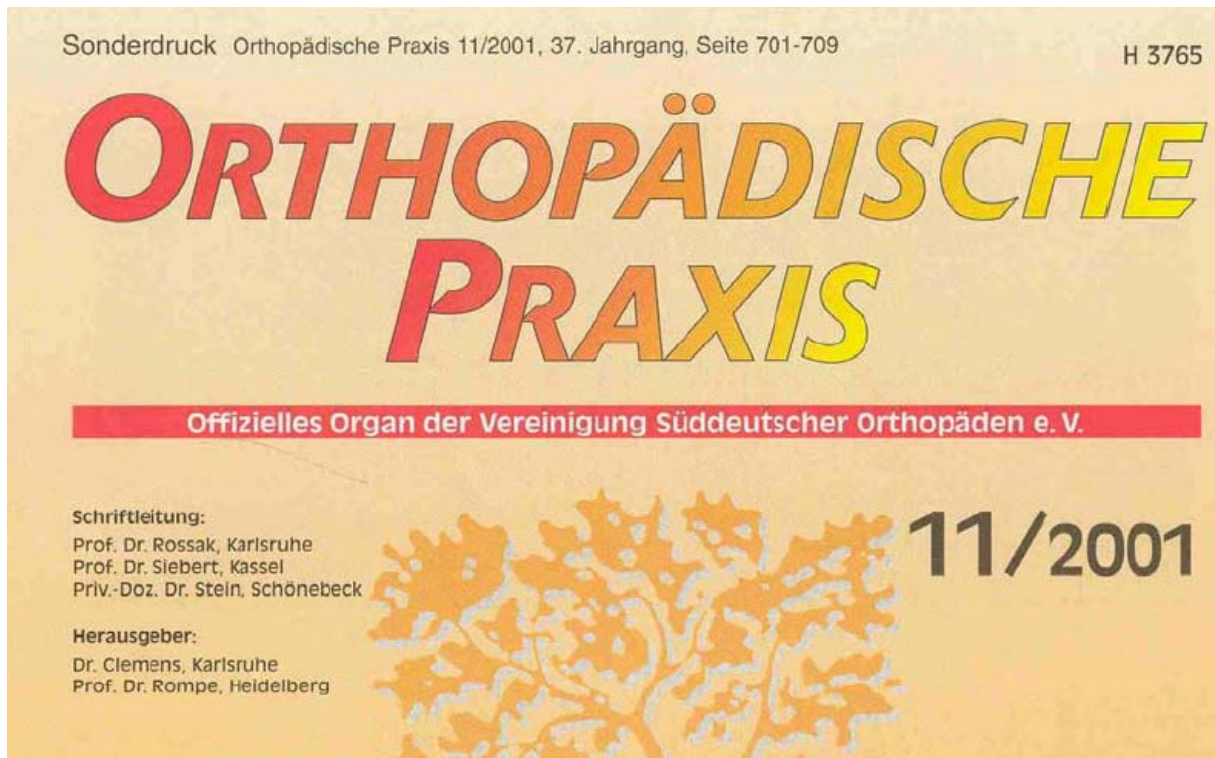


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A Prospective Multicenter Study of Osteoarthritis of the Knee (Kellgren II and III) with Pulsed Signal Therapy (PST™) M. Faensen*, R. Breul

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Summary:

In this prospective, multicenter study (MCS) we examined the effectiveness of Pulsed Signal Therapy (PST™) for arthritis of the knee (Kellgren degree II and III). At the beginning this study included 303 patients from 40 clinics, which were treated by PST™ for one hour on 9 consecutive days. The treatment was only allowed to be interrupted on weekends. At the end, 221 patients participated in the six-month follow-up.

At baseline, after 9 one hour PST™ sessions, six weeks after PST™ and six months after PST™; the patient's self assessment of the parameters of difficulty were recorded using the Lequesne Knee Arthritis Index, the visual analog scale (VAS), the severity of pain and the difficulties of performing daily activities (DA).

All results of the investigated parameters, showed for paired and unpaired tests (parametric and/or non-parametric tests), highly significant results with $p < 0.001$ respectively $p < 0.0001$. The improvement of each recorded parameter varies between 40 and 50 %. On the basis of an improvement of each parameter $> 20\%$, nearly 73% of the patients responded positively to PST™.

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Introduction:

Pulsed Signal Therapy (PST™) has been used increasingly since 1996 in Germany and neighbouring countries to treat osteoarthritis. It builds on the theoretical, experimental and clinical understanding of pulsed electromagnetic fields [PEMF], which is employed in the treatment of pseudarthrosis [14]. As a non-invasive procedure, PEMF is without side effects. The results obtained last more than 6 months and a placebo effect can be excluded unequivocally [13]. This method is based on the observation that the crystalline structure of the hydroxyapatite [12] in the bone is deformed on compression, giving rise to a piezoelectric current. Consequently, a mechanical stimulus in the extracellular matrix is changed by physical transduction into an electrical potential. The biological processes that lead to bone healing have not yet been fully elucidated. However, a series of investigations have shown that delayed bone healing processes are set in train or accelerated by enchondral ossification [30, 31, 32, 33].

Comparatively similar processes apply for cartilage [26, 27], while there is a range of differences because of its specific structure and function. Firstly, hyaline articular cartilage is used for transmission of force between the involved joint components. In this situation, cartilage is capable of absorbing impacts, allowing uniform distribution of force within the joint surface and on the bone structures underneath [3, 9, 16, 19, 22, 24, 25, 28]. It is only by an interaction of all the mechano-electrochemical characteristics of the extracellular matrix [ECM] that cartilage obtains its particular ability to provide sufficient resistance to the high demands of the tissue and to preserve the normal function of the ECM through synthetic processes.

In every compression cycle, the ECM is exposed to a temporally and spatially varying compressive force, causing fluid and ion displacement. Accompanied by hydrostatic and osmotic pressure changes, ions flow past the fixed charges of the sulphated proteoglycan matrix and produce electrical potentials both inside and outside the ECM [10, 16, 17, 18, 21, 27].

Because of these associations, precisely what specific information is transmitted to the chondrocytes under mechanical stress in order to stimulate their metabolism to maintain and repair the cartilage is currently still under discussion. This suggested extending the use of pulsed electromagnetic fields (PST™) to the treatment of arthritis too.

The goal of our investigation is to verify the effect of PST™ on arthritis of the knee, Kellgren stages II and III, in a prospective multicentre investigation in a group of patients selected according to narrow inclusion and exclusion criteria.

Materials and Methods:

This investigation was conceived as a multicenter study [MCS]. Forty-nine practices specializing in orthopedics, surgery, trauma surgery, internal medicine and general medicine participated in the period from January to November 1999 with PST™ treatment equipment.

Patient selection

In order to minimise side effects and increase the reliability of the investigation results, the most homogeneous patient group as possible was assembled for the MCS according to the following criteria:

1. The preliminary selection for this investigation included patients who could be classified by Kellgren's knee arthritis stages II (obvious osteophytes and possible joint space narrowing) and III (moderate multiple osteophytes, obvious joint space narrowing, slight sclerosis and obvious deformity of the joint surfaces).
2. The final selection included only patients who answered the following questions with **YES**: at least 10 points in the Lequesne severity index, pain symptoms for one year, at least 40 mm in one of the pain parameters on the visual analogue scale [VAS], no operative treatment on the lower limb in the past 6 months, no arthroscopy in the past 6 months, no intra-articular injection treatment in the past 4 weeks, no underlying rheumatic disease, no inflammatory changes in the soft tissues, minimum age 30 years, no bilateral arthritis of the hip, no underlying malignant disease, no marked obesity (referring to Body Mass Index [BMI] = weight in kg / (height in m)²); BMI > 32.5 means 30% or more overweight), no alteration in the medical and physical treatment plan 1 month before and during the treatment and follow-up period; this applies also to the dosage of nonsteroidal analgesics/anti-inflammatories, understanding the use of the Visual Analogue Scale (VAS) to estimate the pain or physical activities, no pregnancy and written consent to participate in the study. The Visual Analogue Scale is 100 mm long. The distance marked by the patient was entered in the study protocol as a scale result in cm.

Treatment

The PST™ treatment device consists of a coil system (a toroid coil in an annular arrangement), connected by electronic means to a control unit. At a field strength of approximately 12.5 Gauss, it produces a physiological signal carried on an impulse-modulated elliptical magnetic fields in a range between 1 and 30 Hertz.

Treatments lasting one hour were conducted on each of 9 successive days. This series could be interrupted by one weekend (not > 48 hours). The diseased knee joint was placed in the joint coil according to instructions.

Patient protocols

The following data were recorded for each patient before, after, 6 weeks after and 6 months after PST™ treatment:

- I. The severity of the arthritis graded according to Lequesne, consisting of groups of questions about: a = pain or symptoms, b = mobility, c = daily activities.
 1. According to the patient's responses, the Lequesne arthritis severity is classified into the following scores: 1 – 4 points = mild, 5 – 7 points = moderate, 8 – 10 points = severe, 11 – 13 points = very severe, 14 points or over = extremely severe.
 2. The Lequesne scores were supplemented by self-assessment of pain and impairment/difficulties with daily activities using a 10 cm Visual Analogue Scale (VAS). Before each of the four protocols was recorded, the investigating doctor explained the meaning and graduations of the VAS (0 = none and 10 = most severe pain or greatest impairment/difficulty) to the patient to ensure that it was well understood. The patient entered his/her self-assessment independently by means of a line on the scale beginning at zero:
 - a. the severity of the pain in the knee in the past two days, within the past 24 hours, in the morning on rising and at night in bed;
 - b. pain or difficulties in daily activities (DA) in the past two days, when walking more than one block of houses, going up stairs, going down stairs, standing longer than 15 minutes, getting in or out of a car and getting in or out of the bathtub or shower.

Statistical analysis

For the statistical analysis, the patient protocols were entered in a database (Access) with a data capture mask and were then analysed with the SPSS[®] 9.0 for Windows programs. The following were analysed: means, standard deviations, absolute and relative frequencies.

The results were examined statistically by means of parametric t tests and/or Whitney-Mann and Wilcoxon non-parametric tests for paired and unpaired samples. The initial result = baseline level was compared with the final result = 6 months after PST[™].

The results were represented graphically using Excel[®].

Results:

General information about the patients in the MCS is summarised in Table 1.

Table 1: Age, body weight and body size of the patients, subdivided by sex.

| | | Age Years | Weight kg | Height cm | Body-Mass- Index |
|-------------------------|---------------------------|--------------|--------------|--------------|---------------------|
| Women n = 206 | Mean | 66.4 | 72.8 | 164.9 | 27.0 |
| | Standard deviation | 10.9 | 10.6 | 6.8 | - |
| Men n = 97 | Mean | 60.4 | 83.3 | 176.2 | 26.8 |
| | Standard deviation | 13.3 | 11.1 | 7.4 | - |

With regard to the Body Mass Index, the female patients, with an average of approx. 27, exceeded the normal value of 22 by approx. 19% and the male patients exceeded the normal value of 23 by approx. 15%. On average, there was slight overweight in both sexes, but none of the patients had to be excluded from participating in the MCS because of marked obesity (BMI > 32.5).

Table 2: Numbers of patients in the study before PST[™], immediately after, 6 wks. after and 6 mos. after.

| | before PST [™] | after PST [™] | 6 weeks after PST [™] | 6 months after PST [™] |
|---------------------|-------------------------|------------------------|--------------------------------|------------------------------------|
| Patients (n) | 303 | 298 | 266 | 221(220*) |
| Women (n) | 206 | 204 | 172 | 148 |
| Men (n) | 97 | 94 | 94 | 73 |

* Some of the study results in 1 patient are missing in the 6 month after PST[™] group.

A total of five patients opted for other forms of treatment (conservative, operative, etc.) before the treatment with PST[™]. After 6 months, approx. 26% of the patients (28% women, 24% men) had left the study. The majority of these patients did not belong to the treatment failures (reduction of all symptoms < 20%). Despite repeated invitation (letter, telephone calls etc.) by the treating doctors, most of these patients did not attend the agreed follow-up examinations for various reasons, including holidays, lack of interest etc.

Since no sex-specific difference in the results of Table 1 were observed, men and women are not distinguished in the following analyses.

1) Lequesne knee arthritis index

Table 3 contains the classification of the patients on the 5-point knee arthritis index scale before and 6 months after PST[™] treatment as absolute and relative frequencies as a percentage.

Table 3: Relative and absolute frequencies of the Lequesne Knee Arthritis Index.

| Lequesne Knee Arthritis Index Score | | | | |
|-------------------------------------|-------------|-------------|---------------------|-------------|
| Classification | before PST™ | | 6 months after PST™ | |
| | Frequency | Frequency % | Frequency | Frequency % |
| Mild | 4 | 1.3 | 54 | 24.5 |
| Moderate | 8 | 2.6 | 63 | 28.6 |
| Severe | 73 | 24.2 | 45 | 20.6 |
| Very severe | 111 | 36.8 | 36 | 16.4 |
| Extremely severe | 106 | 35.1 | 22 | 10.0 |

Figures 1 and 2 shows the re

Figure 1: Frequency distribution in percent.

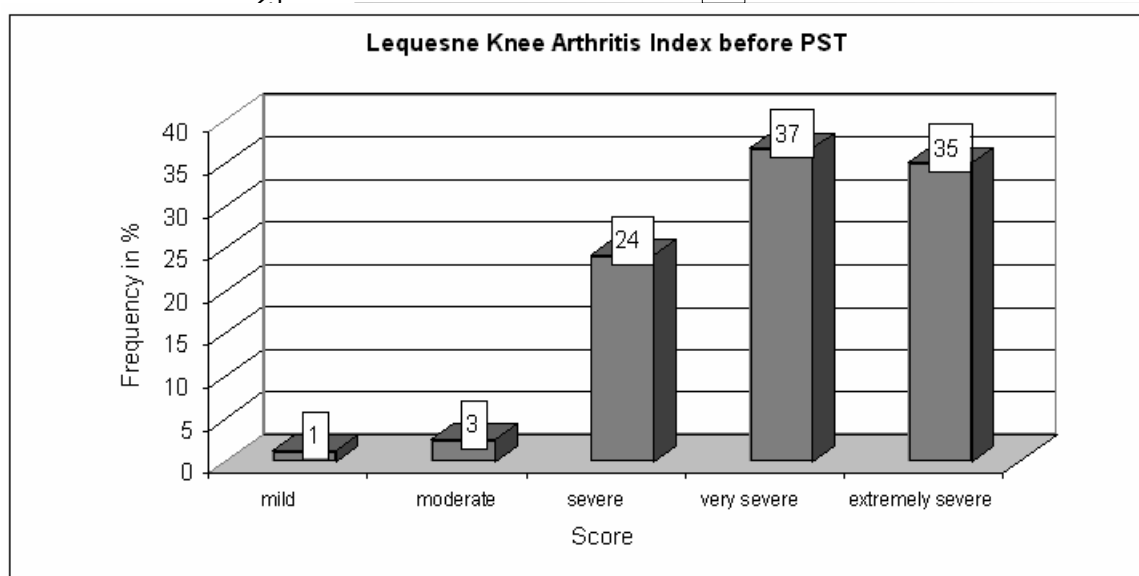
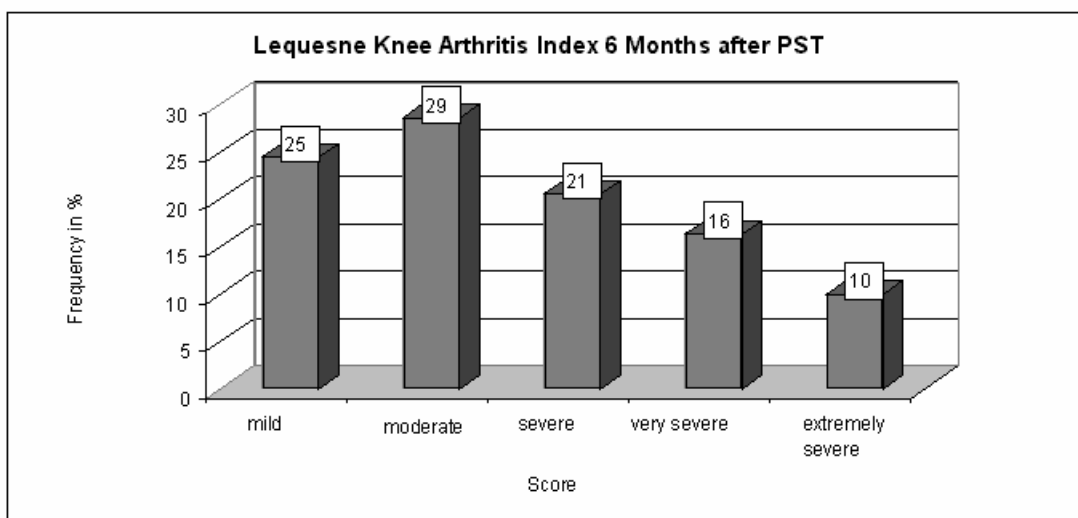


Figure 2: Frequency distribution of the Lequesne Knee Arthritis Index 6 months after PST™-treatment in percent.



These results emphasise that the scores “very severe“ and “extremely severe“ account for approx. 72% of the frequency before the PST™ treatment; in contrast, 6 months after the PST™ treatment, these two scores are reduced by approximately two-thirds of the initial level to approx. 26 %. The scores mild and moderate were 4% before PST™ and approx. 54% 6 months after PST™.

In the unpaired (Table 4a) and paired (Table 4b) rank test, the results of the Lequesne arthritis index were tested for significance before PST™ and 6 months after PST™.

Table 4a: Unpaired results for the Lequesne Knee Arthritis Index before PST™ and 6 months after PST™.

| Lequesne score | N | Mean rank | Rank total |
|---------------------|-----|-----------|------------|
| Before PST™ | 302 | 327.36 | 98862.50 |
| 6 months after PST™ | 220 | 171.09 | 37640.50 |
| Total | 522 | | |

| Lequesne score before PST™ / 6 months after PST™ | |
|--|------------|
| Mann-Whitney-U | 13330.50 |
| Wilcoxon-W | 37640.50 |
| Z | -12.01 |
| Asymp. significance (2-sided) | p < 0.0001 |

Table 4b: Paired results for the Lequesne Knee Arthritis Index before PST™ and 6 months after PST™.

| Lequesne score | Ranks | | | |
|-----------------------------------|----------------|-----|-----------|------------|
| | | N | Mean Rank | Rank total |
| 6 months after < before PST™ | Negative ranks | 169 | 95.5 | 16139.5 |
| 6 months after > before PST™ | Positive ranks | 13 | 39.5 | 513.5 |
| 6 months after PST™ = before PST™ | Bindings | 37 | | |
| | Total | 219 | | |

| Wilcoxon test | 6 months after < before PST™ |
|-------------------------------|------------------------------|
| Z | -11.14 ^{a)} |
| Asymp. Significance (2-sided) | p < 0.001 |
| a) Based on positive ranks | |

For all tests there are significant differences in the ranks compared, some with p < 0.0001 or p < 0.001, i.e., the differences in the measurements in the Lequesne index or score are not by chance but are based on successful treatment.

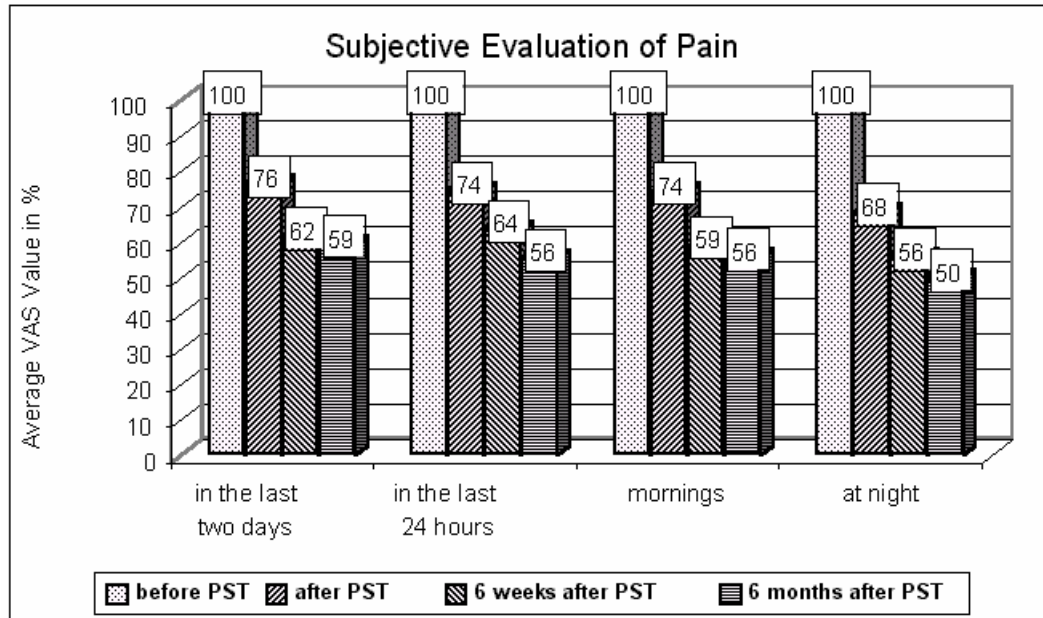
II) Self-assessment using the Visual Analogue Scale (VAS)

a) Pain

Figure 3 shows the results of the self-assessment of four pain parameters as a histogram in percent over the entire study period of 6 months. The results at the initial examination (before PST™) were set at 100% as a baseline. The VAS results concerning pain demonstrate a reduction averaging between approx. 41 and 50% 6 months after the PST™ treatment.

The results of the self-assessment of pain were tested for the significance of the differences before PST™ and 6 months after PST™. Tables 5a and 5b summarise the results of the parametric tests for the unpaired and paired VAS responses concerning pain.

Fig. 3: Representation of the averages of four pain parameters in percent. The inclusion conditions



before the PST™ treatment were set respectively as a basis value to 100%.

Table 5a: Unpaired results for the VAS pain responses before PST™ and 6 months after PST™.

| Pain | N | Mean | Variance | Std. deviation | Std.-error |
|---------------------|-----|-------|----------|----------------|------------|
| Before PST™ | 302 | 48.38 | 358.59 | 18.93 | 1.09 |
| 6 months after PST™ | 220 | 25.79 | 470.50 | 21.69 | 1.47 |

| Mean difference | DF | t | Significance |
|-----------------|-----|-------|--------------|
| 22.59 | 519 | 12.63 | p < 0.0001 |

Table 5b: Paired results for the VAS pain responses before PST™ and 6 months after PST™.

| Before PST™ and 6 months after PST™ | Paired differences | | 95% confidence interval of the difference | | | | T | df | Signif. (2-sided) |
|--|--------------------|-----------|---|--------|-------|------|-----|------------|-------------------|
| | | | Std.-error | Limits | | | | | |
| | Mean | Std. Dev. | Mean | Lower | Upper | | | | |
| Pain in the past two days | 23.01 | 28.90 | 1.9 | 19.2 | 26.8 | 11.8 | 219 | p < 0.0001 | |
| Pain in the past 24 hours | 26.57 | 32.65 | 2.2 | 22.2 | 30.9 | 12.1 | 220 | p < 0.0001 | |
| Pain/stiffness/immobility in the morning | 23.29 | 31.28 | 2.1 | 19.1 | 27.4 | 11.1 | 220 | p < 0.0001 | |
| Pain at night | 19.05 | 29.24 | 2.0 | 15.2 | 22.9 | 9.7 | 220 | p < 0.0001 | |

The tests of significance for paired and unpaired samples show for both the individual pain parameters and for the averaged pain parameters that the differences between the means before PST™ treatment and 6 months after PST™ treatment are significant with p < 0.0001

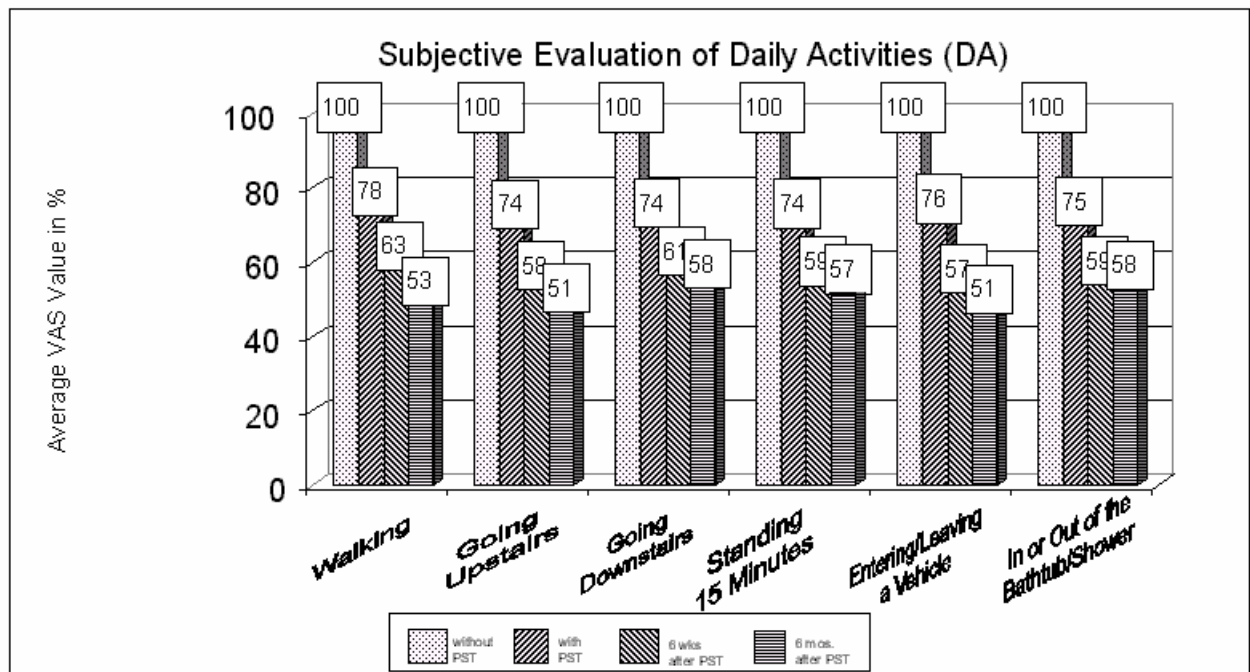
and $p < 0.001$ respectively. The results show that the reduction in pain can be attributed to the PST™ treatment.

b) Difficulties with daily activities (DA)

Figure 4 shows the results of the self-assessment by VAS of six parameters of difficulties in daily activities as histograms in % over the study period of 6 months. The results at the initial examination (before PST™) were set at 100% as a baseline. The VAS results 6 months after PST™ treatment show an average reduction of between approx. 42 and 49%.

The results of the self-assessment of DA's were tested for the significance of the differences of the means in the pairings before PST™ / 6 months after PST™. Tables 6a and 6b summarize the results of the parametric and nonparametric tests for the unpaired and paired VAS results concerning daily activities.

Fig. 4: Representation of the averages of six DA trouble parameters in percent. The entrance condition



before the PST™ treatment was set respectively as a basis value to 100%.

Table 6a: Unpaired results for the DA responses before PST™ and 6 months after PST™.

| Pain/difficulties of DA | n | Mean | Variance | Std.-deviation | Std.-error |
|-------------------------|-----|-------|----------|----------------|------------|
| Before PST™ | 302 | 47.27 | 398.72 | 19.97 | 1.15 |
| 6 months after PST™ | 220 | 25.73 | 540.07 | 23.24 | 1.57 |

| Mean difference | DF | t | Significance |
|-----------------|-----|-------|--------------|
| 21.54 | 520 | 11.35 | $p < 0.0001$ |

Table 6b: Paired results for the DA responses before PST™ and 6 months after PST™.

| Pain/difficulties of DA before PST™ and 6 months after PST™ | Paired differences | | 95% confidence interval of the difference | | | | | Signif. (2-sided) |
|---|--------------------|---------|---|--------|-------|-------|-----|-------------------|
| | Mean | Std.dev | Std.-error | limits | | T | df | |
| | | | | Lower | Upper | | | |
| Walking more than one block | 19.85 | 29.68 | 2.00 | 15.91 | 23.80 | 9.92 | 219 | p < 0.0001 |
| Going up stairs | 24.61 | 28.29 | 1.91 | 20.85 | 28.37 | 12.90 | 219 | p < 0.0001 |
| Going down stairs | 25.21 | 29.43 | 1.98 | 21.30 | 29.12 | 12.71 | 219 | p < 0.0001 |
| Standing longer than 15 min. | 20.04 | 30.39 | 2.05 | 16.00 | 24.08 | 9.78 | 219 | p < 0.0001 |
| Getting in/out of car | 21.71 | 26.65 | 1.80 | 18.17 | 25.25 | 12.08 | 219 | p < 0.0001 |
| Getting in/out of bathtub or shower | 17.73 | 27.62 | 1.86 | 14.06 | 21.40 | 9.52 | 219 | p < 0.0001 |

The tests of significance for paired and unpaired samples show for all DA parameters that the differences between the means of the self-assessment before PST™ treatment and 6 months after PST™ treatment are significant with $p < 0.0001$ and $p < 0.001$ respectively. The results indicate that the reduction in difficulties in daily activities can be attributed to the PST™ treatment.

Discussion:

There have been few published clinical studies of the treatment of degenerative joint diseases with pulsed electromagnetic fields (PEMF) until now. In double-blind placebo-controlled studies [35, 36] a more or less clearly identifiable effect on parameters such as pain and daily activities was found after one month in patients with arthritis of the knee measured by VAS compared to the group treated with placebo, which was found to be statistically significant upon several parameters. The improvements averaged between 35% and 39% in the groups studied. The treated group was treated in 18 sessions for a total of 30 minutes, with 10 – 15 Gauss at 5 Hz, with 15 – 25 Gauss at 10 Hz and with 15 – 25 Gauss at 12 Hz for 10 minutes in each case.

This justifies the question of whether the effects described above can be found in a greater number of patients after an observation period of 6 months.

This study was therefore designed as a prospective multicentre study involving 49 PST™ treatment centres. This had the advantage that a group of over 300 patients could be assembled initially, 221 respectively, 220 of whom were still in the study after 6 months. There were thus adequate data to allow statistically reliable evaluation of the results. Patients were included in the study according to narrowly defined selection criteria in order to exclude interference from side effects and to ensure approximate homogeneity in the composition of the group. The Lequesne arthritis index and visual analogue scales for self-assessment of pain and limitation or impairment of daily activities were used as evaluation instruments. Although these procedures are based on subjective statements by the patients, they form a satisfactory basis for clinical investigations, as has been shown by validation studies of arthritis treatment [7].

The results of our study of the efficacy of PST™ in arthritis of the knee make it clear that a lasting positive effect of treatment can be observed both in the Lequesne arthritis index and in the results for pain and restrictions of DA's as determined by VAS after 6 months. The reduction in pain and restrictions of daily activities and the improvement in the Lequesne arthritis index vary on average between 40% and 50%. Examination for significance of the differences of both means in the unpaired t-test (303 patients before PST™ treatment / 220

patients 6 months after PST™ treatment) shows that the differences can be confirmed as statistically significant with $p < 0.0001$. The representation of our results as histograms emphasises particularly clearly the nature of the positive changes. It is well-known that a placebo effect is associated with every form of therapy, and this applies particularly for new therapies [20]. Nevertheless, the length of the observation period of 6 months argues against such an effect, since a placebo effect can be maintained only for a short time. Thus, the sustained and progressive increase in benefits demonstrated by the Lequesne Arthritis Index and VAS results can be safely assumed to be the result of PST™ treatment.

The clinical results observed by us refer to subjective reports by the patients. In addition to the need for further clinical studies, there is therefore an increased necessity at present to research the biological mechanisms of action of PST™ or PEMF on hyaline joint cartilage. The three-phase model mentioned in the introduction [21, 29] represents a plausible attempt with the detailed description of the mechano-electro-chemical characteristics of hyaline cartilage, in particular taking the viscoelasticity into consideration. It is clearly emphasized that when a load is applied to the cartilage a mechanical stimulus is changed into an electrical potential through transduction. This is caused by the simultaneous displacement of free ions within the ECM and the resulting imbalance in the ion distribution in the ECM. This results in an electrical signal, which passes within the cartilage parallel to the joint loading and which is situated in a low frequency region.

Apart from a few contradictory results from in vitro and in vivo experiments, it must be borne in mind that PEMF increases collagen metabolism, the activity of alkaline phosphatase, the synthesis of cyclic AMP and proteoglycan synthesis etc. [1, 4, 5, 6, 8, 15, 23]. A further effect of PEMF shows that there is a marked increase in intracellular transcription and DNA synthesis within a short time. The electrical potentials produced in the ECM by PEMF are lower than membrane potentials, and a direct transmembrane effect of the PEMF on cartilage cells must be excluded. It is therefore postulated that PEMF at frequencies < 15 Hz acts on receptors on the cell surface and that these then release secondary messengers [2, 11, 15] and/or allow calcium ions to flow through membrane channels into the chondrocytes. As a result, an increased rate of synthesis of glycosaminoglycan is observed [2, 15]. Moreover, the synthesis of glycosaminoglycan can be significantly increased by chondrocytes in cell culture when an intermittent field is employed instead of a continuously acting PEMF [34]. In hyaline cartilage, the glycosaminoglycan content can be increased with PEMF and the degradation of the glycosaminoglycans present can be suppressed [23].

Despite the previous evidence from in vitro and in vivo experiments of possible mechanisms of action of PEMF and PST™ on cartilage cells and cartilage tissue, the biological cause of the clinically observed effects such as reduction in pain etc. are still unknown. It seems plausible that the content of glycosaminoglycans [GAG] is reduced in damaged cartilage. This is associated with alterations in the viscoelastic characteristics of the cartilage and in the distribution of the negative charges of the GAG. As a result, the mechanical loading capacity of the cartilage and thus its ability to resist compressive forces is impaired. Pain can arise subsequently in the subchondral cancellous bone due to microfractures and in the periosteum due to osteophyte formation, since these structures are provided with pain receptors.

Hypothetically, taking these circumstances into account, it could be assumed that the GAG content in damaged cartilage is increased by PEMF or PST™ treatment and thus the biomechanical characteristics of the redistribution and absorption of force are altered positively.

Further experimental and clinical evidence will be required until there is a final explanation of the described associations and possible biological mechanisms of action, especially in the treatment of arthritis with PST™.

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