Analgesic effects of high intensity laser therapy (HILT) for chronic hemophilic artrhopathy: a pilot study on safety, tolerability and clinical outcomes.

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ABSTRACT

The aim of this study was to verify analgesic effects of High Intensity Laser Therapy (HILT) for the treatment of chronic artrhopathy in adult hemophilic patients and to verify its safety and tolerability.

Eleven adult hemophilic patients of any degree with or without inhibitors, diagnosed with chronic artrhopathy, were enrolled in this pilot open-label study by three Hemophilia Treatment Centers. All patients were treated with 3 High Intensity Laser applications/week in the symptomatic joint for 3 consecutive weeks. Clinical evaluations assessed reactions at application site and skin reactions. Outcomes were defined as variations in the Nieschl's and VAS Scores and Hemophilia Joint Health Score 2.0, compared to the baseline, as well as documented adverse events (AEs) and serious adverse events (SAEs).

At the end of the study, after 3 weeks of therapy, we recorded a statistically significant decrease of Nieschl's score (-1.9±2.47) and VAS score (-27.1±30.66) (both at $P<0.05$), while no statistical difference was observed between the basal and last visit with regard to HJH-2.0 scores. Three local reactions at the site of therapy were reported, two of which were non-severe and one (paresthesia) was of moderate intensity. Three adverse events were experienced, such as transient gonalgia of the right knee that was considered to be possibly related to the study treatment. No bleeding at the site of therapy application was reported.

In this pilot study, HILT demonstrated a statistically significant analgesic effect for chronic artrhopaty in hemophilic adult patients; the analgesic effect was evident even after few treatment sessions and it was well tolerated with rare adverse events. Further studies have to be carried out to clarify if different doses and schedule applications could improve the clinical outcomes.

INTRODUCTION

Hemophilia is a hereditary bleeding disorder caused by mutations in the gene for factor VIII (Hemophilia A) or factor IX (Hemophilia B) [1]. Progressive joint destruction resulting from intra-articular bleeding is the major morbidity and disability affecting patients with hemophilia. This process starts in the joints when affected children begin to walk and just few recurrent bleeding episodes in a single joint can determine the onset of a progressive degenerative process that eventually leads to hemophilic arthropathy [2]. The joints most commonly affected are the ankles, knees and elbows. The progressive functional incapacity and chronic pain that requires pain killer medications and surgical intervention, together with manifestations of acute hemarthrosis, are the cause of frequent clinical visits and hospitalization associated with a poor quality of life (QoL) and loss of self-confidence. Disability is directly correlated with pain level [3-4].

High power lasers application in physiotherapy is quite recent; High Intensity Laser Therapy (HILT) performs a pulsed Nd: YAG laser beam that principally induces photomechanical and photo thermal effects at a sufficient depth to irradiate human joints (Figure 1) . The

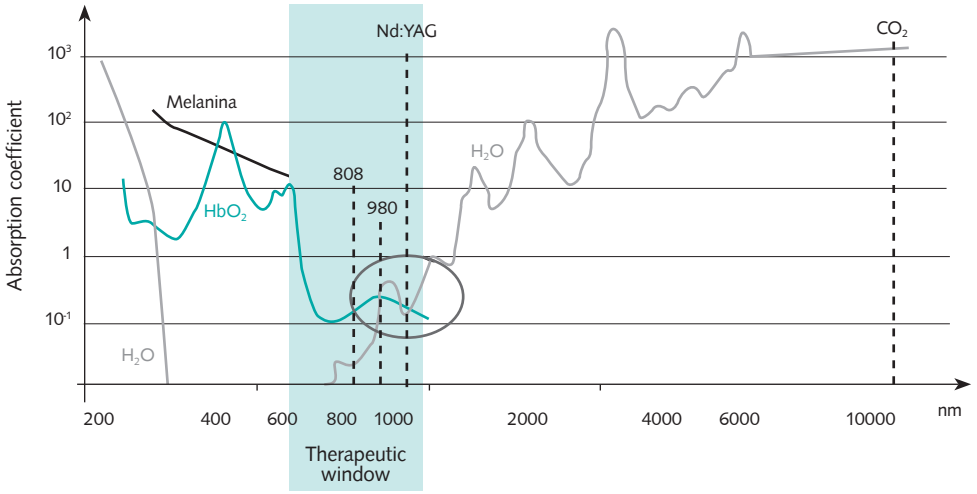

Figure 1: Laser Nd: YAG 1064 λ therapeutic window.

AGE, YEARS (SD)	40.6 (13.4)	
SEVERITY OF HEMOFILIA		
	Moderate	1 (9%)
	Severe	10 (91%)
BLEEDING HISTORY		
	Target joints	11
	Sport Activities	7 (64%)
	Recurrent hemarthrosis	10 (91%)
	Recurrent bleeding	3 (27%)
	Bleeding in the last 7 days	2 (18%)
REASON FOR TREATMENT		
	Back pain	1 (9%)
	Bilateral ankle pain	1 (9%)
	Joint pain	3 (27%)
	Joint pain and stiffness	1 (9%)
	Pain at rest	1 (9%)
	Pain affecting left ankle	1 (9%)
	Pain right ankle	1 (9%)
	Pain right elbow	1 (9%)
	Right shoulder pain	1 (9%)

Table I: Patients characteristics

duty cycle of pulsed Nd: YAG laser used for HILT allows to have photothermal effects without tissue denaturation or extravascular cell membrane lesions [5]. High Intensity Laser Therapy (HILT) peculiarity is its ability to transfer highly energetic photonic packages in deep tissues in a completely non-invasive way, helping to rebalance the homeostasis in the course of chronic-degenerative phenomena [6-8]. Since 1960 Low Level Laser Therapy (LLLT) has been used clinically to stimulate several biological tissues, targeting cell metabolism, reducing post injury inflammatory processes, accelerating soft tissue healing and stimulating new blood vessels growth [9-13].

HILT demonstrated to be more effective than LLLT in pain and disability management showing good results in osteoarticular disease as well as in osteoarthritis [5-7] with consequent QoL improvement [14,15].

Although the pathogenesis of hemophilic artrhopathy has not been fully elucidated, it appears to have similarities with the degenerative joint damage that occurs in osteoarthritis and the inflammatory processes associated with rheumatoid arthritis [16]. The purpose of this pilot study is to verify the safety, tolerability and clinical outcomes of high-intensity laser applications for the treatment of chronic artrhopathy in adult hemophilic patients.

MATERIALS AND METHODS

Eleven hemophilic patients older than 18 years of age, with a mean age of 41, diagnosed with chronic arthropathy were enrolled in 3 Haemophilia Treatment Centers. Ten patients were affected by severe hemophilia, one by moderate hemophilia (Table I). All patients were not infused by replacement therapy before laser exposure, or had taken cortison therapy during or after laser exposure. They were treated with the equipment ASA-SH1, (ASA s.r.l. El.En.Group Italy) laser type Nd:YAG, Class 2a, λ 1064 nm, that emits infrared light. Three non-invasive, transcutaneous HILT applications per week in the target joints for three consecutive weeks were provided keeping within the following parameters: Fluence: 360 to 760 mJ/cm²; Frequency range: 10 - 35 Hz; Total energy: from 500 to 1500 J; Application time: 6

Mean ± S.D.				
	Nieschl's score	VAS score	HJH Global Gait score	HJH Total score
Baseline	4.27±1.95	62.82±22.84	1.18±2.00	27.45±15.05
After 1 week	3.00±1.48	45.64±20.11	1.36±2.00	27.45±15.31
After 2 weeks	2.60±1.51	39.00±19.69	1.40±2.00	26.00±15.78
After 3 weeks	2.50±1.90	38.00±25.41	1.40±2.00	26.00±15.78
Difference vs basal visit				
N. Mean ± S.D.	Nieschl's score	Signed Rank Test Significance	VAS score	Signed Rank Test Significance
After 1 week	11 1.27±2.00	N.S.	11 17.18±18.69	P<0.01
After 2 weeks	10 1.80±2.25	P<0.05	10 26.10±28.85	P<0.05
After 3 weeks	10 1.90±2.47	P<0.05	10 27.10±30.66	P<0.05

Table II: Clinical outcomes

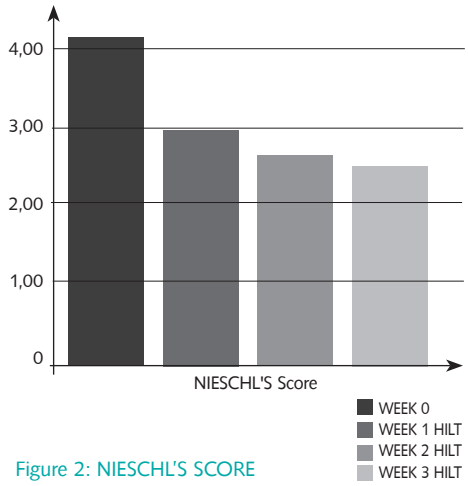

Figure 2: NIESCHL'S SCORE

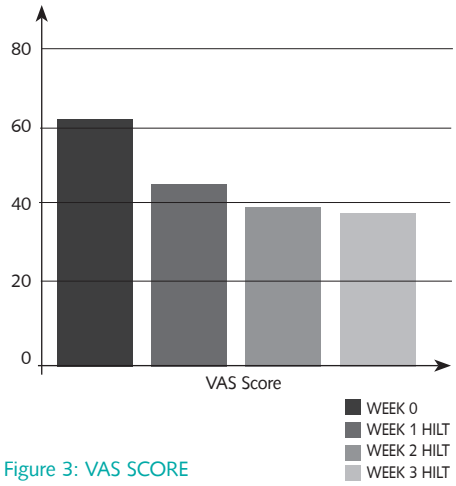

Figure 3: VAS SCORE

- 11 minutes. Treatment time was related with the skin area to be treated, according to the general rule: 50 J/cm². Before treatment all patients underwent clinical evaluations with regards to medical history, presence of antibody to FVIII, frequency of previous total and joint bleedings (average frequency), evaluation of joint damage (hemarthrosis), presence of a target joint, initial assessment of subjective pain evaluated by Nieschl's Score and Visual Analogic Scale - "VAS", initial assessment of the joint status ("Hemophilia Joint Health Score 2.0"), and concomitant medications [17]. All patients signed the Study informed consent form. Patients were monitored during and after the HILT treatment to assess reactions at application site (heat, numbness, loss of feeling and tingling) identified as mild, moderate or severe by the Investigators. Outcomes were defined as variations in subjective pain at baseline, during treatment and at last visit using the Visual Analogue Scale (VAS) score (0 = no pain, 100 = maximum pain) and the Nieschl's Score; joints were evaluated by the "Hemophilia Joint Health Score 2.0", with the same schedule. All bleeding episodes occurred since the previous visit were recorded, as well as documented adverse events (AEs) and serious adverse events (SAEs). The Trial was approved by the local Ethical Committee.

STATISTICAL ANALYSIS

A statistical evaluation of HILT efficacy was performed based on Nieschl's score, VAS score and Haemophilia Joint Health 2.0 scores (HJH-2.0). Non-parametric Signed Rank Test was used in order to evaluate the difference between basal value (Visit 1) and the values after 1 (Visit 4), 2 (Visit 7) and 3 (Visit 10) weeks of therapy at a level of 5% significance. Statistical analysis was performed using SAS software (Ver. 9.2), by SAS Institute Inc., Cary, North Carolina, USA. Descriptive statistics for continuous demographic and clinical parameters were described in mean, standard deviation, median, range and frequency. Nominal or discrete parameters were reported as contingency tables (Table II).

RESULTS

At the end of the study after 3 weeks of therapy, the decrease of Nieschl's score was: -1.9±2.47 (Figure 2) the decrease of VAS score was -27.1±30.66 (Figure 3) both statistically significant (P<0.05) (Table II).

Both scores showed a statistically significant (P<0.05) difference also just after 2 weeks of therapy as compared to basal values.

A statistically significant (P<0.01) pain relief, measured as VAS score, was also observed after a single week of therapy (-17.18±18.69).

No statistical significant differences were observed in term of HJH Global Gate score and HJH Total score (Table II) with respect to baseline values. Regarding tolerability and safety, two patients experienced mild heat at the site of application therapy and one patient suffered moderate local paresthesia. No

bleeding at application site was reported. Three adverse events were reported: a mild episode of esophageal reflux, a mild episode of cough and a moderate episode of gonalgia of the right knee. Only the last event was considered to be possibly related to the study treatment.

DISCUSSION

The weel Known dose–response relationships between non-steroidal anti-inflammatory drugs (NSAIDs) and serious upper gastrointestinal bleeding is a caveat for pain therapy in hemophilia [17,18]. This is the reason that induced our team to look for an alternative therapy, as laser therapy for chronic joint pain in hemophilic patients.

Laser therapy seems to be a promising approach [5,6]. In this pilot study we investigated the role of an innovative treatment called High Intensity Laser Therapy (HILT). HILT should overcome some limitations of traditional laser therapy, as it can achieve good tissue penetration, possibly enabling the repair/regeneration of chronic articular lesions. Recent studies in osteoarthritis confirm that HILT can improve pain control. Under physiological conditions a complex homeostatic mechanism regulates all processes of the chondrocyte.

Such rigid control seems to be the result of a balanced production of anabolic and catabolic cytokines: the production of the constituents of the matrix is in equilibrium with its degradation. HILT seems able to promote the anabolic cytokines which can be able to re-balance the ongoing catabolic process, exerting their effect on the activation of the intrinsic tyrosine kinase which triggers a series of intracellular and extracellular phenomena affecting the homeostasis itself [5,6].

The functional impact and disability of chronic articular inflammatory disease in adult hemophilic patients is well known. The pathogenesis starts early in childhood and the recurrence of intra-articular bleedings causes the common reported symptoms of itching and heat followed by pain, swelling and decreased range of motion [2]. The pathogenesis of the subsequent arthropathy is not fully understood, especially in its early stages, but can be seen as a multi factorial process: inflammation in the synovium and degeneration of articular cartilage. During an episode of acute hemarthrosis, within a few hours the synovium is infiltrated by polymorphonuclear cells and subsequently by lymphocytes and monocytes.

Macrophages remove the blood from the joint cavity, however the recurrence of acute bleedings can reduce their depletion capacity. This gives rise to the formation of substantial hemosiderin deposits that induce synovial proliferation, determine the formation of villi and induce a process of neo-vascularization in the below layer which in turn facilitates the inflammation. The inflamed synovium is highly vascularized and fragile and bleeds easily, even for minimal stress, giving rise to the establishment of a vicious circle that is difficult to stop. Inflammatory cells infiltrating the synovium release cytokines and enzymes which cause the destruction of the cartilage, without allowing any possibility of repair, giving rise to the typical clinical manifestations of debilitating arthritis and complete disruption of the joint architecture. Iron plays a fundamental role in the establishment of the process as it is responsible for the activation of genes involved in cell proliferation [2]. The final result of these mechanisms is represented by the abnormal synovial hypertrophy. Experimental studies seem to support the hypothesis that even a single episode of bleeding can cause irreversible changes in cartilage coating in mice and in human beings. How many repeated bleedings in the joint itself that are required to determine irreversible damage to the articular cartilage is still unknown, however it is common to observe that a few are sufficient to trigger a chain reaction in which the hemarthrosis begins to occur with considerable frequency. Since the amount of blood in the joint cavity affects the magnitude of inflammation and consequently the proliferation and degeneration of synovial and cartilage structures, an early treatment should to be established at any onset of hemarthrosis. Controlling the pain together with maintaining or improving joint functions are considered the principal aims of the therapy [17-19].

We have therefore assessed the safety, tolerability and efficacy of HILT in this pilot treatment of 11 hemophilic patients with chronic artrhopathy. HILT treatment demonstrated to have a significant antalgic effect and was able to obtain a fast pain control after only few applications: Nieschl's score improved after 2 weeks of treatment and 9 HILT sessions, while VAS score was already significant after 1 week of therapy and 3 sessions.

This confirms that HILT can be a useful tool in the management of pain in these patients allowing an ultimate result of a better quality of life. These results confirmed the positive findings obtained in osteoarthritis [14]. Unfortunately it was not possible to assess if these benefits were long lasting, as the protocol was designed to evaluate only the acute effects and no follow up was scheduled. The overall tolerability was good, with one paresthesia of moderate intensity at the application site and three adverse events, none of which were serious. No changes were reported in the Hemophilia Joint Health Scores: different HILT parameters and changes in the duration of the treatment should be further investigated to assess if a longer or more intense application could ameliorate the HJHS.

CONCLUSIONS

The results of this pilot study support

the hypothesis that laser medicine offers potential benefits in treating chronic hemophilic arthropathy. Our results suggest that High Level Laser Therapy is a safe and well tolerated treatment, working quickly and efficiently in the management of pain, even after few treatment sessions. It may be considered as a possible alternative to pain killer medications, due to its analgesic effect. Further studies should be carried out to clarify if different doses and schedule applications can improve or modify the articular status.

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