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A Clinical Trial Evaluating Pulsed Electro-Magnetic Field Therapy on Osteoarthritis Patients: Modeling Ordinal Longitudinal Responses

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Abstract

The effectiveness of the Pulsed Electro-magnetic Field (PEMF) Therapy is investigated statistically considering a real clinical trial in the treatment of Osteoarthritis (OA) patients with longitudinal monitoring. Relevant statistical modelling followed by an appropriate analysis for ordinal longitudinal data is carried out to evaluate the usefulness of the therapy in reducing the symptoms of the indicative characteristics based on the reported trial data.

Keywords: longitudinal data; ordinal data; pulsed electro-magnetic field therapy.

AMS Subject Classification: 62P10.

1. Background and Motivation

The Pulsed Electro-Magnetic Field (PEMF) therapy has been used with success in many orthopaedic diseases. Barker et al. (1994) used PEMF therapy to treat tibial fractures; Bassett and Schink-Ascani (1991) used it in congenital pseudo-arthrosis of the tibia; Bassett et al. (1982) used it in non-united fractures and failed arthrodeses;

Brighton and Pollack (1985) reported the use of PEMF in recalcitrant non-union; Capanna et al. (1994) reported this treatment on massive bone allograft after tumor resection; Frykman et al. (1986) used PEMF in non-united scaphoid

fractures. But a controlled PEMF therapy for the treatment of Osteoarthritis (OA) patients, particularly with a proper statistical design, as far as we know, has not been reported elsewhere, before the pilot study report of Ganguly et al. (1994). In an earlier work of Ganguly et al. (1993), a pilot study has been reported with an objective to investigate the effects of PEMF therapy for the treatment of Rheumatoid Arthritis (RA) patients. In this study, sequentially entering RA patients are put through an 'adjustment period' of 4 weeks during which they are totally withdrawn from any existing medication to remove any possible carry-over effects of medication. Thereafter, they are given 16 weeks of the PEMF therapy, thrice a week and their conditions are monitored once a week. Therefore, we have repeated observations, on each patient's condition, taken during the adjustment and the therapy period. Early analysis of a related uncontrolled trial can be found in the works of Dewanji et al. (2001). The study of Dewanji et al. (2001) reported some short-term beneficial effects of the therapy, at least in terms of symptomatic improvement, under the presumption that any effect of medication is removed during the adjustment period. Biswas and Dewanji (2004a, 2004b, 2004c) reported a real double-blind placebo-controlled clinical trial at the Indian Statistical Institute, Kolkata, during January 1999 to March 2000, with an objective to evaluate the PEMF therapy in reducing primary symptoms of the RA patients. In the trial, a total of 22 patients were treated, where after the first 4 patients, the remaining 18 were allocated following a response-adaptive urn design. For the allocation of any patient, the updated urn was used at that time-point. In a number of monitoring, recurrence status was observed for each treatment group. The final results show the superiority of the PEMF therapy over the placebo, where excluding the 4 initial patients, 14 out of 18 patients (nearly 78%) are treated by the PEMF. Although the responses were multivariate categorical, the allocation were done using a reduced binary response. In addition, for easy understanding and implementation, the covariates were ignored in the allocation design and also in the primary analysis, as reported in Biswas and Dewanji (2004a, 2004b, 2004c).

Descriptions and findings of a number of clinical trials evaluating the effect of PEMF therapy on OA patients are well documented in literature. A comprehensive exposure in this context can be found in the review articles of Leon Scott (2017), Chen et al. (2019) and Yang et al. (2020). Although the trials mentioned in these articles used ordinal scale (e.g. 10-cm. Visual Analogous Scale (VAS) for pain) to measure the responses, but the final analysis was conducted by assigning numerical scores to ordinal categories and subsequently adopting methods

available for continuous responses. Naturally, such a strategy suffered from loss of information and therefore, undermined the validity of the analysis. Moreover, best to our knowledge, none of the trial data are available in the public domain till date. Consequently, in the current work, we consider an available data from a real clinical trial with patients having OA, which evaluates the effects of PEMF therapy in reducing symptoms/characteristics of such a disease based on ordinal categorical responses from the patients. The subjects and methods as adopted in the trial is described in Section 2. In Section 3, a statistical analysis assuming an autoregressive type cumulative logit response model for the trial data is carried out. Finally, in Section 4, we end up with a recommendation set on the basis of the resultsof the analysis of trial data.

2. Subjects and methods

2.1. Patient Enrolment and Eligibility

The study enrolled 303 diagnosed OA patients, based on ACR Clinical Classification Criteria for Osteoarthritis (see Altman et al., 1991). Among them 61 were male and the rest were female, which indicates a high incidence of OA in the female population. The mean age of the subjects, enrolled for the study, was 51.10 years. For the analysis of the condition of an entering patient, the important characteristics were described as pain (PA), tenderness (TE), swelling (SW), joint disability (JD) and joint (functional) disability (FD), each for big joints and small joints. Responses to each of the characteristics were measured in one of the four ordinal categories, namely, (1) Nil (2) MILD (3) MODERATE and (4) SEVERE. Responses to all of the five characteristics, mentioned above, were observed for any patient. Patients with none of the 5 characteristics in severe condition were eligible for enrolment in the trial. If a patient with any/some characteristic in severe condition entered into the system, he/she would be given proper medication with an effort to make him/her eligible.

2.2. Treatment in the Trial

An eligible patient, after enrolment, went through an adjustment period of 4 weeks, during which all the medications were withdrawn. The objective was to eliminate any possible effects of medication(s). The choice of this duration of 4 weeks is based on the advice from the medical experts involved in the trial. Patients' conditions were recorded both at the beginning and at the end of the

adjustment period when the patient was ready to be a part of the trial. After the adjustment period, for the purpose of evaluation, the patients were assigned with PEMF therapy and were monitored for 16 weeks.

Patients were given PEMF therapy thrice a week and their symptoms on the 5 characteristics were noted on the next visit. On each visit, a dichotomous outcome on the general condition of the patients (Recurrence of problem: R or Non-recurrence: N) is also noted. The definitions of R and N are very specific – if for a patient during the trial, any of the already mentioned 5 characteristics becomes severe from moderate or moderate from mild or mild from nil, it is treated as a "recurrence" (R). Once R occurs, it is treated as a failure for that patient. The patient is then given some medicine (e.g. painkiller) for certain duration (7 or 14 or 21 days) by the medical expert depending on the patient's condition. After this duration, the patient is returned back to study in the usual sense. The idea is, during medication, the patient is certain not to have R and hence does not contribute of having R. This possibility is presumed to be back after the medication is over.

2.3. Exclusion from study

An action of emergency is also suggested. If a patient falls seriously ill (according to the medical expert) during the 16 weeks of therapy period, he/she will be immediately "with- drawn from the study" for the comparison purpose. Then the group identity is disclosed to the medical expert. The expert will take appropriate medical course of action, for the benefit of that patient. If the patient is put on therapy at a later time, he/she may be considered only for follow-up purpose. After the completion of study-period following the therapy, the patients may be "out of study". Based on the exclusion criterion, 54 patients were dropped from the study and hence the trial continued with a total of 249 patients.

3. Statistical Analysis

3.1. Data Description

As already noted, a total of 249 eligible patients were treated in the trial with high incidence of female subjects. The response to the therapy is multivariate with ordinal nature for each characteristic. The age-sex pyramid of the enrolled subjects (see, Figure 1) shows the high incidence of OA among the female subjects of ages varying from 31 to 70 supporting the claim of ACR. For the analysis, the response of the patient under each characteristic is measured in an ordinal scale, namely, 0

(NIL) or 1 (MILD) or 2 (MODERATE) or 3 (SEVERE). Figure 2 gives the week wise total and mean response for the PEMF treated patients for each characteristics over the entire phase of study.

The total of responses decreases substantially for each of the characteristics over the weeks except for Joint Deformity. The reason may be that the therapy is not effective in reducing the symptoms of Joint Deformity, because any bone changes, if at all occurs are not reversible except corrective surgical interventions. For better understanding, we further examine a plot (Figure 3) of the week-wise mean values of each of the 5 characteristics and the conclusion regarding the effect of PEMF therapy on Joint Deformity remains unaltered. However, for a confirmatory analysis of the results, we further investigate statistically.

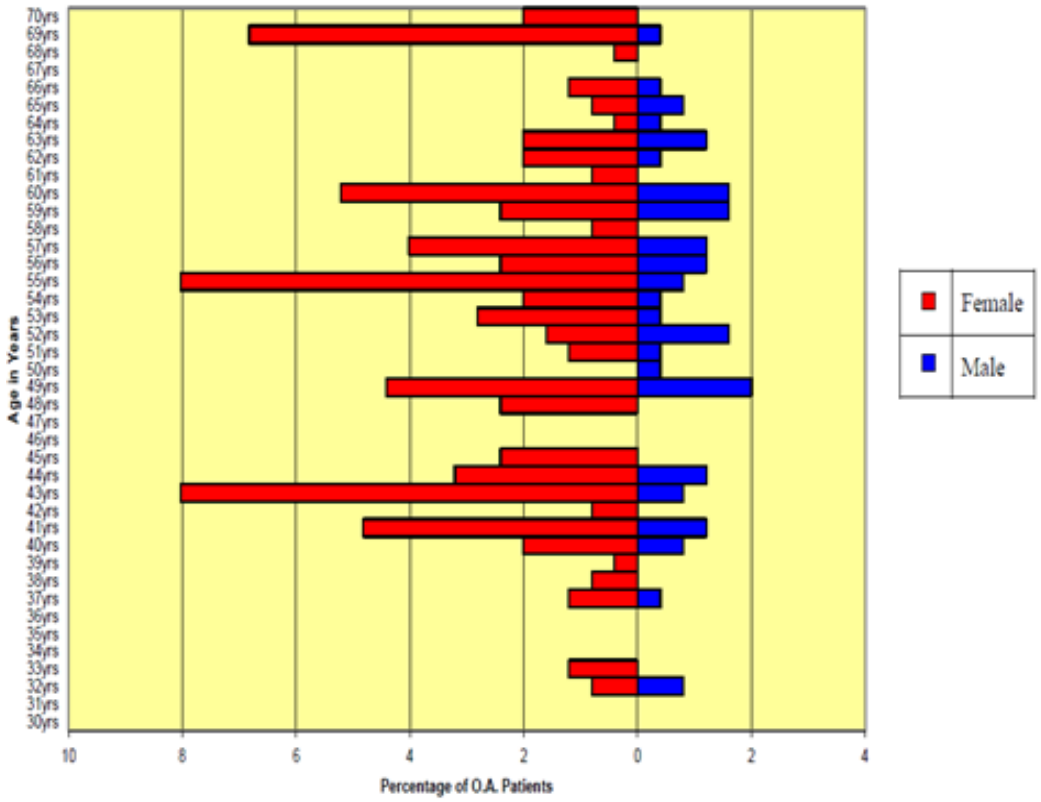


Figure 1: Age-sex pyramid of PEMF treated OA patients

3.2. Statistical Modeling

Thus, it is clear that we are dealing with longitudinal multivariate data having ordinal responses for each characteristic/variable. But, the joint probability distribution of the 5 characteristics under study is not still clear and hence, we treat each characteristic separately through a cumulative logit model (Agresti, 2019) with proportional odds. Suppose y_{kij} denotes the response of the ith subject in the jth time period for the kth characteristic and (x_{1i}, x_{2i}) indicates the covariate vector (Age, Sex) of the ith subject, $j = 0, 1, 2, \ldots, 24$; $i = 1, 2, \ldots, 249$; $k = 1, 2, \ldots, 5$, where $x_{2i} = 1$ or 0, according as the ith subject is male or female.

		INITIAL STATUS	ADJUSTMENT PHASE				P.E.M.F. TREATMENT PHASE															OBSERVATION PHASE			
WEEKS		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
TOTAL	PAIN	523	523	556	609	657	657	657	657	657	657	657	556	498	453	408	408	408	408	400	341	280	280	280	280	274
MEAN	PAIN	2.1	2.1	2.2	2.4	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.2	2	1.8	1.6	1.6	1.6	1.6	1.6	1.4	1.1	1.1	1.1	1.1	1.1
TOTAL	TENDERNESS	523	523	556	609	657	657	657	657	657	657	657	556	498	453	408	408	408	408	400	341	280	280	280	280	274
MEAN	TENDERNESS	2.1	2.1	2.2	2.4	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.2	2	1.8	1.6	1.6	1.6	1.6	1.6	1.4	1.1	1.1	1.1	1.1	1.1
TOTAL	SWELLING	523	523	523	542	609	657	657	657	657	657	657	570	498	453	408	408	408	408	408	395	312	312	312	312	314
MEAN	SWELLING	2.1	2.1	2.1	2.2	2.4	2.6	2.6	2.6	2.6	2.6	2.6	2.3	2	1.8	1.6	1.6	1.6	1.6	1.6	1.6	1.3	1.3	1.3	1.3	1.3
TOTAL	JOINT DISABILITY	523	523	556	609	657	657	657	657	657	657	657	556	498	453	408	408	408	408	400	341	280	280	280	280	274
MEAN	JOINT DISABILITY	2.1	2.1	2.2	2.4	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.2	2	1.8	1.6	1.6	1.6	1.6	1.6	1.4	1.1	1.1	1.1	1.1	1.1
TOTAL	JOINT DEFORMITY	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498	498
MEAN	JOINT DEFORMITY	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Figure 2: Weekly total and mean responses for PEMF assigned patients

The response y_{kij} of the patient is measured in an ordinal scale, namely, 0 (NIL) or 1 (MILD) or 2 (MODERATE) or 3(SEVERE). Then, assuming an autoregressive type of dependence, the cumulative logit model for ordinal longitudinal data can be expressed as

$$\log\left\{\frac{P(Y_{kit}\leq s|y_{kij},j\leq t-1)}{P(Y_{kit}>s|y_{kij},j\leq t-1)}\right\} = \beta_{0s} + \sum_{j=1}^{t-1}\beta_j y_{kij} + \gamma_1 x_{1i} + \gamma_2 x_{2i},\ \text{k=1,2,.. ,5;}$$

$$\text{s=0,1,2.}$$

However, inclusion of all the previous responses induces multi-collinearity as there are time points in which no improvement is observed and consequently the response vector does not change. We, therefore, include only the baseline response, week 8 response and week 15 responses as covariates in addition to Age and Sex assuming that time lag eliminates the possibility of dependence.

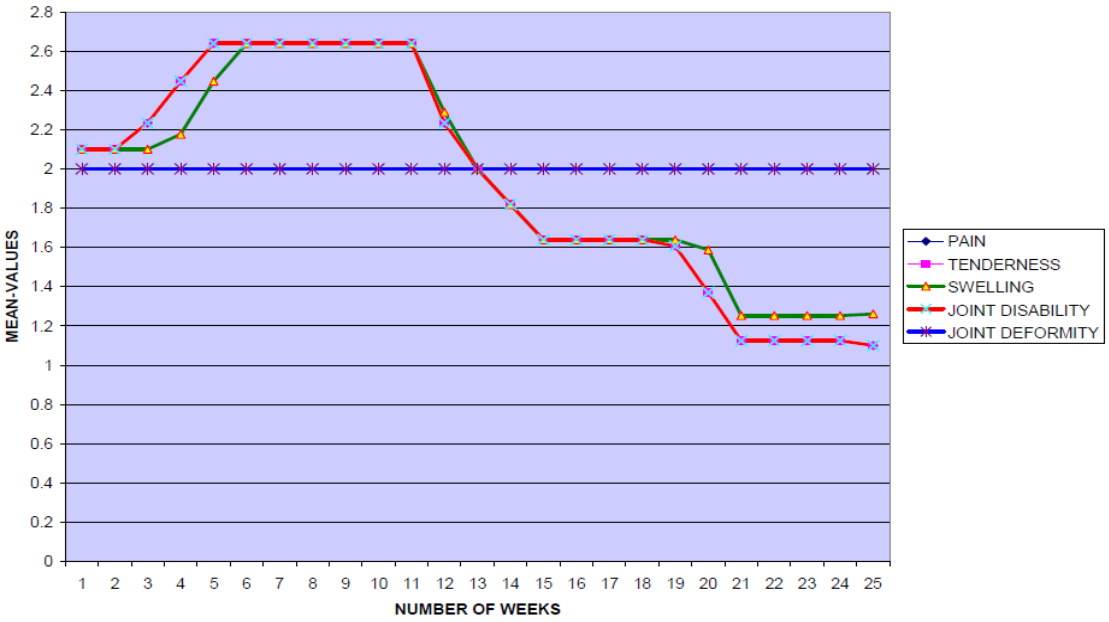


Figure 3: Weekly mean of each characteristics

Now it is worthwhile to mention in the context of the current study that no SEVERE category responses are recorded as the final response for each of the characteristics and hence we combine the categories SEVERE and MODERATE into MODERATE for the purpose of analysis. But presence of even less than 2 % responses in the NIL category for the characteristics Pain, Joint Disability and Tenderness introduced sparsity. Thus, to avoid sparseness for these characteristics, NIL and MILD categories are clubbed and represented as MILD,

in addition. Hence, the final response for these characteristics is reduced to binary (as responses are reported only in the MILD and MODERATE categories) in nature and consequently binary logistic regression model becomes appropriate. However, for Swelling, no NIL category response is obtained as final response and as a result we fit the binary logistic model assuming response categories MILD and MODERATE. Again, as all the weekly responses for the characteristic Joint Deformity fall in the MODERATE category, we do not perform further analysis for it.

4. Results

The binary logistic model with the assumed predictors is fitted in R for each of the characteristics (except Joint Deformity) separately. The estimated coefficients with corresponding standard errors (SE), p value of an associated test of significance, odds ratios (OR) and the corresponding 95 % confidence intervals are reported in Table 1-4. The estimated odds ratio (OR) corresponding to a typical estimated coefficient $\hat{\alpha}$ is nothing but $exp(\hat{\alpha})$, which represents the multiplicative effect on the odds of a unit increase in the corresponding covariate for fixed levels of other covariates. In order to check goodness of fit of the assumed model, the Hosmer and Lemeshow Goodness of Fit statistic is further provided in each table and we find that the assumed model fits good to the data for each of the characteristics. However, as the responses in the Baseline, Week 8 and Week 15 are recorded in ordinal scale and the rate of improvement in symptoms is slow, in general, Baseline Week 8 and Week 15 figures are more or less similar. This induces potential problems of multi-collinearity and consequently, the variable Week 15 is dropped to tackle multi-collinearity (Midi et al., 2010). From these, we observe that for all the characteristics except 'Joint Deformity', the assumed model fits good to the data. In most of the tables we find significantly higher standard errors for the covariates Baseline and Week 8. Although unimpressive but such values are not unusual because for most of the variables, Baseline and Week 8 responses do not differ significantly and hence indicates a mild presence of multi-collinearity. In addition, for each characteristic (except Joint Deformity), we have plotted the predicted probabilities of 'improvement' (i.e. having a final response in the lower category for a patient with higher category responses in the early assessments) for both male and female patients and varying age groups. Specifically, we computed the predicted probability of observing MILD response for a typical patient with MODERATE responses in the Baseline and Week 8 visits by varying age over the interval 30 to 80. Although plots are prepared for each characteristic, for brevity, we provide only the comparative plot (see Figure 4) for 'pain'

considering both sexes. From the plot, we find that the predicted probability of ' improvement' is almost unity for both male and female patients irrespective of age. The same conclusion continues with the other characteristics and hence indicates the usefulness of PEMF therapy.

Table 1: Summary results for Pain

Predictor	Estimated Coefficient(SE)	P value	OR	Lower CI	Upper CI
Constant	-20.35(11658.36)	0.99	-	-	-
Baseline	-19.69(8022.39)	0.99	0.00	0.00	$1.78032X10^{144}$
Week 8	19.73(4229.62)	0.99	368414169.2	0.00	$5.38378X10^{64}$
Age	-0.02(0.02)	0.50	0.98	0.94	1.03
Sex	-.06(0.52)	0.92	.95	0.34	2.62

Hosmer and Lemeshow Goodness of Fit statistic=4.11 with 8 DF and p value=.847. OR and corresponding CI are not reported for" Constant"

Table 2: Summary results for Joint Disability

Predictor	Estimated Coefficient(SE)	P value	OR	Lower CI	Upper CI
Constant	-14.34(256.11)	0.99	-	-	-
Baseline	-13.71(176.80)	0.94	0.00	0.00	$1.78032X10^{144}$
Week 8	13.12(92.93)	0.89	482763.36	0.00	$5.38378X10^{64}$
Age	-0.02(0.03)	0.50	0.98	0.94	1.03
Sex	-0.06(0.52)	0.92	0.95	0.34	2.62

Hosmer and Lemeshow Goodness of Fit statistic=4.11 with 8 DF and p value=.847. OR and corresponding CI are not reported for" Constant"

Table 3: Summary results for Swelling

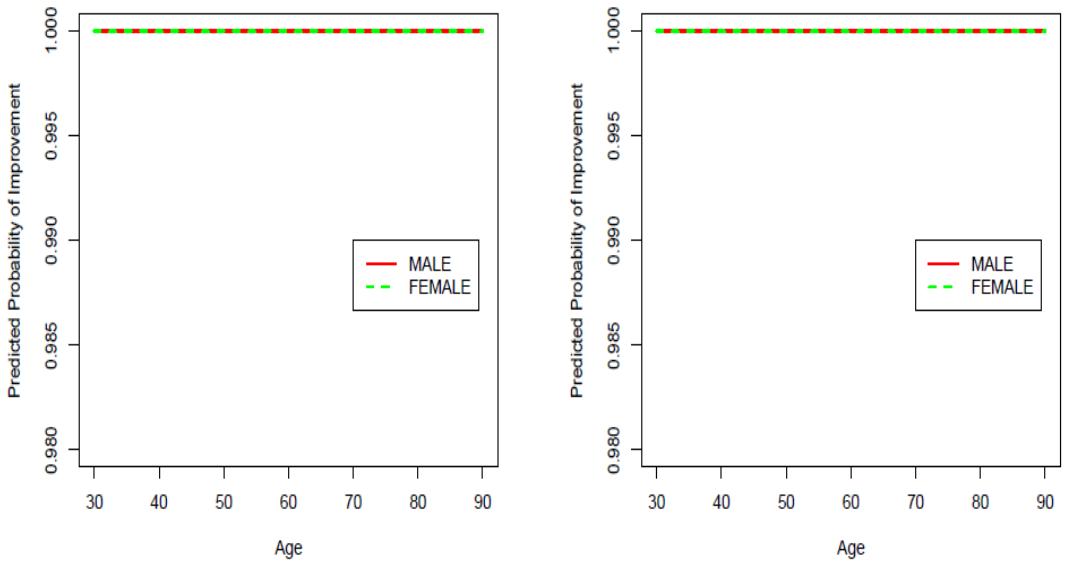
Predictor	Estimated Coefficient(SE)	P value	OR	Lower CI	Upper CI
Constant	-21.78(11660.22)	0.99	-	-	-
Baseline	-21.22(8025.86)	0.99	3.75	1.21	11.65
Week 8	21.19(4229.25)	0.99	1590963957	0.97	1.05
Age	0.01(0.02)	0.53	1.01	0.98	1.05
Sex	-.26(0.40)	0.51	.77	0.35	1.69

Hosmer and Lemeshow Goodness of Fit statistic=2.89 with 8 DF and P value=.941. OR and corresponding CI are not reported for "Constant"

Table 4: Summary results for Tenderness

Predictor	Estimated Coefficient(SE)	P value	OR	Lower CI	Upper CI
Constant	-13.33(259.11)	0.99	-	-	-
Baseline	-14.01(171.80)	0.94	0.00	0.00	$1.78032X10^{144}$
Week 8	12.13(97.93)	0.91	185349.8	0.00	$5.38378X10^{84}$
Age	-0.03(0.03)	0.53	0.98	0.94	1.03
Sex	-0.04(0.49)	0.94	0.95	0.34	2.62

Hosmer and Lemeshow Goodness of Fit statistic=4.01 with 8 DF and P value=.821. OR and corresponding CI are not reported for "Constant"



(a) Pain (b) Tenderness

Figure 4: Predicted probabilities of improvement

5. Conclusions

Use of PEMF therapy resulted better in reducing the symptoms of the OA subjects, enrolled in the trial. All the enrolled subjects show signs of improvement after the therapy was given. In particular, the therapy is observed to be effective in reducing the characteristics, Pain, Joint Disability, Swelling and Tenderness. Although the therapy is not effective in reducing Joint Deformity but it did not show

any adverse effects, that is, increasing the magnitude of Joint Deformity. Therefore, one can recommend the therapy for the effective treatment of OA patients, at least so far, the analysis results of the given data set is concerned.

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