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Self- Management of Pain and Fatigue in Major Thalassemia

Abdollah Dakalirad[1], Ali Ansari Jaberi[2], *Tayebeh Negahban Bonabi[3]

1 MSc, Department of Medical Surgical Nursing, Tropical and Communicable Disease Research Center, School of Nursing and Midwifery; Iranshahr University of Medical Sciences, Iranshar, Iran.

2 Department of Psychiatric and Mental Health Nursing, Social Determinants of Health Research Center, School of Nursing and Midwifery; Rafsanjan University of Medical sciences, Rafsanjan, Iran.

3 Department of Community Health Nursing, Social Determinants of Health Research Center, School of Nursing and Midwifery, Rafsanjan University of Medical sciences, Rafsanjan, Iran.

Abstract

Background: Limited studies have examined the effect of reflexology on pain and fatigue in thalassemia major patients. The aim of this study was to determine the effect of foot reflexology on pain and fatigue in patients with major thalassemia.

Methods: In this double-blinded randomized controlled trial, 90 patients were assigned into 3 groups equally (reflexology, touch, and control) by the minimization method. The reflexology group received an entire foot massage three times a week, for 2 weeks, for 10-15 minutes. No intervention applied in the control group, and in touch group touching was applied with the same pattern as the intervention group. The pain and fatigue score was measured before, immediately and 2 weeks after the intervention on the NRS and FSS scales respectively. Data was analyzed by SPSS version 22, using Chi-square, Fisher Exact, Mann-Whitney U, repeated measure ANOVA tests and statistically modeling at a significance level of 0.05.

Results: There were no significant differences between the groups regarding demographic characteristics. On the reflexology and touch group, the mean score of the pain and fatigue decreased significantly (p=0.001) both at the immediate measurement and two weeks after the intervention. In intergroup comparison, the pain score in the reflexology group was significantly lower than in the two other groups. But the fatigue scores did not make any significant changes.

Conclusion: Reflexology could be used safely in management of pain in major thalassemia patients; but it could not reduce the patients' fatigue.

Key Words: Chronic Pain, Complementary Medicine, Fatigue, Reflexology.

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**** Corresponding Author:***

Tayebeh Negahban Bonabi, Department of Community Health Nursing, Social Determinants of Health Research Center, School of Nursing and Midwifery, Rafsanjan University of Medical sciences, Rafsanjan, Iran. Email: negahbant@yahoo.com.

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1- INTRODUCTION

Thalassemia syndromes, as one of the most serious and common genetic diseases, are endemic in a vast geographical area, and through the migration, they are spreading in areas that have not been affected before (1). In Iran, Sistan and Baluchestan province, has the highest thalassemia rate (2). Despite the correct use of common treatments, beta thalassemia patients suffer from many complications (3). Tissue iron accumulation is the leading cause of mortality and morbidity in thalassemia (4).

Pain as a subjective symptom has become increasingly a common complication of thalassemia (5). Its prevalence is greatly underestimated, but the evidence indicates a high proportion of adults with thalassemia who experience chronic pain (6). Fibromyalgia is 20 times more common in people with thalassemia than in normal people (7). Research has shown that in thalassemia patients, increased pain has been associated with decreased quality of life, increased anxiety, and depression (8). Also, researchers believe that fatigue is a common symptom in patients with chronic conditions (9). In thalassemia major the reduced hemoglobin value, chronic anemia (10) and the repeated transfusion (9) have been associated with fatigue. The results of a research have shown that fatigue is a complex and distressing symptom in patients with hemoglobinopathies that can lead to physiological and emotional burden (11).

Although there are several hematological, surgical, and pharmacological methods for managing pain and fatigue in these patients, available treatment options have limited effectiveness (6, 12); and there may be barriers to accessing the services of the specialized pain teams. So, in most cases, patients have to respond to their pain and fatigue in non-pharmacological and self-managed ways and try to control them; and the role of health professionals is mainly reflected in guiding and facilitating. Physicians, meanwhile, are less prepared to take on this supportive role, and often, nurses play a significant role instead. Researchers have proposed several methods for supporting self-managing the pain and fatigue of thalassemia patients, including the telenursing and exercise training programs (13), smartphone games (14), carnitine and folic acid consumption (15), and Types of psychotherapy on quality of life (16-19). Foot reflexology has also been employed to manage pain and fatigue and improve functional status in some conditions (20-22). It also seems to be useful in thalassemia patients.

Reflexology is an ancient natural treatment that uses energy on the soles of the feet to create a flow of energy in the body. There is a limited understanding of the function of reflexology. It is similar to the Chinese and Japanese ancient natural healing principles (23). Limited studies have examined the effect of foot reflexology on pain and fatigue in patients with thalassemia major. In the existing texts, most reflexology-based interventions have been done in the field of hemodialysis (24, 25), lymphoma (26), and kidney transplantation (21) patients. In thalassemia patients, reflexology has been able to reduce transfusion induced anxiety (27, 28). The aim of this study was to determine the effect of self -administered foot reflexology in the management of pain and fatigue in patients with major thalassemia.

2- MATERIALS AND METHODS

This double-blind randomized controlled trial was performed from June 2019 to October 2019; aimed at determining the effect of foot reflexology on fatigue and pain in patients with thalassemia major who attended the Special Diseases Center in Iranshahr in Sistan Baluchistan province, Iran.

Sample size, based on previous studies (29), was considered to be 90 (30 patients in each group), according to the following formula with a standard deviation of 19; and the minimum expected difference between the means was considered as 18 (based on the minimum difference of significant mean changes) in each group for the fatigue score at the confidence level of 95% and power of 90%.

$$n= 2(z_{1-\alpha/2} + z_{1-}\beta)\ \sigma^2/ d^2 \times \sqrt{1.3}$$

The study population included all patients with thalassemia major referring to Iranshahr Special Diseases Center, who met the inclusion criteria. Sampling was purposeful, and based on inclusion criteria. And, the eligible subjects were randomly allocated into three study groups.

Sampling was performed by the random minimization method (30), based on pain and fatigue in two categories (moderate and severe) for each. The first samples were assigned into the three groups randomly and for the entry of subsequent samples, the sum of samples in each group in each category was considered, such that, the total number of samples in each category of each group was equal. Sampling continued until the required sample size was fulfilled.

Data collection was done by face-to-face interviews. The data collection tools included demographic questionnaire (age, sex, education, and time interval of last treatment), the numerical ranting scale (NRS) for pain severity evaluation and the FSS fatigue intensity scale, used to measure fatigue. The NRS is a 10 cm horizontal line graded from zero to 10, in which zero indicates the absence of pain and 10 indicates the maximum pain intensity. The pain score categories consist of Zero: no pain, 1 to 3: mild pain, 4 to 6: moderate pain, and 7 to 10: severe pain. The FSS fatigue intensity scale is a valid self-report scale designed in 1989 by Krupp et al. (31) consisting of 9 questions. In this scale, five questions are related to the quality of fatigue, three questions to physical and mental fatigue and their impact on the individual's social relationships, and one question is related to the severity of fatigue. The scoring of the questionnaire is based on the Likert scale, from 1 to 7. (Scores 9-18 indicate low, 18–45 average, and scores above 45 high fatigue rates).

After approving the proposal and obtaining the code of ethics with REC number of IR.RUMS1397.240 from research council of Rafsanjan University of Medical Sciences and also presenting an introduction letter to the Special Diseases Center, one of the researchers who had received sufficient training in performing reflexology technique by a traditional medicine specialist, started the primary sampling from patient's health records based on the inclusion criteria. Telephone calls were made to eligible patients, explaining the objectives of the study. In case of informed consent to participate in the study, the patient was invited to attend the center at the appointed time.

After random allocation of samples in the three groups of reflexology, touch, and control, a practical and theoretical training session was held for subjects in the reflexology and touch group. In this session, one of the researchers taught them how to perform the intervention, individually. Then, to ensure learning, the patients were asked to repeat the intervention procedure. If approved by the researcher, the patient could enter the study.

In the reflexology group, the foot massage was performed three times a week, for two weeks, each time 10-15 minutes per foot. In order to perform foot massages, Patients were instructed to remove their rings, and jewelry before beginning the massage, and to wash and dry their hands and feet using water at room temperature and regular soap. Then, in a completely calm and safe

environment that is suitable in terms of light, temperature and ventilation, and where they felt safe, they were to sit on a short chair or pillow, so that they could focus on the therapist's instruction. The patient should have had a clock or timer with him to control the time of movements. The techniques were performed first on the left foot and then on the right foot.

At first the patient should have lubricated his hands with olive oil (which was provided to them by the researcher), placing his calf on the knee of the opposite foot so that he could have enough control on performing the massage.

The initial massage was performed to prepare the patients' feet. Using the palm and fingers of the dominant hand, the patient massages from the calf to the wrist and then the sole of the foot with superficial and medium pressure, then hold the heel of the foot with one hand and rotate the rest of the foot clockwise. These movements were repeated several times during the two minutes.

To perform the reflexology massage, which was the main massage of the intervention, the patients were instructed to place one hand on the back of the foot, the other under the sole of the foot, and gently massage all parts of the sole of the foot, from the toes to the heel and then the ankle, and continue this movement again Using the middle part of the index finger and the fleshy part of his thumb. They should have applied enough pressure so that one third of the nail bed turned white. Then, without interrupting the contact of the toes with the sole of the foot, the massage started from the lower part (fleshy part) of the toes in a circulated form and continued to the end of the heel, and repeated towards the fingers. Finally, thumb walking was performed from the tip of the heel to the toes, and then the entire sole of the foot. Also, at sensitive points (liver, heart, pituitary gland, and solar plexus), three types of pressure were applied: 1- rotated clockwise, 2- continuous (consecutive), and 3- stable or direct pressure (single pressure) was performed.

The intervention was performed three times a week (every other day), at 6 pm for 14 days. It should be noted that, researcher followed-up all patients' daily by phone call, half an hour before the intervention time.

In the touch group, the preconditions and conditions for touch were similar to the intervention group. A soft feet touch (with the same duration) was used, which covered all parts of the patient's sole of the feet without applying deep and effective pressure to the reflex sensitive points. This touch, like the reflexology group, started from the toes and ended at the heel.

In the control group, no intervention was performed.

Patients' pain and fatigue were assessed before, immediately after last sessions and two weeks later by a colleague of the researcher who had no information about the allocation of samples in the study groups (reflexology massage group, touch group and control group), through face-to-face interviews at the Special Diseases Center. The patients were not also aware of the study group they were in.

Data were analyzed using SPSS software version 22, by Kolmogro-Smirnov statistical tests (to determine the normality of quantitative data distribution), Chi-square and Fisher Exact statistical tests (to compare ratios), Mann-Whitney U (to compare means in between the three groups) and to compare time by time, the mean of pain and fatigue score in repeated measurements between and among the studied groups, the repeated measure ANOVA and statistical modeling were used. The significance level was considered at 0.05.

2-1. Inclusion and Exclusion Criteria

Inclusion criteria were no lesions such as wounds, cellulite and burns at the massage site, no history of cognitive disorders and mental illnesses, having more than 15 years of age, achieving a moderate or severe score on the scale of pain and fatigue. Exclusion criteria were failure to perform the intervention for two consecutive sessions or more than two sessions in total intervention period, inability to learn and perform the intervention and reluctance to continue participating in the study.

2-2. Ethical Considerations

In order to observe the ethics in the research, the proposal was approved by the research council of Rafsanjan University of Medical Sciences and the code of ethics was obtained from the research committee of this university (code of ethics: IR.RUMS1397.240). Furthermore, informed and written consent was obtained from the patients. Patients were also informed that their participation or non-participation in the study would have no effect on the quality of services received and the center's routine care. It should be noted that this project was registered at the Iranian clinical trial registry (IRCT.IR) with the identification Code of IRCT20190303042906N1.

3- RESULTS

In this study, the data from 90 Major Thalassemia Patients were analyzed (**Fig. 1**). The results of Kolmogorov–Smirnov showed that all of the quantitative variables were distributed normally. The data analysis results showed that the mean and standard deviation of the age of the samples was 21.59± 4.71 with a minimum of 15 and a maximum of 35 years. 39 of the participants (43.4%) were females and 51 (56.7%) were males. In terms of marital status 4 (4.4%) were married and 86 (95.6%) were single. No statistically significant difference was observed between the study groups regarding age, gender, educational level categories, and time of receiving a previous treatment. (**Table 1**).

Table-1: Comparison of the demographic characteristics across the studied groups

		Reflexology n=30	Touch n=30	Control n=30	P-Value
Gender* N (%)	Male	22(73.3)	15(50)	14(46.7)	0.076
	Female	8(26.7)	15(50)	16(53.3)	
Education** N (%)	Illiterate	5(16.7)	3(10)	5(16.7)	0.146
	Under Diploma	14(46.7)	15(50)	18(60)	
	Diploma	8(26.7)	5(16.7)	7(23.3)	
	Academic	3(10)	7(23.3)	0(0)	
Time interval of receiving treatment** last N (%)	2 weeks	26(86.7)	22(73.3)	76(84/4)	0.122
	More than 2 weeks	4(13.3)	8(26.7)	14(15/6)	
Age*** Mean (SD)		22.73(4.79)	21.13 (5.09)	20.90 (4.13)	0.263

* Chi-square test
**Fisher exact test
*** One way ANOVA

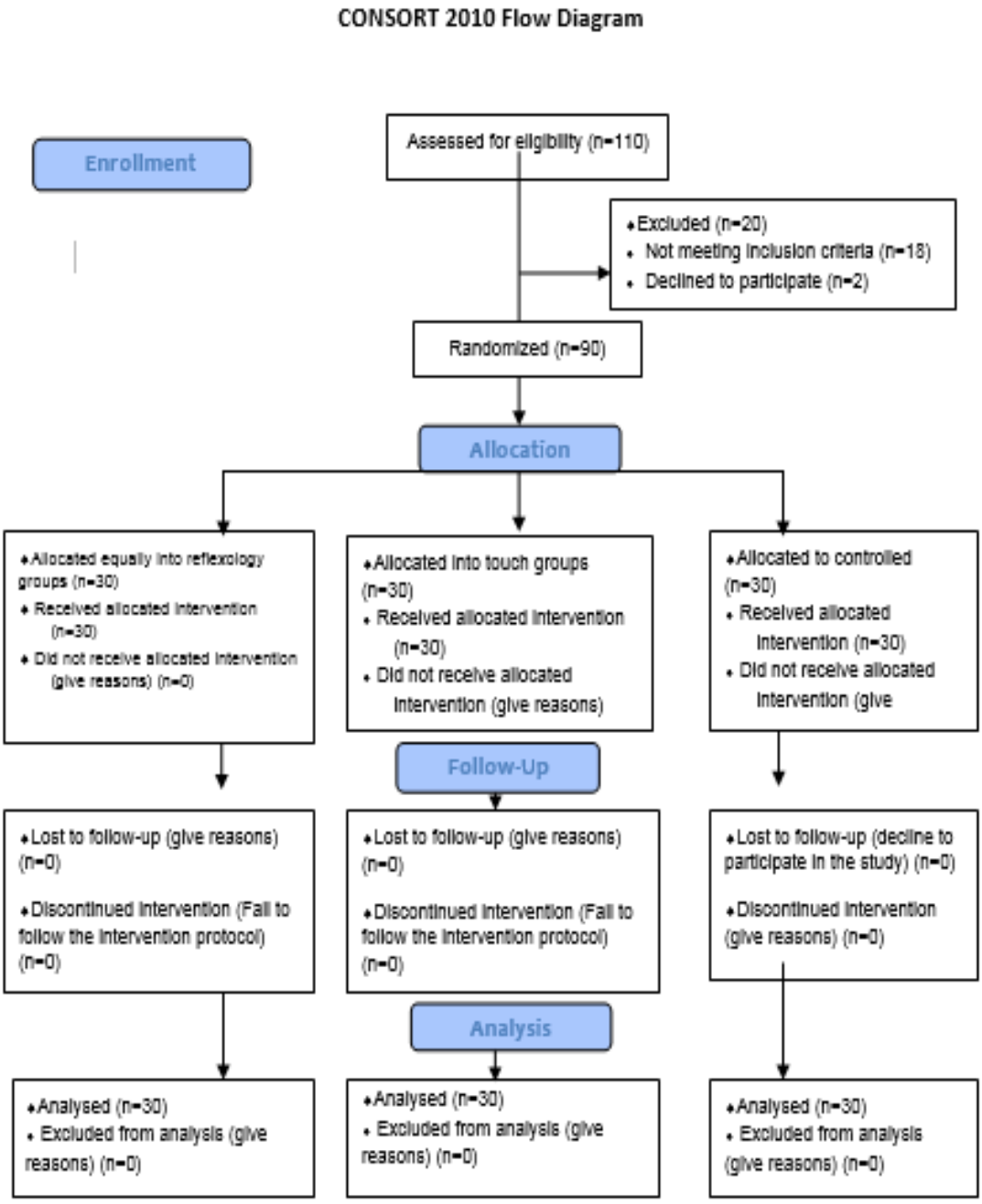

Fig. 1: Consort flow diagram of the study

To examine the changes of the pain score during consecutive measurement times (time effect) and among the study groups over the time (group effect), and pain score changes over time taking into account the effect of groups (interaction between time and group), repeated measure ANOVA was used. The results of Mauchly's Sphericity test showed that the correlation coefficients of the consecutive measurements were significantly different (P <0.0001). So the correlation equation precondition was not accepted. Therefore, Greenhouse-Geisser correction coefficient was used to report P-values. The results of the multivariate test showed that the effect of interaction between time and group (P = 0.001) (**Table 2**), and also the effect of time (P= 0.001) were statistically significant; so to examine the trend of pain

score changes in different groups and times, and the interaction between them in detail, the statistical modeling was used. The results of the Between-Subject Effect Test to evaluate the group effect did not show a statistically significant difference (P = 0.079).

Table-2: The comparison of means and standard deviations of pain scores in the three study groups at the three measurement times

	Reflexology Mean(SD)	Touch Mean(SD)	Control Mean(SD)	P-value*
Before intervention	5.83(1.46)	5.43(1.35)	5.47(1.25)	0.001
Immediately after intervention	4.13(1.38)	5.07(1.11)	4.43(1.25)	
One month after intervention	4.17(1.34)	5.03(1.21)	5.43(1.34)	

* Adjustment for multiple comparisons: Bonferroni

The results of analyzing the trend of pain score changes within each group showed that in the reflexology group, the mean pain score decreased significantly at the immediate measurement and two weeks after the intervention, compared to the pre-intervention phase (P = 0.001). But in the same group, the mean pain scores of the immediate and two-week-later measurements were not significantly different (P = 1.00). The control group showed no statistically difference in consecutive measurements (p>0.05). The results of examining the trend of pain score changes within the touch group in consecutive measurements showed that the mean pain score decreased, significantly, at the immediate and two-week-later measurements in comparison to the pre-intervention phase (P = 0.003). But, similar to the reflexology group, there was no statistically significant difference between the immediate and two-week-later measurements (P = 1.00).

Pairwise comparisons of mean pain score between groups showed no statistically significant difference between the study groups in the pre-intervention measurements. At the immediate and two-week-later measurements, there was a statistically significant difference between the reflexology and touch groups (P = 0.001 for both), and reflexology and control groups (P = 0.029), (P = 0.015) respectively. But there was no statistically significant difference between the touch and control groups (P > 0.05) (**Fig 2**).

Results of fatigue score analyses showed a statistically significant difference (P = 0.001) between the three groups in the three measurements stages (interaction between groups and times) (**Table 3**). The results of examining the trend of fatigue score changes within each group in consecutive measurements showed that in the reflexology group, the mean fatigue score between the pre-intervention and immediately after the intervention and also between the pre-intervention and two weeks after the intervention were statistically significant (P = 0.001). But in the same group, the mean change in fatigue scores between immediately after the intervention and two weeks after the intervention was not statistically significant (P = 1.00). In the touch group, no significant differences were observed in the mean fatigue scores between the pre-intervention stage and immediately after the intervention and also between the pre-intervention stage and two weeks after the intervention.

The results of examining the trend of fatigue score changes within each group in consecutive measurements showed that in the control group, the difference in mean

fatigue scores between the pre-intervention stage and immediately after the intervention and also between the pre-intervention stage and two weeks after the intervention were statistically significant (P = 0.003). But there was no statistically significant difference between the pre-intervention stage and two weeks after the intervention (P = 1.00).

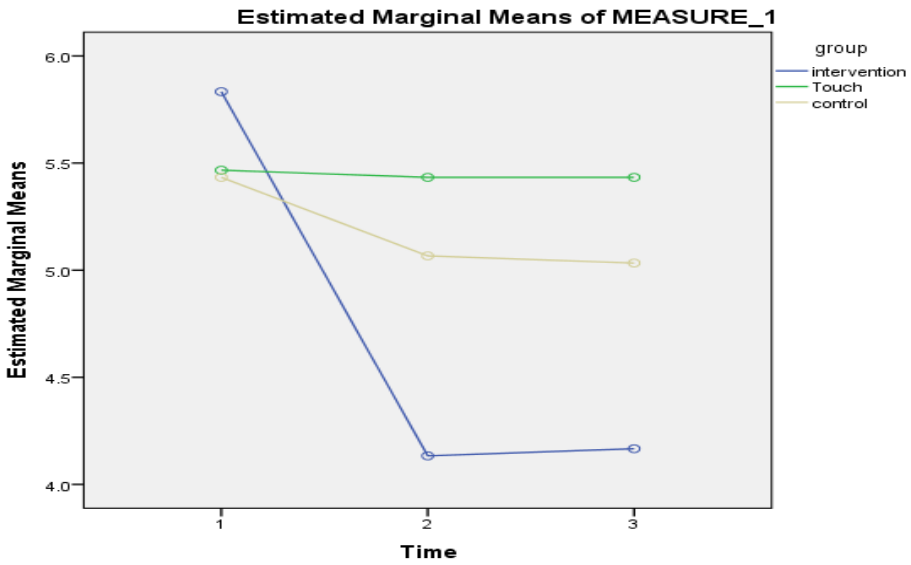

Fig. 2: The pain scores changes in the study groups in the three measurement times.

Table-3: Comparison of mean and standard deviation of Fatigue score in the three study groups at the three measurement times

	Reflexology Mean(SD)	Touch Mean(SD)	Control Mean(SD)	P-value*
Before the intervention	34.43(14.06)	31.13(6.27)	32.23(9.43)	0.001
Immediately after the intervention	26.37(12.03)	28.73(6.99)	31.70(8.78)	
Two weeks after the intervention	26.53(12.50)	28.50(8.04)	31.53(8.72)	

* Adjustment for multiple comparisons: Bonferroni

There is no statistically significant difference between the two groups in pairwise comparisons of fatigue scores before the intervention phase. This means that all three groups had the same fatigue score at the beginning of the study. There was no statistically significant difference in pairwise comparisons of fatigue scores between the study groups in the immediate and two-week-later measurements (**Fig. 3**).

4- DISCUSSION

In summary, the results of this study showed that in intragroup comparisons, the pain score in the control group did not change significantly during the three stages of measurement. But in the touch and reflexology groups, the mean pain scores at the immediate measurement and two weeks after the intervention were significantly lower than those before the intervention. However, in the follow-up stage, no significant change was observed

compared to the immediately after the intervention stage.

These results are probably due to the effect of placebo, the effect of the therapist's presence and the difference in the number of the therapist visits compared to the control group.

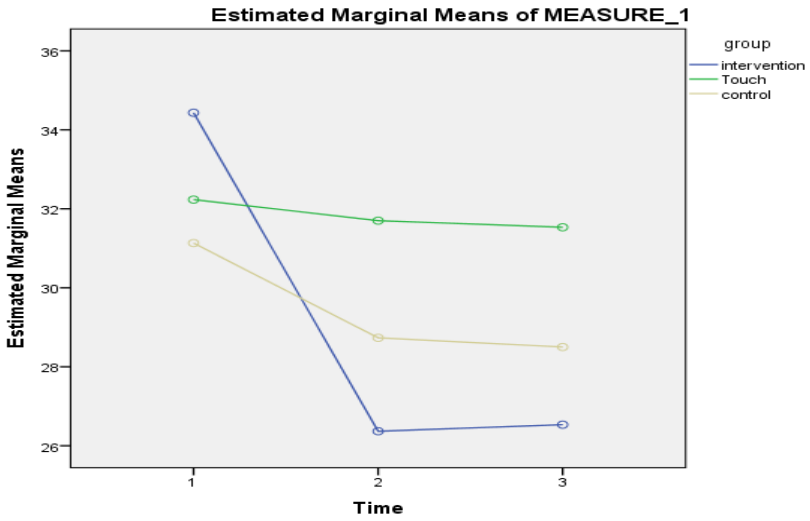

Fig. 3: The fatigue score changes in the study groups in the three measurement times.

Based on the results of this study, at the intergroup comparison, all three groups were similar in baseline mean scores of pain. But at the immediate and the follow up measurements, the reflexology group experienced significantly lower pain scores than the other two groups. However, the mean pain scores in the touch and control groups in the mentioned two stages did not change significantly.

In reviewing the available literature, limited studies have examined the effect of reflexology on pain and fatigue relief in the patients with thalassemia major. But the pain relieving effects of reflexology have been studied in other contexts and similar results to our research have been reported. In a study, Samarehfekri et al. showed that reflexology intervention significantly reduces the pain of patients after kidney transplantation surgery compared to the control group. However, reflexology did not reduce acetaminophen consumption (21). The results of Davodabady et al. revealed that the foot reflexology intervention could not alleviate the pain of burn patients during the dressing change on the second and third day, but on the fourth, fifth and sixth days the pain was significantly less than that in the control group (32). Also, Bakir and et al. showed that foot reflexology intervention after 6 weeks could significantly reduce the pain of patients with rheumatoid arthritis (33).

The results of the present study indicated that although the fatigue score in reflexology and touch group was reduced compared to the before intervention stage, the fatigue score was not significantly different between the three study groups. There is controversial evidence in the existing literature about the effect of reflexology on fatigue in different contexts. Some studies have shown the positive effect of this intervention on fatigue. For instance, Rambod et al. examined the effectiveness of reflexology on fatigue in lymphoma patients and concluded that reflexology could reduce

fatigue in these patients (26). In some other studies the reflexology was found to alleviate the fatigue in pregnant women (34), multiple sclerosis (35, 36), and cancer patients (32, 33). In some other studies, reflexology had no effect on fatigue. Similar to our study, Babazadeh et al. showed that reflexology could not reduce the fatigue of the pregnant women in the first half of pregnancy (34). Also in Chao's study, reflexology had no positive effect on reducing nursing students' fatigue (37).

Researchers in a review study reported that there is limited evidence for the effect of reflexology on fatigue. Instability in fatigue measurement tools, limitation in introducing minimum data on long-term results and cost-effectiveness are also important issues; therefore, it seems that not enough attention has been paid to the mechanisms of fatigue and intervention plans, and due to the complexity of fatigue, future research on exploring individualized approaches is necessary (38). This controversy in the available results may be due to the variety of intervention protocols, the therapist, the target group, and the nature of fatigue in each. In addition, the sensitivity of the repeated measure ANOVA statistical test in examining the data should not be overlooked.

Although in the present study, we have been trying to obtain valid results by matching the three groups in terms of basic pain and fatigue scores, two-way blinding and the use of accurate statistical analysis methods, the role of the personal characteristics and mental status of subjects in understanding and reporting the pain and fatigue levels cannot be ignored. In general, what can be deduced from the available texts is that reflexology has been able to relieve patients' fatigue in some cases. But in fewer studies, the placebo effect has been introduced by researchers. Therefore, based on the available evidence, the role of reflexology in relieving pain and fatigue in thalassemia patients is not clear. More detailed studies are needed to confidently comment on the effect of reflexology on pain and fatigue in thalassemia patients. So in future research, it is also necessary to clearly determine in which patients and at what stage of the disease this method can be used therapeutically.

5- CONCLUSION

In summary, the study showed that Reflexology could be used safely in management of pain in major thalassemia patients. But it could not reduce the patients' fatigue.

6- ACKNOWLEDGMENTS

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7- REFERENCES

1. Angastiniotis M, Lobitz S. Thalassemias: An Overview. IJNS, 2019; 5(1): 16.

2. Miri-Moghaddam E, Naderi M, Izadi S, Mashhadi M. Causes of new cases of major thalassemia in sistan and baluchistan province in South-East of iran. Iran. J. Public Health. 2012; 41(11):67.

3. Bonifazi F, Conte R, Baiardi P, Bonifazi D, Felisi M, Giordano P, et al. Patterns of complications and burden of disease in patients affected by beta thalassemia major. Curr. Med. Res. Opin. 2017; 33(8):1525-33.

4. Origa R. β-Thalassemia. GIM. 2017; 19(6):609-19.

5. Arbabisarjou A, Karimzaei T, Jamalzaei A. The perception of Biological experience in patients with major thalassemia: A

qualitative research. Glob. J. Health Sci. 2015; 7(1):79.

6. Lal A. Assessment and treatment of pain in thalassemia. Annals of the New York Academy of Sciences. 2016; 1368(1):65.

7. Pamuk GE, Pamuk ÖN, Set T, Harmandar O, Yeşil N. An increased prevalence of fibromyalgia in iron deficiency anemia and thalassemia minor and associated factors. Clin. Rheumatol. 2008; 27(9):1103.

8. Trachtenberg F, Foote D, Martin M, Carson S, Coates T, Beams O, et al. Pain as an emergent issue in thalassemia. Am. J. Hematol. 2010 May; 85(5):367-70

9. Aslani ERNMP, Georgios LMMPPD, Maria TP. The Measurement of Fatigue in Hemoglobinopathies: A Systematic Review of Fatigue Measures. Int. J. Caring Sci. 2018; 11(3):1970-81.

10. Prochaska MT, Newcomb R, Jiang D, Meltzer DO. The effect of red-blood-cell transfusion on fatigue in hospitalized patients with anemia. Vox sanguinis. 2018; 113(7):669-77.

11. Post LGMMP. The Measurement of Fatigue in Hemoglobinopathies: A Systematic Review of Fatigue Measures. Int. J. Caring Sci. 2018; 11(3):1970-81.

12. Needs T, Gonzalez-Mosquera LF, Lynch DT. Beta thalassemia. StatPearls. 2020.

13. Abusaad F, Sarhan MM. Exercise Training Program and Telenursing Effects on Depression and Fatigue Level in B-Thalathemia Major Children. AJN. 2016; 5(5):191-200.

14. Firouzkouhi M, Abdollahimohammad A. Effects of Smartphone Games on Levels of Anxiety, Depression, and Fatigue in Patients with Thalassemia. JMUMS. 2020; 30(188):62-71.

15. Tabei SMB, Mazloom M, Shahriari M, Zareifar S, Azimi A, Hadaegh A, et al. Determining and surveying the role of carnitine and folic acid to decrease fatigue in β-thalassemia minor subjects. Pediatr. Hematol. Oncol. J. 2013; 30(8):742-7.

16. Dehkordi AH, Hasani T, Fekri K, Deris F, Etemadifar S. Effects of aquatic exercise on dimensions of quality of life and blood indicators in patients with beta-thalassemia major. IJPM. 2020; 11(1):128.

17. Sadeghloo A, Shamsaee P, Hesari E, Akhondzadeh G, Hojjati H. The effect of positive thinking training on the quality of life of parents of adolescents with thalassemia. IJAMH. 2019; 1(ahead-of-print).

18. Taheri P, Nooryan K, Karimi Z, Zoladl M. Effect of Individual psychotherapy with a Focus on Self-Efficacy on Quality of Life in Patients with Thalassemia Major: A Clinical Trial. J. clin. Care skills. 2019; 1(2):49-54.

19. Jabbarifard F, Sharifi T, Solati K, Ghazanfari A. The effectiveness of acceptance and commitment therapy on perceived stress, resilience, and the quality of life in thalassemia major patients. J Shahrekord Univ Med Sci. 2019; 21(2):91-7.

20. Metin ZG, Ozdemir L. The effects of aromatherapy massage and reflexology on pain and fatigue in patients with rheumatoid arthritis: a randomized controlled trial. Pain Manag Nurs. 2016; 17(2):140-9.

21. Samarehfekri A, Dehghan M, Arab M, Ebadzadeh MR. Effect of foot reflexology on pain, fatigue, and quality of sleep after kidney transplantation surgery: a parallel randomized controlled trial. Evid. Based Complementary Altern. Med. 2020

22. Dikmen HA, Terzioglu F. Effects of reflexology and progressive muscle relaxation on pain, fatigue, and quality of life during chemotherapy in gynecologic cancer patients. Pain Manag Nurs. 2019; 20(1):47-53.

23. Blunt E. Foot Reflexology. Holist. Nurs. Pract. 2006; 20(5):257-9. PubMed PMID: 00004650-200609000-00009.

24. Unal KS, Akpinar RB. The effect of foot reflexology and back massage on hemodialysis patients' fatigue and sleep quality. Complement. Ther. Clin. Pract. 2016; 24:139-44.

25. Roshanravan M, Jouybari L, Bahrami Taghanaki H, Vakili M, Sanagoo A, Amini Z. Effect of foot reflexology on fatigue in patients undergoing hemodialysis: A sham-controlled randomized trial. JMUMS 2016; 26(137):32-41.

26. Rambod M, Pasyar N, Shamsadini M. The effect of foot reflexology on fatigue, pain, and sleep quality in lymphoma patients: a clinical trial. Eur J Oncol Nurs. 2019; 43:101678.

27. Mansouri A, Shadadi H, Poudineh-Moghadam M, Vahed AS, Dehghanmehr S. Evaluation of the effect of foot reflexology massage on vital signs and anxiety after blood transfusions in children with thalassemia. **B**ali Medical Journal, 2017 Jan 1; 6(3):623-9.

28. Dehghanmehr S, Sheikh G, Siyasari A, Sheikh A, Nooraien S, Salarzaei M. The impact of foot reflexology massage on anxiety caused by blood transfusion in children with thalassemia. Int J Pharm Sci Res. 2018; 9(5):7-2053.

29. Özdemir G, Ovayolu N, Ovayolu Ö. The effect of reflexology applied on haemodialysis patients with fatigue, pain and cramps. Int J Nurs Pract 2013; 19(3):265-73.

30. Pandis N. Randomization. Part 2: minimization. AJO-DO, 2011; 140(6): 902-4.

31. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Fatigue severity scale (FSS). InSTOP, THAT and One Hundred Other Sleep Scales Springer, New York, NY.

2011: 167-168).

32. Davodabady F, Naseri-Salahshour V, Sajadi M, Mohtarami A, Rafiei F. Randomized controlled trial of the foot reflexology on pain and anxiety severity during dressing change in burn patients. Burns. 2021; 47(1):215-21.

33. Bakir E, Baglama SS, Gursoy S. The effects of reflexology on pain and sleep deprivation in patients with rheumatoid arthritis: a randomized controlled trial. **Comple**ment. Ther. Clin. Pract, 2018; 31:315-9.

34. Shobeiri F, Manoucheri B, Parsa P, Roshanaei G. Effects of counseling and sole reflexology on fatigue in pregnant women: a randomized clinical trial. Journal of clinical and diagnostic research: JCDR. 2017; 11(6):QC01.

35. Ozdelikara A, Alkan SA. The effects of reflexology on fatigue and anxiety in patients with multiple sclerosis. ATHM, 2018; 24(4):8-13.

36. Sajadi M, Davodabady F, Ebrahimi-Monfared M. The Effect of Foot Reflexology on Fatigue, Sleep Quality and Anxiety in Patients with Multiple Sclerosis: A Randomized Controlled Trial. Arch. Neurosci, 2020; 7(3).

37. CHO G-Y. Effects of Self-Foot Reflexology on the Stress, Fatigue and Sleep Pattern of the Nursing Students. J Fish Mar Sci Educ. 2017; 29(2):386-95.

38. Cramp F. The role of non-pharmacological interventions in the management of rheumatoid-arthritis-related fatigue. Rheumatology. 2019; 58(Supplement_5):v22-v8.