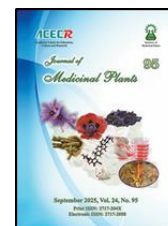




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## Journal of Medicinal Plants

Journal homepage: [www.jmp.ir](http://www.jmp.ir)



### Article

## A comparative analysis of the impact of virtual reality and rose aroma on anxiety, sleep quality, and happiness among patients undergoing dialysis: a randomized control trial with a factorial design

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### ARTICLE INFO

#### Keywords:

Aromatherapy

Hemodialysis

Virtual reality

Anxiety

Sleep quality

Happiness

### ABSTRACT

**Background:** Hemodialysis patients frequently experience anxiety and poor sleep quality, adversely affecting overall well-being. **Objective:** The objective is to evaluate the effects of virtual reality (VR) and aromatherapy (AR), individually and in combination, on anxiety, sleep quality, and happiness among patients undergoing dialysis. **Methods:** A randomized controlled trial was conducted with 80 participants (mean age: 55.19 years) assigned to four groups: control (CL), aromatherapy (AR), virtual reality (VR), and aromatherapy with virtual reality (AR + VR). Assessments included demographic questionnaires, the Spielberger State-Trait Anxiety Inventory, the Pittsburgh Sleep Quality Index, and the Oxford Happiness Questionnaire. Interventions lasted four weeks, with weekly 15-minute sessions, beginning 20 minutes post-dialysis. The AR group received rose essence via a mask, the VR group viewed calming nature scenes, and the AR+VR group received both interventions. **Results:** Analysis (SPSS v19) indicated that the AR + VR group showed a significant increase in happiness scores compared with other groups ( $P < 0.001$ ) and reductions in both state and trait anxiety. The CL group exhibited a decline in sleep quality, whereas no significant sleep-quality improvements were observed in the intervention groups. **Conclusion:** Integrating VR and AR may reduce anxiety and enhance well-being among dialysis patients. Further research is needed to examine long-term effects and optimize intervention strategies.

### 1. Introduction

Chronic kidney disease presents multifaceted challenges that extend beyond the physical realm, significantly influencing the economic, psychological, and social aspects of patients' lives, ultimately affecting their overall quality of

life. The prevalence of end-stage kidney disease demonstrates notable variation across different nations. For instance, European countries report an average incidence of 171 cases per million individuals, whereas the United States shows a higher rate at 336 cases per million. The United

**Abbreviations:** CKD, Chronic kidney disease; SAS, Sleep apnea syndrome; reality; CL, Control; AR, Aromatherapy; VR, Virtual reality

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doi:

Received 4 January 2025; Received in revised form 18 August 2025; Accepted 19 August 2025

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Kingdom records the lowest incidence rate at 100 cases per million. In contrast, Iran faces a concerning situation with an incidence rate of 357 cases per million, and projections indicate that this number could escalate to 95,000 cases by 2021 [1]. The rate of kidney failure in Iran is significantly above the global average, which sees an annual increase of approximately 6-7 %, while Iran experiences about a 12 % rise annually. Predominantly, the leading causes of kidney disease in Iran are diabetes and hypertension [1].

Hemodialysis serves as a vital treatment for individuals with kidney failure, effectively substituting essential kidney functions and enabling patients to lead relatively fulfilling lives [2]. While hemodialysis enhances life expectancy, it can also negatively impact patients' mental health, leading to heightened anxiety, stress, and sleep disturbances [3]. Sleep disorders are common among hemodialysis patients, often remaining unrecognized and potentially leading to conditions like sleep apnea syndrome, excessive daytime sleepiness, and the worsening of cardiovascular and immune system-related illnesses [4]. These sleep disorders can amplify feelings of stress and anxiety, thereby increasing the risk of mortality [3].

Sleep quality is intricately linked to the overall quality of life for dialysis patients, with insomnia posing a significant problem [4]. Research indicates that as many as 80 % of hemodialysis patients experience various sleep disturbances, which may lead to conditions like sleep apnea syndrome (SAS), excessive daytime sleepiness, and the worsening of cardiovascular and immune system-related illnesses [5, 6]. Untreated insomnia can diminish patients' happiness and well-being, potentially shortening life expectancy [7]. The time commitment of

hemodialysis sessions can exacerbate stressors such as fatigue and dietary restrictions, increasing the risk of psychological challenges like anxiety, tension, and depression [3]. Studies have shown that anxiety is prevalent among hemodialysis patients, with symptoms such as headaches, insomnia, changes in appetite, fatigue, and mood fluctuations detrimentally affecting their quality of life. Addressing these sleep and anxiety issues is crucial for improving the overall health and well-being of hemodialysis patients [7].

Various anxiety management strategies exist for hemodialysis patients, including pharmacological interventions, psychotherapy, and behavioral therapies [8]. While pharmacotherapy is an option, it is not always the first line of treatment due to potential adverse effects. Medications for insomnia, like benzodiazepines, may be considered relatively safe in certain situations, but the risk of dependence limits their long-term use [2].

Complementary therapies offer an alternative approach for alleviating anxiety and enhancing sleep quality in hemodialysis patients with minimal side effects [9]. Virtual reality (VR) has demonstrated efficacy in reducing anxiety and fostering relaxation, while aromatherapy utilizes essential oils to promote relaxation through olfactory stimulation [9]. Integrating VR with aromatherapy could provide a synergistic effect, enhancing emotional regulation.

A significant lack of research exists regarding the synergistic effects of VR and aromatherapy for alleviating anxiety, enhancing sleep quality, and promoting overall happiness in hemodialysis patients [10]. The financial implications of implementing and examining these treatments also require further investigation. While some studies have suggested potential benefits of aromatherapy in

mitigating anxiety and improving sleep, findings are often inconsistent.

Considering the challenges and adverse effects associated with conventional treatments, alongside the recognized anxiolytic properties of rose essential oil, this research aims to delve into the combined application of aromatherapy using rose essential oil and VR. The goal is to evaluate how these interventions influence the psychological burdens faced by patients during treatment and to uncover a more economical treatment alternative that minimizes side effects. Addressing the costs associated with psychological therapies is crucial for patient satisfaction and adherence to treatment protocols. Therefore, studies concentrate on analyzing the effects of VR and aromatherapy on anxiety levels, sleep quality, and overall happiness in individuals receiving dialysis, with the intent of identifying effective strategies to enhance their mental well-being during this challenging period.

## 2. Materials and methods

This study employs a semi-experimental framework based on a  $2 \times 2$  factorial design. It was conducted in the Dialysis Department of Mehr Madar Hospital in Torbat-Jam, Iran, which has 15 dialysis beds operating in three shifts: morning, evening, and night. The target population consisted of hemodialysis patients who consented to participate in the research. Inclusion criteria required participants to provide informed consent, have at least three months of hemodialysis experience, and be free from conditions affecting their hearing, vision, or sense of smell.

Exclusion criteria included a history of mental health disorders, serious accidents within the past six years, debilitating diseases such as dementia or Parkinson's disease, sensitivity to

smell, or the use of sleeping pills, anti-anxiety medications, or herbal essences during the intervention period. Participants were also excluded if they passed away, missed an intervention session, or developed sensitivity to essential oils that necessitated withdrawal from the study.

This study adhered to ethical considerations in two key aspects: first, all participants provided voluntary informed consent to participate in the study; and second, participants were assured that all information would remain confidential and that the results would be reported in aggregate form. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1975 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The study protocol, with approval number IR.BUMS.REC.1400.360, was approved by the ethics committee of Birjand University of Medical Sciences. Furthermore, the study was registered with the clinical trial registry under code IRCT20221225056922N1.

A total of 80 patients were randomly assigned to four groups: aromatherapy (AR), virtual reality (VR), a combined approach (AR+VR), and a control group (CR). Initially, the control group did not receive any intervention; however, for ethical reasons, they were offered one of the interventions one week after questionnaire data collection. To prevent aroma exposure from affecting other participants during the aromatherapy sessions, the study allocated specific shifts (morning, afternoon, and night) for each group using block randomization with a block size of four, ensuring a balanced assignment of eligible participants.

### 2.1. Instruments

The study employed a variety of questionnaires to gather essential data. These included a demographic information form, which captured details such as age, gender, marital status, occupation, education level, smoking history, history of hemodialysis, and previous hospitalizations. Additionally, the research utilized the Spielberger State-Trait Anxiety Inventory, the Pittsburgh Sleep Quality Index, and the Oxford Happiness Questionnaire. The psychometric properties of these instruments have been previously validated within the Iranian context [11-14].

To assess anxiety levels among participants, the Spielberger State-Trait Anxiety Inventory, comprising 40 items, was utilized. This inventory is divided into two sections: the first 20 questions evaluate state anxiety, while the latter 20 assess trait anxiety. The instrument has shown considerable reliability, with a Cronbach's alpha coefficient of 0.92 in Iranian studies, affirming its effectiveness in anxiety measurement [11, 13].

Furthermore, the Oxford Happiness Questionnaire, which includes 11 items with four statements each, was employed to gauge the happiness levels of the respondents. Participants rated the statements on a scale from 0 to 3, leading to a potential total score ranging from 0 to 98; higher scores indicate increased levels of happiness. This questionnaire has also demonstrated strong validity and reliability in assessing happiness in Iranian society, with a reported Cronbach's alpha coefficient of 0.93. Thus, the combination of these validated tools provides a comprehensive framework for analyzing the psychological well-being of the study's participants [15].

The Pittsburgh Sleep Quality Index, comprised of seven distinct components, is

utilized to evaluate sleep quality, with scores ranging from 0, indicating no issues, to 3, reflecting severe difficulties [14].

During a four-week intervention period, the project was overseen by a professor from the Torbat Jam Faculty of Medical Sciences, while the researcher and trained colleagues facilitated the intervention. This program included weekly sessions lasting 15 minutes, incorporating both virtual reality and aromatherapy interventions across three separate groups.

In the aromatherapy group, participants were instructed to place an absorbent cloth imbued with three drops of rose water inside their masks for a duration of 15 minutes, ensuring normal inhalation to enhance the treatment's efficacy. The virtual reality group experienced a calming 15-minute session using 3D glasses, featuring serene imagery sourced from Nature online, following the treatment protocol established by Hariss et al. in 2002. The blended intervention group received both therapies; they inhaled rose essence on a cloth placed inside their masks 20 minutes after the commencement of dialysis while simultaneously engaging with the soothing virtual reality visuals. This multifaceted approach aimed to explore the synergistic effects of aromatherapy and virtual reality on improving sleep quality among participants.

### 2.2. Statistical analysis

In this research, quantitative variables were summarized by their means and standard deviations, while qualitative variables were presented as frequencies and percentages. To assess the assumption of normality, the Shapiro-Wilk test was employed. For comparing quantitative variables among different study groups, analysis of variance (ANOVA) was utilized; in cases where the normality

assumption was violated, the Kruskal-Wallis test was implemented instead. The Chi-square test was used to analyze the homogeneity of qualitative variables across the study groups, and when the expected frequencies fell below acceptable thresholds, Fisher's exact test was conducted. To evaluate the impact of the intervention within each group, the paired samples t-test was applied. Statistical analyses were performed using SPSS version 19, with the significance level set at 0.05.

### 3. Results

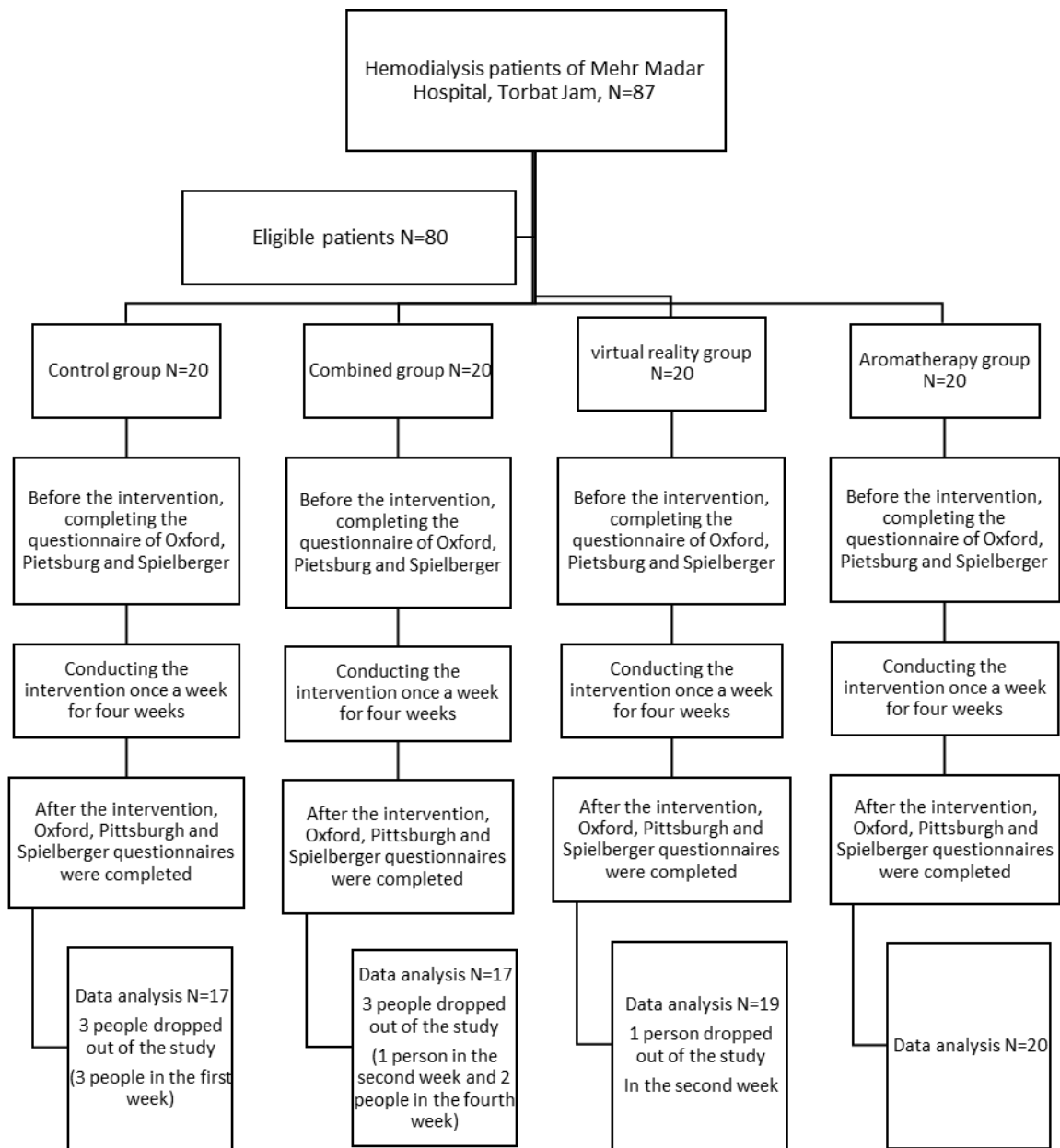
The AR + VR group initially included 17 participants; however, one individual chose to withdraw from the study during the first week, and two others withdrew due to illness in the second week. In addition, three participants from the observation group discontinued their involvement in the first week, citing

dissatisfaction with the research process. Consequently, the observation group ultimately retained 17 members, while the AR group comprised 20 individuals. These two groups showed similarity in several demographic factors, including gender ( $P = 0.6$ ), occupation ( $P = 0.23$ ), educational background ( $P = 0.98$ ), smoking history ( $P = 0.51$ ), and marital status ( $P = 1$ ), as detailed in Table 1. By the conclusion of the intervention, 19 participants remained in the VR group, although one participant withdrew due to experiencing eye pain during the second week. This data highlights the importance of considering participant retention and satisfaction in research studies, particularly in the context of AR and VR interventions. Understanding the reasons behind withdrawals can inform future research design and improve engagement strategies.

**Table 1.** Frequency distribution of demographic variables according to the studied groups

Variable		CL	AR	VR	AR + VR	P-value
Sex	Female	9 (26.5)	11 (32.4)	8 (23.5)	6 (17.6)	0.6 <sup>a</sup>
	Male	8 (20.5)	9 (23.1)	11 (28.2)	11 (28.2)	
Marital status	Single	4 (26.7)	4 (26.7)	4 (26.7)	3 (20.0)	0.98 <sup>a</sup>
	Married	13 (22.4)	16 (27.6)	15 (25.9)	14 (24.1)	
Job	Self-employed	4 (14.3)	5 (17.9)	9 (32.1)	10 (35.7)	0.23 <sup>b</sup>
	Unemployed	6 (42.9)	4 (28.6)	2 (14.3)	2 (14.3)	
	Housewife	7 (23.3)	10 (33.3)	8 (26.7)	8 (16.7)	
Education level	Illiterate	8 (25)	9 (28.1)	9 (28.1)	6 (18.8)	0.98 <sup>b</sup>
	Elementary	6 (22.2)	7 (25.9)	6 (22.2)	8 (29.6)	
	Lower/upper secondary	3 (21.4)	4 (28.6)	4 (28.6)	3 (21.4)	
History of smoking	Yes	2 (11.1)	6 (33.3)	6 (33.3)	4 (22.2)	0.51 <sup>b</sup>
	No	15 (27.3)	14 (25.5)	13 (23.6)	13 (23.6)	

a: Chi-square test, b: Fisher exact test



**Fig. 1.** Consort diagram  
Eligible patients N = 80

*3.1. Changes in sleep quality before and After the Intervention across study groups*

Before the intervention, the average sleep quality scores for the CL, AR, VR, and AR+VR groups were:  $(8.52 \pm 3.53)$  for CL,  $(7.25 \pm 2.04)$  for AR,  $(11.36 \pm 4.29)$  for VR, and  $(7.9 \pm 2.1)$  for AR+VR. After the intervention, these scores

changed to:  $(13.8 \pm 5.9)$  for CL,  $(8.2 \pm 2.5)$  for AR,  $(11.15 \pm 5.2)$  for VR, and  $(7.2 \pm 1.09)$  for AR+VR. Statistical analysis revealed significant differences among the groups ( $P < 0.001$ ), indicating that the CL group experienced the most substantial improvement in sleep quality, with a significant increase in scores ( $P < 0.001$ )



(Table 2). Conversely, the AR+VR and VR groups showed a decline in sleep quality scores following the intervention. Intra-group analysis further indicated that only the CL group demonstrated a statistically significant change from pre- to post-intervention.

### 3.2. Changes in happiness before and After the Intervention across study groups

Regarding happiness levels, prior to the intervention, the average scores did not show significant differences among the groups: CL ( $41.11 \pm 17.1$ ), AR ( $34 \pm 14.8$ ), VR ( $34.36 \pm$

$15.80$ ), and AR+VR ( $35.3 \pm 11.6$ ) ( $P = 0.51$ ). After the intervention, these scores changed to:  $41.9 \pm 16$  for CL,  $39.2 \pm 12.6$  for AR,  $37.5 \pm 14.9$  for VR, and  $45.5 \pm 8.4$  for AR+VR. Despite these changes, the differences remained statistically insignificant ( $P = 0.12$ ) (Table 2). Within-group comparisons revealed no substantial changes for the CL group. However, the AR, VR, and AR+VR groups showed an increase in happiness scores, with the AR+VR group demonstrating a notable advantage over the aromatherapy and VR groups (Table 2).

**Table 2.** Comparison of the Sleep quality, happiness, State-anxiety, Trait-anxiety and Total anxiety among the study groups before and after the intervention

Outcome	Time	CL	AR	VR	AR+VR	F (df <sub>1</sub> df <sub>2</sub> )	P-value
Sleep quality	Before	$8.52 \pm 3.53$	$7.25 \pm 2.04^b$	$11.36 \pm 4.29^b$	$7.9 \pm 2.1^b$	6.25 (3-69)	<0.001*
	After	$13.8 \pm 5.9^a$	$8.2 \pm 2.5$	$11.15 \pm 5.2$	$7.2 \pm 1.09$	8.75(3-69)	<0.001*
Happiness	Before	$41.11 \pm 17.1$	$34 \pm 14.8$	$34.36 \pm 15.80$	$35.3 \pm 11.6$	2.25 (3)	0.51 #
	After	$41.9 \pm 16$	$39.2 \pm 12.6^a$	$37.5 \pm 14.9^a$	$45.5 \pm 8.4^a$	5.8 (3)	0.12 #
State-anxiety	Before	$43.93 \pm 13.87$	$45.10 \pm 11.52$	$44.31 \pm 16.7$	$49.29 \pm 10.89$	0.55(3-67)	0.64*
	After	$44.06 \pm 12.80$	$40.94 \pm 10.15^a$	$44.31 \pm 16.7^a$	$49.29 \pm 10.89^a$	1.25(3-69)	0.3*
Trait-anxiety	Before	$44.37 \pm 12.44$	$45.46 \pm 14.36$	$44.00 \pm 14.40$	$49.52 \pm 11.54$	0.73 (3-69)	0.53*
	After	$44.68 \pm 10.29$	$43.21 \pm 13.26^a$	$41.47 \pm 13.99^a$	$36.47 \pm 8.12^a$	1.45(3-69)	0.22*
Total anxiety	Before	$88.33 \pm 25.8$	$90.78 \pm 24.17$	$88.31 \pm 30.11$	$98.82 \pm 22.11$	0.63 (3-67)	0.59*
	After	$88.75 \pm 22.44$	$84.15 \pm 22.29^a$	$81.57 \pm 27.61^a$	$72.41 \pm 12.86^a$	1.45(3-69)	0.23*

a: significant difference with Before, b: significant difference with CL, \*: ANOVA test, #: Kruskal walis test

### 3.3. Changes in state anxiety before and After the Intervention across study groups

Regarding state anxiety, the pre-intervention mean scores were comparable across groups: CL ( $43.93 \pm 13.87$ ), AR ( $45.10 \pm 11.52$ ), VR ( $44.31 \pm 16.7$ ), and AR + VR ( $49.29 \pm 10.89$ ), with no significant differences observed ( $P = 0.3$ ). However, post-intervention, the AR + VR group showed the most substantial reduction in state anxiety scores. Intra-group analyses further confirmed significant decreases in state anxiety for the AR+VR group, suggesting that the

combined approach may be particularly effective in alleviating anxiety symptoms (Table 2).

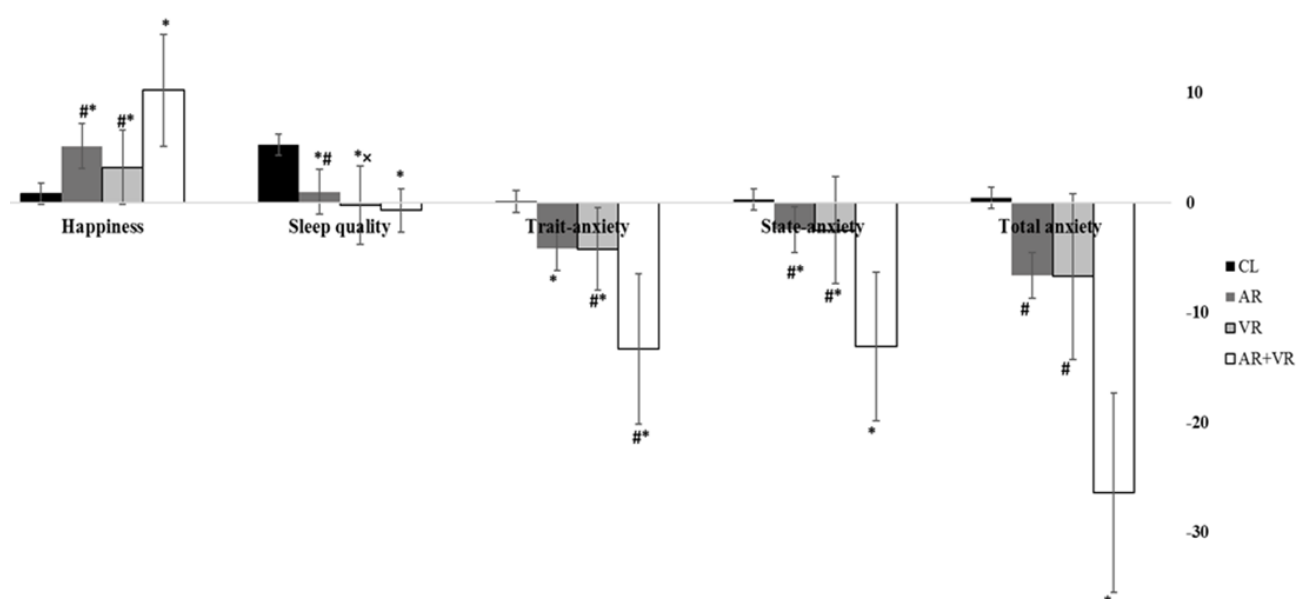
### 3.4. Changes in trait-anxiety before and after the intervention across study groups

Before the intervention, the average trait-anxiety scores across the groups—CL ( $44.37 \pm 12.44$ ), AR ( $45.46 \pm 14.36$ ), VR ( $44.00 \pm 14.40$ ), and AR+VR ( $49.52 \pm 11.54$ )—showed no significant differences. Post-intervention analysis similarly revealed no statistically significant variation in the mean trait-anxiety

scores among the groups ( $P = 0.22$ ) (Fig. 2). However, the blended group (AR + VR) showed the most substantial reduction in anxiety levels, with the virtual reality group following closely. Within-group evaluations further indicated significant reductions in anxiety scores for all groups except for the control group after the intervention (Table 2).

Prior to the intervention, total mean anxiety scores were comparable across groups: CL ( $88.33 \pm 25.8$ ), AR ( $90.78 \pm 24.17$ ), VR ( $88.31 \pm 30.11$ ), and AR+VR ( $98.82 \pm 22.11$ ), with no

statistically significant differences observed ( $P = 0.59$ ). Following the intervention, the total mean anxiety scores changed to:  $88.75 \pm 22.44$  for CL,  $84.15 \pm 22.29$  for AR,  $81.57 \pm 27.61$  for VR, and  $72.41 \pm 12.86$  for AR + VR. Despite these changes, no significant differences were found among the groups post-intervention ( $P = 0.23$ ). These findings underscore the efficacy of the blended approach in reducing anxiety, suggesting that all interventions—except for the control group—led to significant within-group improvements.



**Fig. 2.** Comparison of differences in mean scores of happiness, sleep quality, trait-anxiety, state-anxiety, and total anxiety in the studied groups after the intervention. \*: significant difference with Control group, #: significant difference with AR + VR, x: significant difference with AR

#### 4. Discussion

This study examined the effects of virtual reality (VR) and rose aromatherapy (AR) on anxiety, sleep quality, and happiness in hemodialysis patients. Participants were categorized into four homogeneous groups based on gender, marital status, occupation, education, and smoking habits.

Our findings revealed that the control group experienced the most significant change in sleep quality scores post-intervention; however, this

change indicated a decline in sleep quality, possibly due to the absence of sedative medication during the intervention period. In contrast, previous studies, such as Fattah et al. on the effects of rose aroma on sleep quality in lactating women, and Gharaee et al. on the impact of citrus aurantium in patients with acute coronary syndrome, reported improved sleep quality following aromatherapy. While these studies used different essential oils, our research specifically



focused on rose aroma, which has been recognized for its calming properties [12, 16].

Interestingly, our results showed no statistically significant improvement in sleep quality among the VR and AR+VR groups. This minimal variation may be attributed to the dopaminergic effects of VR, which can increase alertness and energy levels, potentially disrupting sleep patterns. This observation aligns with the findings of Lee et al., who investigated the impact of VR meditation on sleep quality in ICU patients. Their study reported shorter sleep durations but longer deep sleep periods, suggesting that VR may alter sleep architecture. Similarly, Tanriverdi et al. examined the effects of VR-based interventions on sleep in leukemia patients, reporting significant improvements in total sleep time and respiratory disturbance indices. The differences between these studies and our findings may stem from the timing of VR exposure, as our interventions were conducted during dialysis sessions, potentially influencing observed outcomes.

Regarding happiness levels, our analysis indicated that all intervention groups (AR, VR, AR + VR) showed significant increases in happiness scores, whereas the control group exhibited no notable changes. The AR + VR group demonstrated the most substantial improvement, suggesting a synergistic effect between rose aroma and immersive VR experiences. This finding is consistent with Dadkhah et al., who explored the impact of VR-based dream creation on happiness in elderly women, reporting an 83 % increase in happiness scores among participants. Furthermore, our results align with Barati et al., who investigated the effects of rose aroma on anxiety in hemodialysis patients, confirming its positive impact on emotional well-being. Anxiety scores

significantly decreased in all intervention groups, with the AR+VR group showing the most pronounced reduction. This supports the hypothesis that combining aromatherapy with VR can effectively divert patients' attention from environmental stressors, enhancing relaxation [17].

Previous studies, such as Khoshkhati et al., have also demonstrated the benefits of integrating VR with aromatherapy, reporting reductions in depression, anxiety, and stress among dialysis patients [5]. Similarly, Hashemi et al. found that elderly cardiac ICU patients in the control group exhibited no significant changes in anxiety levels, whereas the experimental group showed a statistically significant reduction [18]. Dehkordi et al. further highlighted the therapeutic potential of rose aromatherapy, emphasizing its effectiveness in alleviating psychological distress in hemodialysis patients [5].

### Limitations of the Study

Despite the strengths of this study, several limitations should be acknowledged:

- **Limited sample size** may affect the generalizability of the findings.
- **Difficulty in understanding research terminology** among participants posed a challenge. To address this, questionnaires were administered through interviews, and patients were offered follow-up support via phone or in-person meetings.
- **Potential response bias** may have occurred if participants did not fully express their true feelings. Confidentiality was emphasized to mitigate this risk.
- **Physical, emotional, and psychological conditions** of participants—stemming from the stress and anxiety associated with their illness—may have influenced their responses. To reduce this impact, the researcher personally introduced themselves to each patient and clarified that the

information collected would be used solely for research purposes.

## 5. Conclusion

Findings indicate that virtual reality and rose aromatherapy can significantly enhance happiness and reduce anxiety in hemodialysis patients. However, their effect on sleep quality remains unclear, possibly due to dopaminergic influences of VR and timing of interventions. Future research should investigate long-term outcomes, optimal timing, and integration with other relaxation techniques to improve patient well-being.

### 5.1. Conclusion and recommendations

The results of this study indicated that the combined use of aromatherapy and virtual reality had a significant positive effect on happiness and anxiety (both state and trait), but did not yield significant improvements in sleep quality. While each intervention alone also had a positive effect on happiness and anxiety, the combination of aromatherapy and virtual reality had the greatest impact. Furthermore, compared with other treatment options, such as drug therapy, the costs of these two methods are relatively low, and these methods are highly accessible and easy to implement.

### Human and animal rights

This research did not involve the use of animals. All procedures involving human participants were conducted in accordance with the ethical principles outlined in the 1975 Declaration of Helsinki.

### Consent for publication

In accordance with ethical considerations, the confidentiality of participants' information was maintained, and access to this information was

strictly restricted. Participants' names and surnames were not collected during data acquisition, which was conducted following approval from the Birjand University of Medical Sciences ethics committee.

### Funding

This research was done with the financial support of Birjand University of Medical Sciences.

### Standards of reporting

The STROBE guidelines were followed.

### Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

### Author contributions

F. H: Conceptualization, methodology, data collection. M. N: Supervision, project administration, manuscript writing. F. S: Statistical analysis, data interpretation. I. S: Data validation, manuscript review. Final manuscript. All authors have read and approved the final version of the manuscript.

### Conflict of interests

The authors declare no conflicts of interest, financial or otherwise.

### Acknowledgements

This article is derived from the Master's thesis in Nursing by Fahimeh Heirati, conducted under the supervision of Ms. Manijeh Nasirizadeh. The authors gratefully acknowledge the support of the officials from the Dialysis Department at Mehr Madar Hospital in Torbatjam, as well as the patients who participated in this study.

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How to cite this article: Heirati F, Salmani F, Nasirizadeh M, Sarbisheh I. A Comparative analysis of the impact of virtual reality and rose aroma on anxiety, sleep quality, and happiness among patients undergoing dialysis: A randomized control trial with a factorial design. *Journal of Medicinal Plants* 2025; 24(95): 77-88.

doi: