Original Article

Acupressure for nausea-vomiting and fatigue management in acute lymphoblastic leukemia children

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Abstract

Context: Chemotherapy induced nausea vomiting and fatigue are prevalent problems following chemotherapy and pharmacologic methods are moderately efficient in alleviating them. Acupressure is a substitute approach.

Aims: This paper sought to determine the effectiveness of acupressure application in relieving nausea vomiting and fatigue among children with acute lymphoblastic leukemia in compression with a placebo treatment.

Settings and Design: In this single blind, randomized, placebo controlled clinical trial, 120 hospitalized school age children with ALL, randomly divided into experimental and placebo groups. Subjects rated the intensity of nausea and fatigue by visual analog scales.

Material and Methods: In the experimental group, finger acupressure on p6 and ST36 (true points) and in the placebo group on SI3 and LI12 (sham points) was applied. Symptoms of nausea and fatigue intensity immediately and an hour postintervention evaluated. Then variable of nausea vomiting and Fatigue was also measured 12 h postintervention by the instruments of Adapted Rhodes Index of Nausea and Vomiting for Pediatrics by Child and Fatigue Scale Child, Respectively.

Statistical Analysis Used: Data were analyzed by SPSS version 16.0.

Results: Significant differences were observed between two groups based on the fatigue and nausea intensity immediately and an hour postintervention with confidence interval 95% and $P < 0.001$.

Conclusions: Applying one time acupressure may reduce the intensity of nausea immediately postintervention and fatigue and nausea at one hour post treatment. Hence, acupressure could be recommended as a helpful, nonpharmacologic method for some cancer related fatigue and chemotherapy induced nausea vomiting management.

Keywords: Acupressure, Acute lymphoblastic leukemia, Chemotherapy, Fatigue, Nausea-vomiting

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancers in children. Its accounts for 75%–80% of childhood leukemia[1] With the advance of cancer treatment, children with leukemia at the present time have an enhanced survival rate. Optimal use of existing chemotherapy agents and improved supportive care in contemporary clinical trials has

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improved the 5-year survival rate of childhood ALL above 85% in developed countries. However, this has increased the quantity and severity of side effects and unpleasant symptoms, for instance, pain, nutritional concerns, nausea-vomiting, and fatigue.[2] Chemotherapy-induced nausea-vomiting (CINV) is prevalent and detrimental side effects of cancer chemotherapy treatments, however, studies suggest that the clinical uptake of antiemetic guidelines is often suboptimal, and CINV is a persistent problem for patients receiving chemotherapy even with current advances in pharmaceutical technologies, approximately 60% of patients under chemotherapy despite receiving antiemetic medications have experience nausea and vomiting and may be dispirited from completing their chemotherapy regimen.[3] Moreover, insufficient management of these side effects may result in metabolic imbalance, fatigue, distress, and lowered quality of life.[4,5]

Fatigue is an extensive, distressing, and weakening symptom that has an enormously negative influence on daily activity, involvement in social activities, preservation of interpersonal interaction, quality of life, and individual well-being.[6,7] Despite other cancer symptoms that may disappear as soon as the treatment is completed, fatigue has a continual and long-term impact on children experiencing cancer treatment.[8] Cancer-related fatigue (CRF) is a subjective symptom, the most common side effect after chemotherapy experienced by cancer patients, more upsetting and troublesome to daily activities than, for instance, cancer-related pain.[9] About 73.890.5% of patients receiving chemotherapy experience CRF.[10] About 40% of cancer patients may suffer from fatigue even years after treatments.[11]

Moreover, new advances in understanding the mechanism of CINV have cause to the advancement of efficient antiemetics, such as 5-HT_3 and NK_{-1} receptor antagonists (RA) also the improvement guidelines for efficient CINV management. Despite current approaches in antiemetic therapy, about 60% of cancer patients receiving chemotherapy continue to suffer from CINV. Various complementary and alternative therapies are frequently used to manage side effects and symptoms from cancer treatments including CINV and CRF.[12] Some clinical trial helps to determine the efficacy and acceptance of a self-administered acupressure technique in breast cancer survivors; evidence suggested acupressure in this patients could relieve fatigue,[13] additionally, acupressure was found effective to reduce sleep problems, fatigue, and depression in patients undergoing hemodialysis.[14] Acupressure is a part of traditional Chinese medicine (TCM) which is applying pressure with bands or fingers on the acupoints. Acupressure is simple to do, trouble-free, low-cost, and an effective approach The aim of acupoint stimulation is to return the body to a harmonized, balanced condition.[15] Acupressure has demonstrated in cancer patients and other chronically ill patients. Furthermore, pilot clinical trials have confirmed that acupressure can significantly reduce persistent cancer fatigue by about 38%.[16] Nausea-vomiting and fatigue are side effect of chemotherapy and managed by pharmacologic and nonpharmacologic approaches. Although in many countries, CINV and CRF in both adults and children have received concentration as an important problem and has been studied extensively, regrettably, it has not received enough attention by health-care professionals and researchers in Iran. No studies could be recognized on whether CINV and CRF is a common tolerable neither distressing symptom among Iranian pediatric oncology patients nor have the coping methods for dealing with the nausea-vomiting and fatigue syndrome among these children been methodically studied. In light of the limited research on chemotherapy complications reduction interventions in children with ALL, this study was undertaken examine the effectiveness of acupressure for controlling CINV and CRF in pediatric ALL patients after completing their chemotherapy.

MATERIAL AND METHODS

In a single-blind, randomized controlled clinical trial (IRCT138807152556Nl), participants recruited into the study were 120 children with ALL between the ages of 8 and 12, who randomly divided into experimental and placebo groups, random allocation in to experimental and placebo group was accidentally and blocked. The stratification factors sex (male, female) and age (12–8 years) are to be considered, and 120 patients are to be randomized in a ratio of 1:1 into the experimental and placebo groups (2 × 60 patients), then randomization has to be performed for each separate subgroup. On enrollment, each participant was consigned a random allocation number generated from a random table. The participant with a digital number from 0 to 4 was consigned to the experimental group and from 5 to 9 to the placebo group.

Patients were enrolled from oncology unit of two pediatric educational hospitals in Tehran. Inclusion criteria were ALL diagnosis, agreement to participate in the study and to be randomized in one of the two groups, age 8–12 years, no prior experience of chemotherapy, no prior experience of acupressure, and more than 3 months anticipated survival. Patients were excluded if they had low-platelet count (<50,000), a bleeding disorder (e.g., hemophilia), had hemoglobin levels <9 g/dl and hematocrit <30, or

were on active treatment for anemia (i.e., Erythropoietin or blood transfusions).

After completing a demographic form, baseline intensity of nausea-vomiting and fatigue measured by the visual analog Scales (VASs) at preintervention. In the 2nd day of chemotherapy, finger acupressure was applied for 3 min on ST36 and P6 as true points in the experimental group and on LI12 and SI3 as sham points in the placebo group.

Since in the present study, ALL children who also suffered from CINV and CRF, were chosen, thus applying acupressure on various acupoints could be frustrating for patients. According to the results of the previous study that was done to relieve CINV and CRF, P6 and ST 36 was chosen as the acupressure points and the SI3 and LI12 as the sham point. SI3 and LI12 are not associated with energy in the TCM and were also used as the sham point in the previous studies.[17] In addition, applying acupressure on one point is easy to learn and apply pressure for the patients and their family, therefore, patients and their family can do this intervention to overcome CINV and CRF at home.

We evaluated fatigue intensity using VAS immediately and 1 h after the intervention. Nausea- vomiting and fatigue were again measured 12 h postintervention by the instruments of Adapted Rhodes Index of Nausea and Vomiting (ARINV) for Pediatrics by Child (ARINVc) and Fatigue Scale-Child (FS-C). Routine care was administered to both groups. Patients were recruited from an oncology unit in two pediatric educational hospitals in Tehran.

The VAS uses a 100-mm device (0–10) with the extreme left side representing zero, nausea-vomiting and fatigue and the extreme right, maximal nausea-vomiting and fatigue. The patient indicates nausea, vomiting, and fatigue intensity by moving a pointer on the device, yielding a score measured by the pointer location. Patients were familiarized with the VAS device on the 1st day of hospitalization. The instruments of (ARINVc) to evaluate the frequency, distress, and duration of nausea and the frequency, distress and quantity of vomiting. Fatigue assessments were planned to measure fatigue along multiple dimensions**.** The (FS-C) is a self-report instrument that has 10-item to evaluate CRF.

In 2nd day of chemotherapy, patients in the experimental group received 3 min finger acupressure on p6 point, the acupressure point used to manage nausea and vomiting was p6 point, also called Nei-Guan point or pericardium 6 or Inner Gate. P6 is placed bilaterally on the inner face of the forearm approximately three finger widths proximal to the first-wrist crease [Figure 1][17] and also received 3 min finger acupressure on point ST36, a point traditionally used for "energy,"[10] located lower than the knee in the anterior margin of tibia [Figure 2]. The control group instead received pressure on SI3 placed in the depression proximal to the ulnar part of the fifth metacarpophalangeal joint, at the border (instead of p6) [Figure 3]. Moreover, a point not accompanied with "energy" in TCM.[8] The LI12 point, (instead of SI36) located on the lateral side of the upper arm, with the elbow flexed, on tile border of humerus [Figure 4].[17] Participant in both groups was told that we are evaluating the impacts of two sets of points but were not informed that one set was a sham method.

The study was reviewed and approved by the Research and Ethics Committees of Tehran University of Medical Sciences and Health Services (code: 1744263). Written and verbal information about the purpose and the method of the study, the right to extract and the assure of confidentiality were given to participants and their parents by researchers. In addition, they assured to keep privacy for other participants. For participation in study, verbal assent from children was needed also their parents were signed consent forms. All patients in placebo group were notified, exhibited with the results of the study and instructed how to situate and press the more efficient points at the end of the study, for ethical reasons. All participants were received routine care. However, they did not receive any intervention to reduce CRF and CINV.

For statistical analysis, data were coded and entered into SPSS (SPSS Inc. Released 2007 SPSS for Windows, Version 160 Chicago, SPSS Inc). Descriptive statistics were calculated with all demographic and clinical data, and fatigue and CINV subscale scores. Chi-square and fisher exact tests were also used to test any differences in demographic data among the two groups. Confidence intervals 95% were achieve from *t*-tests between two groups.

RESULTS

In this randomized controlled trail 120, ALL children were enrolled. There were no differences between two groups in any of the demographic or other baseline variables. Mean age of the children in both experimental and placebo group was 9.98 ± 1.55 years. The mean and standard deviation of both groups' ages were equal. Girls accounted for 31.7% and boys for 68.3% of the subjects. About one-third of the experimental group and 40% of the placebo group were first child family. The children's companion in the hospital

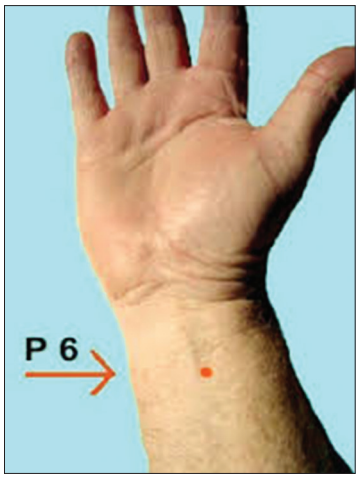

Figure 1: P6

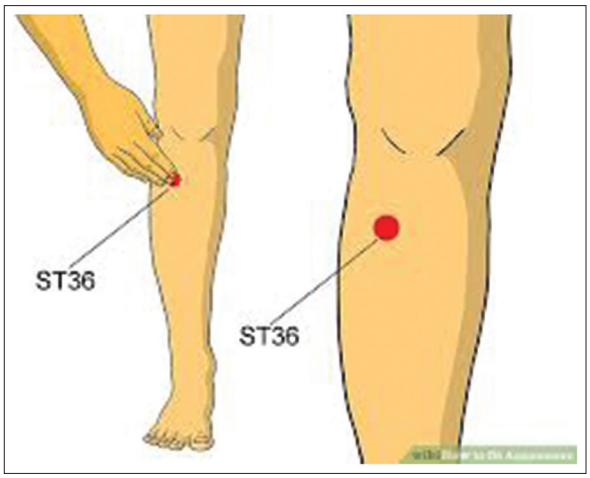

Figure 2: ST36

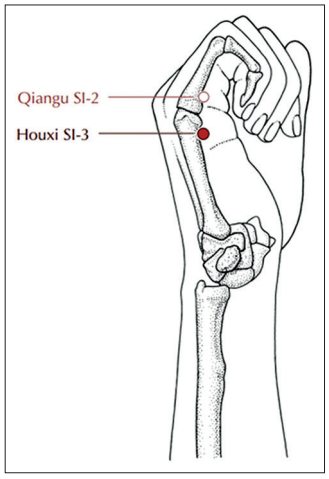

Figure 3: SI3

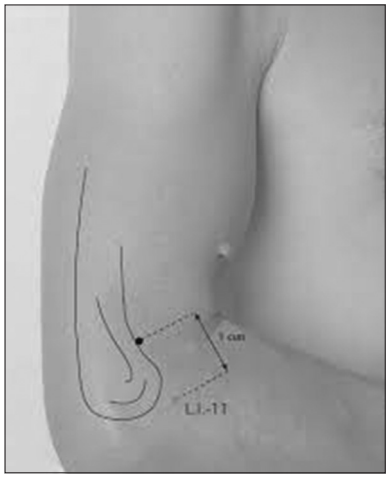

Figure 4: LI12

was their mother in 63.3% of the experimental group and 65% of the placebo group; there was no significant difference between the two groups in this regard ($P = 0.27$). Parents' education and job were not significantly different between the two groups ($P < 0.05$).

Mean score of nausea-vomiting intensity immediately and an hour after intervention in experimental group was lower than the placebo group ($P = 0/02$) [Table 1] ($P \leq 0/001$) [Table 2]. Fatigue intensity of two groups was compared immediately after intervention but indicated no significant difference between experimental and placebo groups ($P = 0.07$) [Table 3]. Most subjects in both groups experienced mild fatigue (score 1–3) so it would be expected that applying one-time acupressure would not reduce fatigue intensity immediately after the intervention. There was also a significant difference regarding fatigue between experimental and placebo groups 1 h postintervention [Table 4] ($P \leq 0.001$) Finally, no significant differences were found between the two groups regarding the variables of nausea-vomiting and fatigue after 12 h postintervention.

DISCUSSION

This randomized, controlled trial addressed the effects of acupressure on nausea-vomiting and fatigue among pediatric patient with ALL and provides some evidence that p6 acupressure in this patient can cause reduction in nausea feeling immediately and 1 h after intervention as well ST36 acupressure reduces the feeling of fatigue 1 h after intervention when compared to the placebo group. However, these effects may not be powerful enough to decrease the prevalence of vomiting and also fatigue for longer period were recognized.

Nausea intensity before intervention in the experimental and placebo group was not significantly different ($P = 0.2$). Miller *et al.* believe that children who received cancer chemotherapy often experience nausea and vomiting,[18] and in this study, p6 acupressure was revealed to decrease

Table 1: The compression of nausea intensity in acute lymphoblastic leukemia children immediately after intervention in tow groups

Nausea intensity	Groups	
	Acupuncture group, *n* (%)	Sham acupuncture group, *n* (%)
Score 0 (no nausea)	13 (21.7)	7 (11.7)
Score 1-3 (mild)	40 (66.7)	40 (66.7)
Score 4-6 (moderate)	7 (11.7)	11 (18.3)
Score 7-10 (severe)	0	2 (3.3)
Total	60 (100)	60 (100)
Mean±SD	1.77±1.5	2.4±1.81
t-test	*t*=2.22, df=114, *P*=0.02	

SD: Standard deviation

Table 2: The compression of nausea intensity in acute lymphoblastic leukemia children 1 h after intervention in tow groups

Nausea intensity	Groups	
	Acupuncture group, *n* (%)	Sham acupuncture group, *n* (%)
Score 0 (no fatigue)	2 (3.3)	0
Score 1-3 (mild)	50 (83.3)	41 (68.3)
Score 4-6 (moderate)	8 (13.3)	17 (28.3)
Score 7-10 (severe)	0	2 (3.3)
Total	60 (100)	60 (100)
Mean±SD	2.08±1.36	3.08±1.52
t-test	*t*=3.7, df=116, *P*≤0.001	

SD: Standard deviation

Table 3: The compression of fatigue intensity in acute lymphoblastic leukemia children immediately after intervention in tow groups

Fatigue intensity	Groups	
	Acupuncture group, *n* (%)	Sham acupuncture group, *n* (%)
Score 0 (no fatigue)	7 (11.7)	3 (5)
Score 1-3 (mild)	30 (50)	27 (45)
Score 4-6 (moderate)	18 (30)	23 (38.3)
Score 7-10 (severe)	5 (8.3)	7 (11.7)
Total	60 (100)	60 (100)
Mean±SD	2.95±2.13	2.30±3.68
t-test	*t*=1.80, df=117, *P*=0.07	

SD: Standard deviation

Table 4: The compression of fatigue intensity in acute lymphoblastic leukemia children 1 h after intervention in tow groups

Fatigue intensity	Groups	
	Acupuncture group, *n* (%)	Sham acupuncture group, *n* (%)
Score 0 (no fatigue)	5 (8.3)	0
Score 1-3 (mild)	38 (63.3)	26 (43.3)
Score 4-6 (moderate)	15 (25)	27 (45)
Score 7-10 (severe)	2 (3.3)	7 (11.7)
Total	60 (100)	60 (100)
Mean±SD	2.68±1.94	4.06±2.09
t-test	*t*=3.9, df=117, *P*≤0.01	

SD: Standard deviation

the nausea intensity immediately and 1 h after intervention in experimental group. Shin *et al.* evaluate the impact of acupressure on CINV in postoperative stomach cancer patients and find similar result[19] shown finger acupressure on p6 reduces nausea intensity in experimental group. The same result could be due to same method, and same acupressure point was used. We also found that acupressure at least control nausea intensity for 1 h after intervention in ALL children undergoing chemotherapy. However, the effect for longer period needs to further investigation.

This study show applying acupressure on children nausea-vomiting, 12 h after intervention is ineffective. The result was coherent with the finding of Alkaissi *et al.* (2005) shown using acupressure on p6 could prevent nauseogenic motion stimulation in woman at high risk for postoperative nausea-vomiting.[20] Moreover, Taspinar and Sirin reported p6 acupressure significantly reduced nausea intensity, but it is not effective on vomiting the reason may related to use of highly emetogenic chemotherapy drug (e.g., cicplatin).[21] Acupressure caused greater fatigue management in comparison to placebo group. About severity of fatigue in subjects 1 h after intervention [Table 3], the independent *t*-test indicated that severity of fatigue 1 h after the intervention was significantly different between the experimental and placebo group ($P \leq 0.0001$). Consequently, it may be inferred that applying the right points at the right time can determine the efficacy of acupressure. Stimulation of ST36 may enhance the flow of Chi or increase a discharge of neurohormon and neurotransmitters[22] and thus reduce the perception of fatigue. Zick *et al.* assume that acupressure could be a helpful therapy in patients with chronic diseases for improving fatigue and sleep quantity and quality.[23] Bastani *et al.* (2015) indicated significant differences in the mean scores of fatigue between two group ($P < 0.001$) in women With multiple sclerosis in addition applying acupressure could provide an substitute method for health-care providers such as nurses to instruct acupressure to the clients with Multiple Sclerosis to fatigue control.[24] Molassiotis *et al.* investigated the effect of acupressure on alleviating CRF. In their study, 47 patients with cancer who suffer from moderate-to-severe fatigue were chosen. They underwent acupressure on ST36 for 2 weeks. Finally, the case group had 19% improvement in fatigue while the control group had 0.6% improvement.[25] The present study used point ST36 to apply acupressure, similar to Molassiotis. By comparing the severity of fatigue in subjects before, immediately after and 1 h after acupressure, paired t-tests showed significant differences in the experimental group before and immediately after, and before and 1 h postintervention ($P < 0.001$). The mean severity of fatigue in the experimental group before intervention was 3.73, but dropped to 2.95 and 2.61 immediately and an hour

postintervention, respectively. This reduction in severity of fatigue before and immediately postintervention, also before and an hour postintervention was significantly different in the acupressure group ($P \leq 0.001$). Patient in the sham acupressure group and acupressure group enhanced in the VAS fatigue immediately after intervention. Massaging the acupoint or nonacupoint itself may create different level of relaxation on the body consequently, create various impact in fatigue.[9]

Considering these results, we can conclude that the effect of acupressure in fatigue reduction immediately after intervention can be attributed to the placebo effect in this group. It is reported that sometimes placebo groups show efficacy of acupressure. For instance, Agarwal *et al.* (2005) reported that anxiety before surgery significantly reduced immediately after applying acupressure on a sham point in the placebo group ($P < 0.001$). They mentioned the effect of massaging and that patients feel some special intervention is being made to their benefit as the reason for this effect.[26] Two theories about the effect of acupressure on sham points may be relevant here first, acupressure on sham points is sometimes authentically effective. Second, subjects' expectation about the efficacy of intervention may be affected simply by the presence of the researcher as a member of therapy team (Hawthorn effect) with therapeutic effect.[14]

Study limitations

Although efforts were made to design a comprehensive study, there were limitations. Several factors may have contributed to the high incidence of CINV and CRF found in this study. This includes basic anxiety that is significantly relevant to nausea intensity because expecting nausea-vomiting can lead to nausea. Other contributing factors are younger age, female sex, physiologic stress such as pain. In addition, measure of nausea-vomiting and fatigue has been argued recently. As nausea and vomiting has been identified as a major quality factor from the patient attitude. Hence, self-reported nausea-vomiting and fatigue experience may have various degree of measurement error such as error related to memory lapse of fatigue and nausea-vomiting. Moreover, finding has limited generalizability because this study was local and small sample were involved.

CONCLUSIONS

Acupressure could reduce nausea-vomiting and fatigue intensity in ALL children immediately and an hour postintervention in the experimental group. Consequently, it is recommended as an complementary, nonpharmacologic method for CINV and CRF management. As nausea-vomiting and fatigue are two different variables and reflects different responses to the treatment approaches, and also applying one-time acupressure was not effective on nausea-vomiting and fatigue 12 h after intervention; hence, it seems that future studies are needed for evaluating acupressure effectiveness on nausea-vomiting as well as fatigue, respectively.

Conflicts of interest

There are no conflicts of interest.

Authors' contributions

All authors contributed equally to the writing of the scientific proposal, data collection, and manuscript drafting. The final manuscript was reviewed and approved by all the authors.

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