Effects of acupuncture on uremic pruritus in patients undergoing hemodialysis

FA Phan¹, A Srilestari¹, H Mihardja*¹ and MBH Marbun²

¹Medical Acupuncture Department, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia
²Hypertension and Kidney Division of Internal Medicine Department, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia

*E-mail: hasanmihardja@gmail.com

Abstract. Uremic pruritus is a problem in patients undergoing hemodialysis because it reduces their quality of life. Even with several advancements in dialysis techniques, recent therapies do not provide optimum results. Acupuncture is a complementary therapy to alleviate the symptoms of uremic pruritus in patients undergoing hemodialysis. This study identified the effects of acupuncture therapy in patients undergoing hemodialysis. Thirty-seven patients with uremic pruritus undergoing hemodialysis were randomly divided into two groups: acupuncture group (n=18), who received acupuncture treatment at a single point (LI11 Quchi), and control group (n=19), who received acupuncture treatment using a placebo needle (the Park Sham Device). This was performed simultaneously with hemodialysis therapy twice a week for 12 times. Pruritus scores were assessed using 5D pruritus questionnaire before treatment; after the 4th, 8th, and 12th acupuncture treatment; and at 4 and 8 weeks follow-up. Significant differences were observed in the 5D pruritus scores of the acupuncture and control groups after the end of acupuncture treatment (7.89±0.832 vs 10.63±3.166; p=0.003) and at 4 weeks follow-up (8.06±1.830 vs. 10.95±3.341; p=0.001). Acupuncture treatment is effective in lowering the pruritus score of patients with uremic pruritus undergoing hemodialysis twice a week.

1. Introduction

Uremic pruritus, or more commonly known as pruritus, that is associated with chronic kidney disease is a frequent and troublesome symptom in patients with advanced or terminal renal failure, which significantly reduces the quality of life [1]. Approximately 40% of patients with chronic pruritus undergoing hemodialysis complain of pruritus in their whole body. The 6th Annual Indonesian Renal Registry report in 2013 presented that the number of individuals with itchiness undergoing hemodialysis was 2,493. Uremic pruritus is difficult to control, and the choice of therapy is limited. The therapies for uremic pruritus include topical therapy, gabapentin, systemic therapy with opioid receptor μ and opioid κ agonist receptor, drugs with anti-inflammatory effects, phototherapy, acupuncture, and others [1]. Medical treatment for uremic pruritus may result in the use of antihistamines, which can cause drowsiness, sedation, and decreased motor activities [2], and patients undergoing hemodialysis should pay attention to potential side effects [3], such as neurotoxicity, insulin-dependent diabetes mellitus, nephrotoxicity, gastrointestinal toxicity, and cardiomyopathy, when using immunosuppressive agents [4].
Kim et al. conducted a systematic review on the effects of acupuncture on uremic pruritus. All the studies (six studies) included in this systematic review showing the beneficial effects of acupuncture, although there was still a risk for bias [5]. In a study by Gao et al using LI11 Quchi and ST36 Zusanli points, 70.6% of the patients who underwent acupuncture therapy recovered without itching for a month, and the condition of approximately 26.5% of the patients was improving. Thus, the efficacy rate reached 97% [6]. Shapiro et al. have used LI11 Quchi, ST36 Zusanli, SP6 Sanyinjiao, and SP10 Xuehai points, and they were effective against uremic pruritus [7,8]. Kılıç Akça et al. have stated that acupressure reduces the intensity of pruritus when used as a single therapy or when combined with pharmacologic therapy [9]. In a study by Che yi et al., acupuncture at one-sided LI11 Quchi points thrice a week for 1 month significantly decreased the pruritis score of patients undergoing hemodialysis thrice a week [8].

Pruritus or itchiness can be classified into pruriceptive, neuropathic, neurogenic, and psychogenic [10]. Mettang et al. have stated that the pathogenesis of uremic pruritus remains unclear, and this condition is activated by the combination of pruritogens, neuropathic dysregulations, and microinflammation; particularly the micro-inflammatory process, because of an increase in the levels of C-reactive protein, Th1 proinflammatory cells, and interleukin (IL)-6 [1]. Acupuncture has anti-inflammatory effects resulting in Th1 and Th2 balance, as explained by Zijlstra et al [9]. Th1 and Th2 balance is affected by β-endorphins released during acupuncture [11]. Acupuncture has a similar anti-inflammatory effect as dexamethasone. Dexamethasone decrease levels of pro-inflammatory cytokines without interfering with levels of anti-inflammatory cytokines while acupuncture doesn’t decrease levels of pro-inflammatory cytokines but increase levels of anti-inflammatory cytokines [12]. Acupuncture does not weaken the immune system. The identification of pruritus was based on a 5D scale (degree, duration, direction, disability, and distribution) [13], as used by the Department of Skin and Venerable Diseases, Faculty of Medicine, Universitas Indonesia.

This study aimed to identify the effects of acupuncture therapy on uremic pruritus, which is performed simultaneously with the patient’s hemodialysis therapy twice a week. Moreover, improvements in the patient’s adherence to both hemodialysis and acupuncture therapy were also assessed. This study used the Park Sham Device in the placebo acupuncture group to perform the procedure that is free of punctures [14]. This was done to prevent a controversial result due to sham acupuncture wherein the punctures have physiological effects [15]. Moffet has performed a systematic review of 38 clinical trials that used sham points with needle insertion in the control group. In 58% (22 of 38 clinical trials) of the patients, the results did not statistically differ, and in 59% (13 of 22 clinical trials) of the participants, sham acupuncture was as effective as the real acupuncture therapy [16]. The results of the present study may contribute to the management of uremic pruritus in patients undergoing hemodialysis. Acupuncture therapy is highly appropriate in patients with kidney disorders because they cannot use substances that may worsen the kidney function.

2. Methods
The study was a double-blinded randomized clinical trial with controls. Both participants and independent evaluators did not know the allocation of research participants to the treatment and control groups. The participants of this study included patients undergoing hemodialysis in Cipto Mangunkusumo General Hospital from February 2015 to May 2015. Patients aged 15–64 years who were undergoing hemodialysis twice a week for at least 6 months, presented with pruritus as assessed using the 5D pruritus questionnaire, had stable hemodynamics, had never been acupuncture, and were willing to follow the study protocol by signing an informed consent were included in the study. However, those who did not present with any primary skin disease, cholestatic liver disease, and malignancy and those who did not use opioid or corticosteroid drugs were excluded from the study.

The participants were classified into the control and treatment groups. The treatment group received acupuncture therapy with the needle verum at the LI11 Quchi point for 1 h while on hemodialysis. The therapy was performed twice a week for 12 times. Meanwhile, the control group used the placebo needle (the Park Sham Device). The participants were dropped out if they have not
been acupunctured for two consecutive times [17] or if they refused to continue participating in the study.

The sample size was calculated, in addition, 17 individuals were included per group by taking the drop out risk set of 10% in each group, and the required number of participants was 19. The participants were selected via simple random sampling using randomized tables after a survey to assess whether they met the inclusion criteria.

Pruritus uremic was assessed using the 5D pruritus questionnaire by an independent evaluator, and the assessment was performed before acupuncture therapy; after the 4th, 8th, and 12th therapy; and at 4th and 8th week follow-up.

Data analysis using statistical test depended on the variables that were analyzed. The comparative hypothesis test of numerical variables with normal distribution and paired group (for intra-group analysis) used paired t-test. If the data distribution was not normal, the Wilcoxon test was used. Unpaired t-test was used for the comparative hypothesis test of numerical variables in data with normal distribution between the two unpaired groups (for inter-group analysis). If the data distribution was not normal, Mann–Whitney U-test was used. If the comparative hypothesis test of p>α (p>0.05) could be interpreted, it was considered there is no significant difference between the variables; if the value of p<α (p<0.05), it was considered that there is a significant difference between the variables. The Statistical Package for Social Sciences software version 20 was used for all the analyses.

This research was approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital on January 12, 2015 (approval number: 38 / UN2.F1 / ETIK / 2014), and the research and data retrieval was also approved by the director of Cipto Mangunkusumo Hospital. A written informed consent was obtained from the participants.

3. Results
Initially, 38 participants were included in the study; however, only 37 successfully completed the study because one participant from the acupuncture group refused to continue participating in the study due to unexplained reasons (uncooperative participant).

The characteristics of the participants are shown in Tables 1 and 2.

**Table 1. Characteristics of the participants.**

| Characteristics      | Acupuncture | Placebo | p value |
|----------------------|-------------|---------|---------|
|                      | n | %   | N | %   |       |
| Sex                  |   |     |   |     |       |
| Male                 | 10 | 55.6 | 11 | 57.9 | 0.886*|
| Female               | 8  | 44.4 | 8  | 42.1 |       |
| Education            |   |     |   |     |       |
| Primary and middle school | 13 | 72.2 | 13 | 68.4 | 0.800*|
| High school          | 5  | 27.8 | 6  | 31.6 |       |

*Χ²test

**Table 2. Age of the participants and duration of hemodialysis.**

| Characteristics          | Acupuncture | Placebo | p value |
|--------------------------|-------------|---------|---------|
|                         | Mean (SD)   | Median (min–max) | Mean (SD)   | Median (min–max) |       |
| Age (y)                  | 45.72±10.075 | 44.50 (31–64)     | 48.37±10.807 | 50 (29–64)       | 0.447**|
| Duration of hemodialysis (y) | 4.78±3.353  | 4.50 (1–12)       | 6±4.497      | 6.00 (1–17)      | 0.425***|

**Unpaired t-test, ***Mann–Whitney test
As shown in Table 3, statistically significant differences were observed between the treatment and control groups in terms of the scores after completing the intervention (12× acupuncture therapy) and follow-up observation 4 weeks after acupuncture therapy.

In this study, acupuncture was performed 216 times (12× in 18 patients) in patients undergoing hemodialysis who received heparin. Bleeding was observed in 13 (6.02%) patients after the needle was removed from the spot, and the bleeding was mild, which could be controlled with the use of cotton and the application of pressure. No serious cases of bleeding occurred. Hematoma, which occurred after bleeding, was observed in four (1.85%) patients. However, the hematoma disappeared without any therapy within 3–10 days. No patients who underwent acupuncture therapy complained of pain. Syncope, infection in the punctured area, nerve trauma, and side effects of acupuncture were not observed in any patient.

4. Discussion
Research on the effect of acupuncture therapy on uremic pruritus in patients undergoing hemodialysis, and the study participants who met the inclusion criteria were included in the analysis and were randomly divided into two groups using a random table. The selection of participants and placements in the randomized groups showed optimal results based on the statistical analysis of the characteristics of the participants (sex, education, age, and duration of hemodialysis), and the initial 5D pruritus uremic score was not statistically different.

The 5D uremic pruritus score significantly differed at the end of therapy (12×) (p=0.003) and 4 weeks of follow-up observation (p=0.001), and these results were consistent with those of Che yi et al. [8], Gao et al. [6], and Kiliç Akça et al. [9], which showed that acupuncture reduces the complications from pruritus in patients, which is proven by the decrease in uremic pruritus score. These results were different from those of Che yi et al. [8], which showed that the benefits of acupuncture therapy in decreasing the uremic pruritus score only lasted for 4 weeks. However, in a study by Che yi et al. [8], the benefit could last for up to 3 months, even though the acupuncture points and the duration of acupuncture were the same. These differences may have been caused by stimulation factors. In the present study, the Park Sham Device needle was used in the placebo group and the verum needle was used in the acupuncture group because this needle holder was difficult to gain de qi by only tapping the needle, which is also similar in the study by Che yi et al [8].

According to Yang et al., de qi was the primary mechanism associated with the acupuncture effects. It releases beta-endorphins from the spine and supra spine, thereby releasing proinflammatory...
neuropeptides and increasing the peripheral circulation, even though there are conflicting evidence on the use of Japanese-type and wrist–ankle acupuncture (WAA, wrist–ankle acupuncture) in clinical settings [18]. A systematic review by Zhang et al. has shown that the present evidence is not sufficient to support the conclusions about the clinical benefits of de qi, although in several studies de qi is related to clinical effectiveness. However, the evidence has low quality [19]. The patter in uremic pruritus score is similar to that by Kiliç Akça et al. [9], in which the score was not significantly different at the beginning of the study, then became significantly different between the two groups, and finally did not differ significantly. This result is attributed to the fact that uremic pruritus is not a usual complaint because sometimes it appears and then disappears [20]. The advantages of the present study compared with that of Kiliç Akça et al. [15] was its random allocation of patients and the use of a single point (LI11 Quchi). Meanwhile, unlike in the study by Kiliç Akça et al. [9], the disadvantage of the present study is that it did not use the TENS acupressure tool, which provides stimuli with more measurable and objective parameters than manual acupuncture.

Although several cases of uremic pruritus have been previously investigated, as per our knowledge, this is the first study in Indonesia to include participants undergoing hemodialysis. The selection of acupuncture point in this study was according to Che yi et al. [8], which only used one acupuncture point, that is, the LI11 Quchi point. Previous studies have used the LI11 Quchi, ST36 Zusanli, Sanyinjiao SP6, and Xuehai SP10 points, which are effective against uremic pruritus [7,8], Duo [21] and Gao et al. [6] have used the LI11 Quchi and ST36 Zusanli points, which were also effective.

The LI11 Quchi point is one of the points that affect immunity other than the LI4 Hegu, ST36 Zusanli, SP6 Sanyinjiao, LR3 Taichong, ST25 Tianshu, ST37 Shangjuxu, GB39 Xuanzhong, GV14 Dazhui, BL11 Dazhu, BL20 Pishu, BL23 Shenshu, BL24 Qihaishu, BL25 Dachangshu, BL26 Guanyuanshu, BL27 Xiaocharmgsu, BL28 Pangguanshu, and CV4 Guanyuan dan CV12 Zhongwan points [22].

The duration of acupuncture was decided in accordance with the research by Che yi et al. [8], and the needle was left for 1 h, which is associated with the stimulation of the punctured tissue during 1 h of inflammation after the coagulation, vasoconstriction, and vasodilation. Acupuncture was performed during the second hour of hemodialysis due to technical considerations to ensure that the action of hemodialysis has stabilized.

The mechanism of acupuncture in reducing pruritus in patients undergoing hemodialysis may be primarily through the mechanism of immunological action. Since the pathophysiology of pruritic uremic is still unclear and complex [1,10,23-26], acupuncture may also work through the μ and κ opioid receptor equilibrium [27] and through neuropathy [28,29]. Because only one point has a significant effect, the mechanism of action in acupuncture in individuals with pruritic uremic works systemically or centrally. Mettang’s opinion on the underlying cause of uremic pruritus due to microinflammation with elevated CRP levels and number of Th1 cells, interleukin (IL)-6 [1], and proinflammatory cells is supported by a recent study by Ko et al. [30] in 2014 showing an elevated IL-31 level in patients with uremic pruritus undergoing hemodialysis. IL-31 is a cytokine marker of inflammation in the skin, which belongs to the family of IL-6. The mechanism of action in acupuncture that influence inflammation is primarily derived from the regulation of Th1 and Th2 balance, which is affected by beta-endorphins [11]. Acupuncture helps secrete calcitonin gene-related peptide, which also shifts the formation of anti-inflammatory cytokines [11]. The synthesis of proinflammatory cytokines is inhibited by the release of acetylcholine and acupuncture [31]. The anti-inflammatory effect of acupuncture has been shown by Da Silva et al. [12]. The effect has been compared with that of dexamethasone, which is a corticosteroid. Acupuncture affects to the activity of the adrenal gland and the adrenal–hypothalamic–pituitary axis. Acupuncture is more effective than corticosteroids because it does not weaken the immune system.

As per our knowledge, this is the first study in Indonesia including participants undergoing hemodialysis using heparin. Therefore, the researchers aimed to identify the safety of acupuncture therapy in patients receiving anti-coagulants. Some of the adverse effects included minimal bleeding, which only needed the use of a cotton and application of pressure to control the bleeding, and this was
observed in 6.02%. This result is consistent with that obtained by Zhang et al. [32] that was published in the WHO bulletin, and the result has shown that mild bleeding or hematoma occurred in 2.1%–6.1% of patients, although Ernst et al. [33] have reported a higher rate of 0.03%–38%. McCulloch et al. [34] have reported that the prevalence rate of hematoma was 14.6% in population who used heparin. Considering the aforementioned figures, the present study had the same prevalence rate for bleeding as those published by the WHO. However, when compared with the specific population who used heparin, this study had a lower prevalence rate. In 6.02% of patients with mild hemorrhage that developed to hematoma, the prevalence rate was only 1.85% (four patients). In one patient, hematoma disappeared within 7 days, and in two patients, it disappeared within 3 days. All patients recovered spontaneously without any treatment. The participants did not complain of any pain, which may be because of acupuncture therapy performed after the patient was pierced with a needle for hemodialysis access, which was significantly larger than the acupuncture needle. The participants did not have other complaints. Based on these data, acupuncture is safe for patients who are receiving anti-coagulants, particularly at the point located in the muscle. However, if acupuncture therapy is performed with deep puncture and at points that affect other structures, such as the synovial joints or internal organs, and cause bleeding that cannot be easily detected, extreme caution must be observed.

The present study was challenging because it used a non-fixed fixture of the Park Sham Device in the placebo group. As a result, when the participants moved their hands, the needle could be dislodged, thereby requiring fixation in the Park Sham Device needle holder with the album vaseline. In addition, the use of the Park Sham Device needle shields in the acupuncture group made it challenging for the researchers to stimulate and observe the de qi sensation that the patient had gained by looking at the skin under the matchmaking region due to fibroblast fibers, as described by Langevin et al. [35].

The present study was based on the clinical condition of patients undergoing hemodialysis who developed uremic pruritus, which was assessed based on the clinical improvement of the reduced pruritus that was indicated by a 5D pruritus score, and the absence of a biomarker examination that can support pathophysiological explanation. The mechanism of action in acupuncture should be considered in subsequent studies. Whether the needle puncture had reached de qi due to the use of the Park Sham Device could not be determined, although the excess of this tool guaranteed placebo acupuncture, and this is considered as another limitation of the study.

5. Conclusion
Acupuncture therapy effectively reduced the complaints related to pruritus uremic in patients undergoing hemodialysis twice a week. The side effects, including mild bleeding and hematoma, that occurred during acupuncture therapy in patients undergoing hemodialysis were controlled with the use of cotton and the application of pressure.

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