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Research article

Role of Bicarbonate-Sulphate-Alkaline-Earthy Mineral Water, Bentonite Clay Mud and Manual Somatic Stimulation in the Treatment of Osteoarthritis

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Abstract: Osteoarthritis (OA) is a joint chronic pathology, characterized by pain, functional limitation and swelling. It can be seriously disabling, so identifying effective therapies is fundamental for its management. A suitable therapeutic approach to OA might be thermal medicine, which exploits the beneficial properties of thermal waters, thermal mud and support techniques like manual therapy; We conducted a pilot retrospective observational study analyzing the data of 87 OA patients (mean age 66 years) who underwent 12 sessions in 2 weeks of an Intensive Thermal Care (ITC) protocol, based on ingestion and inhalation of bicarbonate-sulphate-alkaline-earthy mineral water, local contact application of bentonite clay mud, manual treatment of Key Myofascial Trigger Points performed during inhalations and dedicated hydrokinesitherapy. Patients were assessed before (T0) and after (T1) the protocol through the Numeric Pain Rating Scale (NPRS) for monitoring pain and through the Postural Biometric Index (PBI) for the evaluation of postural-biomechanical dysfunction; At T1 patients treated showed significant reductions in NPRS and PBI scores; ITC treatment is correlated with improvements in pain and postural-biomechanical dysfunction in OA. Due to the absence of a control group and uneven sampling, further studies possibly with an experimental setting, are needed to confirm or disprove our encouraging findings.

Keywords: Rehabilitation; Physical Therapy; Balneotherapy; Mineral Waters; Osteoarthritis; Pain; Posture; Chronic Diseases; Natural Substances; Manual Therapy

1. Introduction

Osteoarthritis (OA) is a very common condition worldwide, which particularly affects certain segments of the population, including the elderly, women and some ethnic groups in underdeveloped or developing countries [1,2]. OA is estimated to be the eleventh leading cause of disability globally [2], although the prevalence and incidence of the disease is constantly increasing [1-3]. It represents a major contribution to the increase in physical, psychological and social disabilities, with a marked impact also on the mortality levels of those affected [1]. This pathology can affect all the various joints of the human body to different degrees and in different ways, from the largest joints such as knees and hips to the smallest ones such as those in the hands [1-3]; however, the typical musculoskeletal signs and symptoms of the disease always consist of the more or less marked coexistence of cartilage degradation, bone deformation, pain, swelling and functional limitation [1-3]. Among the main factors

determining the onset of the pathology are identified genetic predisposition, advanced age, excessive physical activity or sedentary lifestyle and increased bodyweight [3-6].

The standard treatment of the pathology is based first of all on the modification of the lifestyle aimed at weight loss, a reduction of exposure to biomechanical risk factors and education on the correct methods and quantities of physical activity [3,7]. These priority modalities could be accompanied by more specific treatments such as oral or infiltrative administration of drugs and supplements of various kinds such as NSAIDs, Corticosteroids, Viscosupplements, Osteo-Chondral Anabolic Agents, Metformin and many others [3,7,8]. Furthermore, an important role can be played by complementary and alternative medicine and various types of rehabilitation techniques, such as manual therapy, electrotherapy, balneotherapy [7,9]. All of these conservative treatment modalities, regardless of their invasiveness, aim to allow the patient to manage their condition by avoiding surgical treatment of OA, which however becomes necessary when the severity of the symptoms reaches such a severe level that pharmacological or rehabilitative interventions become no longer effective [10].

Among the non-invasive rehabilitation approaches historically most applied in the treatment of musculoskeletal and rheumatic pain, as in the case of OA, there is undoubtedly thermal medicine, also defined as balneotherapy, crenotherapy or spa treatments [11,12]. Thermal medicine is based on the use of natural waters and muds with specific mineral compositions for the treatment of musculoskeletal and respiratory/infectious pathologies, through ingestion, breathing in their vapors, bathing in such waters and contact application [12]. Among these methods, treatments consisting in the ingestion and inhalation of mineral waters rich in sulphurous components would appear to have positive effects on human health and well-being [13,14], especially for bicarbonate-sulphate-alkaline-earthy type waters [15]. Similarly, therapy consisting of local contact application of thermal muds would appear to be effective in reducing the severity of pathological symptoms of some musculoskeletal conditions, such as OA itself [16,17]. Not surprisingly, some studies highlight how an approach based on supplementation in various forms of natural substances, especially herbal ones but not only, could constitute an effective complementary and alternative approach in the containment and management of a widespread and multifaceted pathology such as OA [18,19]; this could therefore also be true for approaches based on the use of natural substances such as thermal mineral waters and thermal muds in combination with rehabilitation techniques such as manual treatment of Key Myofascial Trigger Points (KMTrPs), with the latter representing the somatic expression of visceral and autonomic dysfunction [20]. Considering the mixed mechanical and inflammatory nature of OA, a treatment that combines the potential anti-inflammatory and antioxidant effects of natural substances such as thermal waters and muds with rebalancing effects on the musculoskeletal system such as manual therapy and exercise, could represent a winning approach in the management of OA. The physiological basis of this hypothesis of integrated therapy for OA lies in the well-known integration and communication existing between the somatic and visceral nervous systems, which usually are responsible for the musculoskeletal and autonomic-inflammatory manifestations of a pathology [21-23].

Therefore, we decided to frame the role of a novel specific protocol of Intensive Thermal Care (ITC), based on the ingestion and inhalation of bicarbonate-sulphate-alkaline-earthy mineral water, local contact application of bentonite clay mud and the manual somatic stimulation of KMTrPs, in improving the health status of patients affected by OA. Furthermore, the observation carried out could be useful to verify the possible feasibility, in terms of tolerability and benefits, of any future experimental research on the topic. These objectives are based on the assumption of the therapeutic efficacy demonstrated in the literature for the individual balneotherapy

approaches that make up the protocol, as well as on our research experiences on combined balneotherapy approaches similar to the one proposed but applied in different pathological contexts [24,25].

2. Results

The following table shows the detailed demographic distribution of the patient sample considered for the observations of this study (Table 1).

Table 1. Demographic distribution of the sample.

Variable	Categories	Frequencies	%
Gender	**Men**	30	34.5
	Women	57	65.5
Age (years)	**18-30**	1	1.1
	31-45	2	2.3
	46-60	19	21.8
	61+	65	74.8
Initial NPRS Score	**0**	0	0
	1-3	0	0
	4-6	23	26.4
	7-10	64	73.6
Initial PBI Score	**0-10**	0	0
	>10	87	100

At the end of the treatment protocol (T1), a significant reduction in the NPRS score value was observed ($p < 0.01$, $r = -0.8715$), with patients perception of pain decreasing by an average of 7.5 ± 1.2 to a mean of 4.4 ± 1.4, for an overall reduction of 42% (Figure 1).

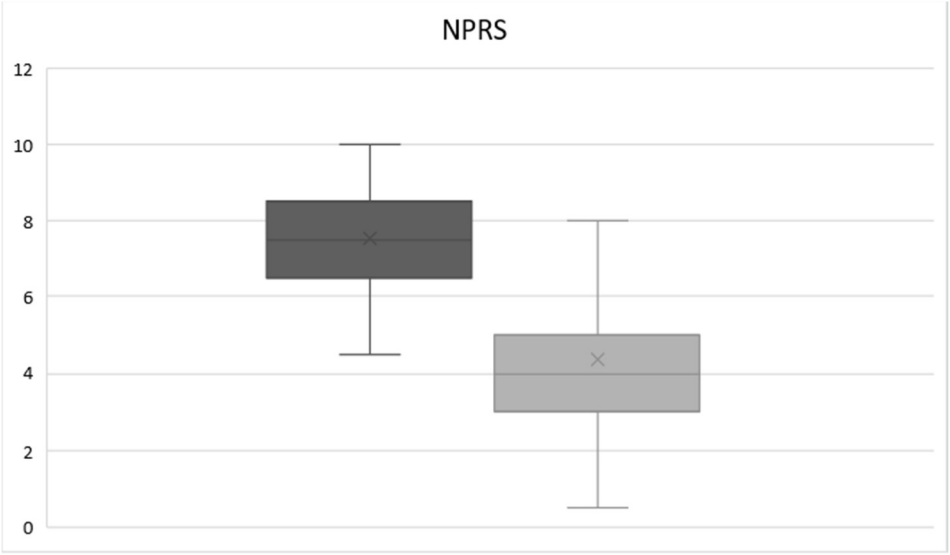

Figure 1. Box plots of the NPRS score variations between times T0 (left) and T1 (right).

Similarly, at time T1, a significant reduction in the PBI score was observed ($p < 0.01$, $r = -0.8706$), with a postural dysfunctionality score that went from a mean of 16.7 ± 3.3 to an average value of 12 ± 3.4, for an overall reduction of 28.3% (Figure 2).

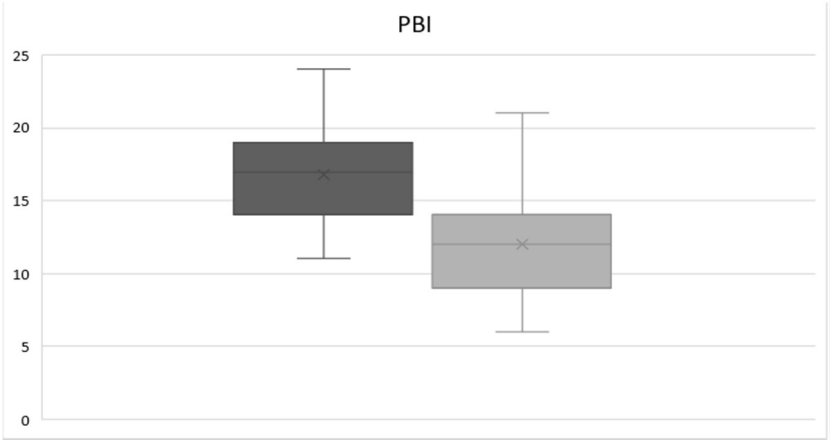

Figure 2. Box plots of the PBI score variations between times T0 (left) and T1 (right).

During the observation period, no drop-outs, side effects of the treatments or non-tolerability of the protocol were reported.

3. Discussion

The application of an ITC protocol for 2 weeks in the observed group of OA patients was associated to a significant decrease in pain, measured through the NPRS, and in postural-biomechanical dysfunction, measured through the PBI.

Pain, as a prevalent symptom in OA, has a very complex characterization. In fact, it is believed that pain in OA is determined by the involvement of complex peripheral nervous sensitization mechanisms, which involve factors such as Neural CCL2/CCR2 signaling, monocytes and macrophages activity and TNF-α receptors stimulation [26]. These nervous mechanisms are probably involved in the peripheral inflammatory processes underlying OA, which determine mechanical sensitization and neuroplastic changes induced by the release of nerve growth factors, cytokines and chemokines [27,28]. In fact, inflammation and the mechanical receptor dysregulations may represent causative and at the same time perpetuating elements of OA [29]. It follows that intervening in a local-peripheral and central-systemic way on the aberrant mechanisms in OA, through the administration of anti-inflammatory substances and corrective mechanical stimuli, may represent a valid intervention strategy in the management of OA, due to the already cited viscero-somatic convergence at the level of the nervous system [21-23]. In this context, spa treatments with thermal mineral waters administered in the context of balneotherapy and crenotherapy through ingestion and inhalation have proven useful in reducing inflammation and, consequently, pain in a multitude of pathological conditions, from nasal infections to rheumatoid arthritis, precisely by virtue of the anti-inflammatory activity of these waters, capable of acting on the modulation of the activity of pro-inlammatory factors such as cytokines and TNF [30-34]. Recent studies in fact attribute to thermal mineral waters, particularly of the sulphurous type like the one used in our research, anti-inflammatory, antioxidant and cytoprotective effects through administration by ingestion and inhalation alongside absorption by skin contact [35-37]. Detoxifying healing properties in the presence of pain and inflammation would also seem to characterize thermal muds of the bentonite clay type: in numerous studies, when applied by contact to painful areas of the body, bentonite clay muds have highlighted healing properties due to their absorbent properties of toxic metals, ammonium and histamine, to the release of bio-compatible minerals such as iron, calcium and sodium and to their bacteriostatic capacities [38-40]. It is even hypothesized that bentonite nanoclays are able to reduce the aggregation of some proteins in the human body, such as Albumin and Lysozyme, which would constitute an interesting further therapeutic property of this substance, which would seem to assume the role of natural

chaperone [41]. Likewise, neuromuscular manual therapy, as somatic stimulation, has repeatedly shown an important therapeutic potential in reducing pain through a series of mechanisms ranging from the activation of the gate control pathway to the balancing of the activity of aberrant somato-visceral nervous circuits in the presence of inflammation and local and systemic biomechanical alterations [42-45].

These mechanisms could explain the efficacy of an ITC-type protocol, such as the one we applied in this study, in significantly improving the NPRS scores of patients with osteoarthritis.

Similar considerations can be made regarding the improvement of the biomechanicalpostural structure of the patients we observed. Postural alteration in terms of alignment and stability is a fairly well-established fact in the context of OA that affects various districts such as knees, hips and spine [46-48]. It is no coincidence that some authors attribute to the static and dynamic postural set-up a predictive value with respect to the progression of OA in patients affected by it [49]. In this sense, it can be hypothesized that, in our study, manual therapy has induced an improvement in the postural arrangement of the observed patients, acting through well-known mechanisms of rebalancing of the basic muscle tone of the treated areas, in particular influencing the improvement of the respiratory mechanics of the patient [50,51]. Furthermore, the analgesic and anti-inflammatory effect of the administration of bicarbonate-sulphate-alkaline-earthy mineral water, may have favored an intrinsic improvement in the posture of the observed patients: in fact, it would seem that exposure in various ways to mineral thermal waters, can induce a relaxation effect on the muscles of the treated patients, measurable for example in an objective variation of the pennation angle of the muscles already observed in the past in these kind of patients [52]. These pathways may underlie the improvement in PBI observed in OA patients considered in our research.

Although the results of this study are encouraging and consistent with current knowledge in the literature in the field of thermal medicine and the action of thermal water administration in the human body, some considerations must be made on critical or limiting aspects of our research. In fact, the observational design of our study, although it allowed us to collect a fairly large sample and volume of data in a relatively short reference period, still limited us in being able to define a sufficiently homogeneous reference population in terms of age and sex. Furthermore, 74.8% of our sample was composed of subjects over 60 years of age, statistically more prone to develop multisectoral OA [53], making it difficult to identify a population with a specific form of arthrosis for a single joint and, consequently, making the results less relatable to the pathological subforms. Although the prevalence of elderly patients in the small population we observed is indicative of a high therapeutic potential of the CIT approach precisely in the age group most at risk for OA [53], it must be considered that such a non-homogeneous distribution of the sample by age group makes it difficult to generalise the results obtained also to OA patients who fall within younger ages. In addition, it should be considered that OA patients seem to be more predisposed to the development of comorbidities, especially metabolic and psychological, which can induce manifestations such as obesity and depression capable of increasing the invasiveness of perceived pain and reducing adherence to treatment protocols [54,55], especially in the elderly population [56]. In this sense, it is encouraging to note that during the observation conducted, no drop-outs or negative effects of CIT treatment were detected in patients, probably by virtue of the low invasiveness and the right degree of involvement of the patient that characterize the approach.

Furthermore, the study, for the same design-related reasons mentioned above, did not include a control group or a follow-up. In fact, the data from the medical records available for the study refer exclusively to patients with OA who voluntarily turned to our center to undertake a CIT-type integrated thermal medicine program; because of this, it was not possible to obtain data from a population of OA patients

with similar characteristics but who underwent treatments other than CIT or no treatment at all in order to make a valuable comparison. Furthermore, since the protocol prescribed for the patients is standardized and did not receive external funding for its implementation, it was possible to observe the patients only for the 2-week treatment period that fell within the reimbursement criteria implemented by the Italian public health system for them, preventing the observation from being extended beyond this duration in the absence of adequate economic resources and possibly organizing a recall of the patients for a follow-up after a period of time from the last evaluation. However, most studies on thermal medicine approaches tend to highlight improvements in various clinical-pathological contexts even with the application of short-term protocols, usually lasting 2-4 weeks, [57-60] consistently with the ITC protocol observed by us.

Despite these critical issues, given the positive and encouraging results observed in this study in a purely observational and pilot setting, it could be important in the future to design new large and in-depth studies on the topic, which should include a more homogeneous sample, a control group and a long-term follow-up. New and more rigorous research on the thermal medicine approach we observed would in fact allow us to better clarify its therapeutic potential and the mechanisms underlying it: infact, the limited pilot observational design that we have been able to implement clearly does not allow us to exclude the influence of a placebo effect on the results, nor to filter the actual magnitude of the effects determined by the individual approaches that make up the ITC protocol: in this regard, in any future studies on the topic, it would be useful to compare the entire protocol to its individual therapeutic modalities in the same setting and on a sample selected a priori following more rigorous criteria. It is important to underline that in the literature several studies have highlighted an important role of thermal medicine in improving the outcomes of various musculoskeletal pathologies when added to exercise programs and other therapeutic modalities [61-64], often by simultaneously applying combined thermal treatments, such as for example water immersion and mud therapy [65,66], similarly to what occurs in the CIT protocol observed by us. In general, the positive effects we observed for the ITC treatment, in the absence of more in-depth evaluation methods than those of clinical evaluation derived from the medical records of the patients, can be discussed merely on a speculative level, based on the literature currently available with respect to the neurophysiological and anti-inflammatory effects observed for the techniques applied in the field of OA and other clinical contexts. Therefore, it is strongly recommended for any future research, where possible, to integrate among the evaluation methods blood tests for the analysis of specific biomarkers for inflammation (such as cytokines, interleukines, TNF, CRP, etc.), instrumental analyses for monitoring pain and nerve conduction (e.g. pressure algometry, localized impedance analysis and/or electromyography) as well as imaging tests (such as MRI and X-ray) for monitoring the musculoskeletal morphology of patients.

Thermal medicine represents an interesting frontier in the clinical and research field today, by virtue of its broad therapeutic potential and its socio-economic value. Therefore, valorizing this medical branch with new studies that can highlight all its strengths and any limitations is of fundamental importance, starting from preliminary pilot studies like ours up to possible rigorous experimental research in the near future [67].

4. Materials and Methods

This research is a pilot retrospective analytical observational study carried out from September to December 2023 at the "Castelnuovo della Daunia Thermal Medicine Center" (Castelnuovo della Daunia, Italy), affiliated with the national health system and the rehabilitation department of the Local Health Authority of Foggia (Italy), in cooperation with the staff of the "Center for Physiotherapy, Rehabilitation and Re-Education – Ce.Fi.R.R." (Chieti, Italy).

The rehabilitation protocol to which the patients were subjected is safe, as all the therapeutic procedures applied to patients comply with the safety regulations of the country where the study was carried out; the protocol is accessible to all patients who do not highlight specific contraindications to the initial clinical evaluation necessary for all patients who access the study facility. The study has been performed in accordance with the Helsinki Declaration and Good Clinical Practice standards [68] and written informed consent was obtained at enrolment from participants who were willing and able, aimed at informing them of the possibility that their clinical data could be used in the future for observational research. Specifically, in accordance with the evaluation and operational routine applied at the study site, the observed data are those registered in the medical chart compiled by doctors in charge of the initial and follow-up evaluations of patients accessing the "Castelnuovo della Daunia Thermal Medicine Center" [69]. The research project falls within the scope of the certification of technical and ethical suitability for the implementation of observational studies (certificate no. IT15/0304) issued to the "Ce.Fi.R.R." institution, in charge of carrying out the study, by the Registered National Accreditation body ACCREDIA in accordance with the UNI EN ISO 9001:2015 regulation.

Data from 87 patients (mean age 66 ± 11 years) affected by OA were collected. The patients involved were all patients originating from the geographical area of reference of the study, who spontaneously turned to the study site to undertake a non-invasive balneotherapy treatment path. All patients presented clinical manifestations of musculoskeletal pain and functional limitations in at least one part of the body. The clinical evaluation of signs and symptoms and the medical history of the patients allowed specialist doctors in physical and rehabilitation medicine or rheumatology to carry out the diagnosis of OA. Patients with severe cardiovascular diseases, neurological diseases and active infections were excluded from the study, in particular in case of cardiac or renal failure, severe hypertension, severe thrombophlebitis, advanced stages of chronic respiratory diseases, acute phases of rheumatic diseases, immunodeficiency, open wounds, psychiatric disorders or severely limited walking ability.

Patients were assessed, before the beginning (T0) and after the end (T1) of the prescribed ITC treatment cycle. The data recorded in the two evaluation times, as routine elements of the clinical evaluation procedure carried out at the study site, were obtained from the medical records of patients who turned to the center to undertake a course of balneotherapeutic treatments in the reference period considered, to then be analyzed at a later time. These evaluation methods consist of:

- The Numeric Pain Rating Scale (NPRS): it is one of the most widespread tools in clinical practice for assessing the pain subjectively perceived by patients. It is a derivate of the Visual-Analogue Scale (VAS) divided into ten levels, usually distributed equidistant on a 10 cm long strip, which correspond to the level of pain perceived by the patient at the time of the evaluation. A value of 0 represents the total absence of pain, a value between 1 and 3 corresponds to mild pain, a value between 4 and 6 corresponds to moderate pai and a value between 7 and 10 corresponds to severe pain, where a score of 10 represents the maximum level of pain imaginable and/or ever experienced by the patient [70]. Tools like the NPRS and VAS proved to be reliable and easy to apply even in the presence of dysfunctions of the musculoskeletal system such as OA [71]. In the case of the present study, patients were asked to express a value from 0 to 10 corresponding to the maximum level of pain perceived at the joint level which was the most insidious points for them.
- Postural Biometric Index (PBI): this is an index calculated on the basis of a stabilometric evaluation carried out by a high resolution multisensor 2D system which acquires data of surface and load every 4 sensors per cm^2 (Diasu Health Technologies, Rome, Italy) [72]. The platform is composed of resistive electronic sensors made in gold-platinum that collect information on the plantar support. This index takes into account the parameters of Center of Pressure, Symmetry of Bipodalic Load,

Symmetry of Retro-Forefoot Load, Angle of Centers of Pressure, Podalic Angle, Location of Maximum Pressure Point, Symmetry of Support Surface and Center of Gravity Deviation - Center of Pressure [72]. These standard postural parameters are then crossed and combined to obtain an index that quantifies the patient's postural state [72], which can often be altered in the presence of OA [73]. The PBI value is typically considered healthy from 0 to 10 and increasingly dysfunctional if >10. To carry out the assessment, the patient is asked to stand for a few seconds on the platform described above, looking at a fixed point traced on the wall in front of him, with his feet positioned parallel and slightly spaced apart (approximately to the width of his shoulders), which would appear to be the optimal position for carrying out stabilometric tests in patients with pathological physical function [74]. Multiple studies have shown that the use of stabilometric platforms can be a valid tool for monitoring postural stability and resilience, as well as proprioception, in subjects affected by various forms of OA [75-78]. Essentially, the PBI value allows to quantify in a unique and rapid way the result of a stabilometric analysis, proving generally reliable and consistent with the individual results offered by a standard digitalized biometric analysis [72].

The ITC protocol applied in the study, consists in the administration of the following stimulation techniques falling in the field of thermal medicine:

- Ingestion of thermal mineral water: also known as hydroponic treatment or crenotherapy; patients were made to drink the bicarbonate-sulphate-alkaline-earthy mineral water from the “Castelnuovo della Daunia Thermal Medicine Center” in a total quantity of 500 cc, administered to each subject on an empty stomach for at least 6 hours. For the convenience of the patients, they were allowed to complete the ingestion of the administered quantity of mineral water during the whole duration of the other ITC treatments described following. Before the ingestion, patients were required to report the time of their last meal to verify that 6 hours of fasting had actually elapsed before ingesting thermal mineral water.
- Inhalations of vaporized thermal water: following the hydroponic treatment completion, patients underwent the inhalation treatment through the administration of direct warm-humid steam jets placed in front of their face, with the patients seated at a distance of approximately 50 cm from a nozzle. The jets are carried out through proprietary individual devices from which the bicarbonate-sulphate-alkaline-earthy mineral water comes out in the form of a homogeneous mist at a pressure of 1.5 atmospheres and at a temperature of 37°C-38°C, lasting about 20 minutes.
- Manual somatic stimulation: it consists of manual treatment with techniques such as kneading, skin rolling and friction, applied to release KMTrPs found in the body of the patient, following the Bio-Physico-Metric approach [24] based on the search and deactivation of MTrPs according to their hierarchical division into active/latent and key/satellites [79,80]. This treatment was performed in two phases: the first phase was performed during the same inhalation session, for all 20 minutes of duration, standing behind the patient's shoulders and performing the indicated stimulation techniques from there on the seated patient; the second phase was performed during a dedicated 30 minutes hydrokinesitherapy session in which the patient immersed himself in a pool of bicarbonate-sulphate-alkaline-earthy thermal water together with the therapist, who continued the manual treatment of the KMTrPs in the pool.
- Contact bentonite clay mud treatment: it is the application of bentonite mud matured in thermal water, that is placed in direct contact with the previously manually treated KMTrPs present throughout the patient's body, according to the same Bio-Physico-Metric approach principles [24]. The application occurs with the patient lying on a soft medical bed, for a duration of 15 minutes, followed by a bath in thermal water with ozone jets hydromassage lasting 15 minutes. This is followed by a reaction phase which consists of having the patient rest in a mild temperature environment for another 20 minutes.

Each patient underwent 6 weekly sessions of ITC for 2 weeks, for a total of 12 treatment sessions lasting around 1 hour and 40 minutes.

At the end of the study, statistical analysis was carried out on collected data using the Wilcoxon Signed Rank test for dependent samples, performed through the Statistics Kingdom online calculator (https://www.statskingdom.com, Melbourne, Australia). Data variations with values of $p < 0.05$ were considered significant. Furthermore, the Effect Size (r) was calculated and reported.

5. Conclusions

According to the results of our observation, which is configured as a pilot in the preliminary evaluation of the efficacy and safety of the studied protocol, in patients with OA, the application of ITC thermal medicine treatments, based on the administration of water in the form of ingestion and inhalation coupled with the execution of somatic manual stimulation of KMTrPs and contact thermal mud application, is associated with a significant reduction in pain and biomechanical-postural dysfunctions typical of the pathology. By virtue of the non-invasiveness of the treatment, its cost-effectiveness and its ability to therapeutically cover large segments of the population in a relatively short time, it will be important to continue with studies in this area, in order to confirm or deny the therapeutic potential of a method that would allow for a more wide-spread management of a pathology such as OA.

Author Contributions: Conceptualization, Giovanni Barassi, Michelina Delli Bergoli and Maurizio Panunzio; Data curation, Giovanni Barassi; Formal analysis, Giovanni Barassi and Pier Enrico Gallenga; Funding acquisition, Giovanni Barassi and Maurizio Panunzio; Investigation, Giovanni Barassi; Methodology, Giovanni Barassi and Piero Galasso; Project administration, Giovanni Barassi and Maurizio Panunzio; Resources, Giovanni Barassi and Michelina Delli Bergoli; Software, Giovanni Barassi and Piero Galasso; Supervision, Celeste Marinucci and Giuseppe Luigi Matera; Validation, Giovanni Barassi and Maurizio Panunzio; Visualization, Celeste Marinucci and Giuseppe Luigi Matera; Writing – original draft, Giovanni Barassi and Loris Prosperi; Writing – review & editing, Loris Prosperi and Pier Enrico Gallenga. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author due to privacy reasons.

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