

Effectiveness of Intensive Short-term Dynamic Psychotherapy on Attachment Styles, Somatization, and Health Anxiety in Patients with Chronic Pain

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ABSTRACT

Objective: The experience of long-term pain and beliefs related to time associated with pain are key factors in understanding the experience of pain and psychological distress in patients. Intensive Short-term Dynamic Psychotherapy (ISTDP) can play an effective role in improving psychological symptoms. Therefore, this study aimed to determine the effectiveness of ISTDP on attachment styles, somatization, and health anxiety in patients with chronic pain. **Methods and Materials:** This quasi-experimental study employed a pre-test, post-test, and follow-up design with a control group. The study population consisted of all patients with chronic pain visiting pain clinics in Tehran in 2023. Thirty participants were randomly and conveniently selected and allocated into experimental (15 participants) and control (15 participants) groups. The experimental group received fifteen 90-minute sessions of ISTDP, while the control group received no intervention. Both groups were assessed for attachment styles, somatization, and health anxiety. Data were analyzed using a two-way analysis of variance with repeated measures.

Findings: Before the intervention, the mean scores for secure attachment, somatization, and health anxiety were 72.25, 58.36, and 24.08 in the treatment group, and 72.12, 59.16, and 23.52 in the control group, respectively ($p < .05$). After the intervention, the treatment group showed a significant increase in the mean scores of secure attachment and significant decreases in avoidant and anxious attachment styles, health anxiety, and somatization compared to the control group ($p < .001$).

Conclusion: The results of this study indicate that ISTDP significantly improves the psychological symptoms examined in the experimental group. With caution, the use of this intervention as an adjunct treatment in patients with chronic pain is recommended.

Keywords: Intensive Short-term Dynamic Psychotherapy, attachment styles, somatization, health anxiety, chronic pain.

1. Introduction

Intensive Short-term Dynamic Psychotherapy (ISTDP) is derived from Freud's psychoanalytic model and was designed and developed by an Iranian scientist named Davanloo at McGill University. In this approach, the long-term, psychoanalytic method is transformed into a short-term, effective, structured, and clear method (Davanloo, 1996; Russell et al., 2022; Shams et al., 2022). This therapy helps patients regulate their anxiety and emotions and change their defenses, thereby becoming stronger and able to confront emotions they have previously avoided (Mahdavi et al., 2019; Mami et al., 2021; Messina et al., 2021). One variable related to the experience of pain is the attachment style. Chronic pain, as a stressor, activates an individual's specific attachment style, ultimately influencing the emotional, cognitive, and behavioral patterns associated with that style (Badaye et al., 2021; Mahdavi et al., 2019; Shams et al., 2022). Such patterns determine how a person interacts with the illness, their biological, psychological, and social responses, as well as the recovery process and quality of life. It has been shown that attachment style plays a significant role in coping with pain and adjusting to it in patients with rheumatoid arthritis and related disabilities (Mahdavi et al., 2019).

Another factor related to chronic pain is one of the most common mental health problems in primary care centers: somatization. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), somatization is classified under Somatic Symptom and Related Disorders. This category is characterized by one or more physical symptoms that are significantly associated with excessive thoughts, feelings, and behaviors. The prevalence of this disorder in the general population is about 5 to 7 percent (Saeed et al., 2019). Stress and anxiety from events can weaken the immune system, making individuals more susceptible to diseases, including COVID-19. Considering that these symptoms occur during anxious states and are also symptoms of COVID-19 disease, in stressful and inflammatory situations like the COVID-19 pandemic, individuals might mistakenly believe they are infected with the SARS-Cov-2 virus without actually having the viral disease. This situation can lead to a vicious cycle that increases the intensity of anxiety and the occurrence of anxiety symptoms (Habibi Asgarabad et al., 2023; Knekt et al., 2021). Health anxiety is a widespread cognitive disorder characterized by incorrect perceptions of bodily symptoms and changes resulting from individual beliefs about illness

or health. Based on clinical observations, health anxiety may be an indicator for other anxiety disorders and tends to exacerbate in various psychological disorders. According to research reported during the COVID-19 outbreak in 2020, exposure to news about the disease has increased health anxiety, particularly in regions affected by the virus, and it has been observed that health anxiety can be transmitted from parents to children (Martino et al., 2020).

The International Association for the Study of Pain defines chronic pain as pain that persists for three months or more. Chronic pain is a global health concern with significant psychological, social, and economic consequences for individuals and society. Surveys indicate that chronic pain can occur at any age and significantly impacts the quality of life and mental health of children and adolescents. Chronic pain can manifest in various forms such as neck pain, back pain, headaches, musculoskeletal pain, and abdominal pain at young ages. A review study by Martino and colleagues indicates the prevalence of headaches at 8.83 percent, abdominal pain at 4.53 percent, back pain at 14.24 percent, musculoskeletal pain at 4.40 percent, and multiple pains at 4.49 percent in children and adolescents. Factors such as being female, anxiety, stress, and lower economic and educational status are significantly associated with the prevalence of chronic pain in children and adolescents (Martino et al., 2020). The lack of awareness of chronic pain at young ages is concerning because individuals may not realize that this condition could affect them into adulthood. The experience of long-term pain and beliefs related to time associated with pain are key factors in understanding the experience of pain and psychological distress in patients. Intensive Short-term Dynamic Psychotherapy (ISTDP) can play an effective role in improving psychological symptoms. Therefore, this study aimed to determine the effectiveness of ISTDP on attachment styles, somatization, and health anxiety in patients with chronic pain.

2. Methods and Materials

2.1. Study Design and Participants

This study was a quasi-experimental research using a pre-test, post-test, and two-month follow-up design with a control group. The research population consisted of all patients suffering from chronic pain visiting a specialized pain clinic in Tehran in 2023. The sample size was determined by referring to Cohen's table, setting at a 95% confidence level, an effect size of 0.30, and a statistical

power of 0.83, with 12 individuals per group. However, to account for potential dropout and to enhance the generalizability of the results, 15 individuals per group were ultimately selected. Initially, 30 individuals were chosen through convenience sampling and subsequently assigned randomly into an experimental group (15 individuals) and a control group (15 individuals) through simple randomization (lottery method).

Inclusion criteria for the study included: full consent to participate in therapy sessions, absence of other diseases (verified by questioning participants), at least a middle school level of education (to comprehend the therapy), no use of psychotropic drugs (such as fluoxetine and sertraline), no psychological services received (like depression or anxiety treatment) in the past three months, and no prior training in Intensive Short-term Dynamic Psychotherapy. Exclusion criteria included missing more than two sessions, developing psychological disorders such as depression, participation in other psychological workshops concurrently, and withdrawal from cooperation. Ethical principles adhered to in this study included informed consent, educating participants about the research methods and goals, maintaining confidentiality of obtained information, and freedom for participants to withdraw from the study at any time.

Sampling took place in February 2023, the intervention started in April 2023, continued until the end of July, and the follow-up phase was completed by the end of September. Interventions were conducted by a trained clinical psychologist (the first researcher) individually on Sundays and Tuesdays from 5 PM to 8 PM at the researcher's clinical practice. There were no dropouts among the participants, and the training was provided free of charge. It should be noted that participants were informed they could leave the study at any time and seek psychological services. After the study concluded, participants in the control group received free psychological services from a clinical psychologist.

2.2. Measures

2.2.1. Attachment Styles

Developed by Hazan and Shaver, this questionnaire consists of 15 questions assessing three attachment styles—avoidant (questions 1-5), secure (questions 6-10), and anxious (questions 11-15)—on a 5-point Likert scale (1=strongly disagree, 2=disagree, 3=somewhat agree, 4=agree, 5=strongly agree). Scores range from a minimum of 5 to a maximum of 25 per subscale, with higher scores

indicating the predominant attachment style of the individual. Hazan and Shaver reported a test-retest reliability of 0.81 and a Cronbach's alpha of 0.87. In a study by Ghanbari et al. on an Iranian sample, the Cronbach's alpha for secure, avoidant, and anxious subscales was reported as 0.86, 0.84, and 0.85, respectively, indicating acceptable reliability. In the current study, the Cronbach's alpha for secure, avoidant, and anxious attachment styles was 0.57, 0.76, and 0.56, respectively, and 0.68 for the overall scale, which is considered satisfactory (Parsakia et al., 2023).

2.2.2. Health Anxiety

This short form questionnaire, designed by Salkovskis and Rimes in 2002, consists of 18 questions, each with four response options reflecting the individual's condition over the past six months. Scores range from 0 to 3, with 14 questions related to the likelihood of disease onset and the remaining four questions addressing the negative consequences of disease onset. The total score range is from 0 to 54, with higher scores indicating greater anxiety. The questionnaire includes three factors: disease onset, disease consequences, and general health concerns. A Cronbach's alpha of 0.75 demonstrates the questionnaire's adequacy, making it suitable for use in various research settings and clinical centers. In this study, the reliability of the questionnaire, determined by Cronbach's alpha, was 0.76 (Habibi Asgarabad et al., 2023).

2.2.3. Somatization

This questionnaire assesses 14 common symptoms as categorized under somatization disorder in DSM-IV, including stomach pain, back pain, headaches, chest pain, dizziness, fainting, palpitations, shortness of breath, gastrointestinal complaints (constipation or diarrhea), digestive issues (vomiting, gas, or indigestion), fatigue, sleep problems, joint or finger pain, and pain or problems during menstruation and sexual intercourse. Symptoms are evaluated over the past four weeks on a three-point scale: 0 (not bothered at all), 1 (somewhat bothered), or 2 (greatly bothered). The total score ranges from 0 to 30, with lower scores indicating minimal somatization and higher scores indicating severe somatization. Cronbach's alpha for this questionnaire in a study by Lee et al. was reported as 0.79. The questionnaire was standardized in Iran by Abdolmohamadi et al., with concurrent validity with the SCL-90 somatization scale at 0.74 and internal consistency with Cronbach's alpha at 0.76. In the current study, the

reliability of the questionnaire was calculated as 0.78 using Cronbach's alpha (Badaye et al., 2021).

2.3. Intervention

2.3.1. Intensive Short-term Dynamic Psychotherapy

According to the Intensive Short-term Dynamic Psychotherapy manual, sessions followed a seven-step questioning process concerning problems, pressure, challenge, transference resistance, direct access to the unconscious, and were conducted according to the psychotherapy guidebook (Mami et al., 2021).

Session 1: Introduction and Initial Assessment

The first session of Intensive Short-term Dynamic Psychotherapy (ISTDP) sets the foundational rules for therapy sessions and includes an initial interview with participants using a dynamic sequence known as "trial therapy." This is designed to conduct a preliminary assessment of the participants' issues.

Session 2: Identifying and Addressing Defenses

In the second session, the focus is on identifying specific defensive patterns (referred to as "defenses") and implementing tailored interventions that are effective for each type. A brief overview of common tactical defenses and corresponding interventions is presented.

Session 3: Working with Tactical Defenses

This session involves addressing tactical defenses such as indirect speech and generalizations. Effective interventions include doubting, challenging, and confronting these defenses to help the patient begin to break down their protective barriers.

Session 4: Specific Words and Indirect Speech

The fourth session examines the specialized terminology used by participants, their tactical defenses in speech, and their pathological and potential thoughts. Effective interventions involve challenging these defenses and clarifying speech to promote clearer communication.

Session 5: Ruminative Defenses

In this session, defenses involving rumination and rationalization are scrutinized. Effective interventions sequentially include clarification, requesting definitive responses, doubting defenses, challenging, and blocking defensive maneuvers.

Session 6: Rationalization and Generalization

Session six addresses defenses of rationalization, generalizations, and broad statements. Effective interventions include clarifying, blocking, and challenging

these defenses to foster a more accurate and grounded understanding of feelings and experiences.

Session 7: Evasion and Forgetting Tactics

This session deals with diversion tactics and forgetting. Effective interventions such as clarification, doubting defenses, and confronting these tactics are employed to help participants face and process avoided emotions.

Session 8: Denial

In this session, the defense mechanism of denial is confronted. Effective interventions include clarification, doubting defenses, and challenging the denial to aid participants in acknowledging and dealing with reality.

Session 9: Externalization and Ambiguity

Session nine focuses on defenses involving externalization and ambiguity. Effective interventions are aimed at clarification and challenging the defenses to reduce blame-shifting and increase personal accountability.

Session 10: Evasion and Obsessive Doubt

This session addresses evasive tactics and obsessive doubt. Effective interventions involve clarification and challenging defenses to help participants deal with uncertainties and ambiguities constructively.

Session 11: Somatization and Acting Out

The eleventh session focuses on somatization and acting out as defenses against emotions. Effective intervention primarily involves clarification to help participants recognize and express underlying emotions rather than converting them into physical symptoms.

Session 12: Rebellion and Regression

This session covers defenses such as rebellion, disobedience, preparatory behaviors, crying, and other regressive defenses. Effective interventions include confrontation, direct engagement, and clarification to address these more primitive defense mechanisms.

Session 13: Talking Instead of Feeling

In session thirteen, the focus is on participants talking about issues instead of feeling them, along with non-verbal cues and compliance. Effective interventions include clarification, doubting defenses, and challenging to encourage a deeper emotional engagement.

Sessions 14 and 15: Consolidation and Closure

The final two sessions are dedicated to consolidating the gains achieved throughout the therapy, planning follow-up, and specifically scheduling the post-test. The sessions conclude with expressions of gratitude towards the participants and officially ending the therapy sessions.

2.4. Data analysis

Data were analyzed using SPSS software, version 26. The statistical method employed for data analysis was two-way analysis of variance (ANOVA) with repeated measures. To examine the demographic characteristics of the subjects, Fisher's exact test was used for nominal variables, and the Kolmogorov-Smirnov test was employed to test for normal distribution. Mauchly's test was used to assess the assumption of sphericity, and Levene's test was used to check for homogeneity of variances. The significance level was set at .05 for all tests.

Table 1

Descriptive Statistics

Variables	Statistical Indicators	Pre-test (Mean ± SD)	Post-test (Mean ± SD)	Follow-up (Mean ± SD)
Anxious Attachment Style	Experimental	7.66 ± 72.25	3.73 ± 51.37	1.28 ± 53.75
	Control	3.27 ± 72.12	2.87 ± 69.37	4.95 ± 74.00
Secure Attachment Style	Experimental	3.67 ± 44.56	3.70 ± 75.40	3.70 ± 75.40
	Control	2.16 ± 45.80	3.38 ± 46.48	3.19 ± 46.12
Avoidant Attachment Style	Experimental	4.23 ± 51.60	3.02 ± 42.84	3.58 ± 41.80
	Control	4.32 ± 50.20	4.15 ± 49.34	3.35 ± 49.12
Health Anxiety	Experimental	3.67 ± 44.56	3.70 ± 31.40	3.70 ± 31.40
	Control	2.16 ± 45.80	3.38 ± 46.48	3.19 ± 46.12
Somatization	Experimental	4.23 ± 51.60	3.02 ± 42.84	3.58 ± 41.80
	Control	4.32 ± 50.20	4.15 ± 49.34	3.35 ± 49.12

As indicated by Table 1, the mean scores of the experimental group improved from pre-test to follow-up. This improvement was observed in the variables of secure attachment style, demonstrating the effect of the Intensive Short-term Dynamic Psychotherapy intervention on the stated variables, whereas no significant changes occurred in the control group.

To analyze the data and examine the hypotheses, two-way ANOVA with repeated measures was used. Before conducting the two-way ANOVA with repeated measures, the assumptions were tested. The Kolmogorov-Smirnov test indicated that the data distribution was normal at the 95% confidence level ($p < .05$). Levene's test result was greater than .05, confirming the homogeneity of variances between the two groups. Mauchly's test of sphericity confirmed that the assumption of sphericity was met for all three components; therefore, the Sphericity assumed test was used. Box's M test was utilized to evaluate the equality of covariance matrices.

The between-group test results indicated that the differences between the intervention and control groups

3. Findings and Results

The mean and standard deviation of age for the experimental and control groups were 43.40 ± 3.92 years and 44.07 ± 4.49 years, respectively ($p = .669$). Independent samples t-tests for age and Fisher's exact test for gender, educational level, and marital status indicated no significant statistical differences between the experimental and control groups ($p < .05$).

As presented in Table 1, descriptive statistics for both groups at the pre-test, post-test, and follow-up stages are shown.

were statistically significant for secure attachment style ($p = .008$), anxious attachment style ($p = .026$), avoidant attachment style ($p = .033$), health anxiety ($p = .024$), and somatization ($p = .013$). The within-group test results (time) showed that the differences between the mean scores of secure attachment style ($p < .001$), anxious attachment style ($p < .001$), avoidant attachment style ($p < .001$), health anxiety ($p < .001$), and somatization ($p < .001$) in the post-test and follow-up stages were significant. Additionally, the results in Table 4 indicate that the interaction effect of group and time on the dependent variables is significant ($p < .001$), demonstrating the impact of the intervention on increasing the mean scores of the variables of secure, anxious, and avoidant attachment styles, health anxiety, and somatization in the post-test and follow-up stages in the intervention group.

Table 2

Results of Two-way ANOVA with Repeated Measures for Testing Hypotheses

Variable	Source of Change	Sum of Squares	Degrees of Freedom	Mean Square	F Value	p Value	Effect Size
Avoidant Attachment Style	Group	179.589	1	179.589	8.546	.008	.377
	Time	79.572	2	39.786	11.881	< .001	.580
	Group*Time	69.001	2	34.500	10.453	< .001	.487
Anxious Attachment Style	Group	1605.589	1	1605.589	7.688	.026	.390
	Time	958.572	2	379.286	40.762	< .001	.780
	Group*Time	924.001	2	462.000	39.888	< .001	.780
Secure Attachment Style	Group	205.589	1	205.589	4.688	.033	.270
	Time	96.572	2	48.286	24.416	< .001	.670
	Group*Time	120.001	2	60.000	30.888	< .001	.710
Health Anxiety	Group	146.974	1	146.974	2.906	.013	.195
	Time	155.753	2	77.876	17.352	< .001	.591
	Group*Time	128.896	2	64.448	13.360	< .001	.545
Somatization	Group	98.822	1	98.822	15.703	.024	.204
	Time	92.822	2	46.411	36.997	< .001	.785
	Group*Time	132.022	2	66.011	18.206	< .001	.653

4. Discussion and Conclusion

This study aimed to determine the effectiveness of Intensive Short-term Dynamic Psychotherapy (ISTDP) on attachment styles, somatization, and health anxiety in patients with chronic pain. The findings indicated that ISTDP led to improvements in attachment styles, somatization, and health anxiety among patients with chronic pain. These findings are consistent prior research (Cyranka et al., 2018; Mahdavi et al., 2019; Mami et al., 2021; Messina et al., 2021; Nabizadeh et al., 2019; Russell et al., 2022; Shams et al., 2022). This consistency might be attributed to the similar ways in which ISTDP and other motivational and social factors influence patients' attitudes and consequently reduce health anxiety.

In explaining the effect of ISTDP intervention on reducing mood non-expression in individuals with chronic pain, it can be stated that in this treatment, due to the patient's confrontation with unwanted emotions, anxiety initially increases, which can in turn exacerbate symptoms. However, after a few sessions, when emotions are externalized, processed, and controlled, mood and emotional symptoms decrease. The active stance of the therapist and the correct application of techniques in this position allow the patient or client to identify the depth of their emotions and thoughts in the shortest time. In the therapeutic process of ISTDP, an individual, by gaining the ability to deeply experience and express emotions, can regulate cognitive processes and arousal through reduced inhibition, develop a realistic understanding of self and capabilities, improve coping skills,

and interpersonal relations, thus facilitating a more appropriate emotional response and emotional expression (Mami et al., 2021). During therapy sessions, when the unconscious is unlocked and emotions are externalized, the sedimented emotions in the individual significantly decrease, and with the regulation of anxiety, defensive styles develop, and the experience of emotional regulation occurs more effectively, allowing the person to better understand positive emotions. In the course of treatment, individuals become more aware of their physical symptoms of anxiety, can identify their emotions in different situations, and learn how to experience, express, and control them, thereby reducing difficulty in mood non-expression. Such confrontations lead to the reorganization of the self and the shedding of pathological defenses, enhancing the individual's mental capacity and ultimately improving their mental health. In ISTDP, when the client gains insight into internal conflicts like the triangle of conflict and becomes aware of how these conflicts are repeated like the triangle of person, they do not hide their emotions behind defenses, driving them toward emotional balance and self-regulation, thereby fostering mental growth (Nabizadeh et al., 2019; Russell et al., 2022).

The findings also demonstrated that ISTDP led to improvements in patients with chronic pain in indices of secure, avoidant, and anxious attachment styles. In confirming the hypothesis, it can be stated that attachment represents a useful adaptation to threatening environments, but as soon as they become conditioned responses to emotions, they generalize to other environments where they are unhelpful or even harmful. According to psychoanalytic

views, childhood traumas create conflicting and anxiety-inducing emotions that can disrupt the experience of feelings (Shams et al., 2022). Consequently, attachment is obliged to manage these conflicts so that the individual does not suffer. Employing these techniques leads to the movement of intense and mixed emotions in transference (patient-therapist relationship) and activates the patient's intertwined defensive layers against these emotions. This conflicting situation revives similar patient conflicts from the past. With the proper use of these techniques, the patient's defense system is broken down, and emotions in the transference are directly touched and expressed, thereby unlocking unconscious experiences and traumas. When the patient consciously confronts what they previously avoided, they no longer rely on defenses that are regressive and self-defeating (Nabizadeh et al., 2019). As a result, the individual faces illness and life challenges in the best possible way and makes decisions accordingly.

The study also found that ISTDP led to improvements in somatization indices in patients with chronic pain. In treatment, we "build ego capacity" so that through defending, patients do not use defense mechanisms to avoid experiencing negative emotions. In fact, by building the ego capacity for the patient, we help improve their condition through bringing them closer to their emotions without using defense mechanisms. In fact, it is the challenge with defenses in the therapeutic process that improves the patient's condition and subsequently improves their quality of life (Mami et al., 2021; Messina et al., 2021).

The inability to regulate emotions is rooted in the early years of life and a failure in the internalization of the "self-care" feature of parents. The self-care ability is a psychological capacity and one of the functions of the ego. This capacity protects the individual from harm and ensures survival. Self-care capacity includes the ability to assess reality, judgment, control, the presence of anxiety functioning as a warning to the individual, and the ability to draw logical conclusions and inferences. Self-care capacity is developed through parent-child interaction and nurturing actions by parents in early childhood. Since individuals with chronic pain lack these internalizations, they have difficulty in self-care ability, maintaining self-esteem, and regulating relationships (Davanloo, 1996; Nabizadeh et al., 2019). Indeed, defects in self-care and self-regulation cause the emergence of painful and confusing emotions in the individual, bringing about significant psychological suffering. In ISTDP, the individual is able to enhance the functioning of the self and increase their self-strength, no

longer needing to use maladaptive behaviors that had functioned for them, and thus can live more comfortably. What happens in the process of short-term ISTDP therapy leads to greater awareness of hidden emotions and feelings during the therapeutic relationship. The client becomes aware of the inappropriateness of their emotional experiences and allows the "self" to assert itself and adapt to changed situations (Russell et al., 2022; Shams et al., 2022).

5. Limitations & Suggestions

Given the results obtained, it is recommended that therapists and counselors learn the ISTDP approach when dealing with patients with chronic pain. Other psychotherapeutic interventions should also be assessed in this population. It is suggested that other specialists and researchers test ISTDP with other variables in different communities.

Research limitations included the inability to screen patients for variables such as personality type, personality organization, motivation to enter therapy, and expectations, which made generalizing results difficult. The psychoanalytic approach itself has limitations that are naturally intertwined with the limitations of this research; the suitability of clients for this therapeutic approach is one factor that must be considered. There are specific disorders that are not suitable for this therapy, and their unsuitability is determined in the early stages of the dynamic sequence. These disorders include severe impulse control disorders, severe states of alcoholism. It is suggested that this study be conducted in other communities and with new variables. Also, given the short-term follow-up conducted, it is recommended that studies with long-term follow-up be conducted.

Overall, the results of the current study indicate that the use of ISTDP is effective in improving mood non-expression, developed defensive styles, and the strength of the self in individuals with chronic pain. Therefore, it is recommended that ISTDP be used for attachment styles, somatization, and health anxiety in patients with chronic pain and alongside other therapeutic methods, this intervention can be utilized in psychosomatic and psychological clinics.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants. The study was registered with the Islamic Azad University of Birjand Ethics in Research Committee under the identifier IR.IAU.BIRJAND.REC.2023.008.

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

All authors equally contributed in this article.

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