



## EFFECT OF ACUPUNCTURE ON SENSORY UREMIA NEUROPATHY IN HEMODIALYSIS PATIENTS

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### ABSTRACT

Background: Hemodialysis is a most common treatment option available for chronic kidney disease patients. End-stage renal disease is known to be related with peripheral neuropathy that includes different presentations such as sensory symptoms. Because of limited and indefinite therapeutic methods, this study was done by the aim of evaluating the effect of acupuncture on sensory uremia neuropathy in hemodialysis patients. Methods: This multi centered randomized clinical trial was conducted during 2015 – 2017 in hemodialysis wards of academic hospitals, Mashhad – Iran. 30 patients that met inclusion criteria were entered the study by convenience sampling and were randomized in two groups, one group was acupuncture intervention and the other was control group received sham acupuncture. We measured VAS score of neuropathy before and after intervention in 2 groups. Results: The mean age of participants was  $49.04 \pm 14.93$  with a minimum age of 23 years and maximum age of 65 years and 17 (65.40%) patients were male and 9 (34.60%) patients were female. we had significant difference after and before in both control and intervention group but the difference score in intervention group was more significant than control group (4.40 versus 1.09). Our study also showed significant differences between two groups after intervention (p-value = 0.007). Conclusion: Our findings indicate that acupuncture as a safe and easy treatment can be a useful and effective option for management of HD patients with sensory neuropathy. Identifying exact neurobiological mechanism of acupuncture to reduce symptoms will remarkably improve the application of new therapies to decrease neuropathy symptoms.

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### Introduction

Chronic kidney disease (CKD) is a worldwide growing public health disease with considerable increasing prevalence, incidence, morbidity and mortality [1, 2]. The mean global prevalence of CKD was 13.4% [3] and the age adjusted prevalence of CKD, stages 3 to 5, in Iran was 14.9% [1].

CKD has different symptoms that commonly include pain, peripheral numbness, fatigue, pruritus, sleep disturbances, depression, sexual dysfunction, nausea and vomiting. Result of these symptoms will be poor quality of life, increased mortality and hospitalization in patients with CKD who are on dialysis [4-6].

Hemodialysis (HD) is a most common treatment option available for CKD patients [7]. End-stage renal disease (ESRD) is known to be related with peripheral neuropathy. Neuropathy in ESRD is defined as a distal symmetrical length-dependent, sensorimotor polyneuropathy. Uremic neuropathy is common among dialysis and no dialysis CKD patients. The prevalence

rate of electrophysiological signs of impaired nerve function was estimated between 60 to 100% in hemodialysis patients, although a lower percentage of them are symptomatic [8, 9]. Recent studies showed that recovery of uremic neuropathy with dialysis is uncommon. Despite the great effort done in this era, the pathophysiology of uremic neuropathy has not been determined yet and just two main hypotheses was proposed: retention of neurotoxic molecules and hyperkalemia [10-14].

Uremic neuropathy present with sensory symptoms including the distal aspect of the lower extremities at first. Early sensory symptoms consist of paresthesia such as tingling or prickling, burning pain and numbness [15]. One of the most common neuropathy symptoms in patients with ESRD is pain with prevalence rate of 50% in hemodialysis patients. Main sources of pain are peripheral neuropathy, musculoskeletal disorders and serious limb ischemia [16].

Proper clinical management has a major role in the optimal care of CKD patients due to the negative effect of untreated or insufficiently treated symptoms [16].

Recently because of adverse effect of most pharmacological interventions and high demand for nonpharmacological approaches, Complementary and alternative medicine (CAM) is being increasingly administered in the treatment of chronic diseases and in other palliative care settings. Yet, further research is required to confirm the efficacy and safety of acupuncture in CKD. Using antiepileptic and tricyclic antidepressant drugs as conventional treatment of neuropathic pain is common, but overall, treatment for decreased other symptom of sensory neuropathy is unsuccessful [17]. Acupuncture is a complex treatment method that originated from East Asian countries and refers to the insertion of needles into specific points on the skin for therapeutic purposes [18]. In CKD, acupuncture has been used to treat different clinical symptoms such as pruritus [19, 20]. Acupuncture points' stimulation can positively affect the circulation of vital energy in the body, while an increase in the opioids blood concentration, including endorphin and enkephalin, may lead to the reduction of fatigue, sensory, cognitive, and emotional dimensions in such patients [5]. Moreover, it may increase the release of serotonin, a hormone that induces relaxation, and therefore could induce sleep and relieve fatigue [16]. To the knowledge of the author, until now no study has been done to evaluate the effect of acupuncture on sensory uremia neuropathy in hemodialysis patients so that we decided to do a study with this aim.

#### **Materials and Methods:**

This multi-centered pilot randomized clinical trial was conducted during 2015 – 2017 in hemodialysis wards of academic hospitals, Mashhad, Iran and compared one acupuncture intervention group with one sham acupuncture control group. 30 patients that met inclusion criteria were entered the study by convenience sampling and were randomized in two groups, one group was acupuncture intervention and the other was control group received sham acupuncture. Allocation concealment was adopted by using sequentially numbered, sealed, opaque envelopes matched for equal size and shape. Both randomization and concealment procedure was done by person who was not concerned with current trial or in management of recruited patients. Inclusion criteria was restricted to; 1: Patients who were dialysis three times a week; 2: older than 18 years and less than 65 years; 3: having been on hemodialysis treatment for at least 6 months; 4: their visual analogue scale (VAS) for sensory neuropathy were at least 4 score; 5: being able to answer questions and 6: consent to participate in our study. Exclusion criteria included: 1: psychiatric disease, liver disease, cancer or disease of the soft tissue or vessels at the extremities; 2: having current infections; 3: having coagulopathy disorders 5. history of using any anti-coagulant drugs. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences and it was performed in accordance to the principles of the Declaration of Helsinki (Version Edinburgh 2000). In addition, a written informed consent was signed by all participants prior to study entrance.

To the authors' knowledge, no clinical trials have yet been performed to evaluate the effect of acupuncture on the treatment of sensory neuropathy in hemodialysis patients. A formal power calculation was not done and we carried out a pilot study. The sample size was 15 per group with a total number of 30 participants, given a possible dropout rate of 20%. This sample size is regarded as the minimum number per group to be considered for pilot studies.

During the study, patients in all the involved hemodialysis wards, were under the usual treatment and care, and no changes were made to the working operations of these wards and we prescribed 200 mg oral gabapentin daily for all the patients in two groups for 6 weeks and referred them to acupuncture clinic of Imam Reza hospital.

We considered subjective sensory neuropathy as loss of sensation (numbness), altered sensation to touch (hyperpathia or allodynia), or uncomfortable spontaneous sensations (tingling, burning or aching) and neuropathic pain that could be burning and dull.

At first we measured VAS score of sensory neuropathy in all patients for entering the trial and then completing the collecting form which included the demographic characteristics (age, sex, occupation, educational level, marriage status) and possible related factors such as dialysis duration. At the end of trial period we again measured VAS score of neuropathy.

For the acupuncture intervention, the specialist of acupuncture who trained in Beijing university of Chinese medicine inserted needles in acupoints by using his fingertips, applying a consistent pressure on the correct acupoint with small rotational movements. Treatment was carried out with the patient lying in the supine position for 30 minutes

The body needling depth was decided based on the location of the acupoints and the patient's body build (10–30 mm). Sensations that a patient experienced during a correctly acupuncture were heaviness or numbness or soreness.

The sham-acupuncture group received the same sessions with same duration of minimal acupuncture by the same physician over 6 weeks. Needles were not stimulated and were inserted superficially, 1 cm distant to the corresponding acupuncture point, outside the meridians.

Acupuncture points of interest were chosen based on the patients' demographic data and the available references; they included Sp6, Sp10, Lv3, Li4 and Li11.

Sensory neuropathy intensity will be assessed using the VAS score as the primary outcome. VAS is an 11-point scale which is scored from 0 to 10; 0 stands for an absence of neuropathy whereas 10 corresponds to maximum neuropathy. The patient will be asked to define mean level of their intense neuropathy.

SPSS software ver. 22 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. For describing the distribution pattern of the data, standard descriptive statistics were used. Normality of the data was determined by the Kolmogorov–Smirnov test. Independent t test and paired t test were applied to compare numerical data with normal distribution between the two groups and pre- and post-intervention, respectively. Chi-square test and Fisher's exact test were used to assess the association significance between the categorical data. Covariance analysis was used to assess the effect of confounder factors on neuropathy intensity. All tests were 2-tailed, and the significance level was set at  $P < 0.05$ .

**Results:**

We had 30 patients in our study who randomly allocated to one of two groups according to inclusion and exclusion criteria (15 patients in per group). Finally, we analyzed 26 participants in our research (15 in acupuncture and 11 in sham acupuncture group). 4 patients in sham acupuncture group could not be included in the analysis because of refusing to continue the study. The data showed that the mean age of participants was  $49.04 \pm 14.93$  with a minimum age of 23 years and maximum age of 65 years and 17 (65.40%) patients were male and 9 (34.60%) patients were female. Table 1 summarizes the patients' characteristics. Except for age, there were no significant differences between two groups in other characteristics; because of this we carried out covariance analysis to assess effect of age on treatment response.

**Table 1:** Basic characteristics of participants in the intervention and control group

Characteristic		Intervention group (Acupuncture) N (%)	Control group (Sham acupuncture) N (%)	P - value
Age (mean ± standard deviation)		54.67±11.40	41.36±16.21	0.03
Sex	Male	9 (60)	8 (72.70)	0.68
	Female	6 (40)	3 (27.30)	
Educational level	illiterate	3 (20)	3 (27.40)	0.30
	Non academic	10 (66.70)	4 (36.30)	
	academic	2 (13.30)	4 (36.30)	
Occupation	Unemployed	2 (13.30)	5 (45.40)	0.37
	Employed	4 (26.70)	0	
	retired	5 (33.30)	2 (18.20)	
	housewife	4 (26.70)	2 (18.20)	
Marital status	Single	1 (6.70)	5 (45.50)	0.05
	married	14 (93.30)	6 (54.50)	
Dialysis Duration (year)	≤ 1	5 (33.30)	5 (45.50)	0.85
	> 1 & ≤ 5	8 (53.30)	5 (45.50)	
	> 5	2 (13.30)	1 (9.10)	

No statistically significant difference was achieved before the intervention in the intensity of neuropathy between the acupuncture and sham acupuncture groups ( $P$ -value=0.33). VAS score of neuropathy before and after the intervention was depicted in table 2. Our study showed significant differences between two groups after intervention ( $P$ -value=0.007). As shown in table 2 we had also significant difference after and before in control group but the difference score in intervention group was more significant than control group (4.40 versus 1.09).

**Table 2:** Neuropathy score before and after intervention in the two groups

Group		Intensity of pruritus(VAS score)	P - value	
Intervention	Before	8.27 ± 1.44	< 0.001	0.007
	After	4.13 ± 2.56		
Control	Before	7.73 ± 1.27	0.006	
	after	6.64 ± 1.29		

After covariance analysis, we found that age of participants doesn't have any effect on intensity of neuropathy and treatment response but variables of sex and initial score of neuropathy have significant effect on treatment response. Patients with

duration dialysis less than one year had higher intensity of neuropathy and also neuropathy score was higher than in female than male (table 3).

**Table 3:** Covariance analysis of patients before and after the intervention

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Intercept	-1.804	2.964	-.609	.550	-8.008	4.400
group=intervention	-3.324	.825	-4.030	.001	-5.051	-1.598
group=control	0 <sup>a</sup>	.	.	.	.	.
Dialysis Duration≤ 1	3.095	1.346	2.300	.033	.278	5.912
1<Dialysis Duration≤5	2.088	1.281	1.630	.120	-.593	4.769
Dialysis Duration>5	0 <sup>a</sup>	.	.	.	.	.
Sex= male	-2.189	.948	-2.309	.032	-4.172	-.205
Sex= female	0 <sup>a</sup>	.	.	.	.	.
Initial neuropathy severity	.881	.323	2.727	.013	.205	1.558
Age	.021	.030	.702	.491	-.041	.083

**Discussion:**

The second main cause of frequent metabolic neuropathy is Uremia. It has been shown that 60 to 100% of dialysis patients undergo neuropathic symptoms. Given the selected diagnostic approach these rates can be different [21]. Despite that WHO has classified peripheral neuropathy (PN) as a disease which can be effectively treated by acupuncture, there are still very little data on PN and acupuncture [17]. To the knowledge of the author, so far no study has been done to evaluate the effect of acupuncture on sensory uremia neuropathy in hemodialysis patients; only few researches have been performed mainly focused on subjective parameters' evaluation and PN treatment by acupuncture.

The results of this pilot study showed that there were statistically significant differences in severity of neuropathy between the intervention and control groups and reduction in the intensity of neuropathy after treatment in the acupuncture group were significantly higher than the control group. Alleviated of neuropathy in control group may be because of gabapentin effect.

In the study by Schröder et al. on 46 diabetic patients with PN considerable improvement in symptoms were reported in 34 cases after six courses of acupuncture treatment while further sessions were needed in only 8 of them. Nevertheless, complete relief of symptoms was reported by 7 of the 34 patients [17].

In a larger survey including 250 patients with HIV-related peripheral neuropathy, the effects of acupuncture, amitriptyline, and placebo were compared. Patients were assigned to receive acupuncture at standardized acupuncture points or at placebo points, or amitriptyline or a placebo. No remarkable difference in pain relief was reported between the real treatments and the placebos. All studied cases received the same treatment as the acupoints studied in this survey were standardized. Acupuncture treatments can be adjusted to fit each individual, and as the study concluded, individualized treatments may have more desirable outcomes [22].

In a clinical trial of 64 patients with PN due to the use of Paclitaxel or Oxaliplatin, acupuncture was more effective than cobamamide therapy in treating peripheral neuropathy after chemotherapy. The effective rate for sensory neural disorders in the acupuncture group was 66.7%, which was higher than 40% in the medication group. Acupuncture was especially effective for moderate to severe neuromuscular disorders caused by Paclitaxel [23].

In a study on pain management, 30 CKD patients aged 35 to 45 years, divided into two equal groups. One group treated with acupuncture combined with medical treatment and the other group only received medication treatment. A significant reduction pain was seen in the acupuncture group [24].

A meta-analysis that examines the treatment of chronic pain using acupuncture in comparison with sham acupuncture or no-acupuncture has shown that acupuncture treatment has significantly better results compared to the other two groups [25].

Several studies in animal models on diabetic neuropathy have revealed the efficacy of electro acupuncture in the control of neuropathic pain and functional deficits [26].

For control of pain symptom in PN, Different human and animal studies have investigated the neurochemical basis of acupuncture. There is no single theory that completely illustrates all the possible effects of acupuncture; however, the mechanisms can to some extent be explained with respect to endogenous pain inhibitory systems.

According to recent studies, release of macrophage (MQ) tumor necrosis factor (TNF), IL-1 $\beta$ , IL-6, and IL-18, could be strikingly limited by vagus nerve stimulation, acting through  $\alpha 7$  receptors which in turn reduces systemic inflammatory responses. The aforementioned results could pave the way to answer some unexplained effects of acupuncture/acupressure.

Acupuncture might be involved in pain alleviation through a physiological mechanism leading to anti-inflammatory effects as pain is associated with acute and chronic inflammation in numerous occasions. An increase in parasympathetic nerve stimulation along with a decrease in pro-inflammatory cytokines has also been proposed in this respect [16, 27-30].

Both peripheral and central nervous systems can be activated through acupuncture by stimulating receptors or producing rhythmic discharges in nerve fibers and a final release of different neurotransmitters by [31].

Serotonergic paths have been involved to reduce pain and difficulties in neuropathy [32]. Accordingly, another suggested hypothesis is the synergistic effect of acupuncture and serotonergic therapy in decreasing neuropathic pain.

Increasing blood flow has been suggested as the role of acupuncture in the extremities by Litscher et al. This increased flow to the vasa nervosa and dependent capillary beds nourishing the neurons maybe beneficial in repairing the nerves with remarkable improvement of axons or myelin sheaths. Moreover, the symptomatic effect of acupuncture can cause morphological changes in the peripheral nerves' anatomy besides complex derangements of central and peripheral regulation [31-34].

The main limitations of the current study were the small sample size and our study did not examine the laboratory findings to detect changing in pruritus score and it was based on subjective findings.

### **Conclusion:**

Our findings showed that acupuncture can be an effective, safe and easy method on sensory neuropathy control in hemodialysis patients through decrease intensity of neuropathy symptom. Identifying exact neurobiological mechanism of acupuncture to reduce symptoms will remarkably improve the application of new therapies to decrease neuropathy symptom. Future studies with larger sample size and objective measurements is recommended to generalize findings.

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### **References**

1. Hosseinpanah F, Kasraei F, Nassiri A.A, Azizi F. High prevalence of chronic kidney disease in Iran: a large population-based study. *BMC Public Health*. 2009; 9:44-52. doi: 10.1186/1471-2458-9-44
2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298(17):2038–2047. DOI: 10.1001/jama.298.17.2038
3. Hill NR, Fatoba ST, OkeJL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease– a systematic review and meta-analysis. *PLoS One*.2016; 1-18. doi: 10.1371/journal.pone.0158765
4. Flaws B, Sionneau P. The treatment of modern western medical diseases with Chinese medicine: a textbook & clinical manual. 2nd ed. Boulder: Blue Poppy Press; 2005.
5. Obaya HE, Khalek MM. Effect of laser acupuncture on hemodialysis male patient. *Int J Ther Rehabil Res*. 2016; 5(4):278-83. doi: 10.5455/ijtr.000000176
6. Barden SK. Managing chronic kidney disease and chemotherapy-induced peripheral neuropathy with acupuncture and herbal medicine: a case study. *J Acupunct Meridian Stud*. 2017; 10(2):139-42. DOI: 10.1016/j.jams.2017.01.001
7. Harwood L, Wilson B, Locking-Cusolito H, Sontrop J, Spittal J. Stressors and coping in individuals with chronic kidney disease. *Nephrol Nurs J*. 2009; 36(3):265-75.
8. Krishnan AV, Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. *Muscle and Nerve*. 2007; 35(3):273–90. DOI: 10.1016/j.jams.2017.01.001
9. Nielsen VK. The peripheral nerve function in chronic renal failure. *Acta Med Scand*. 1971; 190(1-6):105–11. DOI: 10.1111/j.0954-6820.1971.tb07401.x
10. Babb AL, Ahmad S, Bergström J, Scribner BH. The middle molecule hypothesis in perspective. *Am J Kidney Dis*. 1981; 1(1):46–50.
11. Vanholder R, De Smet R, Hsu C, Vogeleere P, Ringoir S. Uremic toxicity: the middle molecule hypothesis revisited. *Seminars Nephrol*. 1994; 14(3):205–18.
12. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. *Brain*. 2005; 128(9):2164–74. DOI: 10.1093/brain/awh558
13. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Kiernan MC. Sensory nerve excitability and neuropathy in end stage kidney disease. *J Neurol Neurosurg Psych*. 2006; 77(4):548–51. DOI: 10.1136/jnnp.2005.079988
14. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Neuropathy, axonal Na<sup>+</sup>/K<sup>+</sup> pump function and activity-dependent excitability changes in end-stage kidney disease. *Clin Neurophysiol*. 2006; 117(5):992–9. DOI: 10.1016/j.clinph.2006.02.002

15. Raskin NH, Fishman RA. Neurologic disorders in renal failure. *N Engl J Med.* 1976; 294:143.
16. Garcia GE, Ma SX, Feng L. Acupuncture and Kidney Disease. *Adv Chronic Kidney Dis.* 2005; 12(3):282-91.
17. Schröder S, Liepert J, Remppis A, Greten JH. Acupuncture treatment improves nerve conduction in peripheral neuropathy. *Eur J Neurol.* 2007; 14(3):276-81. DOI: 10.1111/j.1468-1331.2006.01632.x
18. Kim KH, Lee MS, Kim TH, Kang JW, Choi TY, Lee JD. Acupuncture and related interventions for the symptoms of chronic kidney disease. Lee JD, editor. *Cochrane Database of Systematic Reviews [Internet].* John Wiley & Sons, Ltd; 2011 Nov 9; DOI: 10.1002/14651858.CD009440.pub2
19. Yu Ch, Zhang P, Lv ZT, Li JJ, Li HP, Wu CH. Efficacy of acupuncture in itch: a systematic review and meta-analysis of clinical randomized controlled trials. *EvidBased Complement Alternative Med.* 2015; 2015:208690. DOI: 10.1155/2015/208690
20. Kim KH, Lee MS, Choi SM, Ernst E. Acupuncture for treating uremic pruritus in patients with end-stage renal disease: a systematic review. *J Pain Symptom Manag* 2010; 40(1):117-25.
21. Ramírez BV, Bustamante Gómez PA. Uremic neuropathy: a review. *IntJ Gene Mol Biol.* 2012; 3(11):155-60. DOI: 10.5897/IJGMB11.022
22. Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. *Terry Beinr Community Programs for Clinical Research on AIDS. JAMA.* 1998; 280(18):1590-5.
23. Xu WR, Hua BJ, Hou W, Bao YJ. Clinical randomized controlled study on acupuncture for treatment of peripheral neuropathy induced by chemotherapeutic drugs. *Chinese Acupunct Moxibustion.* 2010; 30(6):457-60.
24. Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat Rev Neurosci.* 2006; 7:535. DOI: 10.1038/nrn1950
25. Shirazian Sh, Aina O, Park Y, Chowdhury N, Leger K, Hou L, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis.* 2017; 10:11–26. DOI: 10.2147/IJNRD.S108045
26. Lee S, Kim JH, Shin KM, Kim JE, Kim TH, Kang KW, et al. Electro acupuncture to treat painful diabetic neuropathy: study protocol for a three-armed, randomized, controlled pilot trial. *Trials.* 2013; 14:225-36. DOI: 10.1186/1745-6215-14-225
27. Borovikova LV, Ivanova S, Zhang M, Yang H. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature.* 2000; 405:458-62. DOI: 10.1038/35013070
28. Tracey KJ. The inflammatory reflex. *Nature* 2002; 420:853-859. DOI: 10.1038/nature01321
29. Wang H, Yu M, Ochani M. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature.* 2003; 421:384-8. DOI: 10.1038/nature01339
30. Son YS, Park HJ, Kwon OB, Jung SC, Shin HC, Lim S. Antipyretic effects of acupuncture on the lipopolysaccharide-induced fever and expression of interleukin-6 and interleukin-1 beta mRNAs in the hypothalamus of rats. *Neurosci Lett.* 2002; 319:45-8.
31. Ogawa K, Ogawa M, Nishijima K, Tsuda M, Nishimura G. Efficacy of contact needle therapy for chemotherapy-induced peripheral neuropathy. *Evid Based Complement Alternat Med.* 2013; 2013:928129. DOI: 10.1155/2013/928129
32. Goodnick PJ, Breakstone K, Wen XL, Kumar A. Acupuncture and neuropathy. *Am J Psych.* 2000; 157(8):1342.
33. Litscher G, Wang L, HuberE, NilssonG. Changed skinblood perfusion in the fingertip following acupuncture needle introduction as evaluated by laser Doppler perfusion imaging. *Lasers Med Sci.*2002; 17(1):19–25. DOI: 10.1007/s101030200005
34. MaS, Cornford ME, VahabnezhadI, WeiS, LiX. Responses of nitric oxide synthase expression in the gracile nucleus to sciatic nerve injury in young and aged rats. *Brain Res.* 2000; 855(1):124–31.