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Clinical and endocrinological changes after electro-acupuncture treatment in patients with osteoarthritis of the knee

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ABSTRACT

Neurobiological mechanisms invoking the release of endogenous opioids and depression of stress hormone release are believed to be the basis of acupuncture analgesia. This study compared plasma β-endorphin and cortisol levels with self assessment scores of intensity of pain, before and after 10 days of electro-acupuncture treatment in patients suffering from chronic pain as a result of osteoarthritis knees. Forty patients of either sex over 40 years with primary osteoarthritis knee were recruited into a single-blinded, sham-controlled study. For electro-acupuncture group the points were selected according to the Traditional Chinese Medicine Meridian Theory. In the sham group needles were inserted at random points away from true acupoints and no current was passed. Both groups were treated for 10 days with one session every day lasting for 20–25 min. Pre- and post-treatment Western Ontario and McMaster Universities (WOMAC) index of osteoarthritis knee and Visual Analogue Scale (VAS) for pain were recorded and blood samples were taken for the measurement of plasma cortisol and β-endorphin levels. Following electro-acupuncture treatment there was a significant improvement in WOMAC index and VAS ($p = 0.001$), a significant rise in plasma β-endorphin ($p = 0.001$), and a significant fall in plasma cortisol ($p = 0.016$). In conclusion electro-acupuncture resulted in an improvement in pain, stiffness and disability. Of clinical importance is that an improvement in objective measures of pain and stress/pain associated biomarkers was shown above that of a sham treatment; hence demonstrating acupuncture associated physiological changes beyond that of the placebo effects.

1. Introduction

Acupuncture is a prominent part of Traditional Chinese Medicine, for over three thousand years it has been used as an effective form of treatment for pain [1]. Due to lack of scientific knowledge about its mechanism of action it has been dismissed for many years by western scientific community. It was only in the 1970s when President Nixon visited China that acupuncture gained popularity in the west [38]. Since then a number of studies have been carried out to determine its scientific basis but to date we do not have an insight to its exact mechanism [45]. Furthermore even a cursory survey of the scientific literature reveals a paucity of high quality research that could assess the mechanism and efficacy of these therapies compared to sham treatments. Moreover results of the various studies published have claimed apposing views as to its efficacy in the treatment of chronic pain [37,48]. Nevertheless, there has been sufficient evidence of acupuncture's value in pain control for its use in conventional medicine to be no longer (particularly) controversial and to encourage further studies on its physiological basis and clinical role [18].

It has long been suggested that acupuncture induces endogenous release of endorphins resulting in analgesia. The endogenous opioid system and pituitary–adrenal axis have a close physiological link. β-Endorphin and Adrenocorticotrophic Hormone (ACTH) share a common precursor, Proopiomelanocortin (POMC) [20]. A study showed that Corticotropin Releasing Factor (CRF) produced within the hypothalamus may cause co-release of ACTH and β-endorphin [26]. In support of this, another independent group found that β-endorphin released physiologically has a close temporal coupling to cortisol release [24]. The effect of acupuncture on plasma levels of cortisol on the other hand is not very clear. Some studies have shown that its plasma levels would fall in response to acupuncture while others showed a rise in the plasma levels of cortisol after acupuncture treatment [12,30,31,34]. This might suggest that acupuncture for chronic pain associated with osteoarthritis may not only increase endorphin levels but also cortisol which may in turn have anti-inflammatory effects.

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This study planned to investigate the effect of electro-acupuncture on pain intensity and plasma levels of endorphin and cortisol. For this purpose patients with osteoarthritis of the knee were chosen, as it is a very common condition. Well-recognized International guidelines for the study of assessment of therapies in Osteoarthritis have been published [3]. Visual Analogue Scale (VAS) and Western Ontario Mac Masters University index for Osteoarthritis (WOMAC) are the validated methods for the assessment of pain and functional status after therapy for osteoarthritis knee [6]. Both VAS and WOMAC were used as pain and functional assessment tools in this study. Although there have been a few studies to demonstrate the effect of electro-acupuncture on Osteoarthritis (OA) of knee [17,8,44], to our knowledge, none has simultaneously measured the objective parameters of pain and functional disability and levels of endocrine markers, cortisol and β-endorphin, in treatment and sham electro-acupuncture.

2. Methodology

This study was carried out at Department of Physiology, Army Medical College, Rawalpindi in collaboration with Holy Family Hospital Rawalpindi, from December 2003 to October 2004. Ethical approval was granted by the local hospital ethical committee. Power calculations had indicated that in an unpaired control study (of 5% Alpha and 95% Power) assuming a 20% standard deviation around means and for a 30% improvement in symptoms compared to sham control, 13 patients needed to be recruited in each arm of the study. However if the variation in SD increased to 30% 28 patients would be required in each group. Based on these figures and intermediate minimum target recruitment was chosen as 20 in each arm of the study.

2.1. Participants/patients

A total of 84 patients of either sex with primary osteoarthritis of one or both knees fulfilling diagnostic criteria for osteoarthritis knee laid down by American College of Rheumatology [2] were recruited in the study. The patients were selected from the pain clinic in the Department of Anaesthesiology at Holy Family Hospital, Rawalpindi. The patients with secondary OA, associated systemic arthropathies, e.g. rheumatoid arthritis and gout, patients on steroids, disease modifying drugs, e.g. methotrexate and azathioprim, patients with recent trauma in the area of acupuncture, pregnancy, history of intra articular injection of steroid within last two months and patients missing two or more sessions of electro-acupuncture consecutively were excluded from the study.

After the diagnosis, the patients included in the study were explained the procedure of study. Written informed consent was taken and relevant history of each patient was recorded.

2.2. Intervention

The sampling technique was non-probability convenience sampling. The patients were divided into two groups "A" and "B" on the basis of the order of presentation at clinic until cohort numbers were reached. The treatment was for 10 consecutive days with group "A" receiving electro-acupuncture and group "B" sham acupuncture. Two tablets of Acetaminophen 500 mg were given stat at the time of first acupuncture session to all the patients in both the treatment and placebo groups because of ethical reasons. They were asked to take two additional tablets if the pain was intractable.

2.3. Electro-acupuncture

Electro acupuncture is a relatively new method of treatment in Chinese Medicine. Just as in a regular acupuncture treatment, needles are inserted into acupuncture points but small crocodile clips are then attached to the ends of needles to connect them to an electro-acupuncture device. In traditional acupuncture the inserted needles are manually vibrated to induce a response whilst in electro-acupuncture the bi-phasic current results in a constant (controlled) vibration of the needles and a direct electrical stimulation. The advantage of using electro-acupuncture is that it provides extra stimulation for a longer duration of time and acupuncturist does not need to manually stimulate the needles [12,49]. Thus, the device allows the practitioner to adjust the frequency and intensity of the electric stimulation in a consistent manner which is not operator dependant.

A qualified Acupuncturist carried out 10 acupuncture sessions in total on each patient with one session everyday. The duration of every session was 20–25 min with patient sitting comfortably in a chair. Acupuncture needles of 30 mm size were used. The needles were inserted into the specific points on the surface of skin (10–30 mm depth, depending on built of patient) in electro-acupuncture group and a De Qi sensation was ensured in this group. The needles were attached to flexible wires connected by crocodile clips (see Fig. 1).

For the group 'A' patients the electro-acupuncture device was a biphasic pulse generator. It was used with maximum tolerable intensity of current and a frequency of 3 Hz. The points were selected according to the Traditional Chinese Medicine meridian theory to treat knee pain [12,40]. The points selected were local points including Liangqiu (St 34). It is 2 cm above and lateral to upper border of Patella, Dubai (St 35). It is in depression on the lateral side of ligamentum patellae. Zusanli (St 36) is located one finger breadth lateral to inferior end of tibial tuberosity. Ququan (Liv 8) is located in the transverse crease of knee joint. Xuehai (Sp 10) is located 2 cm above the medial end of the upper border of patella. One distal point Neiting (St 44) that is located 0.5 cm proximal to the web margin between second and third toes was used. A total of six needles were inserted into each leg by the acupuncturist (the out come measures were not specifically targeted to whether the patient had one or both knees involved). All patients belonging to this group experienced a De Qi sensation, which is a tingling and numbness sensation upon needling of specific points.

2.4. Sham acupuncture

The patients of "B" group were controls. There are different types of controls used in acupuncture trials. We used the control described as sham and by some as minimal acupuncture. This group had the same schedule as the electro-acupuncture group.

Fig. 1. Acupancture points used in the study.

The needles were introduced into random points at least 5 cm away from standard points and 3 cm away from meridians and not in the same dermatome. The depth of the needle insertion was not more than 5–10 mm, depending on the built of patients. The needles were connected to the stimulating device, but the flow of current was not put on. The patients remained unaware of their grouping category because the indicator bulb kept on flashing throughout the 10 sessions in both groups. To facilitate blinding, we tried to separate the treatment and placebo groups by keeping the sham receiving patients together in a group and the treatment-receiving patients in a separate group. Also the patients of sham group were told that this was a new intervention and would require time to have its therapeutic effects. However due to ethical reasons we had asked patients of both the groups to take two tablets of acetaminophen during the study period if the pain was absolutely unbearable. Also, they were allowed to leave the study if they did not want to continue. Same amount of time and attention was given to all patients.

2.5. WOMAC

For both groups, initial assessment of the intensity of pain and functional disability was recorded on Western Ontario Mc master universities index for osteoarthritis knee (WOMAC) and Visual Analogue Scale (VAS). WOMAC is a multidimensional measure of pain, stiffness, and physical functional disability. The pain dimension or scale included five questions asked about pain at activity or rest. The stiffness dimension included two questions. The function dimension asked about the degree of difficulty in 17 different activities. All 24 WOMAC questions were rated on a numerical rating scale ranging from 0 (no symptoms) to 4 (maximum symptoms). The scale was translated into Urdu language for self-assessment of patients. Severity of pain was recorded on the WOMAC questionnaire according to each patient's assessment for all 24 questions, i.e. 0, 1, 2, 3 or 4 and the total calculated was written on the proforma.

2.6. Visual analogue scale

This is an internationally recognized pain scale. It is a 100 mm line starting from 0, which means 'no pain at all' to 100 which means 'pain as bad as it could be' [25]. Each patient marked the level of pain on the scale provided to him/her on the first day of the treatment session and then again on the tenth day after completion of the last session.

After 10 days of daily electro-acupuncture and sham treatment, the patient's pain intensity was again recorded on WOMAC and VAS scales.

2.7. Collection of blood

Two 5 ml blood samples were drawn from each patient from anticubital vein under aseptic measures, one before starting the treatment and one on the tenth day, five minutes after completion of the last session at almost the same time of the day. Blood was drawn and transferred to pre-cooled EDTA tube. It was immediately centrifuged; plasma was drawn with micropipette and divided into two equal parts, one for the estimation of plasma cortisol and other for β-endorphin. The plasma samples were frozen and kept at -70 °C until the time of analysis.

2.8. β-Endorphin and cortisol measurement

All blood samples for the estimation of β-endorphin and cortisol were taken between 9 a.m. and 1 p.m. The before treatment and after treatment timings of sampling in the same patient were tried to match in all patients to avoid any effect of diurnal variation on plasma levels of the hormones.

Quantitative plasma β-endorphin estimation was done using ELISA, i.e., Enzyme Linked Immunosorbent Assay (MD Biosciences, Division of Morwell Diagnostics GmbH Gewerbestrasse 9, Postfach, 8132 Egg b. Zürich, Switzerland) at Armed Forces Institute of Pathology.

Quantitative plasma cortisol estimation was performed on an immulite 2000 at the Armed Forces Institute of Pathology.

2.9. Data analysis

The data were entered into EXCEL data sheets and analysed using STATSDIRECT™ software. All data sets were examined for normality of distribution and descriptive statistics were used appropriately to describe either parametric (means and standard deviation) or non-parametric (mediums and interquartile range) characteristics for numerical data. Since most of the data were not normally distributed Mann–Whitney *U* test was employed to compare the difference in β-endorphin and cortisol levels and pain scores.

3. Results

In total 26 patients were recruited for electro-acupuncture of which 20 completed the study protocol. In the control sham group 58 were recruited in total, but failure to complete was high: 38 dropped out from the study, in our efforts to achieve 20 patients completing sham/control arm of the study (Fig. 2).

No significant adverse effects were seen with respect to the procedure itself, except for mild bruising of the needling site in 3 patients. The demographic data of both the groups are presented in Table 1.

Our study had four quantitative variables; WOMAC score (total and subscores) and VAS pain score, plasma cortisol and plasma β-endorphin.

The WOMAC and VAS scores were recorded for individual patients before and after treatment (Fig. 3). The change in WOMAC score for the sham group was only a 0.7% reduction in the median score (interquartile range 0–4% – Fig. 3b), whilst the median reduction in the score was 72% (interquartile range 53–85% – Fig. 3a) for those receiving electro-acupuncture (Mann–Whitney *U* test – difference in score reduction $p < 0.001$). The reduction in VAS pain score showed a similar trend with the sham group showing no reduction in median score (interquartile range 0–6%, Fig. 3d); whilst electro-acupuncture had a median reduction of 72% (interquartile range 56–85%, Fig. 3c) (Mann–Whitney *U* test – difference in score reduction $p < 0.0001$).

The levels of endorphin and cortisol measured in each group showed a skewed distribution, reflecting the individual nature of endorphin levels (see Table 2). However, interestingly the sham control group had higher basal endorphin levels compared to the electro-acupuncture group ($p = 0.041$). Despite this the electro-acupuncture group had the highest levels of endorphins post treatment ($p < 0.046$). Due to the variability and individual nature of endorphins and cortisol we plotted the magnitude of change in endorphins found for each patients post treatment (Fig. 4). β-Endorphin levels showed a median increase of 170% (interquartile range of 120–570%) in the electro-acupuncture group whilst the sham group showed a small decrease in levels post treatment (median 90% – interquartile range 75–100%). Conversely, cortisol levels fell by a median of 29% in the electro-acupuncture group (interquartile range 4–37%) whilst in patients receiving sham treatment cortisol levels increased by a median of 15% (interquartile range 0–46%).

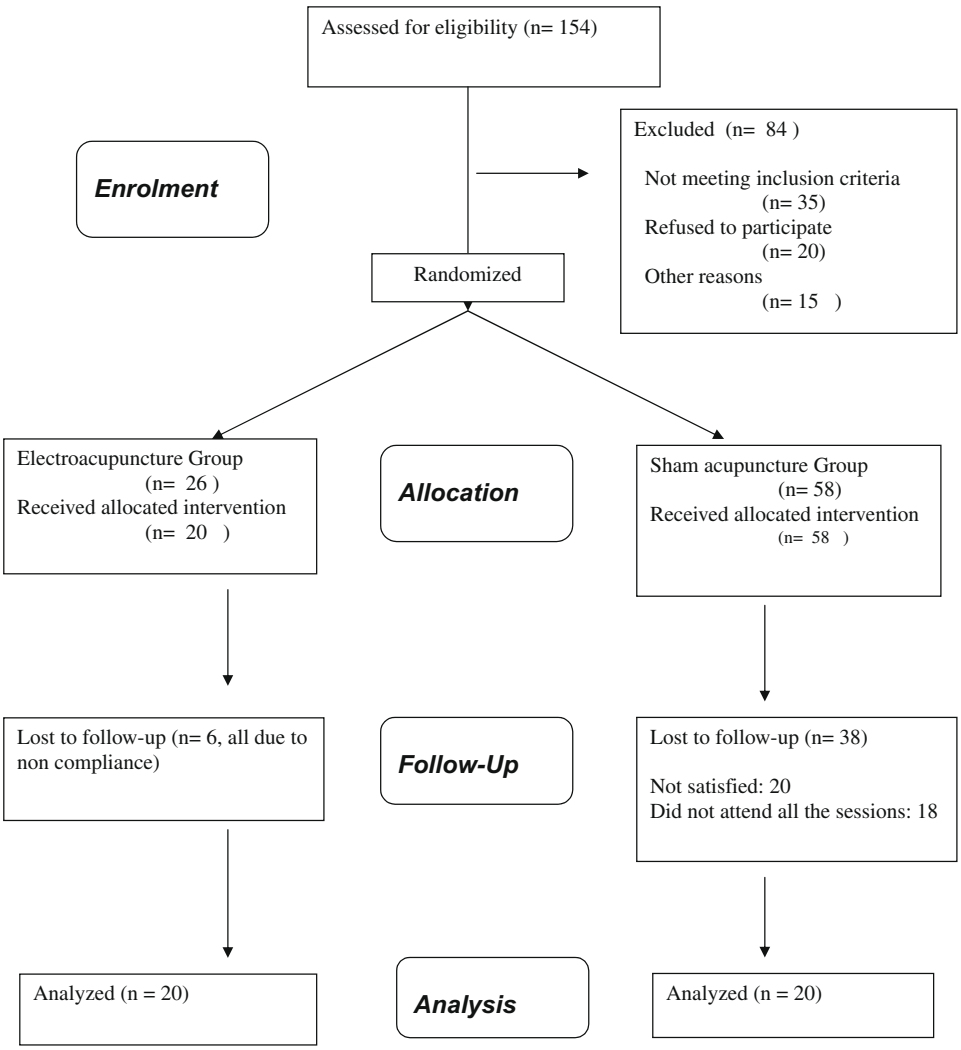

Fig. 2. Consort flow diagram.

4. Discussion

The conclusions of scientific studies on acupuncture efficacy in different clinical trials have been contradictory [5]. Indeed, some studies reported entirely opposite findings when acupuncture was used to treat the same conditions, for example, chronic pain [37,8,15,47]. However, the cause and underlying pathology for chronic pain per se can be various and very different even for the same anatomical location. Nevertheless, there is sufficient practice-based evidence of acupuncture's value to expand its use into conventional medicine and to encourage further studies on its physiology and clinical role [18]. A recently carried out study to record the effect of acupuncture on osteoarthritis pain concluded that acupuncture was effective for relieving pain of osteoarthritis knee [50]. Another study suggested that acupuncture was a safe adjuvant therapy to conventional treatment [14]. Some studies have shown similar results by using waiting list as control group or acupuncture compared with base line treatment [34,9]. The absence of placebo is a serious limitation in these studies and we have tried to overcome this limitation by incorporating a sham treatment group. There are a considerable variety of placebos both invasive and non-invasive. Invasive placebos include sham acupuncture in which there is needle insertion at inappropriate points and no electrical stimulation. Non-invasive placebos are those in which there is no actual needle insertion [17,22,28].We designed a single blinded study and decided to use sham form of acupuncture as placebo. For efficacy studies in which the effectiveness of acupuncture is compared with placebo, sham type of acupuncture appears to be the most appropriate method. Clinical trials indicate that patients blinding is achieved best with the use of sham acupuncture [48]. To facilitate blinding mock connection of electro-acupuncture device with needles was made and we tried to assure that patients belonging to both groups were getting same amount of time and attention.

A study on acupuncture carried out by Ezzo and co-workers in 2001 demonstrated an effective pain relief in osteoarthritis knee [17] but the assessment of quality of life in the form of functional improvement was not considered and needed more studies. Our study has covered this aspect. The objective scales for the assess-

Table 1
Mean age, sex, weight and duration of illness of electro-acupuncture and sham groups (the values of age, sex and weight are given as means ± SD).

Patients	Electro-acupuncture group Means ± SD	Sham group Means ± SD
Age (Years)	51.05 ± 7.73	51.45 ± 8.9
Sex (M/F)	7/13	5/15
Weight (kg)	69.5 ± 9.74	67.27 ± 7.8
Duration of illness (Months)	23.5 ± 17.84	14.45 ± 10.3

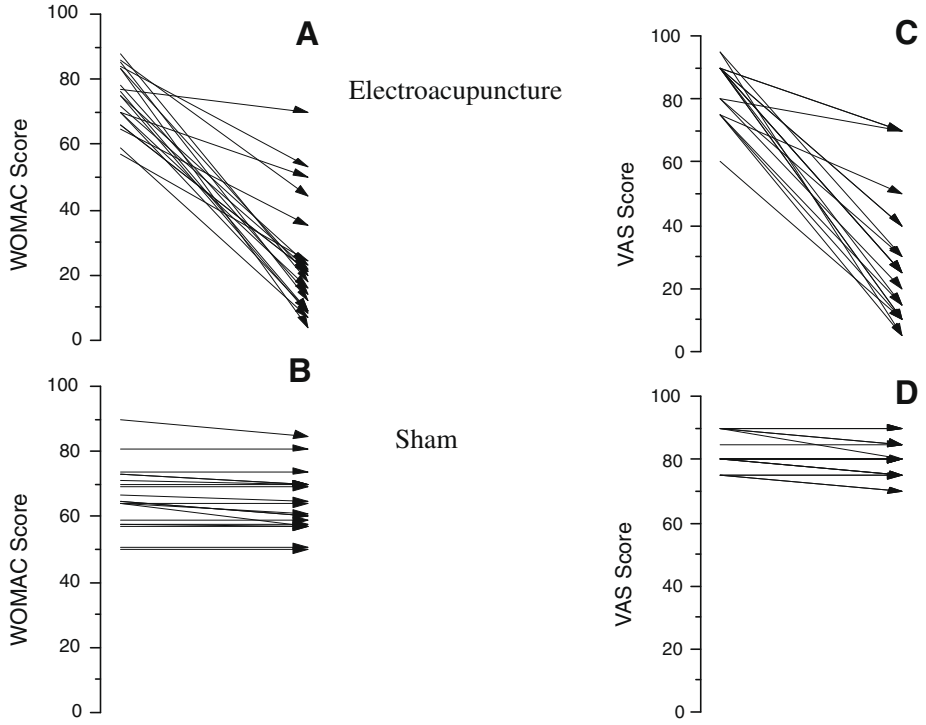

Fig. 3. Change in WOMAC and VAS pain scores for patients in the sham and electro-acupuncture treatment groups.

ment of pain used in our study were WOMAC and VAS. WOMAC is recommended by the OMERACT [7,10] (Outcome Measures in Rheumatology Clinical Trials). VAS is also used in research, as well as clinical practice, especially where changes in symptoms are to be recorded [46]. A recent trial carried out in Selly Oak Hospital, Birmingham, UK by Tukmachi et al. [44] on the effect of acupuncture on the symptoms of knee osteoarthritis also utilized the WOMAC and VAS scales for the assessment of clinical improvement of the symptoms after acupuncture treatment. In this study pain depicted by VAS and all WOMAC sub scores including stiffness and disability in the electro-acupuncture group was significantly reduced. There was some reduction in pain sub-score in the sham group as well but stiffness and disability sub scores were not significantly changed. This showed that electro-acupuncture treatment was more effective than the placebo treatment for pain relief. A small amount of pain relief in placebo group may be attributed to rest and relaxation and a feeling of being provided some effective treatment. Our study results are consistent with those of Tukmachi et al. [44], however, no bio-chemical markers of pain/stress were estimated in their study.

The perception of pain is very complex. The mechanisms involved in chronic pain are different than that in acute pain. In chronic pain conditions there is interaction between many regions of brain including those associated with emotions and cognition as shown by meta-analysis of studies by Zubeta and colleagues on mechanisms involved in modulation and perception of pain in healthy volunteers and patients with chronic pain conditions. .[4].

The involvement of endogenous opioids, including β-endorphin, has been demonstrated as a major factor in bringing about analgesia in chronic pain conditions [19]. A study on rheumatoid arthritis patients showed increase in central endogenous opioid receptor binding in response to inflammatory pain, suggesting an important role of opioids in pain modulation. [27]. Other studies, mostly on animal models, have explored endorphin-related neuro-suppressive/analgesic molecular mechanisms in various parts of the brain [29,36,39,52]. In addition to central actions of opioids, β-endorphin and met-enkephalin also have a peripheral local analgesic action which is blocked by nalaxone [42]. To make the matter more complex inflammatory cells have been shown to produce opioid peptides. There is also increased synthesis of opioid receptors in the dorsal root ganglion neuron and axonal transfer of these receptors to the inflamed site during inflammation [33]. Therefore it appears that endorphins have both peripheral and central actions. While there is a positive correlation between plasma β-endorphin level and analgesia, such correlation has not been found for CSF β-endorphin [35].

Our study showed that plasma β-endorphin levels rose significantly in electro-acupuncture group after treatment whereas in the sham group this change was not seen. This is consistent with another study examining transcranial electro-stimulation in 20 pa-

Table 2
Plasma β-endorphin and cortisol levels and magnitude of change after treatment.

Variables	Group	Before treatment	After treatment	% Change
β-Endorphin (ng/ml)	Sham	0.42 (0.34–0.45)	0.35 (0.32–0.43)	0.90 (0.75–1.00)
	Electro-acupuncture	0.30 (0.09–0.38)	0.48 (0.43–0.49)	1.70 (1.2–5.7)
Cortisol (μg/dl)	Sham	7.4 (6.1–8.25)	7.75 (6.8–10.25)	1.15 (1.00–1.46)
	Electro-acupuncture	9.25 (5.7–12.8)	6.35 (5.5–7.45)	0.71 (0.63–0.96)

$n = 20$.

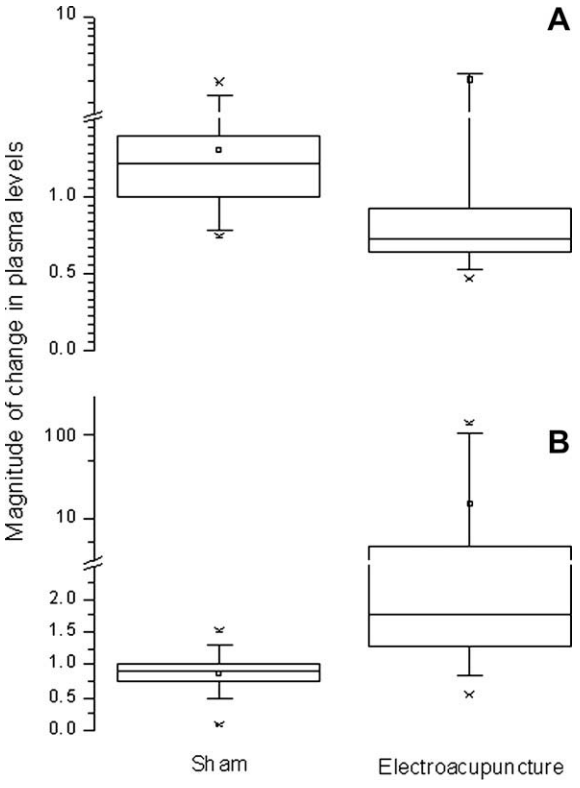

Fig. 4. Magnitude of change (expressed on a log scale) in patients plasma cortisol (upper panel A) and plasma β-endorphin (lower Panel B) after sham and electro-acupuncture treatment.

tients with backache. They demonstrated a significant rise in post treatment blood β-endorphin levels. Such changes in β-endorphin concentration have also been documented by others studying acupuncture treatment in both animals and humans [41,23].

Reviewing the literature, some studies have suggested that electro-acupuncture may have a direct effect on plasma cortisol levels; for example, a study demonstrated a rise in plasma cortisol levels in horses after electro-acupuncture treatment [13]. Another study showed a marked rise in plasma cortisol which brought expected anti-inflammatory effect in rats after electro-acupuncture treatment [51]. Such modulations are not consistent as some studies in humans showed a significant fall in plasma cortisol level after acupuncture analgesic treatment in orthopaedic operations [21]. Bragin [11] showed an association between reduction in blood stress hormones and electro-acupuncture analgesia in patients with spinal osteochondrosis [11]. In our study plasma cortisol level was significantly reduced in the electro-acupuncture group whilst the sham group showed a rise in plasma cortisol. The fall in cortisol levels in our treatment group is comparable with the previous human studies and therefore consistent with the hypothesis that this reflects a reduction in stress [32] of pain rather than a pharmacological increase in the steroid as an anti-inflammatory agent. In the sham group, the rise of plasma cortisol after ten days of treatment may be related to the continuation of stress because of lack of pain relief.

Interestingly, an inverse relationship between cortisol and endorphin has been recorded as early as the 1980s. Taylor and his co-workers [43] proposed that β-endorphin might suppress cortisol release. In their study, cortisol levels decreased below the basal level in response to the infusion of β-endorphin in normal human subjects. They suggested the short feed back loop inhibition of pituitary ACTH or hypothalamic corticotrophin releasing factor by β-endorphin. Thus, in this study, inverse relationship between cortisol and β-endorphin levels following electro-acupuncture is consistent with Taylor et al.'s β-endorphin short loop feed back inhibition hypothesis.

The rank order changes in endorphins and cortisol levels in both the electro-acupuncture and sham treatment groups did not correlate with the rank order changes in WOMAC and VAS scores. Thus, although an efficacy effect can be demonstrated and changes in cortisol and endorphins are also evident, the relationship between clinical assessments of pain relief following electro-acupuncture is not simply explained by changes in the endogenous cortisol and endorphin levels.

Limitation of our study is that despite of translating WOMAC into Urdu language, the investigator completed most of the WOMAC proforma by asking questions because the majority of patients were illiterates, however the grading and questions were explained thoroughly. Also, use of acetaminophen at the start of study was unavoidable due to ethical reasons. We understand that this study focuses only on the short term changes in the clinical and endocrinal markers. However it will form a stepping stone for studies looking into long term effects of electro-acupuncture.

5. Conclusion

In conclusion there are inherent difficulties in acupuncture study designs because of variability in recommendation of matching appropriate control or placebo group, blinding methods, randomization, acupoint specification, needling techniques, number and duration of treatment sessions [28]. Although a double blind randomized placebo controlled trial is the gold standard, studies involving acupuncture, in which both practitioner and patients are unaware of treatment, are virtually impossible to conduct [16].

This study suggests that electro-acupuncture is effective method of relieving pain, stiffness and functional disability associated with primary osteoarthritis knee with minimal side effects. These findings were validated from disease-specific purpose built high performance instrument for evaluative research in clinical trials on knee osteoarthritis. Stress relief in the form of over all clinical improvement in the treatment group was reflected by a significant fall in the plasma cortisol levels. The analgesia brought about by electro-acupuncture was clearly more than sham acupuncture with minimal adverse affects and reflected in changes in the neuro-endocrine modulator β-endorphin. It can be concluded that electro-acupuncture may be incorporated in conventional treatment of osteoarthritis of knee or other musculoskeletal disorders, and provides relief clearly beyond that of placebo effects.

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