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Original Article

The evaluation of the efficacy of steroid iontophoresis in patients with rheumatoid arthritis

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Abstract

Aim: Comparative evaluation of direct current and steroid iontophoresis treatments in patients with active wrist synovitis with rheumatoid arthritis.

Material and Methods: Rheumatoid arthritis (RA) is a chronic, inflammatory disease that causes pain, swelling and limitation of motion, keeping wrist and hand joints symmetrical. In this study, we examined the efficacy of steroid iontophoresis with direct current to the wrists of active RA patients. 20 active patients with RA and wrist synovitis were included in the study. Steroid iontophoresis applied in one wrist of these patients, direct current to the other wrist (control). Patients' number of painful joints (NPJ), number of swollen joints (SJN), hand grip strength (HG), lateral grip strength (LG), Hand Functional Evaluation (HFE), Health Assessment Questionnaire (HAQ), Disease Activity Score-28 (DAS-28) and power Doppler ultrasonography (PDUS) were compared.

Results: Clinical and laboratory parameters were significantly improved according to pre-treatment (Pr-T) and post-treatment (Pst-T). We found significant improvement in Pr-T and Pst-T in the cases of HG, LG, HFE, SJN and NPJ in the wrist in treatment and control, but there was no significant difference between the control wrist and the treated wrist. There were no changes in Pr-T and Pst-T in grades, if any, resistive index (RI) and pulsatility index (PI) values of PDUS with pannus and current in hand wrist.

Conclusions: Our results showed no difference between the steroid iontophoresis and direct current therapy in patients with RA who were active and have wrist synovitis in Pr-T and Pst-T.

Keywords: Rheumatoid Arthritis; Steroid Iontophoresis; Direct Current; Power Doppler Ultrasonography.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease that affects mainly synovial joints, and its etiology is characterized by chronic inflammation (1). It is also referred to as synovium disease because it affects synovial joints and synovial tendon sheaths. Despite being the most affected tissue synovium, in some cases, extra-articular stiffness can be added to different findings (2). Joint stiffness affects hand joints more, and leads to many deformities in hand (3). Case rates have been reported between 0.3% and 1.5% in various studies conducted worldwide for the prevalence of rheumatoid arthritis and there are differences between races. Prevalence ranged from 35 to 45 years, with a female/male ratio ranging from 2/1 to 4/1 and an average of 3/1 (4).

Radiologic imaging techniques play an important role in the diagnosis and treatment of the disease. The earliest radiological changes take place in the hands. Conventional radiography may reveal symmetric soft tissue swelling, juxta-articular demineralization, erosions and cysts around the involved joint. Magnetic resonance imaging allows for early diagnosis in unrecognized RA cases because of changes in synovial tissues and early manifestation of pannus formation (5). Power Doppler ultrasonography (PDUS) allows slow flows and smaller vessels to be visualized, and can be used separately from non-inflammatory fluid collections of inflammatory and infectious fluid collections and helps to detect synovial pannus tissue. (6,7).

Treatment of rheumatoid arthritis is focused on relieving pain and inflammation, starting early treatment and protecting joint functions. Drug therapy should be supported by physical therapy and rehabilitation (8). The aim of using direct current is to release dissolved ions, chemical substances and drugs in the organism for

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therapeutic purposes, epidermis and mucous membranes (9). Iontophoresis is a non-invasive method that can be discontinued when it is needed, it can provide continuous active doses, and it has a wide use area, and has few side effects because of the low amount of locally administered drugs (10). This study is a comparative assessment of direct galvanic current and steroid iontophoresis to the wrist joints in patients with RA.

MATERIAL and METHODS

Twenty female patients with rheumatoid arthritis who met the 1987 ACR criteria were included in the study (11). The study was approved by the local ethics committee and the informed consent forms were filled in with detailed information about the illness, study, and the permissions taken. Patients were active according to Disease Activity Score-28 (DAS-28), with both wrist stiffness and synovitis (12).

Basic characteristics such as age, gender, weight, height, duration of illness, morning stiffness, duration of morning stiffness and other accompanying diseases, if any, were recorded in detail. Patients with active infection and who received steroids above 10 mg/day were not included in the study.

Clinical Evaluation:
Patients' demographic questionnaires and detailed physical examinations were performed to determine the pain, the global assessment of the patient and the physician measured by visual analog scale (VAS), the number of painful joints (NPJ), number of swollen joints (SJN), hand grip strength (HG), lateral grip strength (LG), hand functional evaluation (HFE) was recorded.

In order to evaluate the hand function, we used a board system which we named "nail placement" in a size of 25x25 cm2, which was called "nail placement", with holes drilled on the drill and 20 holes in 4 cm distance from each other. The patient was asked to place the dominant hand first, then the other hand, and the quadrant in the hole, the actions were recorden in seconds with a watch.

A Health Assesment Questionnaire (HAQ) was administered to assess patients' disability status. Complete blood count, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), Rheumatoid factor (RF) values and routine biochemical values of the patients were evaluated.

With the PDUS device, the pannus in the joint, the presence of blood flow, resistive index (RI) and pulsatility index (PI) values were recorded by looking at both wrists and metacarpophalangeal (MCP) (1-5). If blood flow was present in PDUS, the severity of the blood flow was evaluated as grade 1, grade 2, grade 3, and grade 4. RI and PI values were also measured in the blood flow and graded joints.

On the other hand, steroid iontophoresis was applied by 10 sessions of 15 minutes by a physical therapy nurse. Steroid iontophoresis was applied to the same wrist for 10 sessions. After the clinician reconsidered the patient at the end of the treatment, the clinician was informed which wrist was given steroid iontophoresis. Direct current applied wrist was accepted as wrist in control. In iontophoresis, 2 ml of 80 mg of triamcinolone acetonide dissolved in 100 ml of 0.9% NaCl was used as a steroid. For direct current and iontophoresis, 6x8 cm carbon silicon electrodes were used with 9x10 cm sponge pads. In iontophoresis, the active electrode was (+) the inactive electrode was (-).

The Statistical Package for Social Sciences (SPSS for Windows 15.0, SPSS Inc. Chicago IL USA) was performed on a computer using statistical package software. Statistical method results were made using parametric or nonparametric statistical methods according to whether the distribution was normal or not. Comparisons between groups were compared by independent t test for parametric values, Mann-Whitney U test for nonparametric values, t-test for dependent groups if parametric, and Wilcoxon test when group distributions were appropriate for nonparametric tests. The relationship between the parameters was evaluated using the Pearson correlation coefficient. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The mean age of the patients was 54 ± 10,6 and the mean duration of disease was 10 ± 6,3 years, mean height 158 ± 8,3 cm (145-170) and mean weight 70 ± 12,4 kg (51-94) (Table 1).

Table 1. Demographic characteristics of the patients studied

	Patients given direct current and iontophoresis
N	20
Sex (Male / Female)	0/20
Age	54±10,6 (29–68)
İllness Duration (Year)	10±6,3 (2–20)
Height (cm)	158±8,3 (145–170)
Weight (kg)	70±12,4 (51–94)

There was a statistically significant difference ($p = 0,01$ and $p < 0,001$) among patients when pretreatment (Pr-T) and post treatment (Pst-T) CRP compared with ESR, but no significant difference in RF ($p > 0,05$). There was a significant difference when morning stiffness was compared ($p < 0.001$). There was a significant difference in DAS-28 which was used to assess the activity of the patients ($p < 0.001$). There was a significant difference when HAQ values were compared ($p = 0.04$) (Table 2).

When the Pr-T and Pst-T VAS values were compared, pain, self-assessment of the patient, and doctor's assessment of the patient's, the decrease in VAS values were significant. The decrease in pain VAS value was 1.73 ± 1.28 ($p < 0,001$), the patient's self-assessment was VAS 1,57 ± 1,15 ($p < 0.001$), the physician's assessment VAS 1,41 ± 1,23 and $p < 0.001$).

When SJN, NPJ, HG, LG, HFE of both treated hand control hand were assessed, there were significantly improvements in Pr-T and Pst-T periods. In the treatment group, SJN's p rate was found to be <0.05 P value (p <0,001) and control hand was (p = 0,01). In the NPJ, the treated hand value was (p <0,001) and the control hand's was (p = 0,16). There was a significant improvement in hand (p = 0.036), but there was no significant difference in control (p> 0.05). When HFE was compared, it was seen that the treated hand (p <0.001) and the control hand (p = 0.01) improved significantly (shortening of time). When LG was compared, there was no significant difference between treated hand and control one (p> 0.05) (Table 3).

Power Doppler ultrasound is given to patients treated and control wrist the pannus was looked in the MCP and 1-5 joints. Seven of the treated wrists had ulnar styloids and 10 had radial styloid pannus. Among the wrists in control group; 7 had ulnar styloid, 5 had radial styloid and pannus. In the grades of measured blood flows in wrist ulnar and radial styloids, RI and PI values were not statistically significant when compared in Pr-T and Pst-T periods (p> 0,05) (Table 4).

A total of 3 blood flows were detected in the treatment and control MCP joints of the patients. Statistics were not made because the number of joints with blood flow was low.

Table 2. Laboratory and clinic characteristics of the patients studied

	Pr-T	Pst-T	p
ESH (mm/s)	51±17,4	37±17,2	<0,001
CRP (mg/dL)	34±22,3	23±18,1	0,01
RF (u/mL)	154±119,2	153±120	>0,05
Morning stiffness dk	66,7±26,8	36,0±26,8	<0,001
DAS-28	5,45±0,6	4,4±0,9	<0,001
HAQ	32,7±10,5	28,9±9,9	0,04

ESH: Eritrosit Sedimantation Rate, CRP: C-reactive protein, RF: Romatoid factor, DAS-28: Disease Activity Score-28, HAQ: Health Assesment Questionnaire

Table 3. Changes in the number of painful joints, the number of painful joints and the index of articulation

	Treatment Group			Control Group		
	Pr-T	Pst-T	p	Pr-T	Pst-T	p
SJN	2,7±1,3	1,9±1,4	<0,001	2,6±1,4	2,1±1,7	0,01
NPJ	3,8±3,0	2,0±2,0	<0,001	3,6±2,0	2,4±1,7	0,16
HG (kg)	9,7±5,8	10,9±5,5	0,036	9,9±5,8	10,6±5,2	>0,05
LG (kg)	3,1±1,3	3,6±1,5	>0,05	3,0±1,4	3,2±1,4	>0,05
HFE (sn)	69,5±25,0	55,7±14,6	<0,001	69,0±28,9	57,0±17,0	0,01

SJN: Swollen Joint Number, NPJ: Number of Painful Joints, HG: Hand Grip Strength, LG: Lateral Grip, HFE: Hand Functional Evaluation

Table 4. Changes in measurement of wrist ulnar and radial styloid grades, RI and PI

	Treatment Group			Control Group		
	Pr-T	Pst-T	p	Pr-T	Pst-T	p
Ulnar styloid grad	1,5±0,9	1,5±1,0	>0,05	1,2±1,2	1,5±0,8	>0,05
Radial styloid grad	1,7±1,2	1,5±0,8	>0,05	1,3±0,8	1,0±0,7	>0,05
Ulnar styloid Rİ	0,6±0,2	0,5±0,3	>0,05	0,4±0,3	0,6±0,2	>0,05
Radial styloid Rİ	0,6±0,1	0,6±0,1	>0,05	0,7±0,2	0,5±0,3	>0,05
Ulnar styloid Pİ	1,7±0,9	1,3±0,9	>0,05	1,2±1,1	1,6±0,7	>0,05
Radial styloid Pİ	1,5±1,1	1,4±0,7	>0,05	1,9±0,9	1,2±0,9	>0,05

RI: Resistive index, PI: Pulsatility index

DISCUSSION

Inflamed synovium in rheumatoid arthritis leads to pain, swelling, joint arrest, limitation of movement, joint destruction, and deformities. Increased signaling in the synovium that occurs in inflammatory arthritis, hyperemia and hyperperfusion is visualized by PDUS and is claimed to be a useful method in early inflammatory joint diseases (13). In order to reduce the pain, it is necessary to start rehabilitation by using physical therapy methods at the beginning of the disease to maintain function, to prevent tissue destruction and deformity, to correct the loss of function and deformity, and to ensure compliance with the patient. When physical therapy is used together with medication, the effect of treatment increases. In patients with active RA, physical therapy is an integral part of drug therapy (14). Iontophoresis is the most commonly used method for pain and inflammation. Iontophoresis for treatment of locomotor system lesions should be considered as an alternative to peri and intraarticular injections because the drugs used diffuse to the tissues along the dermal barrier and penetrate into the body (15, 16).

Özgöçmen et al. studied a case of a 21-year-old with Ankylosing spondylitis heel pain and VAS rate of right achilles pain was measured as 82 mm, VAS rate of left achilles pain was 80 mm, and CRP 23, ESH 65 mm and PDUS were observed in the laboratory. The right achilles was given steroid and the left was given isotonic iontophoresis for 7 days. After treatment, the pain VAS was measured as 14 mm on the right and 55 mm on the left. Changes were detected in the right achilles but not on the left in PDUS (17).

Grassi et al. studied four different cases regarding the use of PDUS following treatment. In the study Newman et al. performed, they took a patient with 5 RA, one with PsA and one with CPPD, followed by intraarticular injection of steroids after showing active synovitis with PDUS, 40

mg of triamcinolone hexacetonide as a steroid and 1% lidocaine of local anesthetic were applied. Two weeks later, VAS scores and PDUS signal and soft tissue thickness decreased. They stated that PDUS is a useful new method for following treatment (18).

Ston et al. studied 12 patients with active RA had pain VAS, ESR values. With PDUS, at least 3 MCP joints were examined. As a treatment, methyl prednisolone 125 mg IV was given for three days and then 20 mg prednisolone was given orally. Two weeks after the treatment, pain VAS, ESR values were re-examined and the same joints were examined with PDUS. They found that pain level in 10 patients after treatment showed significant difference in VAS, ESR and PDUS. (19).

Teh et al. in their study evaluated 13 patients with active RA had CRP, ESH, HAQ values, PDUS and 3rd MCP joint. They gave 1000 mg i.v. methylprednisolone as a treatment, and after a 6-point reduction in patients' HAQ, they looked again at the parameters. PDUS, CRP, ESH, and HAQ and found significant differences (20).

Kalia et al. took biopsies from the epidermis after iontophoresis and they found steroid deposits in biopsies. However, no steroid deposits were found in the epidermis after oral steroid treatment. In addition, given steroids were detected 2 weeks after iontophoresis in the systemic circulation (21).

Anderson et al. studied 5 people and found that they gave steroid iontophoresis and that ionophore-mediated drugs reached penetration depths of 10 mm in local tissues at pharmacological concentrations (22).

Chantraine et al. studied 94 patients with soft-tissue rheumatism, 47 patients with RA, 25 patients with sports injuries and 22 patients with osteoarthritis. All the patients were treated with steroid iontophoresis. 2 ml of 80 mg of triamcinolone acetonide dissolved in 100 ml of 0.9% NaCl was used as the steroid. The direct current was applied in 0.25-0.35mA for 10-20 minutes and 56% of patients were observed with having less pain and decreased inflammation (15).

Nirschl et al. included 200 epicondylitis patients in their study. Steroid iontophoresis for treatment group, saline solution for control group was applied as 6 sessions in 15 days and evaluated 2 days after treatment. Pain VAS, swelling and tenderness were assessed. Among 200 patients, 99 were treated with steroids and 100 were treated with saline iontophoresis. In pain VAS, improvement was 52% in the treatment group and 33% in the control group, and 48% in the treatment group and 42% in the control group in the global evaluation (23).

In our study, when we looked at pannus, grade, RI, PI rates and blood flow in treated and control hand; there were 7 ulnar styloid on the treated wrist, pannus on 10 radial styloid, 7 ulnar styloids, 5 radial styloids. Although the the treated and control group patients were active and had wrist synovitis, there were 14 blood flows in both wrist ulnar and radial styloids and no flow was detected in the other 6 wrists. These findings were consistent with the above studies.

In our study, two wrists of the patients were given different treatments, one wrist treated with direct current and the other wrist with steroid iontophoresis for 10 sessions. The wrist that we gave the direct current was regarded as control. Several parameters such as age, gender, education status, duration of illness, medication used, level of functional impairment caused by the disease, and deformities were equalized to form groups that did not differ statistically from each other for study. We think that we are able to measure steroid iontophoresis and direct current more efficiently than other studies in patients who we have not treated in different patient groups, but in the same patients.

Steroid systemic circulation through iontophoresis treatment that we applied can pass through and cause steroid effects. Steroid deposits are observed in the tissues after steroid iontophoresis in studies performed, and steroids are found in the plasma up to 2 weeks (21, 22). Steroids reduce joint pain and swelling, fatigue and ESR at low doses. No changes were made to the treatments of the patients we took to study and the same treatment was continued, and a total of 80 mg of triamcinolone acetonide was administered in 10 days.

Iontophoresis is an application made on the direct current ground. Because of this, both the treatment group and the control group are affected by direct flow effects such as analgesia, sensory nerve end-resultant anesthesia, unintentional contraction and vasodilatation resulting from motor nerve stimulation, superficial veins and deeper tissue vessels, resulting in increased back absorption. In addition to these steroids, further reduction of inflammation and pain may explain the significance in Pr-T and Pst-T difference in treated hand, while it is meaningless to control (24).

There was no significant difference between RI and PI values Pr-T and Pst-T ulnar and radial styloid and grade if any. However, when we look at the above studies with Pr-T and Pst-T PDUS, we found significant differences and in our study no significant difference was found. This can be explained by the fact that in our study PDUS and blood flow, if any, grad, RI and PI values were examined. In the above studies, the extent of effusion was examined from the blood flow spread of vascularity.

In our study, low-dose steroids were administered to our patients, but in the above studies high-dose steroids were given and evaluated with PDUS at the earliest 2 weeks after steroid therapy. At the end of 10 days, our patients were reevaluated. The PDUS assessment was applied shortly after the treatment, with time limitations of the assessor, PDUS device intensity, and patients' arrival from the rural areas and requesting to go after the treatment was over. We think that there is no difference in the duration of the vasodilating effect after the direct current is delivered and there is no difference due to the PDUS evaluation during this period (24).

As a result, there is a need for new studies to determine the efficacy of PDUS and iontophoresis, which are just beginning to enter clinical practice.

LIMITATIONS

Our work has some limitations. Especially the patients included in the study consist only of female gender, which is the cause of the patient profile that we follow. The fact that RA is seen more frequently in women than in men makes this limitation negligible. Another limitation is that the study is a cross-sectional study and the number of patients is relatively small. Patients included in the study were having active wrist stiffness and with synovitis, whic was caused the number of patients to be restricted. Our assessment with PDUS after the end of treatment at 10 days is another limitation to be applied immediately after the treatment. The time constraint of the assessor is due to the PDUS device's density and the patients' arrival in the rural area.

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