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APPLICATION OF METHYLPREDNISOLONE SUSPENSION BY IONTOPHORESIS IN PATIENS WITH ARTHROSIS OF THE KNEE

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PRIMENA SUSPENZIJE METILPREDNOZOLONA JONTOFOREZOM KOD PACIJENATA SA ARTROZOM KOLENA

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ABSTRACT

The knee arthrosis is very frequent rheumatic degenerative disease. It primarily represents a damaged joint cartilage, which causes pain and reduction in mobility, inability to walk and associated symptoms. In this clinical syndrome we found synovitis as attendant symptom of „activated knee arthrosis". Therapeutic regiment is based on applications of non-specific inhibitors of inflammation, non-steroidal inflammatory drugs, and application of physical therapy. Later on, preparations of hyaluronic acid have been given. Application of corticosteroid by iontophoresis is not so common in clinical practice, instead of intraarticular injection of cortisone preparations (e.g. poorly soluble suspensions of methylprednisolone and betamethasone). In this work we have shown the importance of application of corticosteroids with iontophoresis in patients with arthrosis of the knee joint. The optimal iontophoretic application of methylprednisolone acetate in the cases with knee joint arthrosis was performed by the following protocol: application of the drug with negative electrode, the current of 120 mA*min/cm^2, with the average time of application (depending on to patient individual sensitivity) of 20 minutes. The improvement of the signs and symptoms and the subjective discomfort in the knee joints were measured by Hubertus test and VAS scale. Our results showed that clinical and subjective improvement was larger and more sustained in the group which was treated with iontophoretic application of methylprednisolone, than in the group treated with placebo (distilled water).

Abbreviations: VAS - visual analogue scale, NSAID - non-steroidal anti-inflammatory drugs, TENS - transcutaneous electrical nerve stimulation

Key words: knee arthrosis, corticosteroids, iontophoresis

SAŽETAK

Gonartroza je vrlo često degenerativno reumatsko oboljenje. Ona se primarno odlikuje oštećenom zglobnom hrskavicom, što izaziva bol, redukciju pokretljivosti, nemogućnost hoda i pridružene simptome. U ovom kliničkom sindromu se sreće i sinovitis kao prateći simptom „aktivirane gonarthroze". Terapijski program se zasniva na primeni inhibitora zapaljenskih nespecifičnih medijatora, nesteroidnih inflamatornih lekova, i primeni fizikalne terapije. Kasnije se daju preparati hijaluronske kiseline. Primena jontoforeze kortikosteroida nije tako česta ukliničkoj praksi za razliku od intraartikularnog davanja kortizonskih preparata (npr. slabo rastvorljive suspenzije metilprednizolona i betametazona). U ovom radu je pokazan značaj primene kortikosteroida putem jontoforeze kod artroze kolenog zgloba. Optimalna primena metilpredizolon acetata putem jontoforeze kod artroze kolena je sprovedena po sledećem protokolu: aplikacija leka sa negativne elektrode, doza od 120mA*min/cm^2, a prosečno vreme aplikacije leka (u zavisnosti od individualne osetljivosti pacijenta) je oko 20 minuta. Poboljšanje simptoma i znakova i subjektivnih tegoba kod atroze kolena je mereno Hubertus testom i VAS skalom. Naši rezultati su pokazali da je kliničko i subjektivno poboljšanje bilo veće i dugotrajnije kod grupe koja je primala metilprednizolon putem jontoforetske aplikacije, nego u grupi lečenih placebom (destilovana voda).

Skraćenice: VAS - vizuelno analogna skala, NSAIL - nesteroidni antiinflamatorni lekovi, TENS - transkutana elektrostimulacija

Ključne reči: artoza kolena, kortikosteroidi, jontoforeza

INTRODUCTION

The knee arthrosis is the most common degenerative rheumatic disease. Its primary properties are: damaged joint cartilage, pain, motility reduction and inability to walk. In clinical picture, we often find synovitis as a symptom of „activated" knee arthrosis (1). Primary knee arthrosis most often does not have clear etiology, and secondary knee arthrosis is caused by bad position of the genu valgum or genu varum, by inflammatory processes, metabolic joint damage (chondrocalcinosis, gout, diabetes mellitus), by traumatic damage (ligaments damage, chondromalacia), by bleeding in the joint (haemophilia), aseptic necrosis and troubles during growth. Localization defines the type of joint arthrosis: medial, lateral or patellofemoral arthrosis. If all three forms are found, then we can talk about arthrosis of the whole knee joint (2).

Therapeutic regiment is based on application of inhibitors of inflammation nonsteroidal anti-inflammatory drugs and application of physical therapy. Recently, with the disease at the initial phase, various preparations of hyaluronic acid were given. The use of corticosteroids through iontophoresis has not been much researched so far, but iontophoretic techniques with corticosteroids, some non-steroid antiinflamatory drugs (e.g. sodium diclofenac), and acetic acid were thought to be effective treatment mode for inflammations in several areas of the body (3). Formulated as water soluble salt, the corticosteroid molecule has a negative charge and, during the iontophoresis, such preparations are delivered from the cathode. Dexamethasone sodium phosphate was

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the most used corticosteroid agent during the iontophoretic procedures (4). It was experimentally proved that the drug penetration into tissue following iontophoresis in primates was considerable (more than 1.5 cm) and included joint capsules (5).

On the other hand, methylprednisolone was occasionally used during iontophoresis probably due to its inability to penetrate the intact skin in significant amount (6). If used, the soluble salt, methylprednisolone succinate, was chosen (7). We were unable to find the study which investigates the iontophoretic penetration of the methylprednisolone or its compounds. However, the esters of methylprednisolone, such as the acetate, sodium succinate, hemisuccinate and the phosphate, were rapidly converted in vivo to parent molecule. In addition, it has been recently reported that in patients receiving the methylprednisolone acetate injection, the drug could be detected in biological fluids with the advanced electrochemical techniques, across the wide range of its concentrations and pH values (8). Electrocatalytic oxidation of methylprednisolone was probably primary involved in its conversion to electrochemically active compound (9, 10).

Obviously, the use of methylprednisolone during iontophoresis was poorly investigated so far which strongly contrast the fact that in routine clinical practice, intraarticular injection of corticosteroid preparations, among which methylprednisolone was the one (e.g. Lemod depoR) is widely used (11). Taking into account the available evidence about the electrical properties and behaviour of methylprednisolone molecule and its pharmaceutical preparations we hypothesised that the iontophoretic application of methylprednisolone acetate depot formulation could exert valuable clinical utility in knee arthrosis.

PATIENTS AND METHODS

The study had single blind, prospective, placebo-controlled design. The study was performed in Specialized Hospital „Vrnjacka Banja", from September, 2005. to December, 2006. The sixty adult subjects with knee arthrosis were randomly assigned into two equal groups. The patients in both groups were treated with the same basic therapeutic protocol - application of drug therapy (NSAIL, other analgesics) and conventional physical agents: ultrasound 0,8 W/cm^2 with 5 minutes duration, TENS therapy, paraffin application, kinesytherapy.

In experimental group, iontophoresis of corticosteroids was applied which consisted of methylprednisolone acetate (Lemod depoR) in the dosage of 40 mg (prepared as liquid suspension in 1 mL), once daily, with duration of ten days. Methylprednisolone was applied in liquid solution, put on filter paper, from the negative pole of the electrode. For iontophoresis, milliampere dosage was applied with 120 – 150 mA*min/cm^2. According to individual sensitivity, the time of the procedure for each subject was adjusted. In another group of patients, beside the basic therapy, placebo was applied by iontophoresis, with the same current parameters of electrotherapy as in experimental group.

For evaluation of the applied therapy effect in the patients with joint arthrosis, we used Visual Analogue Scale (VAS) for pain evaluation (12), Hubertus test (13), muscular test for quadriceps femoral muscle (14) measures of motion range in degrees and of treated knee joint, as well as reduction of the doses of NSAIDs. All parameters are measured three times: the time before therapy application (baseline), after ten therapeutic procedures and after a month of therapy. The study was approved by the Institutional Review Board.

The sample size was calculated for two independent arms in order to detect the significant difference in VAS score between treatment groups. The data for primary variable were based on previous research and medical history database at our institution. The statistical analysis included descriptive statistics as well as the hypothesis testing for continuous or categorical variables (15), according to the intention-to-treat principle. There were no missing data for outcome variables. Before testing, the Kolmogorov Smirnov test was used to examine the normal distribution of the data and then parametric or non-parametric statistics were used depending on distribution pattern. In general, t-test, one/two-way ANOVA and Pearson chi-square were primarily used. The probability of $p=<0.05$ for all statistical calculations was selected.

RESULTS

Sixty patients were allocated in two equal groups, which were comparable according to the main demographic and clinical variables (table 1). The differences in frequency of the following parameters were not significant: age (Mann Whitney U test; p=0.362), gender (χ^2-test; p=0.259), side of the disease (χ^2-test; p=0.436), occupation (χ^2-test; p=0.495), working experience (t-test; p=0.250), body height (t-test; p=0.920), distance knee-floor (t-test; p=0.305), foot length (size) (Mann Whitney U-test; p=0.940), body weight (t-test; p=0.529), time of the maximal pain (χ^2-test; p=0.313), seasonal pain pattern (χ^2-test; p=0.206), family history (χ^2-test; p=0.796), target muscle hypotrophy (χ^2-test; p=0.001 and p=0.002), synovitis (χ^2-test; p=0.071), crepitating joint (χ^2-test; p=0.002), and palpable tenderness (χ^2-test; p=0.313).

Table 1. Demography and clinical properties of the patients.

Variable		Experimental group (n=30)	Control group (n=30)
Age (years)		65.27+10.79	61.53+13.6
Gender	male	8 (26.7%)	10 (33.3%)
	female	22 (73.3%)	20 (66.7%)
Diagnosis	unilateral arthrosis	15 (50%)	18 (60%)
	bilateral arthrosis	15 (50%)	12 (40%)
Occupation	retired	11 (36.7%)	12 (40%)
	unemployed	13 (43.3%)	15 (50%)
	merchants	2 (6.7%)	3 (10%)
	nurses	1 (3.3%)	0 (0%)
	clerks	2 (6.7%)	0 (0%)
	pupils	1 (3.3%)	0 (0%)
Working experience (years)		31.875+6.06	29.5+5.35
Height (cm)		164.34+8.92	164.59+9.51
Body distances, knee-floor (cm)		49.58+2.75	48.03+2.16
Body distances, foot length (cm)		24.75+1.96	24.58+1.6
Weight (kg)		79.47+12.54	77.6+10.17

The values shown: represent the mean ± standard deviation or the number of patients (percent)

The analysis of the variables between the groups was made in relation to the time of examination in order to evaluate the influence of corticosteroid iontophoresis on patient's health. During the application of methylprednisolone acetate, statis-

tically significant reduction in pain has been noticed, which was evaluated according to VAS pain scale (Friedman test; $p<0.001$). In a group of patients treated with iontophoresis with distilled water statistically significant improvement has been also noted (Friedman test; $p<0.001$). However, average value of pain before the therapy in experimental group was significantly higher than in comparator group (Mann-Whitney U test; $p=0.026$). After 10 days of therapy the VAS scores were comparable between groups (Mann-Whitney U test; $p=0.072$). Finally, reduction of pain at the end of the study was significantly bigger in experimental than in control group (Mann-Whitney U test; $p=0.000$). Therefore, overall VAS scores in active treatment group were much lower than in comparator group indicating better treatment outcome (table 2, figure 1).

Table 2. VAS scale in the study patients.

Visit	Experimental group (n=30)	Control group (n=30)
At baseline	7.87+0.9	7.1+1.35
After 10 days	5.33+0.96	6+1.51
After 30 days	4.37+1.13	5.77+1.36

The values shown: the mean± standard deviation

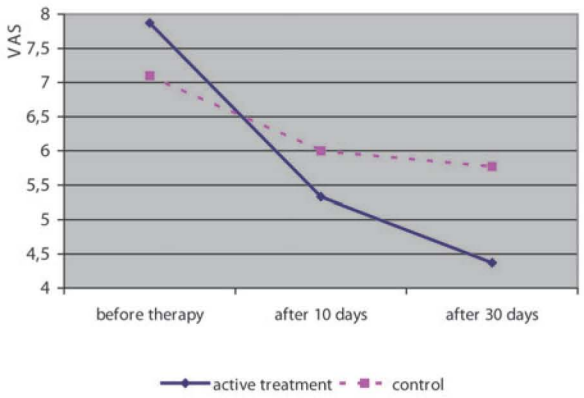

Figure 1. Pain evaluation according to VAS scale during the application of the therapy.

Apart from reduction of pain after application of iontophoresis with methylprednisolone, functional improvement was also achieved; Hubertus test showed positive therapeutic effect in both groups (Friedman's test; $p<0.001$) (table 3, figure 2). In experimental group, the values of the test, recorded before the therapy, were significantly lower than in control group (Mann Whitney U test; $p=0.002$). However, after 10 days of the therapy the difference between groups was not significant (Mann Whitney U test; $p=0.693$) as well as in the next 20 days (Mann Whitney U test; $p>0.05$).

Table 3. Values of Hubertus test in study subjects.

Visit	Experimental group (n=30)	Control group (n=30)
At baseline	23.73+2.3 (23)	26.2+3.08 (27)
After 10 days	29.93+2.98 (30)	30.37+5.76 (30)
After 30 days	30.03+2.92 (30)	29.57+6.76 (30)

The results of the test of femoral muscle strength as well as the magnitude of the affected knee contracture are showed in detail bellow, in tables 4 and 5 as well as in figures 3 and 4. The femoral muscle strength was significantly improved in the experimental group, (Friedman's test; $p=0.018$), but not in the control group (Friedman's test; $p=0.097$). The difference was noted after 10 days (Mann Whitney U test; $p=0.012$), and continued throughout the study (Mann Whitney U test; $p=0.045$).

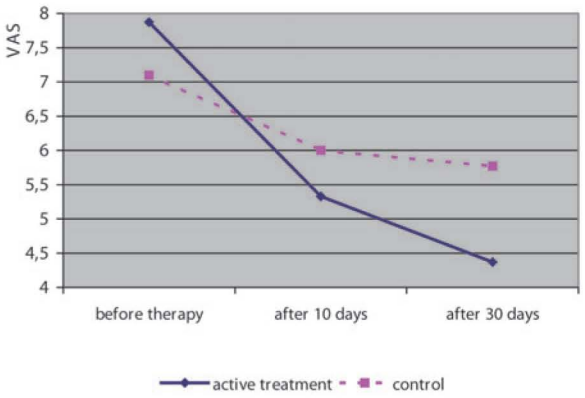

Figure 2. Values in Hubertus test in study subjects.

Table 4. The values of the test for quadriceps femoral muscle.

Visit	Experimental group (n=30)	Control group (n=30)
At baseline	3.77+0.43	3.63+0.49
After 10 days	3.93+0.26	3.67+0.48
After 30 days	3.93+0.26	3.73+0.45

The values shown: the mean± standard deviation

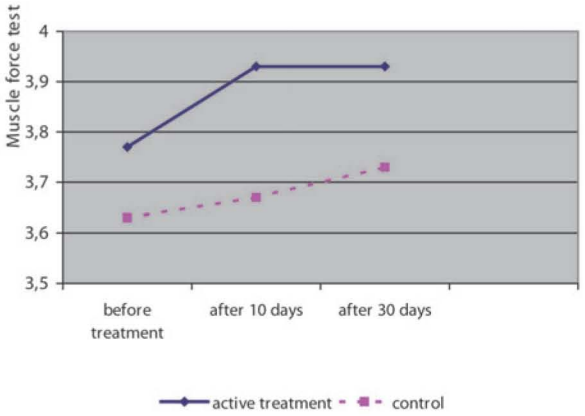

Figure 3. The values of muscle strenght (force test) for quadriceps femoral muscle.

On the other side, there improvement in the knee contracture was noted neither in the experimental (Friedman's test; $p=0.174$), nor in the control group (Friedman's test; $p=0.052$). The groups were similar at baseline (Mann Whitney U test; $p=0.577$), at 10th day (Mann Whitney U test; $p=0.401$), and at the study end (Mann Whitney U test; $p=0.361$).

Table 5. Contracture of treated knee joint, in degrees.

Visit	Experimental group (n=30)	Control group (n=30)
At baseline	6.17+10.72	3.28+6.16
After 10 days	5.67+9.8	2.67+5.04
After 30 days	5.5+9.4	2.33+4.5

The values shown: the mean± standard deviation

Frequency of subjects who gave the data about dose reduction of NSAIDs, in the period from 10th to 30th day from administration of the therapy, was significantly different between the tested groups (χ^2-test; $p<0.001$).

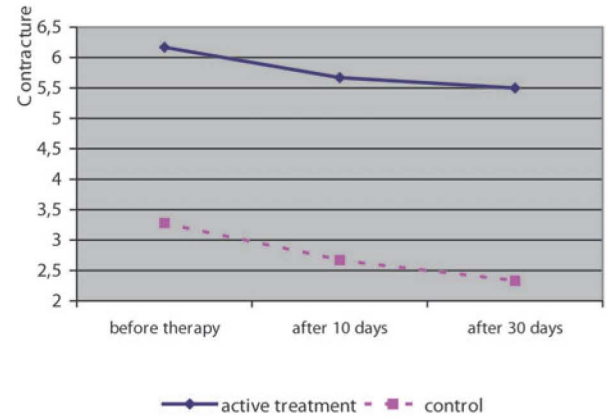

Figure 4. Contracture of the knee joint (degrees).

Table 6. Reduction of NSAIDs in tested groups.

Visit		Experimental group (n=30)	Control group (n=30)
After 10 days	Yes	27 (90%)	15 (50%)
	No	3 (10%)	15 (50%)
After 30 days	Yes	23 (76.7%)	6 (20%)
	No	7 (23.3%)	24 (80%)

The values shown: the number of patients (percent)

During iontophoretic therapy administration, in the group with methylprednisolone acetate the dose reduction of NSAIL was found in 76.7% of the subjects, while in the group where distilled water was used, reduction of the drug dose was found in 20% of the patients, only. The difference was statistically significant (χ^2-test; $p<0.001$).

During the study and in the follow up period adverse events, related to methylprednisolone (corticosteroid local or systemic effects) or iontophoresis itself like burns, or formation of undesirable vesicles and bullae in skin were not recorded.

Reduction of NSAIDs use and doses during the study (after 10 and 30 days) in the control and the experimental group were show in the figure 5 and 6.

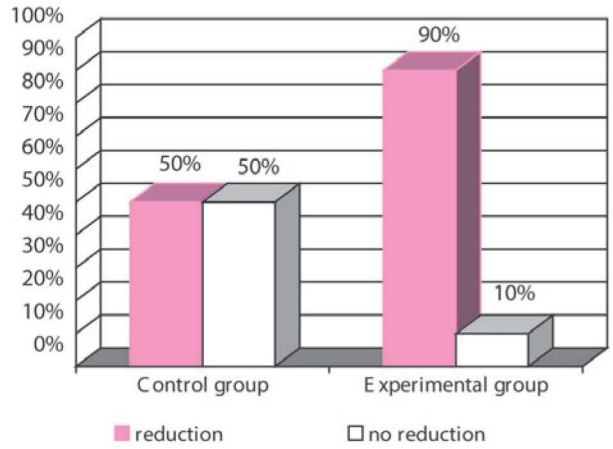

Figure 5. Reduction of NSAIDs use (first column) and dose (second column) after 10 days.

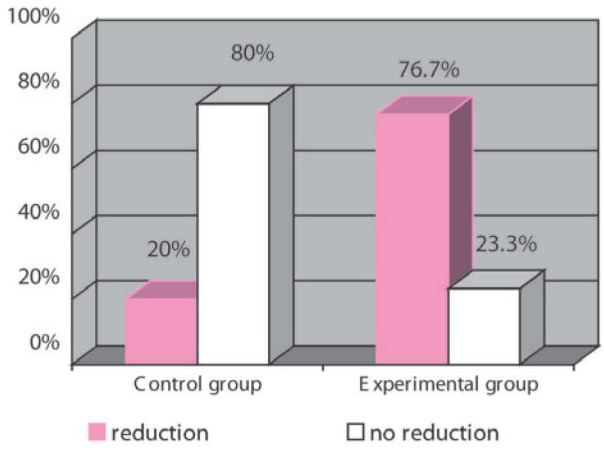

Figure 6. Reduction of NSAIDs use (first column) and dose (second column) between 10th and 30th day of the therapy in the subjects of the tested groups.

DISCUSSION

Iontophoresis augments penetration of electrically charged drugs through skin by administration of electric current. The two prerequisites for the treatment are: preparation of sufficiently charged drug in sufficient amount, and localisation of the disease at or near the body surface. Our results clearly point to valuable clinical advantages of methylprednisolone iontophoresis. Although our experimental drug, methylprednisolone acetate, was exceptionally used during iontophoresis due to difficulties of skin penetration of its suspensions (6), low water solubility and modest electrical behaviour (8), we confirmed its clinical utility. During application of methylprednisolone, statistically significant reduction in pain has been noted, much more than with placebo, as evaluated with VAS pain scale. It is known that, apart from characteristics of the drug, many other factors affect iontophoresis such us the current, formulation factors, biological factors and electrical and endo-osmotic flow (7, 16). Therefore, it is very likely that the properties of the pharmaceutical preparations of methylprednisolone acetate used in our study contribute to its utility recorded in our study. Some of the factors which might add to electrochemical behaviour of the preparation are: drug concentration, pH, ionic strength, and viscosity.

In addition, it is very likely that synergistic effects of drug and electrical current have been recorded. The significant part in reduction of the clinical symptoms might be, in fact, the effect of galvanic current itself. It is known that this physical agent has analgesic effect, especially „the anode galvanization"; positive pole of the electrode releases oxygen, makes acid reaction, vasoconstriction, produces analgesia and reduces bleeding and osmotic pressure (17).

Besides reduction of pain after therapeutic application of iontophoresis with methylprednisolone, functional improvement was also made. Although average value of Hubertus test was lower in control subjects at the end of 30-day period of testing, the difference was not statistically significant. Analysis of other clinical variables also support superiority of active treatment in comparison with the control. The patients treated with methylprednisolone experienced better quadriceps muscle strength and less contracture of the affected knee than patients treated with placebo.

Particular positive therapeutic effect of this methodology was reduction of NSAIDs doses after ten days. Frequency of subjects who reduced dose of NSAIDs was significantly different between the groups. In actively treated patients the dose reduction of NSAIL was found in about three quarter of subjects which is far more than in control group where the doses were reduced in a fifth of patients.

In conclusion, our results show that methylprednisolone acetate was superior to placebo when applied with iontophoretic method in the patients suffered from knee arthrosis. Several subjective and objective parameters of disease activity were improved more by active treatment than by sham iontophoresis. The further, large-scale, randomized clinical studies should confirm our results before introduction of this method in routine practice.

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