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Research Paper

Effects of Acupressure on Fatigue in Patients with Cancer Who Underwent Chemotherapy

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Abstract
Fatigue is the commonest symptom in cancer patients; despite high levels of clinically significant persistent cancer-related fatigue, few treatments are currently available. The aim of this study was to evaluate the efficacy of acupressure on fatigue in patients with cancer who underwent chemotherapy. The study was designed as a randomized and controlled trial. Ninety samples were selected using the convenience sampling method, and random block sampling was used for allocation of groups (30 for each group). The three groups were similar by age and gender. The experimental group underwent acupressure at the Zusanli (ST-36), Hegu (LI-4), and Sanyingjiao (SP-6), whereas sham pressure was used in the placebo group and no intervention was applied in the control group; the level of fatigue of participants in three groups was calculated in three phases, before, during, and after chemotherapy. Data were analyzed using SPSS, version 22. The results showed that the mean of visual analog score of fatigue is significantly different in three groups at the end of chemotherapy ($p = 0.021$). The mean visual analog score of fatigue in the acupressure group was meaningfully lower than that in the control group

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after chemotherapy ($p = 0.028$). Results of this investigation showed that acupressure has short-term effectiveness on the cancer-related fatigue of patients undergoing chemotherapy.

1. Introduction

Cancer is a major life-threatening disease worldwide. Approximately 14.1 million patients were newly diagnosed with cancer, and 8.2 million people died from cancer in 2012 worldwide [1]. Fatigue is the commonest symptom in patients with cancer [2]. Cancer-related fatigue, defined as an unusual, constant, subjective sense of tiredness which cannot be improved after resting [3], has an extremely negative effect on daily routine activity, social activities, interpersonal relationships, well-being, and quality of life in cancer survivors [4,5], and it is sometimes underdiagnosed and not treated [6]. Current treatment options need access to a trained practitioner and are associated with high costs or have unacceptable side effects [7]. Side effects of medications and nonsuitable relief of fatigue with medications shift the patients to complementary and alternative medicine [8]. Different forms of complementary and alternative medicine interventions examined included acupuncture, massage, yoga, and relaxation training for cancer-related fatigue [9]. Acupressure is a type of touch therapy that uses pressure in fingers for provoking different points on the body surface, resulting in relief and suppression of various symptoms by reducing pain [10]. This intervention is used frequently by nurses in clinical settings [11] and is considered as a clinical and comprehensive nursing intervention [12]. Using acupressure among nurses can help improve the quality of nursing care and reduce the side effects of the invasive methods [13]. The benefits of this procedure are as follows: it is cost-effective, there is no need for equipment, it is simply educated to patients, and it involves a noninvasive procedure [12]. This practical intervention can be used for cancer-related or other chronic disorder—related fatigue and is used in different studies [14]. Previous studies showed the application of acupressure for different cancer survivors after completion of their treatment to relieve fatigue, and depression improved after it [7,10,15]. In a study conducted by Molassiotis et al [16], effect of acupressure on fatigue and depression in patients with breast cancer was significantly effective. On the other hand, Tsay [17] concluded that acupressure was not significantly effective in reducing patients' fatigue after the intervention. Contradictory studies and insufficient evidence to conclude with certainty the effectiveness in reducing cancer-related fatigue [9], increasing prevalence rate of cancer, and limited number of studies on acupressure led us to conduct research that has rigorous design and methods to increase the strength of evidence of the effectiveness of acupressure on fatigue in patients with cancer who underwent chemotherapy.

1.1. Trial Design

This study was a randomized clinical trial in which the effect of acupressure on fatigue in all patients with cancer who underwent chemotherapy referring to Razi Hospital of Rasht was studied during 2014—2015. The proposal is registered in the Iranian Registry of Clinical Trials with the registration number of "IRCT201207141174N9".

1.2. Participants

The participants included patients with cancer who underwent chemotherapy between November 2015 and March 2016 in the hematology ward of Razi referral center, Rasht, Northern Iran. The sample was selected using the convenience sampling method, and random block sampling was used for allocation of groups. The three groups were similar by age and gender.

1.3. Sample Size

Estimates of variability for outcomes of fatigue were obtained from a pilot study and power calculation [$\alpha = 0.05$; $(1 - \beta) = 0.90$; effect size $= 0.84$]. Therefore, 30 participants were required for each group.

1.4. Inclusion criteria

Patients with any type of cancer with complete consciousness, with a pathology test result confirming the cancer, aged $\geq$25 years, who are not amputee, with second or higher stage of cancer, who started chemotherapy less than 1 month ago, who were hospitalized for at least 6 continuous days for chemotherapy, with hemoglobin $>$ 9 mg/dl, with platelet levels greater than 100000 mg/dl, with no ulcer in pressure points, and/or with a moderate or higher fatigue level in the base, beside undergoing common treatments and willing to participate in the study, were included in the study.

1.5. Exclusion criteria

Patients with infection or skin disorders or other dermatologic problems, without willingness to continue the treatment, and/or with systemic disorders including ischemic heart disease, hypertension or hypotension, or hemorrhagic disorders were excluded.

1.6. Interventions

The intervention was performed by a researcher who was a certified acupressure practitioner. Different

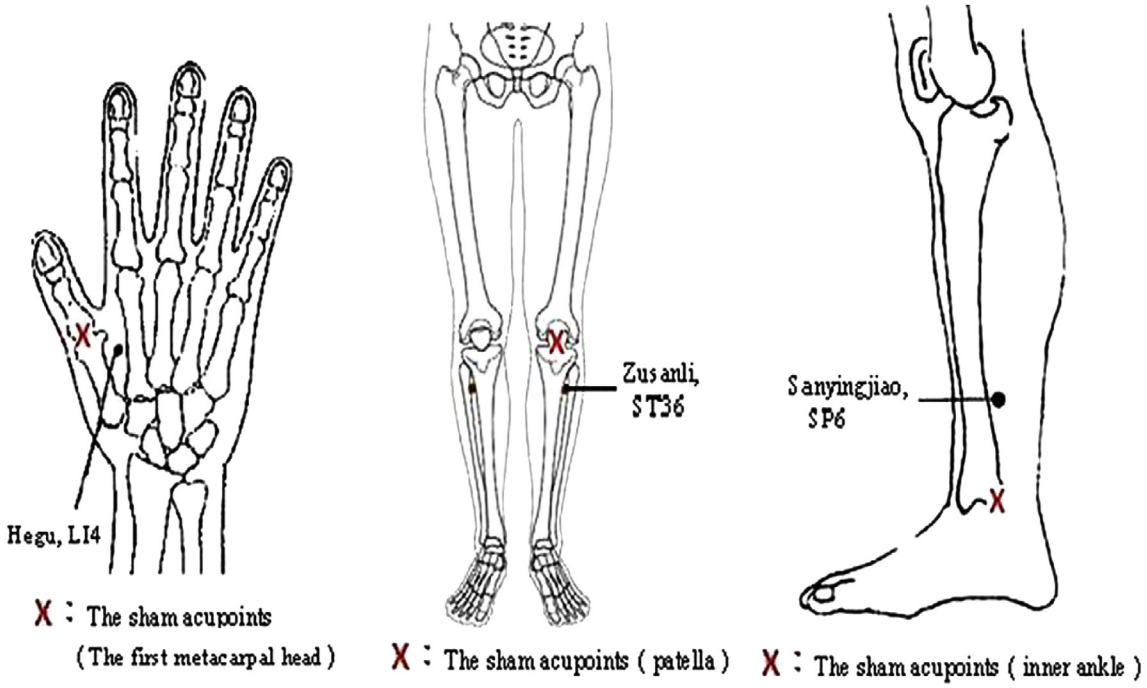

Figure 1 Acupoint location.

points have been used in previous studies [18,19]. The researcher selected three acupoints li-4 (middle of bisector between the first and second metacarpus) or Hegu acupoint[13], ST36 (width of one finger lateral to lower edge of tibia tuberosity and 4 fingers lower than knee joint) or Zusanli acupoint, and sp-6 (4 fingers above the medial ankle and posterior of tibia) or Sanyingjiao acupoint [20] (Fig. 1), which have been related to energy in the human body and were shown to alleviate fatigue in patients with cancer.

In the intervention group, pressure point were pressed for 2 min [13,21] symmetrically immediately after the start and the end of the one session of chemotherapy. Fingers were pressed gently on the point, and pressure was increased gradually until there was a sensation of soreness.

In the placebo group, all points at a distance of 1.5 cm from the main acupoints were pressed. These points are called ineffective or sham pressure points. These three locations have no acupoints, are not related to improving fatigue, and are in the same dermatome region as our three acupoints. No intervention was performed in the control group. Level of fatigue before, during, and after the chemotherapy was calculated and recorded.

Ninety patients participated in this study. Thirty patients were randomized to receive acupressure. Another 30 patients were randomized to the sham acupressure group. The remaining 30 patients were randomized to the control group.

We recruited 95 patients for this study, five of whom were excluded because they did not meet the study's eligibility criteria. Three patients experienced nausea and vomiting during the process and refused to continue the intervention. One of the patients was transferred to the intensive care unit because of dyspnea and reduced consciousness. Another patient refused to continue the intervention without mentioning the cause (Fig. 2).

1.7. Measurement Tools

In this study, two standard questionnaires and a checklist of demographic data and other related factors were used. Age, gender, occupation, marital status, literacy, residency, diagnosis, and time from diagnosis were recorded for each patient.

1.8. Visual Analog Scale

This tool is a fatigue severity ruler divided into 10 states; we put "fatigue free" in the left as zero and "maximum of fatigue" in the right as 10 points. The visual analogue scale (VAS) is applied to many cases, and its standard is approvable [22]. In this study, to determine the reliability of the VAS, the Cronbach a coefficient was used to check its internal consistency. In this regard, 10 patients from the research population who had the profile of the patients with cancer under the study filled out the questionnaires, and by using the results, the Cronbach a coefficient for VAS (r $^{1}/_{4}$ 0.84) was calculated. This scale is developed for evaluation of the intensity or severity of various symptoms. We asked patients to determine their subjective experience of fatigue by rating its severity.

1.9. Statistics

The data were statistically analyzed, using statistical package for the social sciences (SPSS, version 22.0) (Chicago, USA). We used Chi-square and independent *t* test for quantitative and qualitative demographic variables and Fischer exact test for disorder-related variables. Repeated-measure analysis of variance and Tukey honestly significant difference (HSD) test were used to

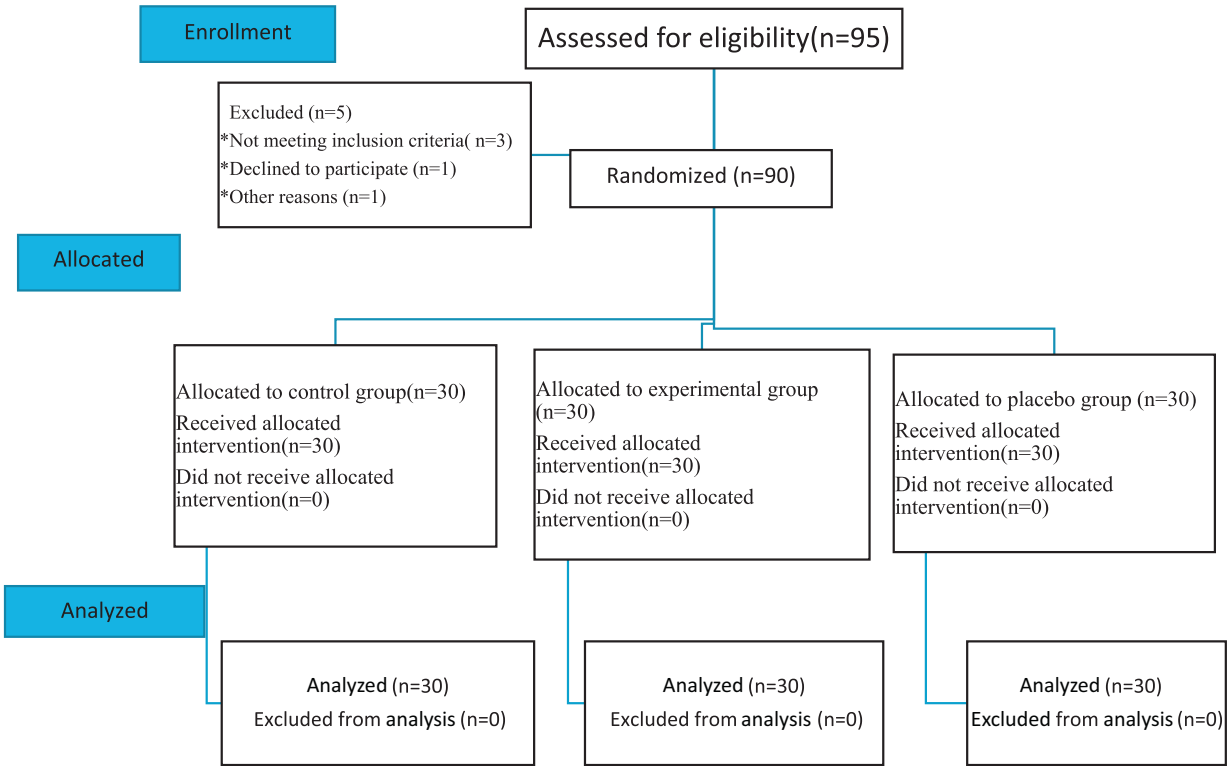

Figure 2 CONSORT diagram.

determine comparison of VAS score of fatigue differences between three groups. Paired *t*-test was used to compare the inter-group before and after. Data were expressed as mean ± standard error of mean, and a P-value less than 0.05 was considered statistically significant.

1.10. Ethics

The study was approved by the Research Committee of the Guilan University of Medical Sciences. Written informed consent was obtained from the participants before collecting data. The study was registered in Iranian Registry of Clinical Trials on 12/28/2014 (IRCT201207141174N9).

2. Findings

2.1. Demographic and Clinical and Laboratory Characteristics between Three Groups

The average duration of the chemotherapy was very similar in patients in the acupressure group, placebo group, and control group (1 vs. 1.1 min, p 1/4 0.51). No serious side effects or discomfort related to acupressure was reported by patients in acupressure and placebo groups.

The results show that there were no significant differences between participants' variables between three groups, and all characteristics were distributed normally. The participants' age average was 52.12 ± 14.4 years. Majority of participants were male (58.9%), were married (91.1%), and had elementary education (91.1%) (Table 1).

Most of the patients had gastrointestinal cancers (31, 34.4%). The mean hemoglobin level in all patients was 11.34 ± 1.51 g/dl. Furthermore, the results show that the type and dose of the drugs were the same in all three groups, and there was no significant difference between them ($p > 0.05$) (Table 2).

2.2. VAS score of fatigue changes in different stages of treatment between three groups

The results show that the mean VAS score of fatigue is not significantly different before and during chemotherapy ($p = 0.275$; $p = 0.496$); it is significantly different in three groups after chemotherapy ($p = 0.021$) (Table 3).

The results of this study show that the mean VAS score of fatigue after chemotherapy is not significantly different between the acupressure and placebo group ($p = 0.930$) and placebo and control group ($p = 0.068$). However, the mean VAS score of fatigue in the acupressure group was meaningfully different between acupressure and control groups after chemotherapy ($p = 0.028$), in which the score (1.2 ± 0/46) was lower in the acupressure rather than in the control group (Table 4).

Results of paired *t* test showed that the VAS score of fatigue before chemotherapy (7.6 ± 1.57) after two stages of acupressure treatment decreased (6.03 ± 1.90) significantly ($p < 0.0001$). We showed that the VAS score of fatigue is decreased significantly in comparison with before and during, before and after, and during and after chemotherapy ($p < 0.0001$) in the acupressure group. In the placebo group, there were significant differences between before and during ($p = 0.003$) and before and after

Table 1 Demographic characteristics between three groups.

Characteristics		Acupressure	Placebo	Control	*p*
Age (Mean ± S.D)		50.43±15.03	51.83±12.8	54.10±15.47	0.615
BMI (Mean ± S.D)		24.26±5.09	26.14±4.83	25.21±5.24	0.362
Sex (%)	Female	46.7%	30%	46.7%	0.317
	Male	53.3%	70%	53.3%	
Marriage (%)	Married	93.3%	90%	90%	0.679
	Unmarried	6,7%	10%	10%	
Education (%)	None	13.3%	30%	30%	0.617
	Elementary	40%	36.7%	43.3%	
	High school	33.3%	26.7%	20%	
	College and above	13.3%	6.7%	6.7%	
Resident (%)	Urban	70%	70%	60%	0.638
	Rural	30%	30%	40%	
Occupation (%)	Jobless	73.3%	63.3%	60%	0.392
	Employee	10%	6.7%	10%	
	Farmer	6.7%	10%	10%	

BMI= Body Mass Index.

Table 2 Clinical and laboratory characteristics between three groups.

Characteristics		Acupressure	Placebo	Acupressure	*p*
Rate of Chemotherapy (Mean ± S.D) Number		5.10±2.93	4.87±2.57	4.43±2.87	0.051
Hb (Mean ± S.D) g/dl		10.83±1.35	11.45±1.34	11.76±1.72	0.317
Hct (Mean ± S.D) %		43.81±4.31	35.90±4.09	35.32±4.89	0.492
Cancer Type (%)	GI	43.3%	33.3%	26.7%	0.538
	Breast	20%	6, 20%	26.7%	
	Leukemia+Lymphoma	16.7%	10%	23.3%	
	MM+ Osteosarcoma	3.3%	13.3%	6.6%	
	Lung	13.3%	6.7%	6.7%	
	Ovary and Cervix	0	10%	3.3%	
	Prostate and Testis	10%	3.3%	6.7%	
Dose of Treatment Type (Mean ± S.D)	Alkylating agents	132.83±233.47	158.33±291.50	82.33±12979	0.426
	Isomerase-I agents	26 ±67.50	12.33±51.97	10±54.77	0.522
	Isomerase-II agents	33. 3±18.26	1.67±9.13	0	0.551
	Antimetabolite agents	535±577.17	398±583.67	441.33±615.84	0.659
	Anti-tumor agents	24±92.68	45.83±139.88	31.83±57.3	0.706
	Mitotic inhibitor agents	15.83±33.94	64.50±219.31	28.17±48	0.332
	Other agents	13.47±73.01	26.8±101.45	37.13±167.2	0.748

Table 3 Comparison of VAS score of fatigue in three groups in different stages of treatment.

VAS score of fatigue	Groups	Mean±S.D	CI (95%)		Min	Max	*p*
			Lower	Upper			
Before chemotherapy	acupressure	7.60±1.57	7.01	8.19	5	10	0.275
	placebo	7.03±1.40	6.51	7.56	5	9	
	Control	7.05±1.65	6.43	7.67	5	10	
During chemotherapy	acupressure	6.73±1.64	6.12	7.35	4	10	0.496
	placebo	6.62±1.38	6.10	7.13	5	9	
	Control	7.70±1.54	6.49	7.64	5	10	
After chemotherapy	acupressure	6.03±1.90	5.32	6.74	3	10	0.021
	placebo	6.20±1.92	5.48	6.92	1	9	
	Control	7.23±1.46	6.49	7.78	5	10	

Table 4 Comparison of mean differences of VAS score of fatigue in three groups after chemotherapy.

VAS score of fatigue	Gorup(l)	Gorup(j)	Mean Differences ±S.D	*p*
After chemotherapy	acupressure	placebo	0/17±0/46	0/930
		control	1/20±0/46	0/028
	placebo	control	1/03±0/46	0/068

($p = 0.006$) chemotherapy, but not during and after chemotherapy ($p = 0.141$). In each stages in the control group, there were no significant differences in the VAS score of fatigue ($p > 0.05$).

Repeated-measures analysis of variance test results showed that changes in the mean VAS score of fatigue in three groups of this study were significantly different in all stages of before, during, and after chemotherapy ($p < 0.0001$). These results showed that in all stages of chemotherapy, acupressure can decrease the mean VAS score of fatigue significantly rather than the two other groups ($p < 0.0001$) (Table 5).

Tukey HSD test showed that the mean VAS score of fatigue of the acupressure group before and during chemotherapy in comparison with the placebo group ($p = 0.046$) and with the control group ($p < 0.0001$) was significantly different.

Fig. 3 showed that acupressure treatment with a meaningful gradient decreased the VAS score of fatigue rather than two other groups.

3. Discussion

The results of this study show that acupressure was effective in decreasing fatigue level in patients with cancer who underwent chemotherapy. The results of other studies also showed a decrease in fatigue scores of the intervention group compared with the placebo pressure groups [18,22]. Consistent with our results, Tsay [17] designed a study to investigate the effectiveness of acupressure on fatigue which showed that there were significant differences between the acupressure group and the control group ($p = 0.01$) and between the placebo group and control group ($p = 0.003$). In another study, Molassiotis et al. [23] showed significant improvements with regard to general fatigue ($p < 0.001$), physical fatigue ($p = 0.016$), activity ($p = 0.004$) and motivation ($p = 0.024$) and that at the end of the intervention, there was a 36% improvement in fatigue levels in the acupuncture group, while the acupressure group improved by 19% and the sham acupressure by

Table 5 Comparisons of mean differences in the VAS score of fatigue in three groups in different stages of treatment.

VAS	Groups	Mean Differences	S.D	S.E	CI (95%)		Min	Max	*p*
					Lower	Upper			
Before chemotherapy	acupressure	0.87	0.89	0.16	0.53	1.19	0	3	<0.0001
	placebo	0.42	0.70	0.12	0.15	0.67	0	3	
	Control	0.02	0.53	0.09	0.21	0.18	1	2	
During chemotherapy	acupressure	0.70	0.85	0.15	0.38	1.01	0	3	<0.0001
	placebo	0.42	1.51	0.27	0.14	0.98	3	5.5	
	Control	0.17	0.48	0.08	0.34	0.01	1.5	1	
After chemotherapy	acupressure	1.57	1.43	0.26	1.03	2.1	0	5	<0.0001
	placebo	0.83	1.53	0.27	0.26	1.4	1	7	
	Control	0.18	0.71	0.13	0.44	0.8	1.5	2	

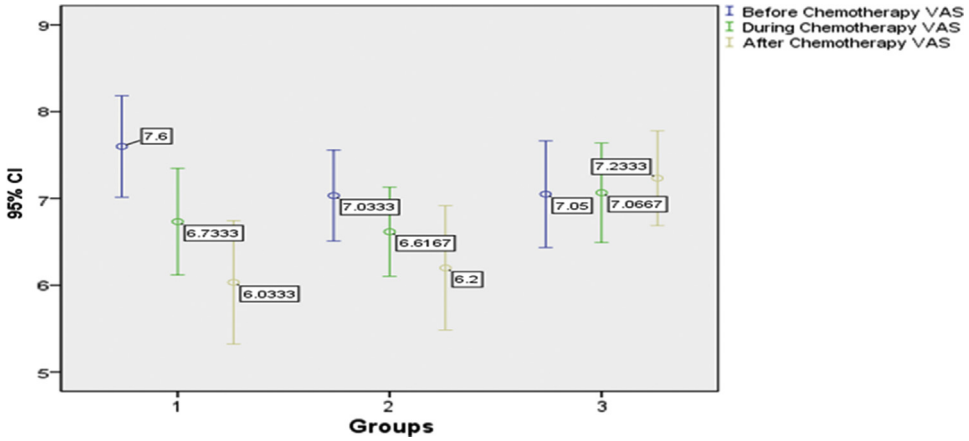

Figure 3 Differences between the VAS score in different stages of treatment within three treatment groups: Group 1, acupressure treatment group; Group 2, placebo group; Group 3, conservative routine treatment.

0.6%. Lan et al. [22] showed that acupressure can improve fatigue in 62 patients with hepatocellular carcinoma during treatment with acupressure but did not alleviate depression.

The results of this study show that the level of fatigue in the intervention group was not significantly reduced compared with the control and placebo group during chemotherapy, while Tang et al. [15] expressed a decrease in fatigue levels even during chemotherapy ($p = 0.02$). This difference may be due to the different study duration in the two studies.

The results of this study show that the level of fatigue in the intervention group was significantly reduced compared with the control and placebo group after chemotherapy. The results of the study by Beykmoradi et al. [18] show that the level of fatigue decreased after intervention. The results of other studies show a similar decrease in the level of fatigue [22].

In this study, the level of fatigue score was significantly different between before and during chemotherapy in the placebo group. This reduction can be due to psychological and physiological effects of the touch. This finding is in agreement with the results of previous studies [18,24]. In another study, Zick et al. [25] found that fatigue was significantly reduced across all treatment groups with significantly greater reductions in the relaxation acupressure group.

In this study, the level of fatigue in the control group was not reduced, but it increased. In the study conducted by Beykmoradi et al. [18], there was no significant difference in the fatigue level in the control group.

Implications for Practice:

* Our results show that application of acupressure in patients undergoing chemotherapy reduced fatigue.
* Teaching acupressure to patients can be effective in reducing fatigue in patients undergoing chemotherapy.
* Acupressure is cost-effective and does not require professional and long-term education for patients and nurses.
* Acupressure would be a suitable intervention in clinical settings where the patient undergoing chemotherapy experiences high levels of fatigue.

4. Conclusion

In this study, we tried to perform a comprehensive study with three groups and involving the effects of the placebo group to remove the limitations of the previous study. Results of this investigation showed that acupressure in three points L14, ST36, and sp-6 has short-term effectiveness on cancer-related fatigue of patients undergoing chemotherapy. Regarding high incidence of fatigue in patients with cancer, we suggest acupressure as a nontoxic and harmless nonpharmacological therapy to reduce adverse events in patients with cancer.

5. Limitations

One of the limitations of this study was using the VAS score for assessing the fatigue. We recommend using other tools to measure fatigue. Numerous factors could influence the fatigue scores. Controlling for these factors was impossible for the researcher because of personal differences and cultural, mental, and psychological factors. We recommended using different acupoints for performing acupressure in these patients in future studies. Long term efficacy of acupressure is recommended for evaluation of other comorbidities related to cancer like pain, anxiety and etc. with nursing-aid or self-treatment methods. Due to limited studies on the effect of acupressure on fatigue in chemotherapy patients, the author believes that further studies should be done in this area. Further studies, systematic reviews, and meta-analyses are required to comment on effects of acupressure on fatigue in patients with cancer who are undergoing chemotherapy.

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Disclosure statement

All authors declare any competing interest.

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