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THE THERMOGRAPHIC ASSESSMENT OF VASOMOTOR DISORDERS IN CHRONIC REGIONAL PAIN SYNDROME UNDER THE ACTION OF PELOIDOTHERAPY

SUMMARY OF THE PHD THESIS

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CONTENTS

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I. COMPLEX REGIONAL PAIN SYNDROME TYPE I - THE KNOWLEDGE IN THE DOMAIN

CRPS type I is a pathological condition described for over 125 years, which still remains a poorly understood and frequently unknown syndrome.

CRPS type I is found in a variety of clinical forms, generating much controversy regarding the different aspects that define its nosological framework. The confusions were generated by the acts: of defining the notion, identifying the triggering etiological factors, elucidating the pathogenic mechanisms that contribute in the complex symptoms of this pathological condition; as well as the determination of objectives, therapeutically means by which they propose a more efficient approach and maximum benefit to patients with complex regional pain syndrome type I.

However, the diagnosis criteria recommended by IASP were never completely validated, some experts doubting of their clinical and scientific value (especially because these criteria have a low diagnostic specificity, being able to cause over diagnosis of AND) [1].

CRPS type I is a syndrome that usually affects the limbs, being characterized by pain and/or other sensory abnormalities, oedema, motor abnormalities (limited range of motion), vascular anomalies (vasomotor instability) and changes in the superficial and deep tissue, trophic changes (skin changes, „patchy" bone demineralization)[2].

Not all of these elements are necessarily present at the same time. It is estimated that 2-5% of people with peripheral nerve injury and 20% of those with hemiparesis will suffer due to CRPS type I [3]. Uncertainty remains about how can CRPS type I be effectively managed. CRPS type I is a multisystem syndrome with various simptoms, usually affecting one or more extremities, but virtually can affect any part of the body.

The overall direction of research in this area is moving towards scientific substantiation of etiopathogenic mechanisms involved in the appearance of chronic regional pain syndrome type I, to establish an investigative protocol used as a "gold standard", the potential role of thermography as a diagnostic method in this pathological condition and to develop an optimal therapeutic protocol in terms of cost-benefit, respecting the principles of evidence based medicine.

Research direction. Recently, extensive research on the effects of peloidotherapy in patients with various pathological conditions is being developed, including chronic pain syndrome with various etiologies[4,5] (fibromyalgia, posttraumatic status). There are, until now, studies conducted both, abroad and in Romania, about thermography as a diagnostic tool, applicable in many specialties: neurology and neurosurgery, orthopedics, oncology, rheumatology, dentistry, internal medicine, medical hydrology and rehabilitation, surgery (thermal scans pre-and post-operative), sports medicine.

The current state of research regarding the thermographic assessment of vasomotor disorders, important clinical feature in CRPS type I and the therapheutic benefit of peloidotherapy in this pathological condition. Currently, in Romania, any similar study dealing with this topic has never been developed before.

In the present, there are being made internationally trials to centralize scientific research, meta-analyzes, to scientifically proof, that CRPS type I is an important pathological condition, as the subject discussed by 4606 publications. Infrared thermography is an underestimated diagnostic tool, 891 studies existing in this regard, of which only 17 studies have focused on the relationship between the CRPS type I and infrared thermography. From the viewpoint of evolution of the patients with CRPS type I under the action of peloidotherapy is important to note that there is only one study, completed in December 1968 in Italy trying to establish the effects of this type of therapy in this pathology[6].

To this purpose, we investigated the standard medical data bases: Medline, Embasse, Database, Scirus, PubMed, Cochrane Controlled Trials Registry UpToDate, analyzing the works and studies made in light of the requirements of codes of medical ethics and evidence-based medicine.

II. MOTIVATION OF CHOOSING THE TOPIC

The topic that I approached is the study subject of several medical specialties, including neurology and neurosurgery, orthopedics, oncology, rheumatology, general and internal medicine, surgery, sports medicine, medical rehabilitation and medical hydrology. The study of CRPS type I is currently in ongoing scientific research, the subject creating much controversy regarding the etiology, pathogenesis and pathophysiological conditions that trigger and maintain the pathology, diagnostic methods and therapeutic approach as effective. Despite these advances, there has been no national study on the influence of peloidotherapy over local temperature variations at patients suffering from CRPS type I to improve clinical status.

1. I started this research project due to questions that occurred during clinical practice and the desire to discover a new concept concerning the methods to approach patients with CRPS, following international trends in the treatment of this condition by intercepting its pathophysiological mechanisms.

2. I have to mention that I found no national study in all my scholar research, and in the international literature only one study has attempted to highlight the effects of mud therapy in patients with CRPS type I.

3. Through this research project I wanted to show the effects of peloidotherapy in the treatment of CRPS type I by assessing changes in local skin temperature of the affected extremity, given the benefit of mud therapy in patients with this pathology.

I wanted to contribute scientifically, to show the benefit of peloidoteraphy, as a new approach in treating patients with CRPS type I, objectified by the improvement of clinical signs and symptoms, which result from the thermographic measurement

CRPS type I is a multiple system dysfunction accompanied by severe pain, often chronic and disability, can be triggered by a minor injury, which has fascinated and perplexed scientists and clinicians for years[7]. As there is no consensus regarding etiology, clinical presentation, diagnosis and management, there is an obvious interest for an old method of treatment (balneal treatment), with recognized therapeutic effects but not validated by rigorous scientific studies. One of the major diagnostic criteria is the increase in local temperature of the region affected by more than 1°C. In trying to understand the therapeutic efficacy of balneal therapy in CRPS type I, I used thermography as objective tool to assess the vasomotor disorders, for both: diagnostic and treatment response. Thermography is used to measure many symmetrical points on the affected and unaffected extremity by comparing between the two limbs. A difference of 0.5°C is considered to be slightly asymmetric, while a difference of 1°C is considered significant[8]. Unlike other internationally trials, where they put more emphasis on physical and kinetotherapy, this research project is original through the importance that provides to natural therapeutic factors.

In CRPS type I there is no single pathophysiological mechanism to explain the diversity and heterogeneity of symptoms (such as edema, vasomotor disturbances, limited range of motion). Currently, several mechanisms are accepted to be involved in the appearance and development of this syndrome.

Pathophysiological mechanisms that underlying the appearance of CRPS type I include changes in skin innervations, central and peripheral sensitization, altered function of the sympathetic nervous system, low levels of circulating catecholamine, increased levels of inflammatory cytokines, genetic and psychological factors[9].

Recent evidence demonstrates that oxidative stress is associated with the appearance of clinical symptoms in patients with CRPS type I[10]. However, the most important mechanism seems to be the inflammatory process, because all the classic signs of inflammation are evident in the early stages of CRPS type I[11].

According to the international medical world, the Balneal and Rehabilitation Sanatorium of Techirghiol, develops an intense research activity, including clinical studies of therapeutic effects and pathophysiological mechanisms of Techirghiol mud by dosing markers of the oxidative stress[12], determining pro-inflammatory cytokines[13] and evaluating the hormonal status[14], respectively: as it positively influences the outcome of patients with different pathologies.

III. CONSIDERATIONS ABOUT THERMOGRAPHY

Thermography is a valuable tool for the study of human body temperature. Modern thermal imaging systems are highly developed and produce a two-dimensional digital image of the skin temperature[15].

Asymmetric thermograms appear in response to a variety of abnormalities, particularly vasomotor dysfunctions[16]. Thermography reports aspects of the vasomotor function/dysfunction rather than anatomical issues[17]. The advantages of thermography are obvious, this technique being able to show rapid changes in blood flow, in a large area, by measuring the temperature with a high resolution[17]. However, as reported in the literature, there are disadvantages, namely: the lack of standardization in how the measurements are made, a few thermographic data analysis methods, and the lack of knowledge on the mechanisms that underlying the occurrence of temperature differences, and the need for dynamic measurements[17]. In conclusion, thermography provides information that is useful in the diagnosis of CRPS type I and is able to follow-up the various therapeutic interventions across[17]. Hendler said that "at a minimum level, diagnostic studies that could facilitate CRPS type I diagnosis could be thermography and bone scan"[18]. Also other rheumatic pains can benefit of this technology, both for diagnosis and for monitoring response to treatment. We can list here: sinovitis of various causes, Paget's disease, fibromyalgia, stress fractures, cervical and lumbar nerves irritations and pain syndromes of the soft parts[19].

Further studies are required to define the place of thermography in these specific conditions.

IV. SAPROPELIC MUD FROM TECHIRGHIOL LAKE

Although known and used since ancient times, today the mud still raises discussions on their efficacy, the points of view are different, from denying some therapeutic effects to the "proximity" with a universal remedy. The complexity of the chemical composition, the interrelations between his components, and its many therapeutic effects make difficult the detection of therapeutic active factors. They are supplemented to the presence of microorganisms themselves with a rich "therapeutic benefit." Logic and rational can not deny the therapeutic action of mud, but scientific h is difficult to show which of properties determine the positive effect. Physiologic and therapeutic effects are caused by the physical and chemical composition of mud and depend on the method of application.

But the most common form of mud application is general and its effects are manifested in all organs and systems. Mud therapy as it "classic form" is a holistic therapy, addressing to the whole of the human body. The mechanisms by which immersion in mineral or thermal water and mud application improves these conditions are not fully understood.

The net benefit is probably the result of a combination of mechanical, thermal and chemical factors; the human body entirely is subjected to mud application. It is difficult to distinguish which of the elements is significantly more active and involved in the effects. According to gate theory, the pain relieve may be due to pressure and temperature of water on nerve endings from the skin, they may influence the muscle tone and intensity of pain. Peloidotherapy increase plasma levels of β-endorphins, the secretion of cortisol, adrenocorticotrophic hormone, growth hormone and prolactin. There are evidence of beneficial effects on oxidative status, peloidotherapy with a reduction in the release of reactive oxygen species (ROS)[20] and nitric oxide (NO). Many other nonspecific factors may contribute to the beneficial effects observed after balneal treatment in some rheumatic diseases[21].

The changing of the general reactivity and the links, already mentioned: endocrine, metabolic, neural, immune and defense, are the therapeutic implications of mud. Current literature contains studies about history of peloidotherapy current concepts of its mechanisms of action and review of methods of application. A special interest is put on the lack of relevant information on selected aspects of peloidotherapy, questionable ways of its implementation and the mechanisms of action[22].

V. AIMS AND OBJECTIVES

The aim of this study is to assess the vasomotor disorders by termography , significant clinical feature in CRPS type I under the action of peloidotherapy, showing the possibility of a new therapeutic approach to patients with this pathological condition.

The main objective of this study is:

1. **Thermographic assessment of vasomotor disorders in patients with CRPS type I under the action of sapropelic mud from Techirghiol Lake.** In order to achieve this aim we considered vasomotor disturbances, namely, increased of local skin temperature, assessed by thermography. For this purpose, we measured the temperature of the affected extremity compared with the temperature of unaffected extremity, in the first day of treatment, to prove the existence of temperature differences. At the end of treatment, we performed the same measurements and analyzed these values to show the effect of peloidotherapy in this pathological condition.

The secondary objectives of this study were:

2. **The assessment of clinical features (pain, swelling, range of joint motion) in patients with CRPS type I under the action of peloidotherapy** and to identify the relationship between temperature and the other clinical features. To achieve this, we assessed pain using the visual analog scale (VAS), edema using perimetry in the maximum affected area and range of motion using goniometry, in the first and the last day of treatment.

3. **The analyzes of biologic and radiologic parameters and their contribution to support the positive diagnosis of CRPS type I.** For this aim we analysed the following parameters: erythrocyte sedimentation rate, C-reactive protein, hemoglobin at baseline. We performed standard radiographs of the affected extremity to obiectivate the „patchy" osteoporosis. In addition, we tried to identify correlations between skin temperature of affected extremity and demographic characteristics of subjects included in the study: gender, age, location of lesion, the affected part of the body, diagnosis, surgery, Sudeck phenotype. We also examined whether the existence of surgery, of treatment before and period of treatment influences clinical features.

VI. MATERIAL AND METHOD

The method of the research project

This research is based on the study of 41 patients who received complex balneal-physical-kinetic treatment- in Balneal and Rehabilitation Sanatorium of Techirghiol, between 2010-2011, all subjects signed an informed consent from being part of this study.

Patients received the following treatment protocol: a mud bath alternatively with a salt bath (in the pool), two or three adjuvants electrotherapy procedures, one session of massage therapy and one kineto therapy session.

Patients were assessed at admission and at the end of treatment. The assessment in admission included: fill up the informed consent; the demographic questionnaire - age, gender, phenotype Sudeck, location of lesion, the diagnosis, the affected part of the body and the existence of surgery; clinical features: visual analogue scale for pain, sudomotor (edema), vasomotor (temperature) and motor (range of motion) disorders; the existence of treatment before, period of treatment. Regarding laboratory tests were analysed at admission: hemoglobin, VSH, CRP and standard radiographs were performed to detect the presence of „patchy" osteoporosis

At the end of treatment, patients were assessed again by the terms of clinical features VAS, sudomotor (edema), vasomotor (temperature) and motor (range of motion) disorders.

Inclusion criteria of subjects in the study were: patients diagnosed with CRPS I, according to Budapest criteria, with age between 20 and 80 years, having as trigger event of pathology the traumatism, with or without surgery. Positive diagnosis of CRPS type I, was made according to Budapest criteria as follows:

A. The patient has continued pain that is disproportionate to the triggering event.

- ❖ sensory disorders: allodynia (painful sensation to a number of stimulus, normally painless, to easy touch or joint movement) and/or hyperalgesia (exaggerated pain to a painful stimulus such as a bite).

- ❖ vasomotor disorders: instability and/or skin temperature asymmetry and/or skin color disturbance.
- ❖ sudomotor disorders /edema: instability and/or swelling asymmetry and/or edema.
- ❖ motor/trophic disorders: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

B. The patient has at least one sign in two or more of these categories.

C. At least one patient reported symptoms in three or more of these categories.

D. No other diagnosis can better explain signs and symptoms.*

Budapest criteria (A-D should apply). A plain abnormal radiography in a characteristic pattern of CRPS type I, can substitute one of the signs of these criteria.

(*) For example, increased systemic inflammatory markers are not associated with CRPS type I, even in the initial inflammatory phase, such a finding needs to search for an alternative or concomitant cause.

Exclusion criteria from the study were:

- ❖ other causes of CRPS type I: by peripheral nerve injury, myocardial infarction, stroke,
- ❖ conditions that contraindicate application of adjuvant procedures of electrotherapy (cardiovascular, respiratory, digestive, renal, neurological diseases, cancer, presence of inflammatory rheumatic diseases, pregnancy, skin disorders)
- ❖ restrictions for thermographic examination: alcohol addiction, certain drug therapies (vasodilators, anti-inflammatory) and physicaltheraphy, burns, fever, women during menstruation,
- ❖ Eritrocyte sedimentation rate > 40 mm/h.

From 49 patients who were initially evaluated according to described protocol, 8 patients were excluded because they had one or more exclusion criteria (peripheral nerve injury, stroke), the present research contains a total of 41 patients. In the present study we dont have a control group, but I considered the unaffected extremity as control.

With a centimeter we measured the volume of the distal affected and unaffected extremity. In this study we used as clinical parameter the difference of edema, the difference between the volume of the two limbs, to remove the inconveniences derived from morphotype.

The measurements of range of motion used a goniometer. Although there is no standardization of measurement decided by any international forum consensus, freely accepted, is used the numeric expression system of movement based on the „0-180°".

To perform a thermographic measurement, the patients should remove the clothes (related segment). The basic condition is the need for a comfortable room temperature. For adults the comfort temperature is 20-25 ° C. The room temperature is maintained by using the air conditioning equipment. To prevent the falling of sunlight directly on the camera or on the patient, during the examination, the best solution was fitting with dark blinds of the windows. The period of thermo adaptation for patients was about 5-7 minutes. The focusing distance between the camera and the hand was adjusted to 68 cm and the focusing distance between the camera and the foot was adjusted to 90 cm, to cover the entire limb. The body segment of patients was examined such that in the picture were included the both extremities. Both, upper limb and lower-limb temperature was measured on the dorsal side.

Table no.1. - Temperature values in different segments of normal human skin

Author	Forehead	Upper lip	Neck	Thorax	Abdomen	Dorsal hand	Anterior thigh	Dorsal foot
Slonim AD	33,2	33,6	34,0	32,2	33,4	30,8	32,5	30,1
Milimivca ME	33,5	-	35,1	34,0	34,4	-	34,3	30,0
Dosacev EA	32,8	32,0	34,0	33,4	34,2	32,1	33,2	30,4

The table no.1 shows that the temperatures of different parts of human body present large variations and can not have great importance in diagnosis. However, the temperature distribution on the surface of the skin, in healthy individuals, has characteristic particularities, the most important being the symmetry. From the literature, for over a hundred years, it has been shown that skin temperature is the same in symmetrical segments, in healthy people.

Statistical analysis of the present study used the programme SPSS 17. Tests which were performed: the $\chi 2$ test of comparison (association), independent samples t test, t test for difference between means of two dependent samples (pairs), one-factor analysis of variance (One Way ANOVA), linear Pearson correlation.

VII. RESULTS AND DISCUSSION

THE THERMOGRAPHIC ASSESSMENT OF VASOMOTOR DISORDERS IN CRPS TYPE I UNDER THE ACTION OF SAPROPELIC MUD FROM TECHIRGHIOL LAKE

Despite the IASP criteria or Budapest criteria, CRPS type I diagnosis remains a challenge because the symptoms and signs have individual variations, including vascular disorders. Previous studies have shown that skin temperature asymmetries, objectivate by thermography, between the affected and unaffected extremity, around 2ºC are useful for diagnosis of CRPS type I [23] (**Figure no.1., Figure no.2**.).

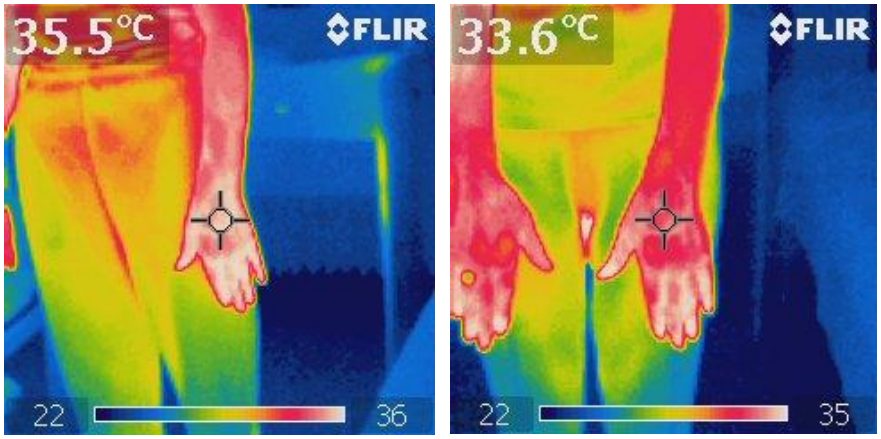

Figure no.1. And Figure no. 2. - *The local skin temperature of the affected upper extremity in admission and at the end of treatment*

CRPS type I is characterized by vascular disorder, which affects primary the microcirculation of the involved distal extremity[24], which is important clinical feature of these patients. The sympathetic nervous system is considered to be involved in the occurrence of these disorders. Neuroendocrine system is another mechanism which is implicated in the occurrence of this disturbance. Almost all hormones have an influence on the terminal territory of circulation[25]. Prostaglandins, products of arachidonic acid metabolism, by the action of cyclooxygenase-2, with a part in the development of inflammation and local pain, also have demonstrated effects on the vasomotor tonus[25].

Temperatures of affected/unaffected extremity at admission / end of treatment

In this study, we measured the temperature of the affected and unaffected extremity at admission, to show the existence of temperature differences between the two limbs. At the end of treatment, we performed the same measurements to show the therapeutic response. Since the study did not include a control group of patients, we considered the unaffected extremity of each subject as the control limb.

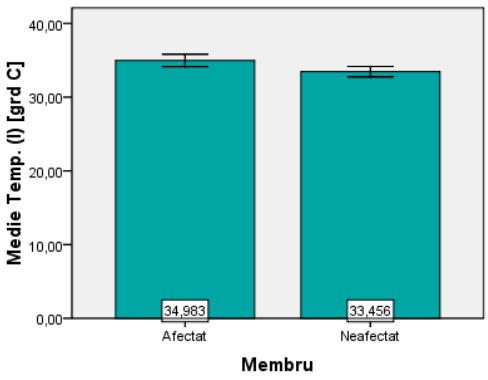

Chart no. 1. Graphical representation of the mean values of temperature of affected and unaffected extremity in admission

Analyzing the results, using **independent samples t test** comparing the mean values of temperature in the affected extremity in admission with the mean values of temperature in affected extremity at the end of treatment, in the study group, we obtained the following: because p <0.001 <α = 0.05 (significance level chosen), is accepted the hypothesis that between the mean values of temperature in the affected extremity in admission and at the end of treatment are statistically significant differences in the two points. (**Chart no.1.).**

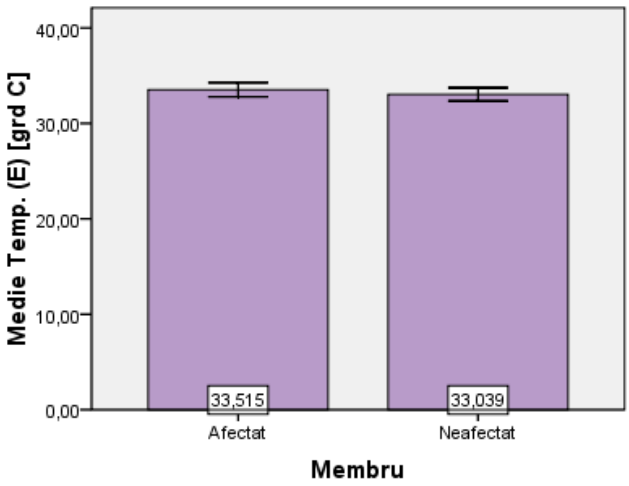

Chart no. 2. - Graphical representation of the mean values of temperature in affected and unaffected extremity at the end of treatment

We can say that between the mean values of temperature in affected extremity at the end of treatment and the mean values of temperature in unaffected extremity, at the same time, still exists statistically significant differences (p = 0.004 <α = 0.05) but the tendency is to the alignment of the two values (33.51 ° C, 33 , 09 ° C). (Chart no.2.).

Temperatures in affected extremity at admission/the end of treatment

Next we analyzed the mean values of temperature in affected extremity in admission compared with the mean values of temperature in affected extremity at the end of treatment.

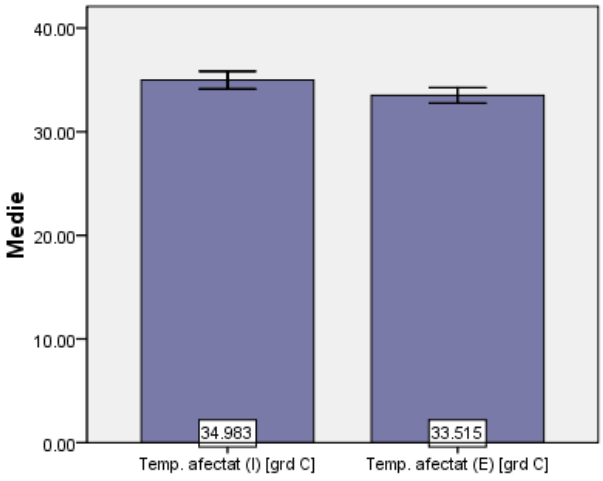

Chart no. 3. - Graphical representation of the mean values of temperature in affected extremity in admission and at the end of treatment

Analyzing the results of **paired sample t test** comparing the mean values of temperature of the affected extremity in admission and at the end of treatment, in the study group, we obtained the following: because $p < 0.001 < \alpha = 0.05$ (significance level chosen), is accepted the hypothesis that **there are statistically significant differences** between the two values, in the two moments. (Chart no.3.).

The mechanism by which the temperature of affected extremity at the end of treatment decreases compared to the temperature at admission of the same extremity (Figure no.3., Figure no.4.) under the action of peloidoteraphy is represented by the interference of pathophysiological mechanisms of CRPS I with the physiological and therapeutic mechanisms of Techirghiol mud, effects demonstrated and sustained by the histological study of skin and muscle[26]. The blood flow circulation is the functional link the most involved in adapting the organism to mud application, therefore the blood flow is the „carrier" of body heat, harmonize the body temperature in its various segments The histological aspects, namely, increasing the number of opened capillaries and neoangiogenesis, is the morphological proof of functional circulatory effects of mud, produced by its termopexic qualities[26].

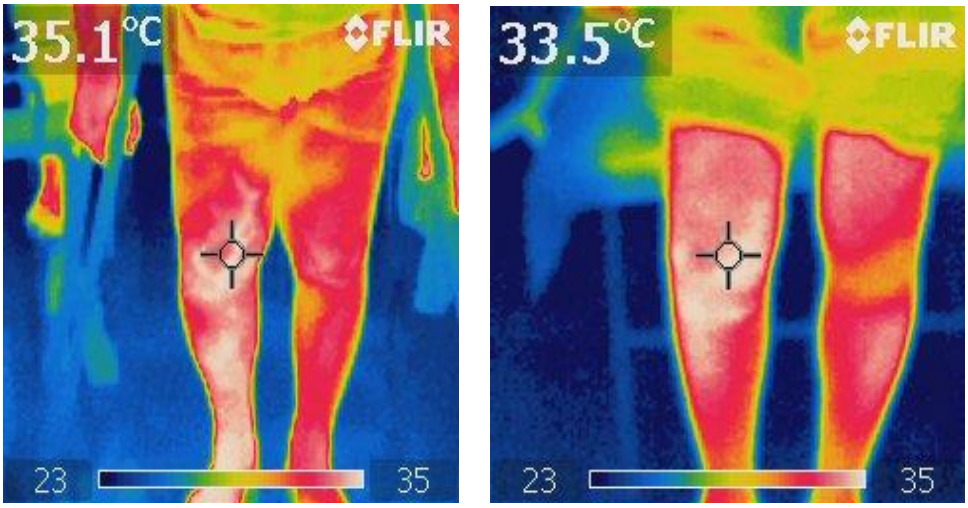

Figure no.3. And Figure no.4. *- The local skin temperature of the affected lower extremity in admission and at the end of treatment*

In the same time, under the action of mud takes place a harmonic stimulation in all glands with the increase of the enzymatic activity and synthesis, but keeping the specificity of each of them, the neuroendocrine system being an important element involved in the occurrence of vasomotor disorders. Also mud stimulate the activity of the hypothalamic-pituitary-adrenal axis, with consequence on the catecholamine secretion, which has a major influence on the sympathetic nervous system also involved in the pathogenesis of CRPS I. So is modulated the general reactivity, oriented towards normal parameters and are corrected the vegetative traumas[27].Oxidative stress is another mechanism involved in the development of CRPS type I and modulate by the action of peloidoteraphy. Recent studies show the decrease of superoxide dismutase (SOD), also, with beneficial effect in patients with CRPS type I.[28, 29].

THE ASSESSMENT OF CLINICAL FEATURES IN CRPS TYPE I UNDER THE ACTION OF PELOIDOTHERAPHY

To assess the clinical features in CRPS I under the action of peloidoteraphy I used:

- Visual analog pain scale (VAS) to assess pain
- Perimeter to assess swelling;
- Goniometry to assess the range of motion.

The assessment of these parameters was made in the first day of treatment and after 10 or 15 days of treatment. Also in this chapter we tried to identify if between the skin temperature and the clinical features are some correlations, using mathematical methods of statistical analysis.

Visual analogue scale (VAS)

In the present study, we noted that at the end of treatment, the mean values of VAS decreased statistically significant ($p < 0.001 < \alpha = 0.05$) than the corresponding mean values of VAS in admission (**Chart No. 4**.), as we expected, because of benefit of treatment with the natural factors. These results are in accordance with studies from international databases which showing the decrease of pain statistically significant, assessed by visual analogue scale for pain (VAS), under the application of complementary therapies[30].

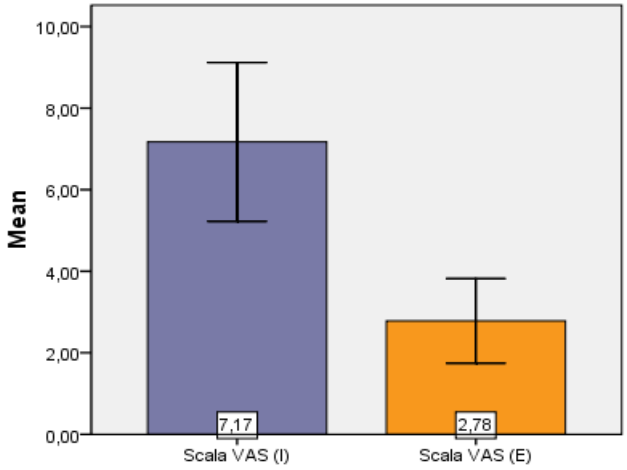

Chart no. 4. Graphical representation of the mean values of VAS in admission and at the end of treatment in affected extremity

Edema

According to Budapest criteria of CRPS I from 2003, which replaced the IASP criteria from 1993 due to low specificity, we evaluated the sudomotor disorders, namely, the difference of edema, using perimetry method of measuring the swelling of the affected area, as compared to the symmetrical unaffected extremity.

Due to individual features, we could not quantify edema as a numerical value to each participant in the study but, for objectivity, we used the difference between the affected and unaffected extremity, so I removed the inconveniences arising from morphotype.

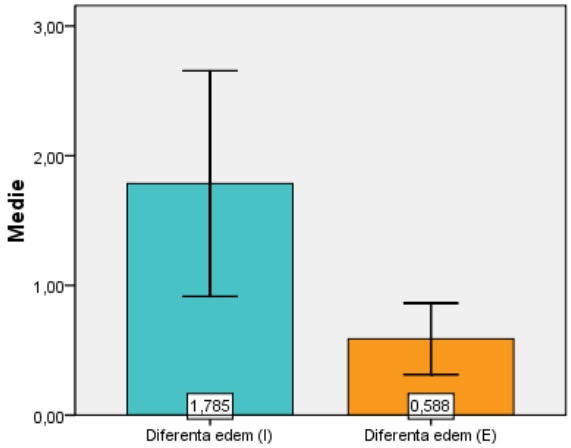

Chart no. 5. Graphical representation of the mean values of difference in edema at admission and at the end of treatment in affected extremity

In this research, we noted that at the end of treatment, the mean values registered for the difference of edema, in the study group, were significantly decreased compared to the mean values from admission (**Chart No. 5.),** which can be explained by antiinflammatory properties of mud, being known that classical inflammatory mechanisms may contribute by the secretion of proinflammatory cytokines, including IL-1β, -2, -6 and TNF-α, to the increase of plasma extravasations and to the occurrence of edema[31]. Prostaglandins, products of the arachidonic acid metabolism by the action of cyclooxygenase-2, have, also role in the

development of inflammation and local pain[25]. The anti-inflammatory effect of Techirghiol mud was demonstrated by the assessment of oxidative stress markers[28, 32], proinflammatory cytokines and the hormonal status, mechanisms involved in the occurrence of local pain and inflammation in CRPS I[33]. The results of this research project are in accordance with the results from international databases, which using complementary therapies in various pathological conditions, including CRPS I, had demonstrated the nutrition of the bone and the soft tissue, the improving of blood circulation and the removing of blood stasis[34]

The range of motion

According to Budapest criteria of CRPS type I, motor/trophic disorders as, limited range of motion (ROM) and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin), with the pain and edema characterize the clinical picture of CRPS type I. The mechanism by which appear the limited range of motion (**Figure no.5., and Figure no.6.)** is due to pain, exaggerate with the triggering event, and edema of the soft tissues, leading to severe impaired function of the joint.

Figure no. 5. and Figure no. 6. - Limited range of motion of lower extremity in CRPS I

According with inclusion criteria, we considered only traumatic etiology, establishing four clinical forms of presentation, as follows: F-PC Pouteau-Colles fracture (fracture of the distal extremity of radius), FG knee joint trauma (fracture of the upper extremity of tibia and fracture of patella) F-GL ankle trauma (fracture of lower extremity of tibia, fracture of perroneous and sprains of ankle), FP leg trauma (fracture of achilean tendon, fractures of talus, calcaneus's and metatarsus bone).

Analysis the range of motion for flexion in affected extremity at admission/end of treatment.

Were performed goniometric measurements of radio-cubito-carpal joint for the upper limb and the knee and ankle joints for the lower extremity

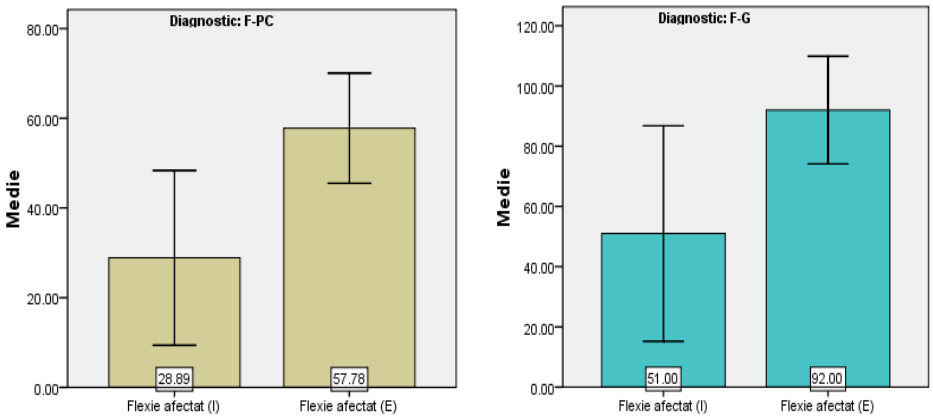

Chart no. 6. And Chart no. 7. Graphical representation of range of motion for flexion in affected extremity in admission and at the end of treatment for Pouteau-Colles fracture and knee trauma.

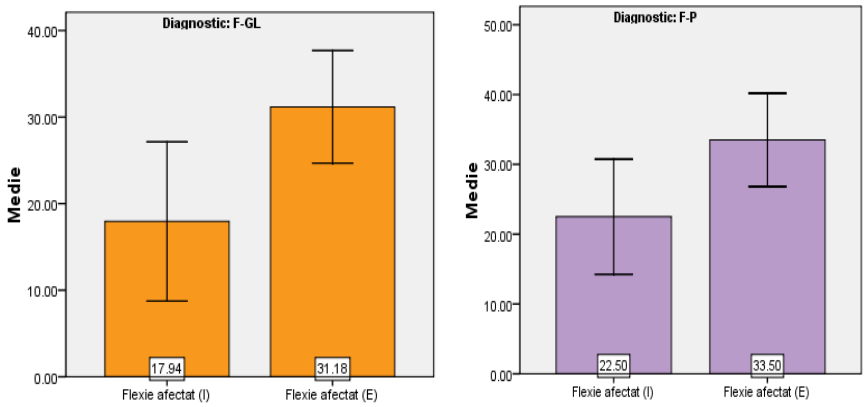

Chart no. 8. And Chart no. 9. Graphical representation of the range of motion for flexion in affected extremity in admission and at the end of treatment for ankle and foot trauma.

For all four presentation of CRPS type I (**Figures no.6, no.7, no.8, and no. 9.)** is a statistically significant increase ($p < 0.001$, $p = 0.009$, $p < 0.001$, $p < 0.001$) of range of motion for flexion explained by the reduction of pain and edema.

Analysis the range of motion for extention in affected extremity at admission/end of treatment.

Were performed goniometric measurements of radio-cubito-carpal joint for the upper limb and the knee and ankle joints for the lower extremity

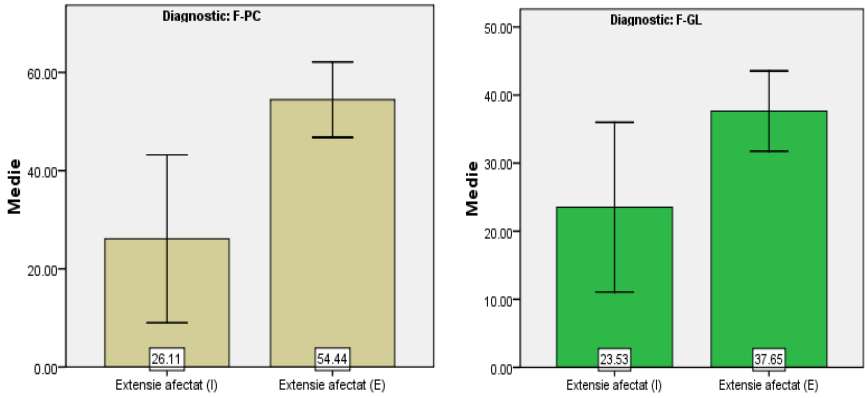

Chart no.10. and Chart no. 11. Graphical representation of range of motion for extension in affected extremity in admission and at the end of treatment for Pouteau-Colles fracture and ankle trauma.

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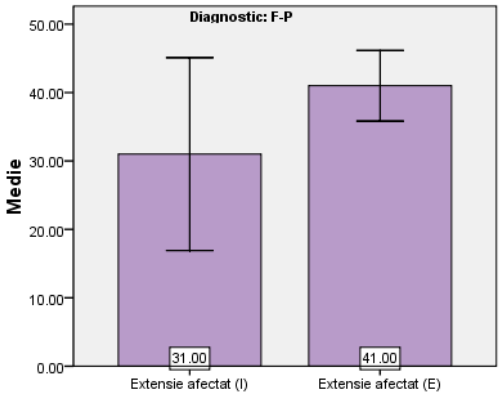

Chart no. 12. Graphical representation of range of motion for extension in affected extremity in admission and at the end of treatment for foot trauma.

For all four presentation of CRPS type I (Figures no.10, no.11, and no. 12.) is a statistically significant increase ($p < 0.001$, $p = 0.789$, $p < 0.001$, $p = 0.008$) of the range of motion for extension.

Histological comparative study of the skin under the action of Techirghiol mud[26, 35], shown that, the systematic, sustained and repeated mud application, produces structural changes in the skin and muscle. The study of blood gases under the action of peloidotherapy, by measurement of the parameters in the peripheral blood, showed an increase of the value of the partial pressure of oxygen, the oxygen saturation and the binding capacity of oxygen Therefore, the release of oxygen to tissues is improved, also the local perfusion, which may explain the improvement of muscle metabolism with the increasing of exercise capacity of muscle and hence the range of motion[36].

THE ANALYZES OF BIOLOGIC AND RADIOLOGIC PARAMETERS AND THEIR CONTRIBUTION TO SUPPORT THE POSITIVE DIAGNOSIS OF CRPS I

We analyzed these parameters in order to establish if exists a non-specific inflammatory process, which is an exclusion criteria for this study. To perform this objective we used: VSH, CRP, hemoglobin and we made standard radiographs of the affected extremity. We excluded from the study patients who had VSH>40 mm/h. In CRPS I don't exist a protocol of laboratory tests for the positive diagnosis, it is known that the diagnosis is primary anamnesis and clinical, the laboratory tests are typically in the normal range (VSH, CRP, and fibrinogen) or in the upper limit of normal[25]. These measurements were performed only on admission, because according to the literature, they usually remain frozen, at the initials values, during the evolution[25].

Erythrocyte sedimentation rate

Table no.2. The mean, standard deviation for erythrocyte sedimentation rate

	N	Minimum	Maximum	Mean	Std. Deviation
VSH [mm/h]	41	5.00	36.00	17.3902	8.34230

C-reactive protein

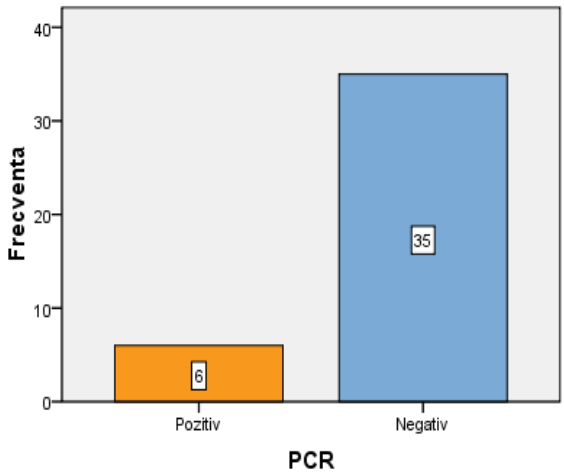

Chart no.13. - Graphical representation of PCR in the study group

In conclusion, laboratory tests which reveal a nonspecific inflammatory process are not altered in CRPS type I (Chart no.13. and Table no.2.).According with Budapest inclusion criteria increased systemic inflammatory markers are not associated with CRPS type I, even in the initial inflammatory phase, such a finding would raise markers to search for an alternative or concomitant cause.

Patchy Osteoporosis

According to the Budapest criteria, used in this research, an abnormal radiograph in a characteristic pattern of CRPS I can substitute other clinical diagnostic criteria. The sympathetic nervous system is involved in the development of osteoporosis with particular location, important clinical feature in CRPS type I [37]. Bone remodeling is considered to be partially controlled by the hypothalamus, a process mediated by the autonomic transmission routes and neurotransmitters[37].

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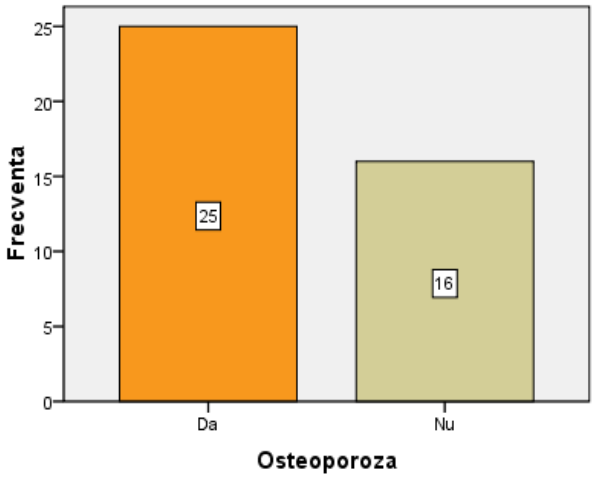

Chart no.14. Graphical representation of the presence of osteoporosis in the study group

In the study group 25 patients presented the "patchy" osteoporosis on the radiological examinations and 16 patients did not show this sign. (**Chart No. 14.).**

Figure no. 7. And Figure no. 8. Patchy" osteoporosis of the calcaneus's bone before and the end of treatment.

Bone changes had inconstant appearance, more frequent in young and elderly than adults[25], and this explains probably the results of our study, where an abnormal radiography is not present in all subjects, because the population included in this study is not homogeneous in terms ofage.

TEMPERATURE ANALYSIS BY DEMOGRAPHIC CHARACTERISTICS

The temperature by gender

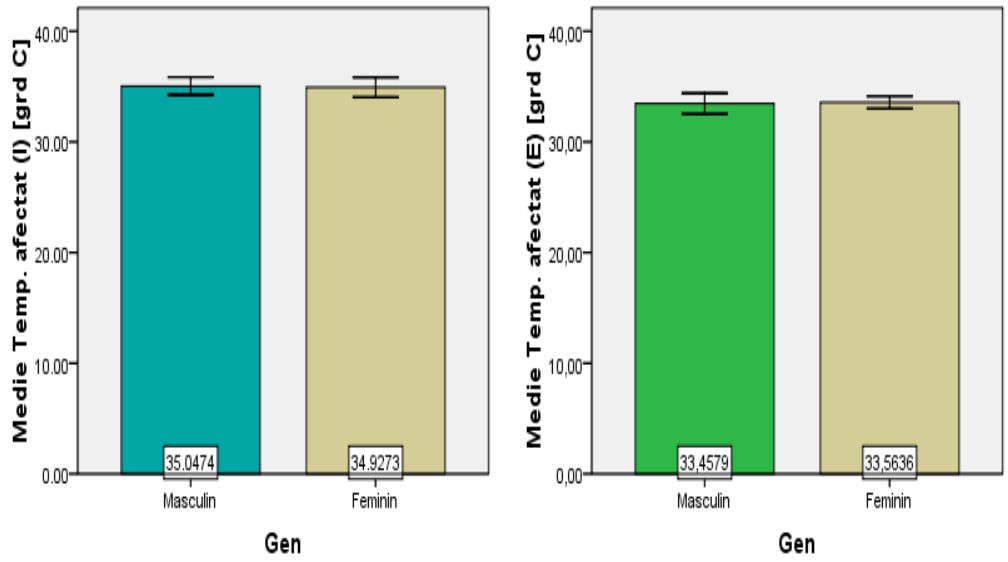

Chart no.15. And Chart no.16. Graphical representation of distribution of the mean values of temperature in admission and at the end of treatment in affected extremity by gender

The mean values of temperature of affected extremity in admission, in males, are increased compared to females (Chart no.15, Chart no.16), probably male is predisposed to severe injuries, by nature of their activities, which involves surgery in most of the cases.

At the end of treatment, the ratio women: men is no longer maintained, males had a higher receptivity to mud application.

Temperature by age intervals

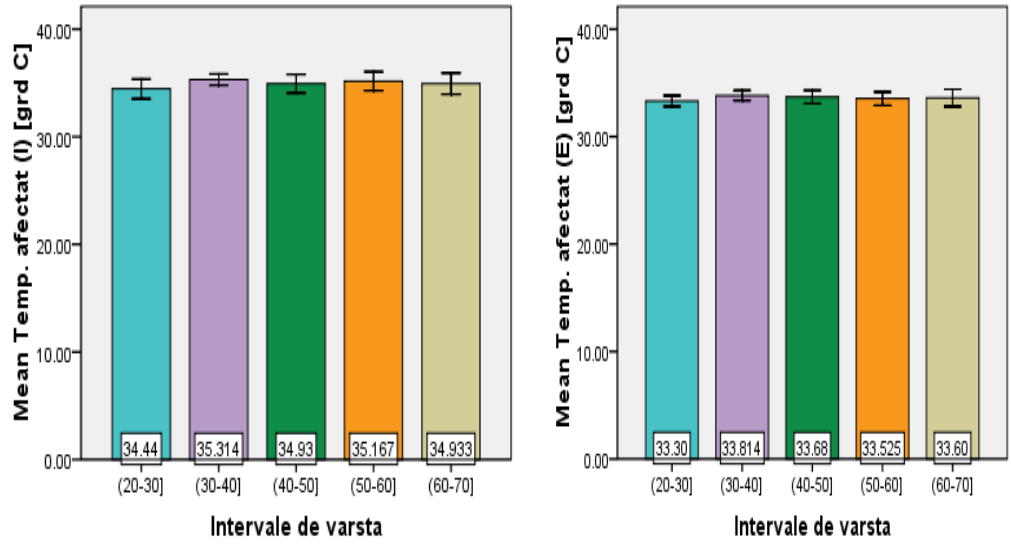

Chart no.17. And Chart no.18. - Graphical representation of the distribution of mean values of temperature in admission and at the end of treatment in affected extremity by age

Between the mean values of temperature in affected extremity corresponding to considered age intervals, in the two moments, are not statistically significant differences, the lowest values have been distributed in 20-30 and 70-80 age intervals. (Chart no.17, Chart no.18.).

Temperature by phenotype Sudeck

The neuroendocrine and autonomic constitution or functional status of these systems is discussed as predispositions factors in the occurrence of CRPS type I, by different authors[1]. Was described even a so-called "Sudeck phenotype", anxious people, emotional instability, with significant vegetative trauma[25]. Other clinical studies shows that changes in behavior and personality observed in patients with CRPS type I, especially depression and anxiety, are a consequence of persistent pain and resistance to treatment, and not the cause of CRPS type I [39].

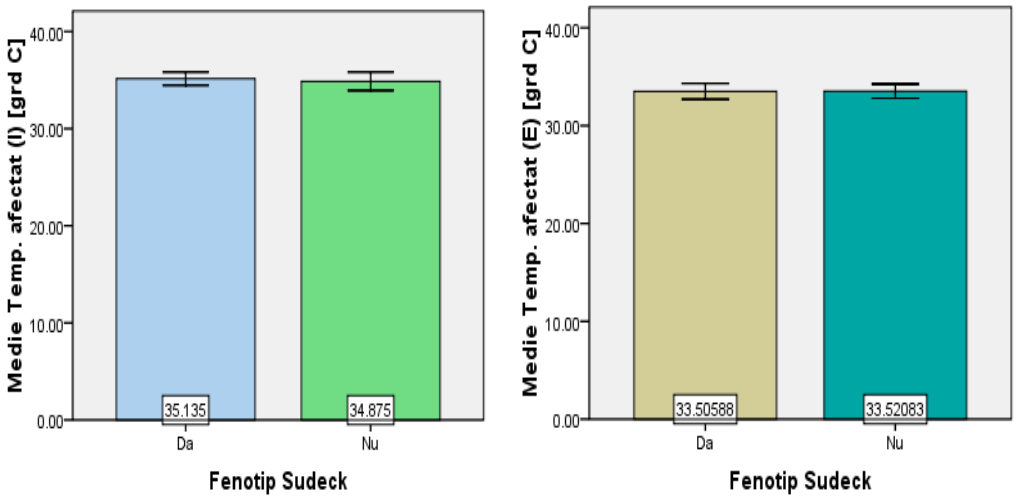

Chart no.19. And Chart no.20. Graphical representation of distribution of mean values of temperature in admission and at the end of treatment in affected extremity by phenotype Sudeck

From these data results that patients who present Sudeck phenotype had increased the mean values of temperature in affected extremity. (Chart no.19. and Chart no.20.) Probably the changes observed in behavior and personality of these patients, emphasizing the vasomotor disorders, with the increasing of the local skin temperature.

Temperature according to the location of the lesion

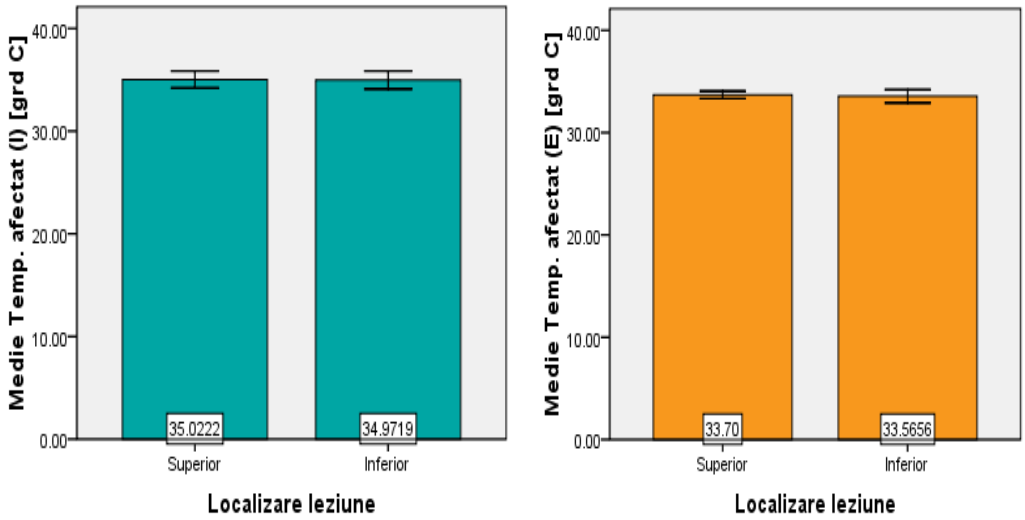

Chart no.21. And Chart no.22. Graphical representation of distribution of the mean values of temperature in admission and at the end of treatment in affected extremity by lesion location

The mean values of temperature is increased in upper extremity compared to the lower extremity, in the two moments (Chart no.21.,Chart no.22.), probably the hand is the most complex segment of the human body. It is not used just for prehension (the hand to catch the action with your fingers) and the most important

discriminative sensibility, but at the same time, is the organ of the human personality, of the expressiveness and the most elaborate professionalism.

Temperature according to the diagnostic

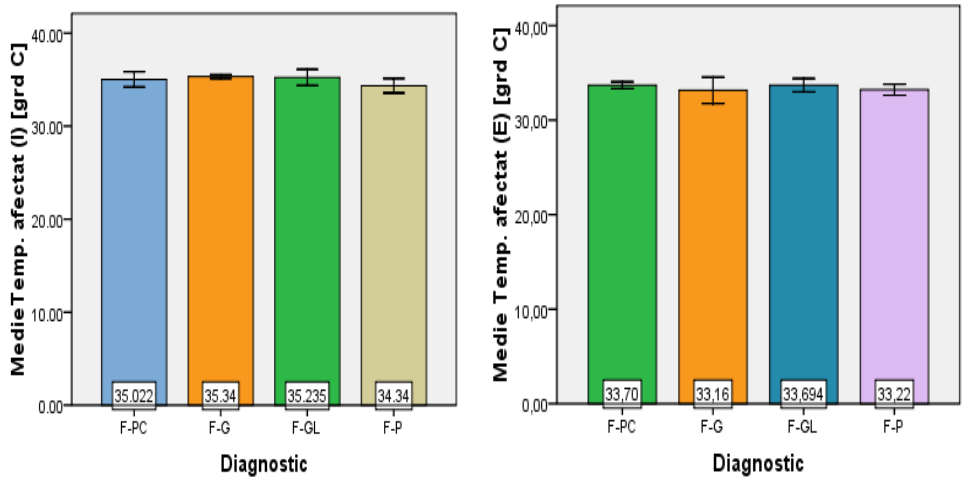

Chart no.23. And Chart no.24. Graphical representation of distribution of mean values of temperature in admission and at the end of treatment in affected extremity by diagnostic

In admission and at the end of treatment, between the mean values of temperature in affected extremity, in the four locations, are not statistically significant differences (Chart no.23., and Chart no.24.), which sustain that the temperature is a consequence of functional changes of the vascular structures, no matter of the diagnosis and the lesion location.

Temperature according to the surgery

CRPS type I is not unusual complication after surgery. For the upper limb, this condition can occur as a complication of surgery and determine a more prolonged recovery[40].

In our study, 16 participants were subjected to the surgical cure, while the 25 participants had been conservatory treated, by immobilizing of the fracture, in a cast, for various periods of time, depending on the severity of the disease, no longer than six weeks.

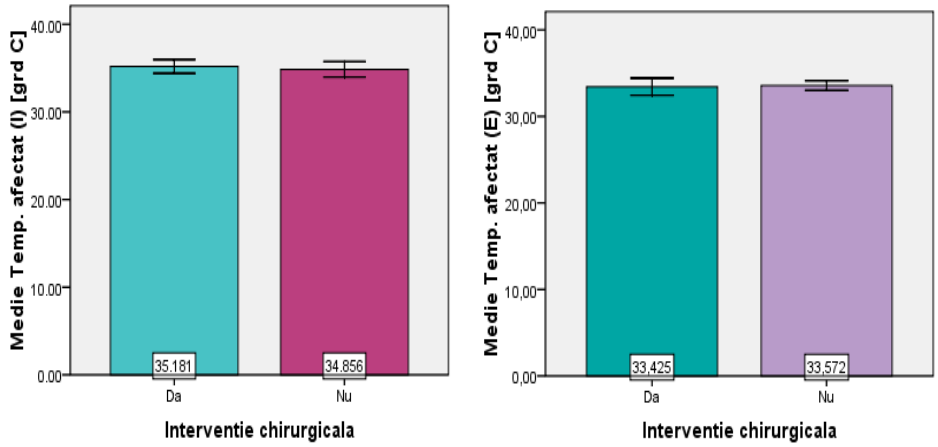

Chart no.25. And Chart no.26. Graphical representation of distribution of the mean values of temperature in admission and at the end of treatment in affected extremity with or without surgery

We could say that surgery is a trauma, at the same time, by enhance the local inflammatory process, determine the increase of mean values of temperature in affected extremity, in admission in patients who were surgical treated.

The mean values of temperature in affected extremity, at the end of treatment, in the two groups, were closed (33.42°C, respectively 33.57°C), showing that both groups of patients had reacted similarly to mud therapy (Chart no.25., and Chart no.26), reflecting the benefit of treatment with sapropelic mud from Techirghiol Lake.

CORRELATION OF CLINICAL FEATURES WITH SURGERY, THE EXISTENCE OF TREATMENT BEFORE AND THE PERIOD OF TREATMENT

Correlation of clinical features with surgery

CRPS type I remains a poorly understood pathological condition, characterized by clinical signs and symptoms that occur frequently in the periphery, after various injuries[40]. Pain is the main symptom; it is disproportionate to the triggering event[40]. In addition edema, limiting range of motion, color changes and the skin temperature in affected extremity occurs[40]. Diagnosis and treatment are a challenge for any clinician and often requires a multidisciplinary approach[40]. This condition often occurs as a complication of surgery, in the upper or lower extremity, leading to a more prolonged recovery.

Next we analyze if between clinical features (VAS, difference of edema, ROM, temperature of affected extremity) in patients with/without surgery, are significant differences. These parameters were assessed only at admission.

Pain and surgery

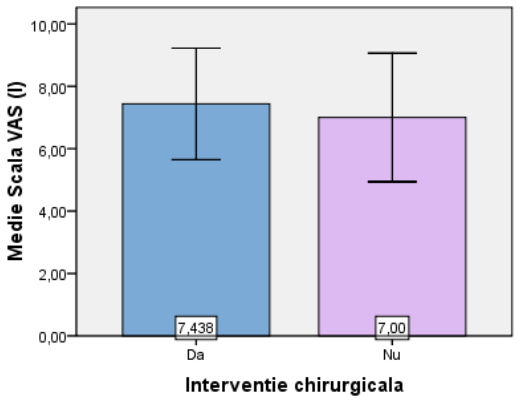

Chart no.27. Graphical representation of the mean values for VAS in admission according to surgery

Patients after surgery had the mean values of VAS elevated, in admission, compared with the mean values of VAS in the group who did not subjected to surgical treatment. (Chart no.27.).

Difference of edema and surgery

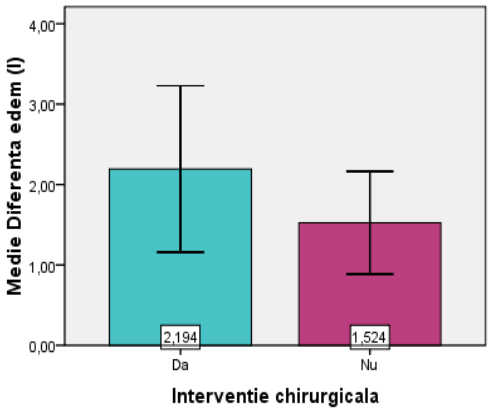

Chart no.28. - Graphical representation of the mean values of difference in edema in admission according to surgery

In admission, between the mean values of difference of edema, in both groups, are not statistically significant differences (p = 0.030) (Chart no.28.), because patients after surgery without CRPS type I, may present signs of inflammation: pain and swelling in affected extremity. Despite major interest for this pathology, there are a few data about which patients are at increased risk for developing CRPS type I after surgery[41].

The range of motion - the existence or not of the surgery

The range of motion is defined as an arc of movement determined by muscular strength to obtain joint movement. The range of motion was assessed using the goniometer. In the upper extremity was measured the dorsal flexion (extension)/the palmary flexion (flexion) of the radio-cubit-carpal joint and for lower extremity was measured dorsal flexion (flexion)/plantar flexion (extension) of the ankle joint and flexion/extension for knee joint. The range of motion of affected extremity was multiplied by 100 and divided by the range of motion of unaffected extremity. The result was set on a scale of numerical value graded from 1 to 5 as follows: 1. -> 95% representing no limitation of range of motion, 2. - 70-94% representing slight limitation of range of motion 3. - 45-69% representing moderate limitation of range of motion 4. - 15-44% being severe limitation of range of motion and 5 < 15% meaning the maximum limitation. I chose this scale because the study group is not homogeneous in terms of joint damage, meaning that subjects had affected radio- cubit carpal joints, ankle joint, knee joint, each of them having different degrees of freedom.

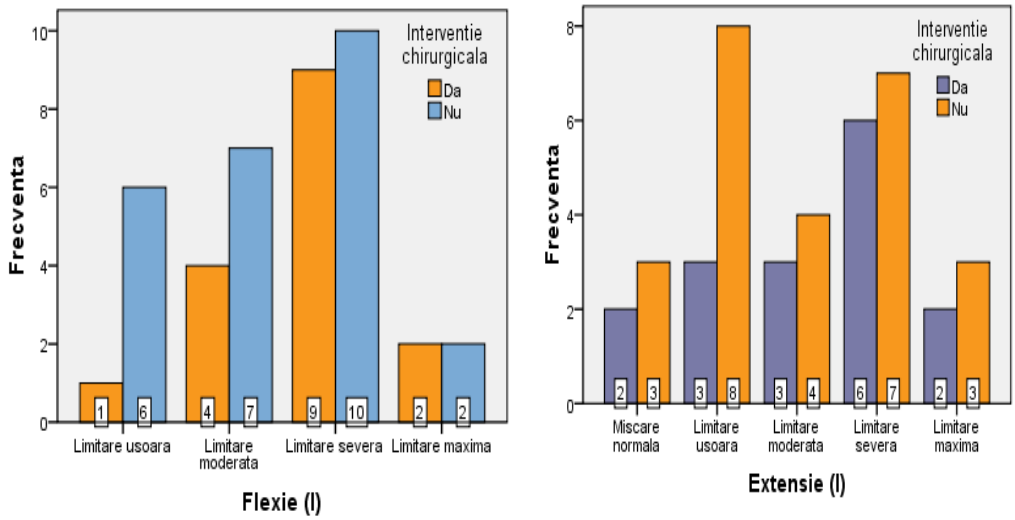

Chart no.29. And chart no.30. Graphical representation of range of motion for flexion and extension of the affected extremity in admission according to surgery

From the total of 16 patients who were surgical treated, 2 patients had maximum limitation the range of motion, 9 patients had severe limitation, 4 patients had moderate limitation and one patient had slight limitation of the range of motion for flexion (Chart no.29.). Because in the appearance of this severe limit of the range of motion an important contribution have the pain and edema, probably explains why the majority of patients, who were surgical treated, had severe and maximum limitation of the range of motion (15% -44 % from normal mobility).

From the total of 16 patients who were surgical treated, 2 patients had maximum limitation the range of motion, 6 patients had severe limitation, 3 patients had moderate limitation, 3 patients had slight limitation of extension and 2 patients had normal range of motion for extension (Chart no.30.). As shown from the data presented the range of motion for extension at admission, is less affected compared to the range of motion for flexion, probably in knee trauma, the flexion was more affected than extension.

Correlation of clinical features and the existence of treatment before

According to the data from the literature, except for studies to elucidate the etiology and pathogenic mechanisms of CRPS type I, are conducted researches to find the best therapeutic approach. Previous studies suggest several therapeutic attitudes: pharmacological therapy, physical therapy, sympathetic block and

sympathectomy, neuromodulation techniques (spinal electro stimulation) injection or infusion therapies[42]. Some of these techniques have many disadvantages, the most pronounced being the major financial and economic implications and the clinical efficiency poorly supported by randomized clinical trials. When they are used alone or the combination of these therapies often gives unfavorable results[42].

Pain and the existence or not of treatment before

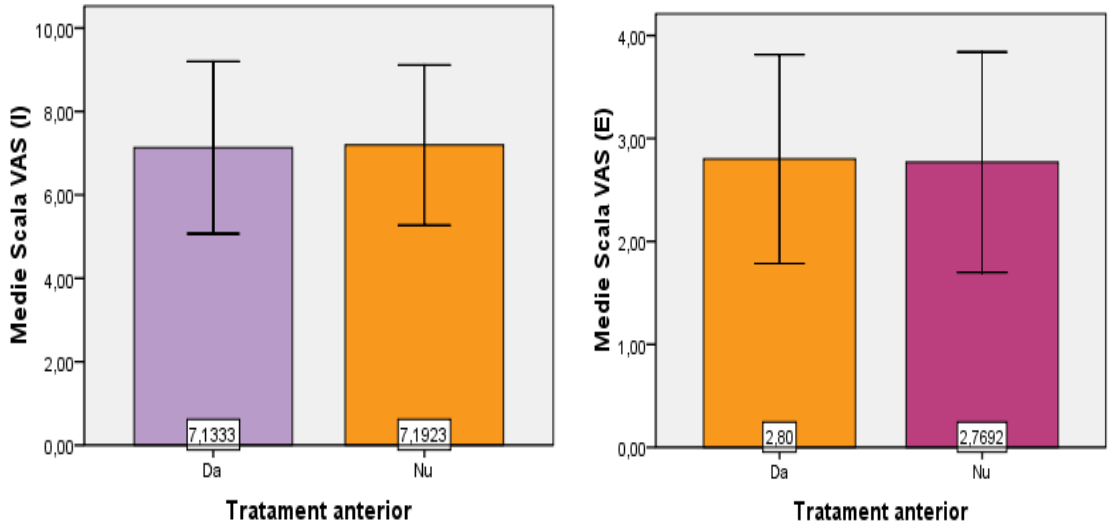

Chart no. 31. And Chart no.32. Graphic representation of mean values of VAS in admission and at the end of treatment according to the existence of treatment before

Because between the mean values of VAS, in admission, in the two groups are not statistically significant differences (Chart no.31.), we can say that physical therapy alone did not influence the pain assessed by VAS, in patients with CRPS type I.

At the end of treatment, the mean values of VAS are similar with the mean values of VAS from general study group (Chart no.32.), meaning, no matter if they received or not physical therapy before, pain assessed by VAS presents an improvement in both groups.

Difference of edema and the existence or not of treatment before

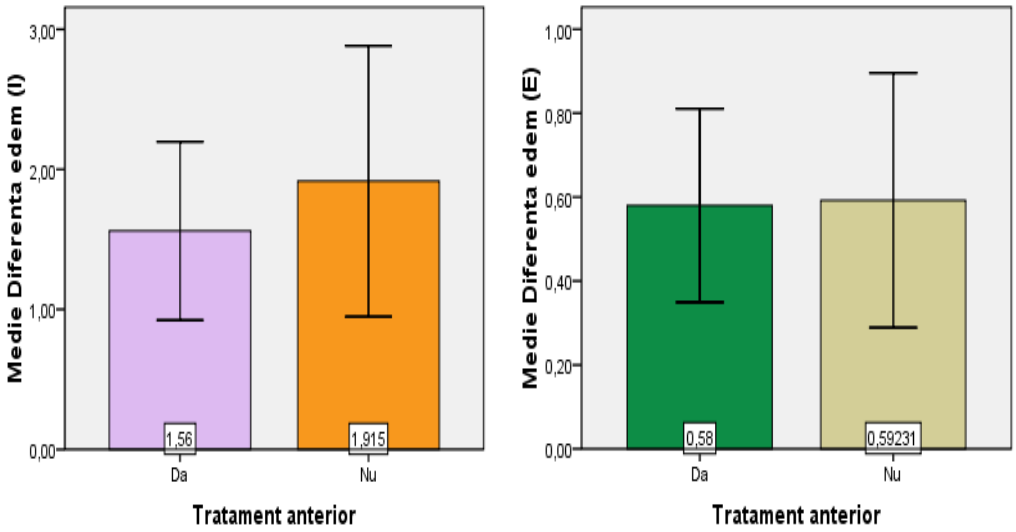

Chart no.33. And Chart no.34. Graphical representation of the mean values of difference in edema in admission and at the end of treatment according to the existence of treatment before

It is important to note that the edema is more an objective feature, while the VAS is a subjective feature. In addition to the involvement of the autonomic nervous system in the appearance of edema may be incriminated the local accumulations of products of catabolism, electrolyte and pH changes in the affected area. Because, between the mean values of difference in edema, in admission, in the two groups, are statistically significant differences, we can say that local electrotherapy with anti-inflammatory and resorptive effect has proven the benefit, as shown in Chart no.33.

Between the mean values of difference in edema at the end of treatment, in both groups, are not statistically significant differences. In admission, physical therapy alone has proven the benefit, but the association of mud therapy determined an additional response of the body, in the group with physical therapy before, the mean values of difference in edema decreased from 1.56 cm to 0.58 cm (Chart no.33., Chart no.34.).

Range of motion and the existence or not of treatment before

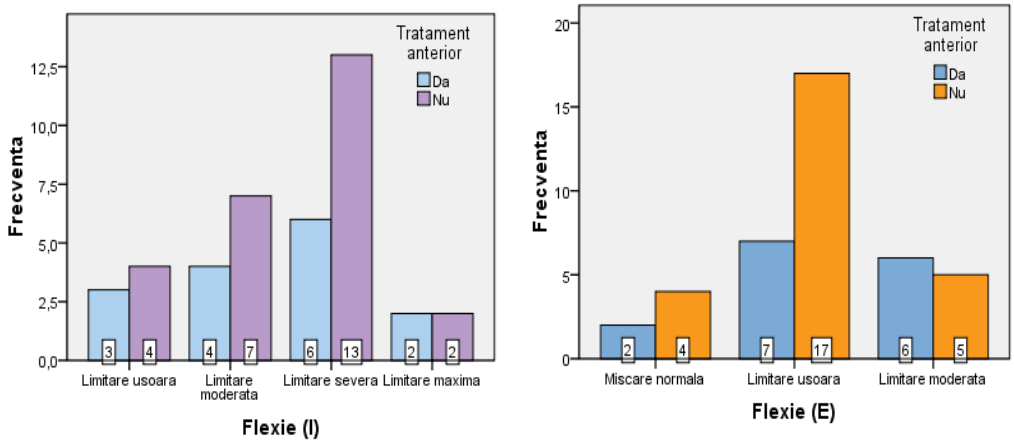

Chart no.35. And Chart no.36. Graphical representation of range of motion for flexion in the affected extremity in admission and at the end of treatment according to the existence of treatment before

In admission, the range of motion for flexion in groups of patients who had not received treatment showed that 22 patients had moderate, severe and maximum limitation from total of 26 patients (Chart no.35.). Even if those who had not received treatment before were superior numerical representation, the ratio of the two subgroups did not vary significantly.

At the end of treatment, in the two study groups, we observed an improvement in range of motion for flexion (Chart no.36.), by increasing the number of patients in the mild and moderate intervals with the disappearance of the intervals with severe and maximum limitation of range of motion, which demonstrates the benefit of combined therapeutic intervention of mud and kinetotherapy in the swimming pool and gym room.

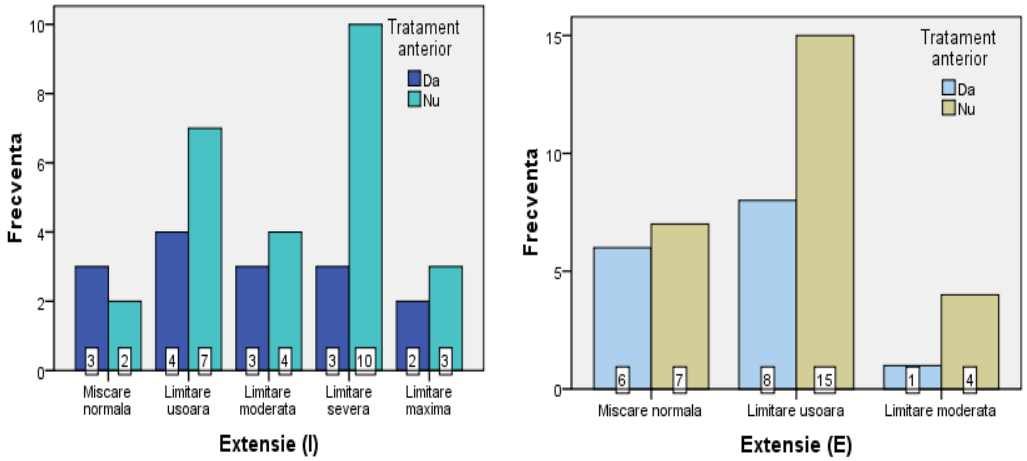

Chart no.37. And Chart no.38. Graphical representation of range of motion for extension in the affected extremity at admission and at the end of treatment according to the existence of treatment before

At the end of treatment, there is a similar behavior of the range of motion for flexion, in the two study groups, as meaning that the disappearance of subjects with severe and maximum limitation. However the evolution of extension, in studied joints, is superior to flexion (Chart no.37, and Chart no.38.).

Temperature and the existence or not of treatment before

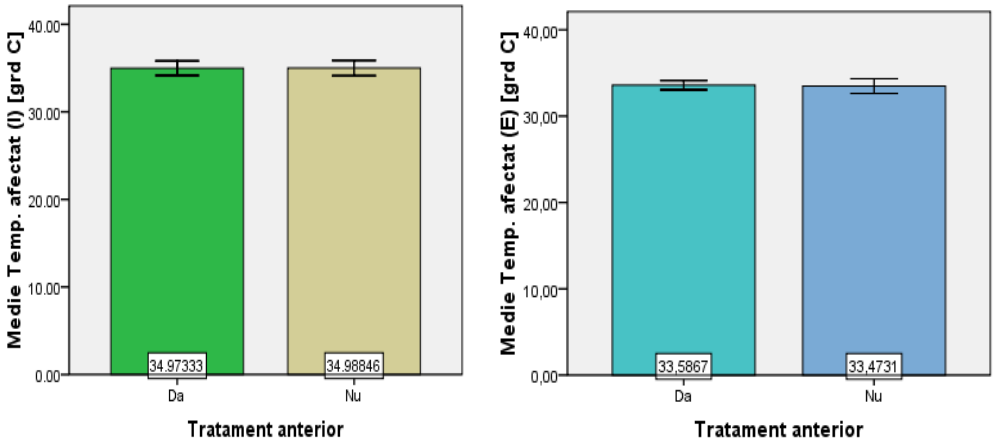

Chart no.39. And Chart no.40. Graphical representation of the mean values of temperature in admission and at the end of treatment according to the existence of treatment before

Vasomotor disturbances, in this study objectified by thermography; by increasing the local temperature, are important clinical features in patients with CRPS type I. SNS is the main cause of these vascular abnormalities[25]. Neuroendocrine system is another cause of vascular disorders. Almost all hormones have an influence on the terminal territory of circulation[25]. Prostaglandins, products of arachidonic acid metabolism, by the action of cyclooxygenase-2, with a part in the development of inflammation and local pain, also had demonstrated effects on the vasomotor tonus[25]. Because in the occurrence of vasomotor disorders contributes the mentioned mechanisms, this explains the fact that there are not statistically significant differences between the mean values of temperature in affected extremity, in admission, in the two groups, probably physical therapy alone can not influence these pathogenic mechanisms (Chart no.39. and Chart no.40.).

Correlation of clinical features with the period of treatment

In the Balneal and Rehabilitation Sanatorium of Techirghiol patients receive treatment for 10 or 15 days. We tried to identify if treatment period influence the evolution of the clinical features in CRPS type I. In our study group 32 subjects received 10 days of treatment, and 9 subjects performed 15 days of treatment. We analyzed pain using VAS, swelling using perimetry, range of motion by goniometry and temperature in affected extremity, their values at the end of treatment.

Pain and period of treatment

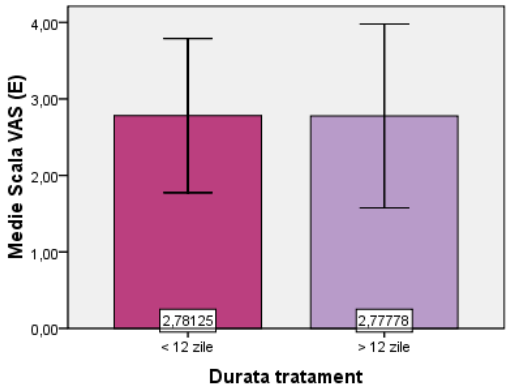

Chart no.41. Graphic representation of mean values of VAS at the end of treatment according to the period of treatment

At the end of treatment, the mean values of VAS in the group which received treatment for 15 days continues to decrease, not statistically significant, compared to the mean values of VAS of those which were treated for 10 days (Chart no.41.). The study shows that mud therapy adjusts the general reactivity, modulates the endocrine secretion to the new physiological conditions, set the adaptive response "à la longue" for a few months (at least 3-6 months).

Difference in edema and the period of treatment

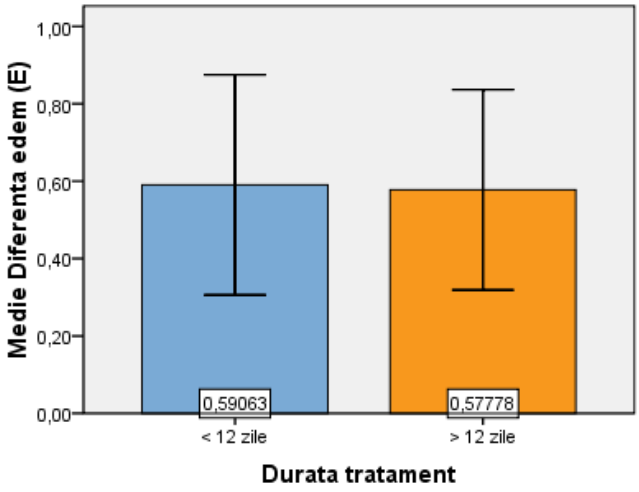

Chart no.42. - Graphic representation of mean values of difference of edema at the end of treatment according to the period of treatment

The same favorable evolution presents the mean value of difference in edema at the end of treatment in group who performed more than 15 days of treatment (Chart no.42.). Probably local structural changes and clinical features are subjected to the continuing effects of balneal therapy.

The range of motion and the period of treatment

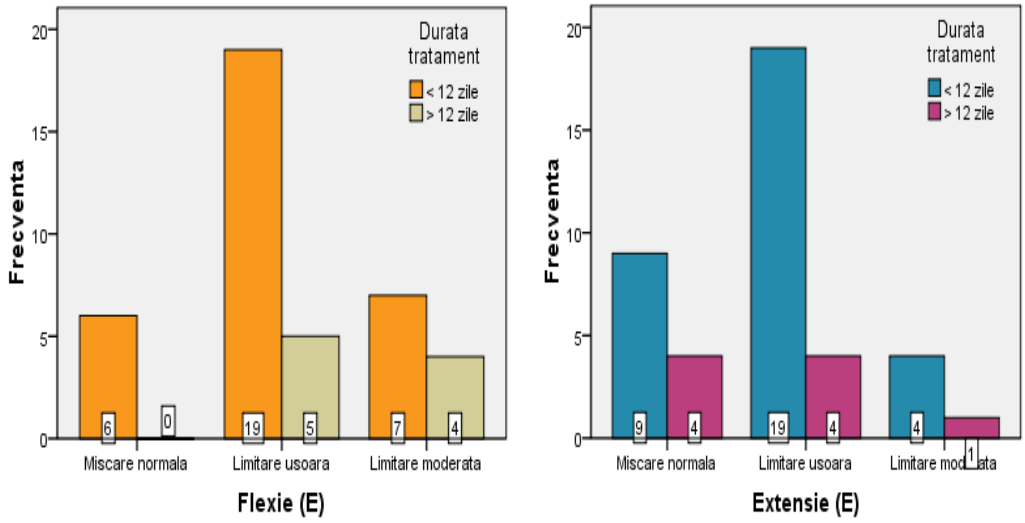

Chart no.43. And Chart no.44. Graphic representation of range of motion for flexion and extension at the end of treatment according to the period of treatment

The range of motion for flexion and extension had favorable evolution whatever the period of treatment. Unlike the range of motion for flexion, extension (dorsal flexion of the radio cubit -carpal joint plantar flexion of the ankle and extension for knee joint) has a higher improvement, 13 patients from 41 patients achieving normal mobility. (**Chart no.43. and Chart no.44.**)

Temperature and the period of treatment

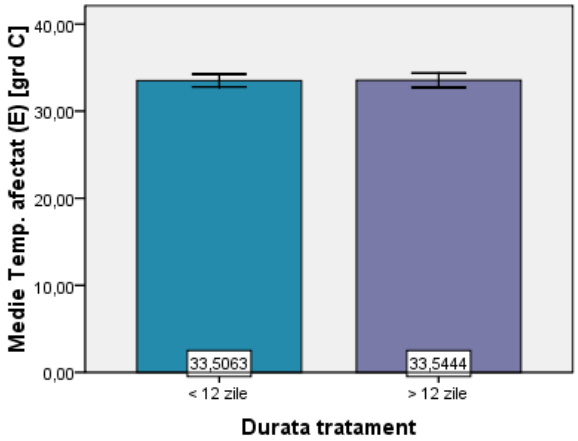

Chart no.45. Graphic representation of mean values of temperature at the end of treatment according to the period of treatment

At the end of treatment, the mean values of temperature in affected extremity, in the two groups, presented similar values (33.50ºC, 33.54ºC). It means that, temperature develop independent and its decrease in both groups means improving of clinical status and efficacy of Techirghiol mud whatever of the period of treatment (Chart no.45.).

The balneal environment through physical, chemical, biological, psycho-social agents by a certain intensity and duration, given systemically, rhythmic, determine multiple adaptative processes. The changes have a positive neuropsychic component and the biological responses generate endocrine-metabolic reactions that are able to provide the restore of homeostasis balance [43].

VIII CONCLUSIONS

CRPS type I is a pathological condition described over 125 years that is still a poorly understood and often unrecognized syndrome. Confusion appeared regarding the pathogenic mechanisms that contribute to the complex symptoms of these pathological conditions, as well as the determination the objectives, therapeutic means by which they propose a more efficient approach and maximum benefit to patients with CRPS type I.

The originality of this study results from a new therapeutic approach to CRPS type I, peloidotheraphy, an old method of treatment, established and improved over time, to achieve maximum benefit for patients with this condition.

For drawing conclusions on thermographic evaluation of patients with vasomotor disorders in CRPS type I, under the action of peloidotherapy, we grouped the obtained results from the goals that I have set. Where data was found in the literature, in the country or abroad, were compared with the results obtained in this study.

1. Thermographic assessment of vasomotor disorders in patients with CRPS type I under the action of sapropelic mud from Techirghiol Lake, in admission, showed a statistically significant increase ($p < 0.001$) of mean values of temperature in affected extremity compared with the mean values of temperature in unaffected extremity. We can say that, in this study, the existence of temperature asymmetries between the affected and unaffected extremity was diagnostic criteria

At the end of treatment, the mean values of temperature in affected extremity decrease statistically significant ($p < 0.001$), compared with admission, the values of the two extremities have the tendency to be the same.

The vascular disorders are an important clinical feature in CRPS type I. Several mechanisms, the sympathetic nervous system, neuroendocrine mechanism, almost all hormones contribute in the occurrence of these disorders. Prostaglandins, products of arachidonic acid metabolism, by the action of cyclooxygenase-2, with a part in the development of inflammation and local pain, also have demonstrated effects on the develop of vasomotor disorders. The mechanism by which the temperature of affected extremity decreased is due to, probably, the interference of pathophysiological mechanisms of CRPS type I with the physiological and therapeutic mechanisms of Techirghiol mud. Blood circulation is the functional link most involved in the body's adaptation to the mud application, and the blood is "carrier" body heat, harmonizing the body temperature in its various segments. Histological aspect revealed the increasing the number of open capillaries and neoangiogenesis, as a morphological proof of functional circulatory effects produced by termopexsis qualities of mud.

2. Evaluation of clinical features in patients with CRPS type I under the action of peloidotherapy.

We evaluated in this paper the following clinical features: pain, swelling and range of motion. All the parameters have a statistically significant improvement. All these represent the evidence for clinical effectiveness of the complex balneal treatment in this condition. Trying to establish if between the mean values of temperature in affected extremity and the mean values of the three parameters are correlations: we concluded that there are not strong correlations between them. The only variables that have been correlated moderately were the objective parameters: temperature and the difference of edema in affected extremity, measured in admission

3. Analysis of biological and radiological parameters and their contributions to sustain the positive diagnosis of CRPS type I. The analysis of VSH, PCR in admission showed that they are normal, as expected. According with the Budapest criteria, increased systemic inflammatory markers are not associated with CRPS type I, even in the initial inflammatory phase; such a finding requires searching for an alternative or concomitant cause. Radiological changes are not present in all subjects included in the study, usually are more common in young and elderly, and the population included in this study is not homogenous in terms of age.

4. The mean values of temperature in affected extremity in admission are increased in males, but not statistically significant. Males are probably susceptible to severe injury by the nature of their activities and often involve surgical intervention.

5. I noticed that the lowest mean values of temperature in affected extremity in admission and at the end of treatment was between: 70-80 years and 20-30 years, probably, CRPS type I is a pathologic condition that affects with predilection the adults.

6. The mean values of temperature in affected extremity on admission are increased in patients with Sudeck phenotype. Perhaps, in this study, the consequence of the observed changes in the behavior and the personality of these patients, were the emphasizing of vasomotor disorders with the increasing of the local skin temperature.

7. The mean values of temperature in affected extremity were higher in the upper limb, in two points, probably due to the fact that the hand is the most complex segment of the body. It is not only the organ of prehension and the most important segment for discriminative sensibility, but at the same time, is the organ of the human personality, of the expressiveness and of the most developed professionalism

8. The mean values of temperature in affected extremity, in admission and at the end of treatment, are not different according to the diagnosis of the lesion. What makes the case for the fact that the temperature is a consequence of functional changes of vascular structures, whatever the diagnosis and lesion localization.

9. The mean values of temperature in affected extremity in admission are increased in patients who received surgical cure of the lesion, knowing that surgery enhances the local inflammatory syndrome.

10. The existence of surgery in personal pathological antecedents of these patients showed higher values of clinical features, statistically significant for difference of edema, the association of surgery amplifying the local inflammatory syndrome.

11. We found that physical therapy, alone, does not influence clinical features (pain, swelling, range of motion, temperature). The mean values of these clinical features, measured in admission, did not reveal significant difference between two groups, with or without physical treatment before the balneal cure.

12. The analysis of clinical features (pain, swelling, range of motion, temperature) according to the period of treatment, at the end of treatment, showed that some of these parameters continue to decrease, although not statistically significant, probably due to the continuing effects of applications of the natural factors.

In conclusion, support the hypothesis that peloidotherapy is a valuable therapeutic option in the treatment CRPS type I by intercepting its pathophysiologycal mechanisms.

Proven mechanisms of action of mud: the anti-inflammatory role, stimulating the activity of hypothalamic-pituitary-adrenal axis, modulating the general reactivity and correction of the vegetative traumas, increasing the oxygen release in tissues with improved local perfusion, could explain the efficacy of this therapy, as demonstrated in this paper by decreasing the temperature and inflammation in CRPS type I.

REFERENCES

1. Stanton-Hicks M, Jänig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. *Reflex sympathetic dystrophy:changing concepts and taxonomy.* Pain. 1995 Oct;63(1):127-33;
2. Marcu V, Tarcău E. FEFS-Kinetoterapie-Universitatea Oradea. *Procedures, techniques and methods under recover kinetic in complex regional pain syndrome.* Conference 2005 Top athletic performance between hypotheses and confirmation-October 2005;
3. Veldman, PH, Reynen, HM, Arntz, IE, Goris, RJ. *Signs and symptoms of reflex sympathetic dystrophy: Prospective study.* Lancet 1993; 341:1012; 342:1012-1016;
4. Giannitti C, Bellisai B, Iacoponi F, Petraglia A, Fioravanti A. *[New evidences on spa therapy in fibromyalgia].* Clin Ter. 2008 Sep-Oct;159(5):377-80;
5. Bender T, Karagülle Z, Bálint GP, Gutenbrunner C, Bálint PV, Sukenik S. *Hydrotherapy, balneotherapy, and spa treatment in pain management.* Rheumatol Int. 2005 Apr;25(3):220-4. Epub 2004 Jul 15;
6. Bianchi C, Campacci R, Trinchi E. *Physical therapy in Sudeck's syndrome.* Fracastoro. 1968 Nov-Dec;61(6):748-68;
7. Johan Marinus, G Lorimer Moseley, Frank Birklein, Ralf Baron, Christian Maihöfner, Wade S Kingery, Jacobus J van Hilten *Clinical features and pathophysiology of complex regional pain syndrome.* The Lancet Neurology, Volume 10, Issue 7, Pages 637 - 648, July 2011;
8. Rho RH, Brewer RP, Lamer TJ, Wilson PR. *Complex regional pain syndrome. Mayo Clin Proc.* 2002 Feb;77(2):174-80;
9. Harden R, Bruehl S, Perez R, et al. *Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome.* Pain 2010;11:1115-25;
10. Taha R, Blaise GA. *Update on the pathogenesis of complex regional pain syndrome: role of oxidative stress.* Can J Anaesth. 2012 Sep;59(9):875-81;
11. Bruehl S. *An update on the pathophysiology of complex regional pain syndrome.* Anesthesiology 2010;113:713-25;
12. Marin V., Profir D., Ionescu E., Başa M., Roşoiu N., (2009), *Effects of Techirghiol mud in oxidative stress at patients with osteoarthritis,* Archives of the Balkan Medical Union, 44, 3, 196-200;
13. Profir D., Marin V., Surdu T.V., Roşoiu N., (2011), *Variation of Serum Level of Proinflammatory Cytokines after Mud Therapy in Patients with Osteoarthritis,* Archives of the Balkan Medical Union, 46, 2, 114-119;
14. Surdu Traian-Virgiliu. *Complex adaptive responses under Techirghiol mud sapropelic therapy.* Ovidius University, Faculty of Medicine, Constanta, 2011;
15. Anna Jung, Lanusz *Yuber, Francis Ring, Casebook of infrared imaging in clinical medicine*, Medprerss Warszawa, 2003;
16. Baron R, Janig W: *Complex regional pain syndromes – how do we escape the diagnostic trap?* Lancet 2004, 364(9447):1739-1741;
17. Niehof Sjoerd Petrus, Lamberts S.W.J., Klein J., van der Helm F.C.T., Hovius S.E.R., Stam H.J., Huygen F.J.P.M., Zijlstra F.J. *Video thermography: complex regional pain syndrome in the picture*. Rotterdam, 2007, 8.6 Medicine and thermography; 138-139;
18. Hendler N.: *Reflex Sympathetic Dystrophy and Causalgia. Handbook of Chronic Pain Management.* Editor; C. David Tollison, PhD. Williams & Wilkins, 1989;

19. BY R. K. WILL, E. F. J. RING, A. K. CLARKE AND P. J. MADDISON.: *Infrared thermography: what is its place in rheumatology in the 1990s?* British Journal of Rheumatology 1992;31:337-344;

20. Marin V., Profir D., Ionescu E., Başa M., Roşoiu N., (2009), *Effects of Techirghiol mud in oxidative stress at patients with osteoarthritis,* Archives of the Balkan Medical Union, 44, 3, 196-200;

21. Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M. *Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there?* Rheumatol Int. 2011 Jan;31(1):1-8;

22. Badalov NG, Krikorova SA. *[Peloid therapy: the theoretical and practical aspects, problems and prospects of its development].* Vopr Kurortol Fizioter Lech Fiz Kult. 2012 May-Jun;(3):50-4;

23. Krumova EK, Frettlöh J, Klauenberg S, Richter H, Wasner G, Maier C. *Long-term skin temperature measurements - a practical diagnostic tool in complex regional pain syndrome.* Pain. 2008 Nov 15;140(1):8-22;

24. Wasner G. *Vasomotor disturbances in complex regional pain syndrome--a review.* Pain Med. 2010 Aug;11(8):1267-73;

25. Degeratu Cornelia, *Complex regional pain syndrome.* Editura Medicală Bucureşti,1983. pag.23-37; 49-51; 53; 68-73; 91-95;

26. Surdu Olga. *Comparative histological study of the action of Techirghiol sapropelic mud on skin.* Ovidius University, Faculty of Medicine, Constanta, 2007;

27. Teleki N., Munteanu L., Stoicescu C., Teodoreanu E., Grigore L., 1984, *Spa cure in Romania*, Sport-Travel Publishing, Bucharest, 50-52, 76-82;

28. Marin V., Profir D., Ionescu E., Başa M., Roşoiu N., (2009), *Effects of Techirghiol mud in oxidative stress at patients with osteoarthritis,* Archives of the Balkan Medical Union, 44, 3, 196-200;

29. Taha R, Blaise GA. *Update on the pathogenesis of complex regional pain syndrome: role of oxidative stress.* Can J Anaesth. 2012 Sep;59(9):875-81;

30. Schencking M, Bohmhammel J, Keller C. *[Inpatient treatment for CRPS I by use of complementary medicine].* Forsch Komplementmed. 2009 Apr;16(2):117-22;

31. Bruehl S. *An update on the pathophysiology of complex regional pain syndrome.* Anesthesiology. 2010 Sep;113(3):713-25;

32. Profir D., Marin V., Surdu O., Roşoiu N., (2007), *Variation of serum level of proinflammatory cytokines after mud therapy in patients with ankylosing spondylitis,* FEBS Journal, Volume 274, Supplement 1, July 2007, pp.1-378, 32nd FEBS Congress, "Molecular Machines", Vienna, Austria, F1-76, 283;

33. Profir D., Marin V., Surdu T.V., Roşoiu N., (2011), *Variation of Serum Level of Proinflammatory Cytokines after Mud Therapy in Patients with Osteoarthritis*, Archives of the Balkan Medical Union, 46, 2, 114-119;

34. Xu RS, Zong XH, Li XG. *[Controlled clinical trials of therapeutic effects of Chinese herbs promoting blood circulation and removing bloodstasis on the treatment of reflex sympathetic dystrophy with type of stagnation of vital energy and blood stasis].* Zhongguo Gu Shang. 2009 Dec;22(12):920-2;

35. Surdu Olga, et al *„Histological study on the skin tissues modifications induced by mud-pack therapy"*, 35th Congress of the International Society of Medical Hydrology and climatology, june 6-10, 2006, Istanbul, Congres Book pag 96;

36. Marin V., Profir D., Roşoiu N., Petcu L., (2011), *Evaluation of Blood Gases Pressure in Patients Treated with Sapropelic Mud of Techirghiol,* Archives of the Balkan Medical Union, 45, 1, 69-74;

37. Kurvers HA, Jacobs MJ, Beuk RJ, Van den Wildenberg FA, Kitslaar PJ, Slaaf DW, Reneman RS. *Reflex sympathetic dystrophy: evolution of microcirculatory disturbances in time.* Pain. 1995 Mar;60(3):333-40;

38. He JY, Jiang LS, Dai LY. *The roles of the sympathetic nervous system in osteoporotic diseases: A review of experimental and clinical studies.* Ageing Res Rev. 2011 Apr;10(2):253-63;

39. Lesky J. *[Sudeck syndrome (CRPS) caused by unique personality traits: myth and fiction].* Z Orthop Unfall. 2010 Dec;148(6):716-22;

40. Field J. *Complex Regional Pain Syndrome: a review.* J Hand Surg Eur Vol. 2013 Jan 22;

41. Reuben SS. *Preventing the development of complex regional pain syndrome after surgery.* Anesthesiology. 2004 Nov;101(5):1215-24;

42. Happak W, Sator-Katzenschlager S, Kriechbaumer LK. *Surgical treatment of complex regional pain syndrome type II with regional subcutaneous venous sympathectomy.* J Trauma Acute Care Surg. 2012 Jun;72(6):1647-53;

43. Surdu Traian-Virgiliu. *Complex adaptive responses under Techirghiol mud sapropelic therapy.* Ovidius University, Faculty of Medicine, Constanta, 2011;