

## *Effect of the Duration of Electrical Stimulation on the Analgesic Response in Patients with Low Back Pain*

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**Background:** Electrical stimulation of peripheral nerves produces acute analgesic effects. This randomized, sham-controlled, crossover study was designed to evaluate the effect of differing durations of electrical stimulation on the analgesic response to percutaneous electrical nerve stimulation in 75 consenting patients with low back pain.

**Methods:** All patients received electrical stimulation for four different time intervals (0, 15, 30, and 45 min) in a random sequence over the course of an 11-week study period. All active percutaneous electrical nerve stimulation treatments were administered using alternating frequencies of 15 and 30 Hz three times per week for 2 consecutive weeks. The prestudy assessments included the health status survey short form questionnaire and 10-cm visual analog scale scores for pain, physical activity, and quality of sleep, with 0 being the best and 10 being the worst. The pain scoring was repeated 5–10 min after each 60-min study session and 24 h after the last treatment session with each of the four methods. The daily oral analgesic requirements were assessed during each of the four treatment blocks. At the end of each 2-week treatment block, the questionnaire was repeated.

**Results:** Electrical stimulation using percutaneously placed needles produced short-term improvements in the visual ana-

log scale pain, physical activity, and quality of sleep scores, and a reduction in the oral analgesic requirements. The 30-min and 45-min durations of electrical stimulation produced similar hypoalgesic effects ( $48 \pm 21\%$  and  $46 \pm 19\%$ , respectively) and were significantly more effective than either 15 min ( $21 \pm 17\%$ ) or 0 min ( $10 \pm 11\%$ ). The 30- and 45-min treatments were also more effective in improving physical activity and sleep scores over the course of the 2-week treatment period. In contrast to the sham treatment (0 min), the health status survey short form revealed that electrical stimulation for 15 to 45 min three times per week for 2 weeks improved patient function.

**Conclusion:** The recommended duration of electrical stimulation with percutaneous electrical nerve stimulation therapy is 30 min. (Key words: Electroanalgesia; lumbago; stimulation interval.)

THERAPIES for low back pain (LBP) include physical therapy, epidural steroid injections, opioid and nonopioid analgesic medications, implantable spinal cord-stimulating devices, and various psychologic and behavioral modification programs. Although these therapeutic methods may be effective for patients with acute LBP,<sup>1</sup> they are unsatisfactory for many patients with chronic LBP. If pain symptoms persist, the use of pharmacologic therapy can interfere with physical activity and sleep patterns and produce unwanted side effects.<sup>2</sup> These concerns have increased interest in nonpharmacologic therapies for LBP, including transcutaneous electrical nerve stimulation (TENS),<sup>3</sup> acupuncture,<sup>4</sup> electroacupuncture,<sup>5</sup> and percutaneous electrical nerve stimulation (PENS).<sup>6-8</sup>

Percutaneous electrical nerve stimulation is a novel, nonpharmacologic analgesic therapy that combines the advantages of transcutaneous electrical nerve stimulation (*i.e.*, peripheral dermatomal-based electrical nerve stimulation) and electroacupuncture (*i.e.*, electrical stimulation at specific acupoints *via* percutaneously placed needles). This therapy involves the placement of acupuncture needle probes in the soft tissues or muscles to stimulate peripheral sensory nerves at the dermatomal (or sclerotomal) levels corresponding to the local dis-

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ease. The effect of the duration of the electrical stimulation on the short-term analgesic response to PENS therapy has not been studied previously.

Therefore, we designed a randomized, single-blind, crossover study to evaluate the analgesic effectiveness of different durations of electrical stimulation of PENS therapy in patients with LBP. In addition, the comparative effects of the different durations of stimulation on the patients' levels of physical activity and quality of sleep, as well as daily oral analgesic requirements, were assessed over each 2-week treatment interval.

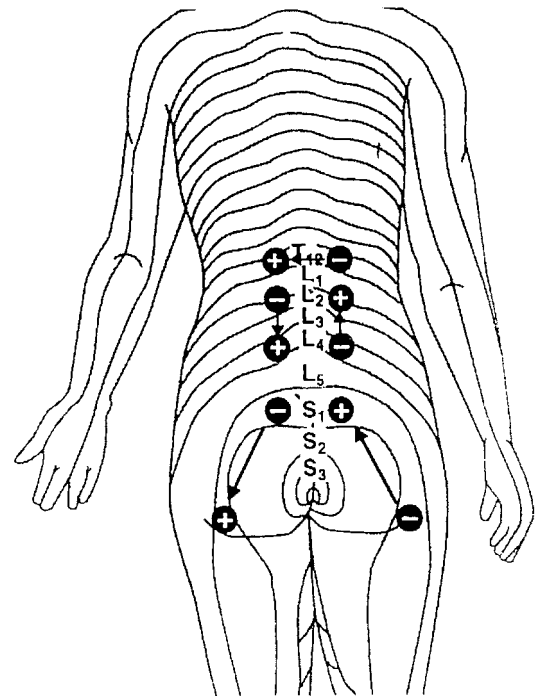
### Materials and Methods

After obtaining local institutional review board approval and written informed consent, 75 patients (34 men and 41 women, ranging between 21 and 76 yr of age) with LBP secondary to radiologically confirmed degenerative lumbar disk disease received electrical stimulation *via* acupuncture needle probes for periods of 0, 15, 30, and 45 min, according to a randomized, single-blind, crossover study design. Inclusion criteria included age older than 18 yr and a history of LBP related to degenerative lumbar disk disease with a pain level that remained unchanged over a period of at least 3 months before enrolling in the study. Forty-two percent of the study patients had undergone previous back surgery. Exclusion criteria included LBP with a radicular component (sciatica), a history of drug or alcohol abuse, previous experience with acupuncture, a change in the character or severity of the pain within the last 3 months, a recent change in analgesic medications (or current use of opioid-containing drugs), and the inability to reliably complete the health status survey short form (SF-36),<sup>9</sup> daily assessment tools, or the global assessment questionnaire.

All patients were told that each treatment session would last for 60 min, with varying periods of electrical stimulation (producing either no sensation or a light tapping sensation), three times per week (on Monday, Wednesday, and Friday afternoons) for 2 consecutive weeks, with 1 week "off" before each treatment modality. Patients were exposed to all four stimulation intervals in a random sequence over the course of the 11-week study period.

#### Treatment Methods

Ten 32-gauge stainless steel acupuncture needle probes (ITO, Tokyo, Japan) were placed into the soft



Needle insertion sites

**Fig. 1.** The location of the needle probes for the percutaneous electrical nerve stimulation and nonelectrical ("sham") needle treatments. Each of the five bipolar leads are connected to a pair of needles, alternating the positive (+) and negative (-) connections as shown in the illustration.

tissue or muscle to a depth of 2–4 cm in the low back region according to the dermatomal (or sclerotomal) distribution of the pain for a period of 60 min, as shown in figure 1. The 10 probes were connected to five bipolar leads (with each lead connected to one positive and one negative probe) from an investigational low-output electrical generator and stimulated for a period of 0, 15, 30, or 45 min at an alternating frequency of 15 and 30 Hz.<sup>10</sup> The intensity of the electrical stimulation was adjusted to produce a tolerable tapping sensation without muscle contractions. The maximum amplitude of the electrical stimulation produced by the generator was 25 mA using a unipolar square-wave pattern and a pulse width of 0.5 ms. The electrical current was direct and the duty cycle was continuous.

#### Assessment Procedures

Before initiating any of the four treatments, patients were required to complete the SF-36 questionnaire.<sup>9</sup> The physical component summary and mental component summary scores of the SF-36 were used to assess patient

response to each of the different stimulation intervals.<sup>11</sup> All patients were also asked to assess their level of LBP, physical activity, and quality of sleep during the 24-h interval before the first treatment and after the last (sixth) treatment for each of the four different timing intervals, using three separate 10-cm visual analog scales (VAS), with 0 being the best and 10 being the worst score. Subsequent VAS assessments of the degree of pain, physical activity, and quality of sleep were performed three times per week before each treatment session. In addition, the pain VAS assessment was repeated 5–10 min after completion of each treatment session to determine the acute analgesic response to the therapy. Patients were instructed to record in their diaries (which were checked by the investigators at each clinic visit) the number of oral nonopioid analgesic pills they used each day. The SF-36 questionnaire was again filled out after completing all six treatment sessions with each of the four stimulation intervals.

#### Data Analysis

The Number Cruncher Statistical System (NCSS) software package (NCSS 6.0.1 statistical system for Windows; NCSS, Kaysville, UT) was used for all statistical analysis. An *a priori* power analysis with  $\alpha = 0.05$ ,  $\beta = 0.10$  (power = 90%), and standard deviations of 2.0 and 1.5 determined that a group size of 75 should be adequate to show differences of 20 and 10% between the VAS scores and the daily oral analgesic requirements (pills per day), respectively, for the four treatment intervals studied. The changes in the VAS scores and daily oral analgesic medication usage were analyzed using repeated measures analysis of variance (ANOVA) and the Student *t* test. Changes and differences in the SF-36 scores were analyzed by paired *t* tests. Data are presented as mean values ( $\pm$  SD for tables and  $\pm$  SEM for figures) and percentages, with  $P < 0.05$  considered significant.

#### Results

Seventy-five patients with a mean age of  $47 \pm 18$  yr, a mean baseline VAS pain score of  $7.4 \pm 2.2$ , and a mean duration of pain of  $38 \pm 13$  months, were enrolled in this study. The prestudy SF-36 evaluation suggested that this LBP population reported significantly lower health-related “quality-of-life” scores compared with the general population. The mean prestudy scores were  $32.7 \pm 7.6$  and  $41.8 \pm 5.9$  for the physical and mental component

**Table 1. Comparison of the Acute Analgesic Effects of the Four Stimulation Intervals on the VAS Pain Scores Immediately before (Pre) and After (Post) Each Treatment Session**

Treatment Number	0 min	15 min	30 min	45 min
1 Pre	6.2 $\pm$ 1.9	6.8 $\pm$ 1.7	6.4 $\pm$ 1.9	6.3 $\pm$ 1.9
Post	5.8 $\pm$ 1.7	5.9 $\pm$ 1.9	3.9 $\pm$ 1.8†	3.8 $\pm$ 1.8†
2 Pre	6.3 $\pm$ 1.7	6.2 $\pm$ 1.7	5.8 $\pm$ 1.8	5.9 $\pm$ 1.8
Post	5.8 $\pm$ 1.9	4.9 $\pm$ 1.8*	3.1 $\pm$ 1.7†	3.2 $\pm$ 1.7†
3 Pre	6.1 $\pm$ 1.8	5.5 $\pm$ 2.0	5.4 $\pm$ 1.9	5.4 $\pm$ 1.7
Post	5.7 $\pm$ 2.1	3.8 $\pm$ 1.8*	2.9 $\pm$ 1.7†	2.9 $\pm$ 2.0†
4 Pre	6.2 $\pm$ 1.9	4.9 $\pm$ 1.6	4.8 $\pm$ 2.2	4.9 $\pm$ 1.6
Post	5.6 $\pm$ 1.9	3.0 $\pm$ 2.0*	2.2 $\pm$ 1.8†	2.3 $\pm$ 1.9†
5 Pre	6.1 $\pm$ 2.2	4.3 $\pm$ 1.9	4.5 $\pm$ 1.8	4.2 $\pm$ 1.8
Post	5.5 $\pm$ 1.5	2.7 $\pm$ 1.7*	2.0 $\pm$ 1.7†	1.9 $\pm$ 1.6†
6 Pre	6.0 $\pm$ 1.6	3.8 $\pm$ 1.9	4.5 $\pm$ 2.1	4.6 $\pm$ 1.5
Post	5.4 $\pm$ 1.9	2.0 $\pm$ 1.7*	1.6 $\pm$ 1.8†	1.5 $\pm$ 1.4†

Values are mean  $\pm$  SD.

VAS = Visual analog scale; 0 = the best to 10 = the worst.

\* Significantly different from values before (pre) each treatment session ( $P < 0.05$ ).

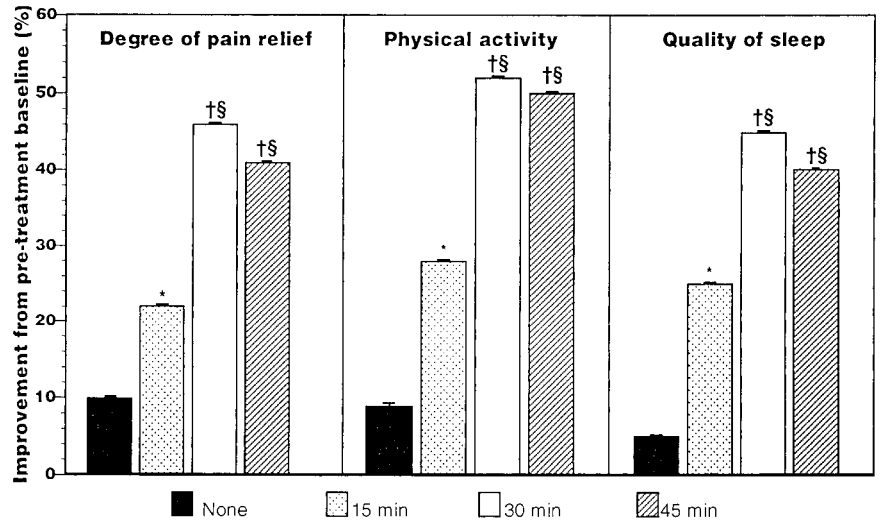
† Significantly different from values before (pre) each treatment session ( $P < 0.01$ ).

summaries, respectively, compared with general population norms of 50 for these two variables. The post-treatment SF-36 test results revealed that electrical stimulation for 15 to 45 min produced significant improvements compared with the sham (0 min) treatments with respect to the physical and the mental components of the survey ( $P < 0.01$  for 15 min and  $P < 0.001$  for 30- and 45-min stimulation intervals). However, the absolute mean magnitude of the changes in physical and mental components with the 30-min (+7.4 and +3.1, respectively) and 45-min (+7.1 and +2.9, respectively) stimulation intervals were significantly greater than with the 15-min stimulation interval (+5.4 and +2.1, respectively;  $P < 0.01$ ). Although the improvements after the 30-min interval were greater than those after the 45-min interval, the differences were not statistically significant.

Electrical stimulation produced significant decreases in pain scores immediately after each treatment, with  $P < 0.05$  for the 15-min and  $P < 0.01$  for the 30- and 45-min stimulation intervals (table 1). Compared with the values 24 h after the completion of the sixth treatment with each method, mean (overall) percentage changes in the degree of pain, physical activity, and quality of sleep from the baseline values 24 h before starting each treatment block were statistically significant for the 15-min interval ( $P < 0.05$ ) and the 30- and 45-min stimulation

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Fig. 2. Comparison of the percentage improvements from the baseline (24 h before and after the first treatment session with each method) in the degree of pain, physical activity, and sleep quality at the end of each 2-week treatment period. Data are mean values  $\pm$  SEM. Significant differences compared with nonelectrical needle therapy values are designated as follows: \* $P < 0.05$ ; † $P < 0.01$ . Significant differences compared with 15-min values are designated by § $P < 0.05$ .



intervals ( $P < 0.01$ ) (fig. 2). In addition, there were significant differences between the 30- and 45-min treatment intervals compared with the 15-min treatment interval.

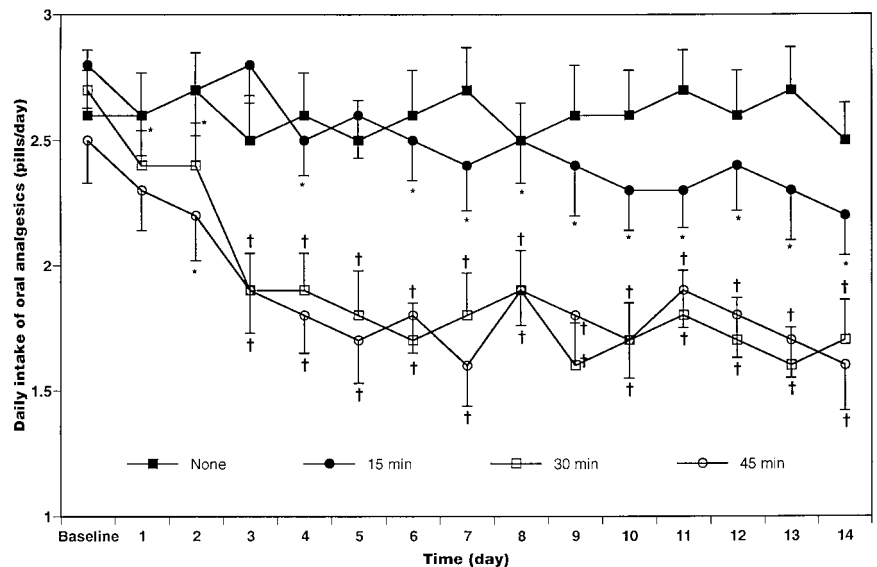
The daily requirements for oral nonopioid analgesic medications (pills per day) are summarized in figure 3. Compared with baseline values, the need for oral analgesic medications was decreased by an average of  $8 \pm 11\%$ ,  $21 \pm 13\%$ ,  $38 \pm 16\%$ , and  $35 \pm 17\%$  over the course of the 2-week treatment period for the 0-, 15-, 30-, and 45-min stimulation intervals, respectively. Compared with no electrical stimulation, it was found that a 15-min stimulation interval ( $P < 0.05$ ) and both the 30- and the 45-min stimulation intervals ( $P < 0.01$ ) were

more effective in decreasing the daily oral analgesic requirements. Moreover, the overall decrease in the daily oral analgesic requirements was greater with the 30- and 45-min (*vs.* 15-min) stimulation intervals ( $P < 0.05$ ).

Discussion

Preliminary studies with PENS therapy showed that this therapy produces short-term benefits in patients with chronic LBP secondary to osteoarthritis<sup>6</sup> and degenerative disk disease,<sup>8</sup> and acute herpes zoster pain.<sup>7</sup> This crossover study showed that the duration of electrical stimulation with PENS therapy influences the degree of

Fig. 3. Changes in the daily oral intake of nonopioid analgesic medications (pills per day) during the 2-week treatment period with each of the four methods. Data are mean values  $\pm$  SEM. Significant changes from the values 24 h before the first treatment (baseline) are indicated as follows: \* $P < 0.05$ ; † $P < 0.01$ .





acute pain relief and the improvement in function over a 2-week treatment period. Although there were no significant differences between the 30- and 45-min durations of electrical stimulation, both intervals were more effective than the 15-min interval and the no-electrical-stimulation ("sham") treatments. These data suggest that the recommended duration of electrical stimulation for PENS therapy should be 30 min because no additional benefit was achieved with a longer stimulation interval.

These findings are consistent with a study by Romita *et al.*<sup>12</sup> in rodents. Using a rat model to study electroacupuncture-induced analgesia, these investigators found that electrical stimulation for a period of 20 min elicited a greater and longer lasting antinociceptive effect than 10- or 40-min intervals of stimulation. Moreover, a study by Chung *et al.*<sup>13</sup> showed that a 5-min train of electrical stimulation elicited a poststimulation inhibition of spinothalamic tract cells lasting less than 2 min. If the same stimulus was maintained for 15 min, these investigators reported, the inhibition persisted for up to 30 min.<sup>14</sup> These data suggest that more prolonged stimulation may allow summation of central mechanisms, thereby producing a more persistent analgesic effect. However, with continuous electroacupuncture the evoked antinociceptive effect appears to gradually decrease as a function of the time of stimulation.<sup>15</sup> Although short-term electroacupuncture stimulation produces marked analgesic effects, prolonged electroacupuncture stimulation appears to result in the development of tolerance.<sup>16</sup> Other investigators also have reported that prolonged periods of electrical stimulation are associated with the development of tolerance to the electroanalgesic effect.<sup>17</sup>

It has been proposed that the accumulation of antiopioid substances within the central nervous system may account for the development of tolerance to electroacupuncture.<sup>18,19</sup> During prolonged electroacupuncture stimulation, release of endogenous opioids activates the cholecystokinin octapeptide system, which can counteract the analgesia produced by endogenous opioid substances. Moreover, electroacupuncture appears to enhance the release of endogenous orphanin FQ<sup>20</sup> in the brain, which can also antagonize electroacupuncture-induced analgesia. Therefore, orphanin FQ may play an important role in the development of tolerance to the analgesic effects of electrical stimulation.

In electroacupuncture studies, the effects of the duration of electrical stimulation on the analgesic response also have been reported to be highly variable. For example, it was found that 30 min of stimulation produced hypoalgesic effects lasting several hours,<sup>21-23</sup> whereas a

40-min period of stimulation produced analgesia lasting for only 30 min.<sup>24</sup> If the electrical stimulation was applied for 75 min, the duration of analgesia lasted for only 15 min<sup>24,25</sup> Consistent with these electroacupuncture studies, our data suggest that 30 min is the optimal stimulation interval for PENS therapy. The results of the SF-36 assessment further support this clinical finding by providing an additional outcome measure that shows the superiority of the 30-min electrical stimulation interval (*vs.* intervals  $\leq$  15 min). These data revealed that if PENS therapy was administered for 30 min at each treatment session, it was more effective in improving the physical (*e.g.*, fewer limitations in self-care, less severe body pains) and mental (*e.g.*, less psychologic distress, less disability resulting from emotional problems) health and well-being of patients with chronic LBP compared with shorter stimulation intervals.

The major limitations in the study design include (1) potential bias because of inability to "blind" the patient to the electrical stimulus, (2) the "placebo effect," resulting from placement of the needles, and (3) the failure to show a sustained analgesic effect after the PENS treatments, with the pain levels returning to baseline values within 1 week after discontinuing each method. Although the investigator collecting these data was blinded to the duration of the electrical stimulation, it was not possible to blind the patients. However, the patients were told that they "may or may not actually feel the stimulus" and they were not informed as to the duration of the electrical stimulation they received at each session. All treatment sessions lasted for 60 min. The placebo (analgesic) effect of the needles alone appeared to be very limited, consistent with previous studies involving PENS therapy.<sup>8,10</sup> Finally, the short-term analgesic effects of PENS are consistent with previous studies in this patient population.<sup>8,10</sup> Future studies need to evaluate the long-term effect of PENS therapy.

In conclusion, this study shows that the duration of electrical stimulation influences the short-term outcome with PENS therapy. Of the different durations of electrical stimulation studied, the 30-min interval appears to be the most suitable for this LBP patient population.

## References

1. Frymoyer JW: Back pain and sciatica. *N Engl J Med* 1988; 318: 291-300
2. Hadler NM: Workers with disabling back pain. *N Engl J Med* 1997; 337:341-3
3. Melzack R, Vetere P, Finch L: Transcutaneous electrical nerve

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stimulation for low back pain: A comparison of TENS and massage for pain and range of motion. *Phys Ther* 1983; 63:489-93

4. Liao SJ: Acupuncture for low back pain. *Acupunct Electrother Res* 1992; 17:249-58
5. Lehmann TR, Russell DW, Spratt KF, Colby H, Liu YK, Fairchild ML, Christensen S: Efficacy of electro-acupuncture and TENS in the rehabilitation of chronic back pain patients. *Pain* 1986; 26:277-90
6. Sun R, Kim DW, White PF, Craig WF, Taylor S, Handel D: A randomized comparison of non-pharmacologic therapies for the relief of chronic back pain (abstract). *Anesth Analg* 1997; 84:S339
7. Ahmed HE, Craig WF, White PF, Ghoname EA, Hamza MA, Gajraj NM, Taylor SM: Percutaneous electrical nerve stimulation: An alternative to antiviral drugs for acute herpes zoster. *Anesth Analg* 1998; 87:911-4
8. Ghoname EA, Craig WF, White PF, Ahmed HE, Hamza MA, Henderson BN, Gajraj NM, Huber PJ, Gatchel RJ: Percutaneous electrical nerve stimulation for low back pain: A randomized crossover study. *JAMA* 1999; 281:818-23
9. Ware JE, Sherbourne CD: The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992; 30:473-83
10. Ghoname EA, Craig WF, White PF, Ahmed HE, Hamza MA, Gajraj NM, Vakharia AS, Noe CE: Effect of stimulus frequency on the analgesic response to electrical stimulation in patients with chronic low back pain. *Anesth Analg* 1999; 88: 841-6
11. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A: Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: Summary of results from the Medical Outcomes Study. *Med Care* 1995; 33(suppl): AS264-79
12. Romita VV, Sul A, Henry JL: Parametric studies on electroacupuncture-like stimulation in a rat model: Effects of intensity, frequency, and duration of stimulation on evoked antinociception. *Brain Res Bul* 1997; 42:289-96
13. Chung JM, Lee KH, Hori Y, Endo K, Willis WD: Factors influencing peripheral nerve stimulation produced inhibition of primate spinothalamic tract cells. *Pain* 1984; 19:277-93
14. Chung JM, Fang ZR, Hori Y, Lee KH, Willis WD: Prolonged inhibition of primate spinothalamic tract cells by peripheral nerve stimulation. *Pain* 1984; 19:259-75
15. Chen XH, Han JS: Analgesia induced by electroacupuncture of different frequencies is mediated by different types of opioid receptors: Another cross-tolerance study. *Behav Brain Res* 1992; 47:143-9
16. Han JS, Li SJ, Tang J: Tolerance to electroacupuncture and its cross-tolerance to morphine. *Neuropharmacology* 1981; 20:593-6
17. Woolf CJ, Thompson JW: Stimulation-induced analgesia: Transcutaneous electrical nerve stimulation (TENS) and vibration, *Textbook of Pain*. Edited by Wall DD, Melzack R. New York, Churchill Livingstone, 1994, pp 1191-2008
18. Han JS, Tang J, Haung BS, Liang SL, Zhang NH: Acupuncture tolerance in rat: Antioioid substrates implicated. *Chin Med J* 1979; 92:625-7
19. Ungar G, Ungar AL, Malin DH, Sarantakis D: Brain peptides with opiate antagonistic action: Their possible role in tolerance and dependence. *Psychoneuroendocrinology* 1977; 2:1-10
20. Tian JH, Zhang Y, Xu W, Grandy DK, Han JS: Endogenous orphanin FQ: Evidence for a role on the modulation of electroacupuncture analgesia and the development of tolerance to analgesia produced by morphine and electroacupuncture. *Br J Pharm* 1998; 124:21-6
21. Fox JE, Melzack R: Transcutaneous electrical stimulation and acupuncture: Comparison of treatment for low-back pain. *Pain* 1976; 2:141-8
22. Mannheimer C, Carlsson CL: The analgesic effect of transcutaneous electrical nerve stimulation (TENS) in patients with rheumatoid arthritis: A comparative study of different pulse patterns. *Pain* 1979; 6:329-34
23. Melzack R: Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. *Pain* 1975; 1:357-73
24. Andersson SA, Ericson T, Holmgren E, Lindquist G: Electroacupuncture: Effects on pain threshold measured with electrical stimulation of teeth. *Brain Res* 1973; 63:393-6
25. Andersson SA, Holmgren E: On acupuncture analgesia and the mechanism of pain. *Am J Chin Med* 1975; 3:311-34