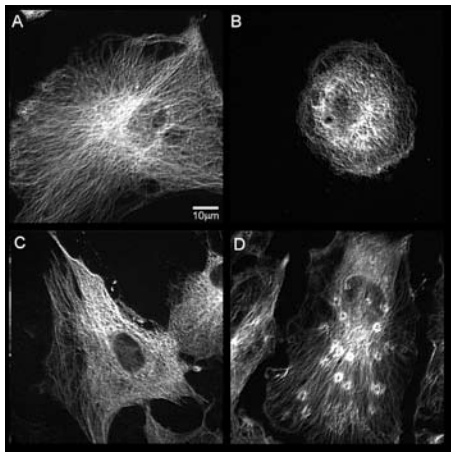


Figure 1: Immunofluorescence Microscopy. Cells from connective tissues (A, B, C) stained with specific anti-human monoclonal antibodies in order to assay tubulin expression. In comparison with controls (A), the microtubules decrease significantly in the peripheral area of the cells exposed to pulsed Nd:YAG laser (B, C), while in the perinuclear area the network often becomes even closer (C). Numerous microtubule organizing centres can be found (see the endothelial cell in D).

The actin ring, which is a network of actin microfilaments subtending the plasma membrane, was clearly evident in control, non treated cells (Figures 2A and 2B), but quite completely disappeared in the treated ones (Figures 2C and 2D). Transcytoplasmatic stress fibres, long and parallel filaments which crossed the cell from end to end, strongly increased in cells of the connective tissues after the treatment (Figure 2C), while in endothelial cells actin was associated with membrane structures resembling ruffles (Figure 2D). It is known that stress fibres are related to the formation of focal adhesions, connection points between cell cytoskeleton and extracellular matrix components, through membrane proteins known as integrins [16]. Indeed, after laser treatment, changes in distribution of membrane integrins have been observed too (data not shown).

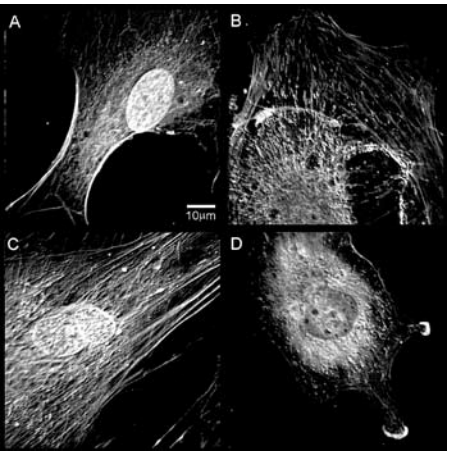


Figure 2: Immunofluorescence Microscopy. Human mesenchymal (A, C) and endothelial cells (B, D) stained with specific anti-human monoclonal antibodies in order to assay actin expression. The actin ring, which is a network of actin microfilaments subtending the plasma membrane, is clearly evident in control, non treated cells (A, B), but quite completely disappears in the treated ones (C, D). Transcytoplasmatic stress fibres strongly increase after treatment with pulsed Nd:YAG laser (C), while in endothelial cells actin is associated with membrane structures resembling ruffles (D).

2) Extracellular Matrix

The extracellular matrix (ECM), that is the extracellular part in animal tissues, provides support and anchorage for cells, regulates intercellular communication and cell's dynamic behavior, modulates the release of growth factors, acts as a compression buffer against mechanical stress [17]. The ECM, which is composed by glycoproteins and glycosaminoglycans, is produced by the cells themselves and its formation is essential for processes like growth, wound healing and tissue repair. The ECM is the defining feature of connective tissues, whose mechanical properties change rapidly, adapting to changes in load [18]. It has been widely demonstrated that mechanical factors regulates the production of ECM [19, 20]. Therefore, part of our study has been devoted to verify whether the PM stress produced by pulsed Nd:YAG laser irradiation was effective in affecting the production of ECM molecules by connective tissue cells. After laser treatment, we analyzed the expression of relevant ECM components in different cell types: collagen II and aggrecan in chondrocytes, collagen I and fibronectin in fibroblasts.

Fibronectin production was assessed also in endothelial cells, because of its importance in reparative processes. In cells of the connective tissues, the treatment significantly enhanced the expression of the ECM molecules considered: in chondrocytes, collagen II (Figure 3) and aggrecan (Figure 4) increased of about 60% ($p < 0.0001$) and 70% (0,0002), respectively, in comparison with controls; in fibroblasts, collagen I increased of the 25% ($p < 0.01$), while fibronectin increased of the 30% ($p < 0.003$) and significantly changed its distribution: thick and ordered fascicles appeared around the cells, connecting them to the substrate. Similar changes in the distribution of fibronectin fascicles were found in endothelial cells: the randomly distributed network of fascicles observed in control cells was replaced, in treated cells, by fascicles ordered in parallel (Figure 5). Besides, the treatment increased both cell spreading and cell-cell interactions (data not shown).

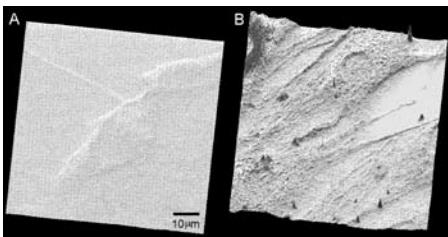


Figure 3: Immunofluorescence Microscopy. Human chondrocytes stained with specific anti-human monoclonal antibodies in order to assay collagen II expression. In comparison with controls (A), the samples treated with pulsed Nd:YAG laser (B) show an increase of about 60% in collagen II expression.

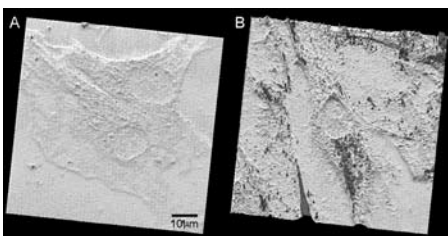


Figure 4: Immunofluorescence Microscopy. Human chondrocytes stained with specific anti-human monoclonal antibodies in order to assay aggrecan expression. In comparison with controls (A), the samples treated with pulsed Nd:YAG laser (B) show an increase of about 70% in aggrecan expression.

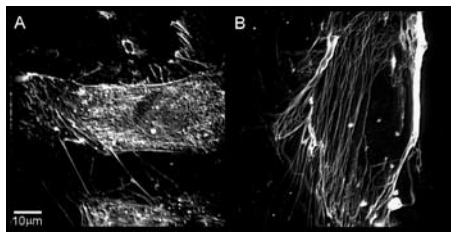


Figure 5: Immunofluorescence Microscopy. Endothelial cells stained with specific anti-human monoclonal antibodies in order to assay fibronectin expression. The randomly distributed network of fibronectin fascicles observed in control cells (A) was replaced, in treated cells (B), by fascicles ordered in parallel.

3) Cell Differentiation

Cellular differentiation is the process by which a pluripotent cell acquires a defined "cell type", this means that the cell becomes specialized in order to perform a specific function, as in the case of a neuron, a blood or a bone cell [21]. During differentiation, both genotypic and phenotypic expression of a cell may change dramatically. A marker of differentiation is a molecule whose expression is particularly intense in a specific type of cell, in one or more differentiation steps. Therefore, the monitoring of one or more differentiation markers in a cell is useful to recognize the type and differentiation degree of the cell itself. Physical stimuli, in particular the mechanical ones, but also gravitational stress, electromagnetic fields, etc..., are known to affect cell differentiation [22, 23, 24]. In order to assess the effect of pulsed Nd:YAG laser irradiation on cell differentiation, we carried out experiments with HMSc able to differentiate through the osteoblastic, chondrocytic and adipocytic pathways. After the laser treatment, we analysed HMSc by immunofluorescence microscopy in order to evaluate the expression of Sox 9, Runx 2 and PPAR γ , major differentiation markers of osteoblastogenesis, chondrogenesis and adipogenesis, respectively. The results showed that in control samples all the considered differentiation markers were weakly expressed (Figures 6A, 7A, 8A), as expected in undifferentiated cells. In treated samples we found a significant increase in expression of Sox

9 (Figure 6B) and Runx 2 (Figure 7B), transcription factors which have a key role in the activation of chondrocyte-specific [25] and osteoblast-specific [26] genetic programs, respectively. Transcription factors are proteins that control the transcription of genetic information: Sox 9 and Runx 2 control the expression of genes involved in chondrocyte and osteoblast differentiation. Contrariwise, in the treated cells the expression of the nuclear receptor PPAR γ (Figure 8B), which has been identified as a dominant regulator of adipogenesis [27, 28], was even lower than in the control ones.

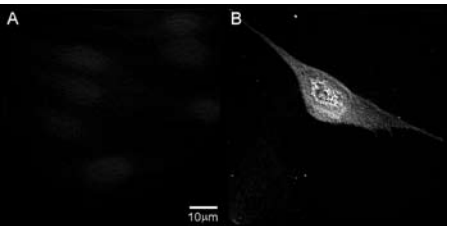


Figure 6: Immunofluorescence Microscopy. HMSC stained with specific anti-human monoclonal antibodies in order to assay Sox 9 expression. The protein is weakly expressed in control cells (A) but strongly increases in cells exposed to pulsed Nd:YAG laser irradiation (B).

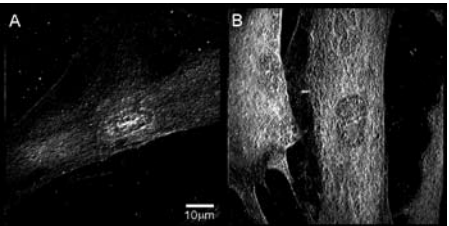


Figure 7: Immunofluorescence Microscopy. HMSC stained with specific anti-human monoclonal antibodies in order to assay Runx 2 expression. The protein is weakly expressed in control cells (A) but strongly increases in cells exposed to pulsed Nd:YAG laser irradiation (B).

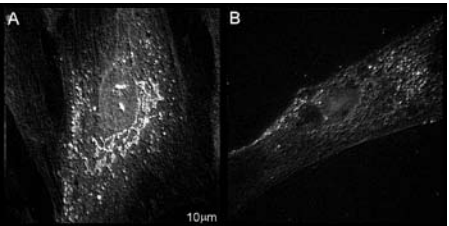


Figure 8: Immunofluorescence Microscopy. HMSC stained with specific anti-human monoclonal antibodies in order to assay PPAR γ expression. The protein is weakly expressed in control cells (A) and further decreases in cells exposed to pulsed Nd:YAG laser irradiation (B).

4) Genetic expression

In order to verify whether the changes in phenotypic expression of connective tissue cells induced by pulsed Nd:YAG laser had a match at genotypic level, we analysed gene expression profile in connective tissue cells exposed to the laser irradiation. Moreover, we compared the gene expression profile induced by pulsed Nd:YAG laser with the one induced by loading, because important studies demonstrated that alterations in the cellular force balance due to mechanical stress can influence gene expression in the nucleus [29]. Gene expression profiling revealed that in laser-treated cells many important pathways were overexpressed (Figure 9). Among them, the “general transcription regulation pathway” and the “cytoskeletal regulation by Rho GTPase pathway”, in agreement with the changes observed at phenotypic level in protein expression and cytoskeleton organization. Considering the expression of single genes, we found a significant upregulation of the genes MEN1, NF1 and GIL1 ($p<0.05$), which are involved in the commitment of multipotential mesenchymal stem cells into the osteoblast lineage [30], in bone development and remodelling [31], in the control of chondrocyte and osteoblast differentiation [32], respectively. This result is in agreement with the increase in Sox 9 and Runx 2 expression found at phenotypic level. Contrariwise, the gene encoding for PPAR γ resulted strongly downregulated, in agreement with the observed decrease in protein expression. Interestingly, we obtained similar results in cells exposed to overload (Figure 9).

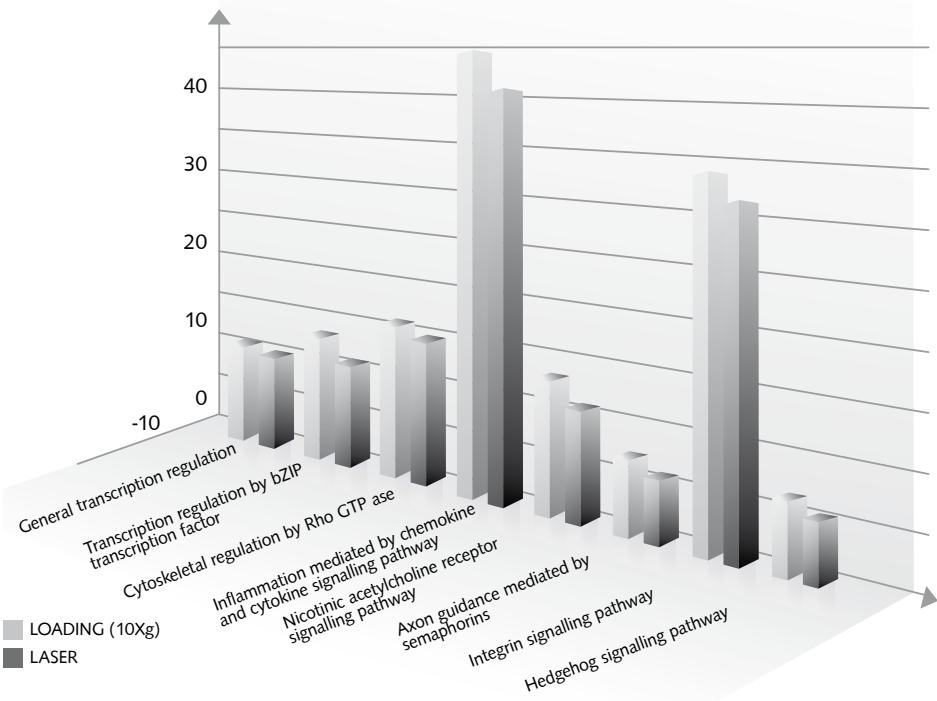


Figure 9: Gene expression profiling reveals that in laser-treated cells many important pathways are overexpressed in comparison with controls.

DISCUSSION

The results clearly demonstrate that the treatment with pulsed Nd:YAG laser affected cytoskeleton organization in all the cell types (endothelial, mesenchymal, connective tissue cells) which have been investigated in our experiments. The rearrangement concerned both the distribution of the three major cytoskeleton components (microtubules, microfilaments, intermediate filaments) and the expression intensity of the proteins

responsible for their assembling, tubulin, actin and vimentin, respectively. Besides the changes in cytoskeleton network, differences in distribution of membrane integrins were found. These findings are consistent with the hypothesis that pulsed Nd:YAG laser radiation induces mechanical stress on cells, likely changing the mechanics of the cell microenvironment. Indeed, very similar effects have been found in the same cell types exposed to loading [33], which is a kind of mechanical stress normally occurring in physiological conditions. Mechanical stress is ever present in the cellular environment, whether through external forces that are applied to tissues or endogenous forces that are generated within the cytoskeleton. Over the past decade, in vitro studies have demonstrated that cells may sense mechanical stress through changes in the balance of forces that are transmitted across transmembrane adhesion receptors (integrins) which link the cytoskeleton to the ECM and to other cells. These changes, in turn, alter the ECM mechanics, cytoskeletal organization, cell shape and nuclear scaffold [34]. Actually, the more advanced research deals with possible mechanisms by which applied forces, cell-generated forces and changes in substrate mechanics can exert changes in cell function through common mechanotransduction machinery [35]. Mechanotransduction, that is the process of translating external forces acting on a cell into a biological response, involves the ECM, integrins, calcium channels, guanosine triphosphatases (GTPases), adenylate cyclase, phospholipase C (PLC) and mitogen-activated protein kinases (MAPKs), all of which play important roles in early signalling triggered by mechanical stress. Cytoskeleton has a central role in mechanotransduction, orchestrating multiple signal pathways [15]. Moreover, it has been discovered that many of the signalling molecules that are turned on by integrins are not floating around in membrane lipid bilayer; rather, they are immobilized on the cytoskeleton structures and specifically concentrated

within the anchoring sites. This suggests that the mechanism of signal integration is based on the spatial organization of signaling molecules associated with cytoskeleton elements within the anchoring sites. [36, 37]. For example, it has been demonstrated that mechanical stress enhances the proliferation and metabolic activity of osteoblast-like cells through the essential role of microtubules and microfilaments, respectively [38]. Further support to the hypothesis that cells sense pulsed Nd:YAG laser irradiation as a mechanical stress, and respond to it by activation of mechanotransduction machinery, was supplied from the results of our investigation on the effect of laser treatment on the production of ECM. The exposure to pulsed Nd:YAG laser stimulated the synthesis of ECM molecules in connective tissue cells. In particular, enhanced expression of collagen II and aggrecan was observed in chondrocytes, while collagen I and fibronectin increased in fibroblasts. These findings are in agreement with many reports of other authors describing fibroblast and chondrocyte activation and control of ECM production by different kinds of mechanical stress [39, 40, 41]. Moreover, in a previous study, we demonstrated that the effects of pulsed Nd:YAG laser on ECM production by connective tissue cells are very similar to the ones induced by loading [33], which is a physiological stimulus because connective tissues have antigravitational function. Interestingly, we observed that pulsed Nd:YAG laser radiation affected also fibronectin distribution and the assembling of fibronectin fibrils. In fact, in treated fibroblasts, thick bundles of fibronectin fibrils appeared. The same effect was observed by other authors in fibroblasts cultured in hypergravity, that is in loading conditions [42]. In treated endothelial cells, a highly organized array of fibrils replaced the randomly distributed network showed by control samples. Fibronectin, which is synthesized by all the cell kinds (tumor cells excluded), is particularly important in ECM organization: it is able

to bind collagen and cell membrane, thus connecting ECM macromolecules each other and with cell surface. It is involved in cell growth and differentiation, cell adhesion and migration. In particular, it mediates cell adhesion preventing cell migration [43]. The effectiveness of pulsed Nd:YAG laser in controlling ECM production and arrangement of fibronectin molecules could be of consequence in wound healing, tissue repair and regeneration. On the other hand, our very preliminar experiments (not yet published data) showed that in unloading conditions, which are known to delay wound healing, both fibroblasts and endothelial cells produce an impressive quantity of fibronectin. It forms an intricate network which catches cells, thus increasing their adhesion and hampering migration. In particular, the fibronectin rearrangement induced by pulsed Nd:YAG laser could affect adhesion, spreading and migration of endothelial cells and, consequently, angiogenesis and endothelium permeability. These effects on endothelial cell function could be at the basis of the irradiation-mediated improvement in tissue repair and oedema resolution. The efficacy of pulsed Nd:YAG laser in favouring tissue repair processes could be partly due to its ability in inducing specific cell differentiation patterns. In fact, our experiments demonstrate that pulsed Nd:YAG laser irradiation can also affect cell differentiation, which is one of the three major genetic programs in cells, together with growth and apoptosis. Indeed, laser treatment was effective in inducing specific differentiation patterns in HMSC, without the cooperation of added biochemical factors. In comparison with controls, we found in treated HMSC a significant increase in expression of Sox 9 and Runx 2, major markers of chondrogenesis and osteoblastogenesis, respectively, while the expression of PPAR γ , specific marker of adipogenesis, decreased. We demonstrated that the same differentiation patterns were induced in HMSC by loading, while unloading enhanced the expression of PPAR γ , and

depressed that of Sox 9 and Runx 2 [44]. The close likeness between the effects of pulsed Nd:YAG laser and loading on HMSc differentiation together with the fact that laser treatment promoted chondrogenesis and osteoblastogenesis, maturation processes of cells belonging to tissues with antigravitational function, strengthen the hypothesis that cell response to the stimulation by pulsed Nd:YAG laser occurs via mechanotransduction machinery. Finally, our experiments demonstrated that pulsed Nd:YAG laser can affect gene expression. A close relationship between phenotypic and genotypic expression in connective tissue cells exposed to pulsed Nd:YAG laser irradiation has been found. In fact, in comparison with controls, important pathways involved in cytoskeleton regulation and integrin signalling, as well as genes involved in chondrogenesis and osteoblastogenesis resulted overexpressed. Moreover, once again the changes produced in gene expression profile by pulsed Nd:YAG laser resulted nearly the ones produced by loading.

CONCLUSIONS

In conclusion, the results of our experiments demonstrate that pulsed Nd:YAG laser may deeply affect cell behaviour. The exposure to laser radiation induces:

- reorganization of cytoskeleton network, observed in all the cell populations studied;
- increase in production of ECM by cells of connective tissues, which could be of consequence in tissue repair and regeneration;
- regulation of fibronectin production/distribution and fibril arrangement, which may strongly affect endothelial cell function;
- induction of specific differentiation patterns in HMSc, which undertake maturation pathways typical of the specialized cellular elements belonging to tissues with antigravitational function;
- changes in gene expression profile, in agreement with the changed phenotypic expression.

These effects, occurring at molecular and cellular level, are consistent with the systemic ones observed in patients treated with pulsed Nd:YAG laser, therefore they can be regarded as the cellular response at the basis of Hilterapia®. Moreover, the findings show that the irradiation with pulsed Nd:YAG laser induced in cells of the connective tissues as well as in HSMc and endothelial cells a biological response very close to the one produced by loading. Contrariwise, unloading conditions often induce opposite effects. The findings suggest that cells “sense” pulsed ND:YAG laser irradiation as a mechanical stress and respond to it through mechanotransduction machinery. We hypothesize that the interaction tissue- laser radiation and consequent energy release, alters the mechanics of cell microenvironment thus acting on the cell as a mechanical stress.

ACKNOWLEDGEMENTS

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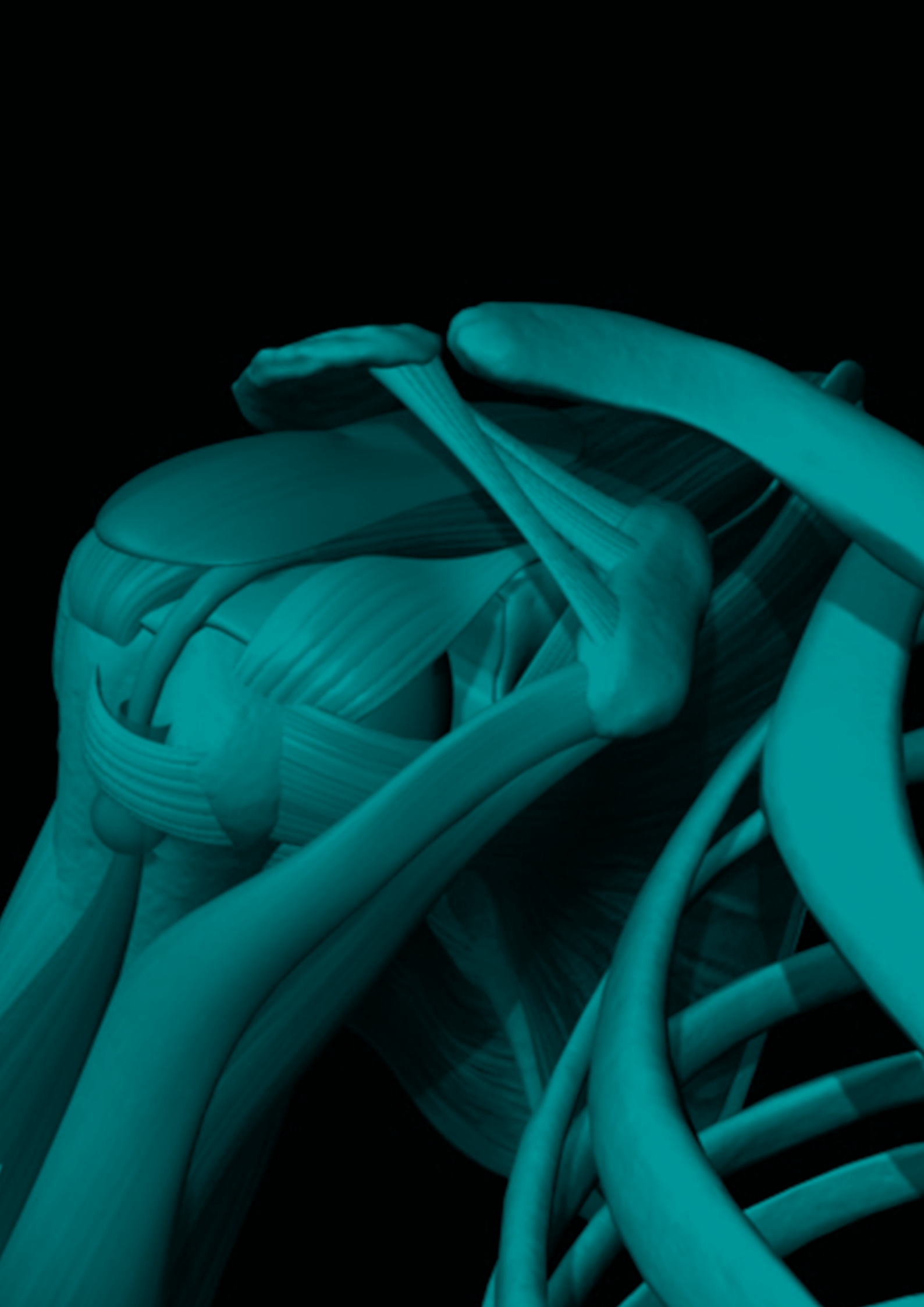
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ABSTRACT

Key words: Ankle pain, Hilterapia®

Hilterapia® and chronic ankle pain syndromes.

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ABSTRACT

According to the third Newton's principle, the ground produces equal and opposite forces to those of a subject in leaning phase. Baumhauer and collaborators demonstrated that joint laxity, foot length, ankle anatomical alignment and ligaments stability are not significant risk factors for chronic ankle pain syndromes, while they registered an higher sprain incidence in subjects with muscle strength imbalance. According to Wright, once the foot has touched the ground, in a position potentially able to cause sprain, ankle pronator muscles must be able to rapidly react to prevent excessive supination and chronic pain syndromes. Freeman and collaborators hypothesized that ankle chronic traumas could damage the capsule and ligaments mechanoreceptors and concluded that the partial deafferentation of these receptors could contribute to the functional instability.

In this study, a marked reduction in chronic pain symptomatology has been observed after Hilterapia® (pulsed Nd:YAG laser, mod. Hiro 3, ASA s.r.l., Vicenza, Italy) and the postural optimisation has been quantified with optoelectronic systems (Digital Biometry Images Scanning). Several scientific papers have been published about the analgesic and bio stimulating effect of Hilterapia®. Various authors have also highlighted its utility in accelerating the articular recovery process and in promoting ligament lesions healing. From our experience, we can assert that a rehabilitation protocol integrated with Hilterapia® is extremely effective, and could be considered the gold standard in the treatment of soft tissues pathology as well as in I and II degree chondropathies of the tibia-fibula-astragalus region.

Key words: Osteoarthritis, High Intensity Laser, Hilterapia®, Low level laser, Ultrasound.

Clinical experience using Hilterapia® in “knee arthrosis”.

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ABSTRACT

Knee osteoarthritis (OA) is a common musculoskeletal disorder in Saudi population. Functional disability “like walking and squatting”, and pain are the most common complaints by OA patients. The aim of this study was to compare the efficacy of Hilterapia® against LLL and US in combination with exercises in relieving knee pain, walking distance without pain and squat in patients with knee early osteoarthritis. Thirty subjects with knee early OA, males and females, age between 40 and 72 years, were enrolled. The inclusion criterion was knee/s pain no more than two years, with clinical and radiological confirmation of the diagnosis of OA. Participants were randomly and equally classified into three groups. All participants received exercise program for knee in combination with one of the therapeutic modalities compared (Hilterapia, LLL, US). Participants at group (1) received Hilterapia®, in group (2) received LLL and in group (3) received US therapy. All participants received six treatments for three weeks (two treatments/week).

Equipments used were 3.0 HIRO (ASA S.r.l., Vicenza, Italy), Low level laser (ASA S.r.l., Vicenza, Italy) Ultrasound Unit (Zimmer Medizin System). Evaluation parameters were: perceptive pain using VAS, walking distance without pain (in meters), and squat with/without pain. Measurements were taken pre-treatment and after completion of the six sessions. The results obtained show that: Hilterapia® was more effective than LLL and therapeutic US in inhibition of pain, increasing walking distance without pain and improvement of ability to squat than LLL in people with early OA. LLL and US had some efficacy, but no differences between LLL and therapeutic US have been observed in inhibition of pain, in increase of the walking distance without pain and improvement of the ability to squat in people with early OA. Therefore, Hilterapia® in combination with exercises can be considered as an effective plan for relieving pain, and improving functions in patients with knee osteoarthritis.

Key words: Lateral epicondylitis, Hilterapia[®], ESWT (Extracorporeal Shock Wave Therapy)

Comparison of the clinical results of Hilterapia[®] and eswt in the lateral epicondylitis.

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ABSTRACT

Lateral epicondylitis, so called tennis elbow, is the term used to describe the pain of uncertain pathogenesis that is centered over the common extensor origin, at the lateral aspect of the elbow, and that interferes with the activities of daily living, sports and work. Tennis elbow is a degenerative condition of the tendon fibers that attach on the bony prominence (epicondyle) on the outside (lateral side) of the elbow. The tendons involved are responsible for anchoring the muscles that extend or lift the wrist and hand. The aim of this study was to compare the efficacy of Hilterapia[®] against ESWT (Extracorporeal Shock Wave Therapy) in patients with lateral epicondylitis of the elbow. Fifty subjects, subdivided in two groups, have been included in the study. The inclusion criterion was: lateral epicondylitis with failure of at least 6 months of conservative treatment. One group was treated with Hilterapia[®] (9 sessions, three time a week) and the other

group with ESWT (3 sessions, one/week). Results have been evaluated by using VAS (visual analog scale) and SET (simple elbow test) score at baseline and after one, three and six months. After nine months, the patient's satisfaction index has been evaluated by Roles and Maudsley score. Equipments used were HIRO 3 (ASA, S.r.l., Vicenza, Italy) and EvoTron (Switech Medical AG, Kreuzlingen, Switzerland). Each group achieved improvement at each follow up, in all parameters measured. The major improvement was achieved in both groups during the first months and continued to a lesser extent for up to six months. No significant differences between Hilterapia[®] and ESWT groups were detected across the different time periods in any measured parameter. This study suggests that Hilterapia[®] could be considered as safe, effective and noninvasive treatment modality for lateral epicondylitis. Another one attractive merit of the Hilterapia[®] is that patients do not have pain or side effects during the treatment and therefore the satisfaction index of patients is very high.

