

Comparing the Effect of Clonazepam Tablets with Noma Syrup (Lettuce Leaf Extract) on the Severity of Insomnia in Hemodialysis Patients*

Arash Azad Farzin¹ , Masoumeh Bagheri-Nesami^{2,3} , Javad Setareh⁴ , Mahmood Moosazadeh⁵ ,
Fatemeh Espahbodi⁶ , Assie Jokar² 

¹Critical Care Nursing Student, Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

²Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

³World Federation of Acupuncture-Moxibustion Societies (WFAS), Beijing, China

⁴Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁵Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁶Division of Nephrology, Mazandaran University of Medical Sciences School of Medicine, Sari, Iran

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ABSTRACT

Background: The goal of the present study was to compare the effect of clonazepam tablets with Noma syrup (lettuce leaf extract) on the insomnia severity in hemodialysis patients.

Methods: This randomized controlled clinical trial study was carried out with 95 eligible patients that were included in 2 groups: intervention (n = 46) and control (n = 49). Noma syrup (20 mL) was prescribed to the intervention group half an hour before going to sleep every night, and 0.5 mg of clonazepam tablets was also given to the control group half an hour before going to bed for 2 weeks. The insomnia severity index (ISI) was completed by both groups before and 2 weeks after the intervention.

Results: The insomnia severity in the noma syrup and control groups before the intervention was 8 ± 1.77 and 20.81 ± 1.86 , respectively ($P = .009$). But the postintervention insomnia severity in the Noma and clonazepam groups was 17.45 ± 4.13 and 16.46 ± 3.01 , which was not significant ($P = .184$). The analysis of the preintervention insomnia severity index did not reveal a significant relationship among the studied groups in relation to the postintervention sleep scores.

Conclusion: According to the results, Noma syrup and clonazepam tablets were equally efficient in treating the insomnia of hemodialysis patients.

Keywords: Insomnia, hemodialysis, lettuce leaf extract, sleep disorders, clonazepam

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INTRODUCTION

Insomnia is a common psychological problem that is related to at least one of the three characteristics of the patient's complaints of inability to fall asleep, stay asleep, or lack of invigorating sleep.¹ Despite the fact that insomnia is very common, it is identified and treated only in less than 20% of patients.² One of the most common sleep problems among hemodialysis patients who suffer from various sleep disorders due to internal or external reasons is insomnia. External factors like dialysis-induced pains, chronic pain, cannulation

pain, or muscle cramps are common and potentially cause sleep disorders in these patients.³

Bone pains, itching, anxiety, immobility caused by hemodialysis, and the tendency to take a nap during treatment can cause nighttime insomnia in these patients.⁴ Also, chronic insomnia, the most common sleep disorder among hemodialysis patients, is identified by complaints of difficulty falling or staying asleep or a lack of enough sleep for at least 1 month.⁵ The overall prevalence of insomnia ranges between 49% and



98% among hemodialysis patients.³ It has been reported at 57% and up to 80% in some studies.^{6,7}

It has also been reported that the insomnia prevalence is significantly higher among patients who have been undergoing hemodialysis treatment for more than 1 year.⁸ Poor sleep affects mental health, quality of life, and daily performance, as well as increases the complications and risk of mortality.⁹ Drug treatment and cognitive behavior therapy are among the most common methods for treating insomnia.¹⁰ Overall, the insomnia medications include allosteric modulators of GABA A receptors, including benzodiazepines, suvorexant, and melatonin.¹¹ Other sleeping medications used in the treatment of insomnia include antihistamines such as chlorpheniramine, diphenhydramine, triprolidine, and promethazine.¹²

Benzodiazepines (including clonazepam) are the most common drugs that are prescribed for treating insomnia.¹² These drugs would have several side effects, for example, memory disorders, drug resistance, dependence, and drug abuse.¹³ Clonazepam, which belongs to the benzodiazepine group, is extensively used as an antianxiolytic, antispasmodic and also for the treatment of sleep disorders.¹⁴ Along with its positive therapeutic effects, clonazepam may have side effects such as drug dependence, cognitive problems, falls, and bone fractures.^{12,15}

Also, herbal drugs have been prescribed to cure insomnia in hemodialysis patients. One of the herbal drugs used to treat insomnia is lettuce, which leaves and seeds are used in Iranian conventional medicine for their hypnotic properties.¹⁶ Lettuce is a diuretic and is known to heal the bladder and urinary tract ulcers. The lettuce leaf extract contains a very low amount of minerals, such as magnesium, and it is reported to be harmless for patients with kidney failure; such as patients undergoing hemodialysis.¹⁷

The hypnotic and soothing effects of capsules containing lettuce seed oil in improving the insomnia symptoms of patients with or without anxiety and clients of outpatient clinics and psychiatric centers have been pointed out in several studies.¹⁸⁻²⁰ In these studies, a comparison with clonazepam is lacking in all these patient groups.

The effectiveness of clonazepam and zolpidem tablets on the sleep quality of hemodialysis patients was investigated

clinically. However, there was no study on the impact of Noma syrup (lettuce leaf extract) on the sleep quality of the hemodialysis patients. The present study aimed to compare the impact of clonazepam tablets with Noma syrup (lettuce leaf extract) to reduce the insomnia severity in hemodialysis patients.

MATERIAL AND METHODS

This randomized controlled clinical trial study was carried out in the Shahrvand Dialysis Center and Fatemeh Zahra Hospital in Sari, Mazandaran city. Participants were selected by using convenience sampling, and eligible people were assigned into 2 groups randomly. Eligible participants were selected from April until September 2021. The sample size was determined, according to Dashti et al's study,¹⁸ the confidence interval = 95%, test power = 90%, for the two-tailed test using the G-power software for comparing 2 means, and the required sample size was estimated 86 people (n = 43 per group). Considering 20% dropout, 8 people were added to each group, and finally, 51 participants enrolled in each group.

A ready-made medicine containing lettuce leaf extract, which is produced in the form of syrup and marketed under the brand name

Noma, has been used in the present study. The intervention group was given Noma syrup (20 mL) half an hour before bedtime every night, and the control group was given 0.5 mg clonazepam tablet half an hour before bedtime for 2 weeks.

Inclusion criteria included Iranian nationality, being aged 18 years and older with insomnia, undergoing hemodialysis 2 to 3 times a week, being mentally alert and able to respond questions, absence of delirium, cognitive problems, stroke, terminal diseases such as cancer, severe hearing and vision problems, and drug abuse. Exclusion criteria also included using anti-anxiety or hypnotic drugs due to psychoneurocognitive diseases, using adjuvant treatments such as acupuncture, herbal medicines, and hypnosis or yoga, being reluctant to participate in the study, experiencing an extreme form of insomnia symptoms, occurrence of delirium, occurrence of an allergic reaction, or patient's death.

Ethical Considerations

This study was confirmed by Ethical Committee of Mazandaran University of Medical Sciences (ethical code: IR.MAZUMS.REC. approval date was 2021/6/2) and obtaining permission from the responsible authorities (IRCT20110906007494N37). Written informed consent was obtained from all the participants after explaining the objectives of the research and assuring them about the confidentiality of the information.

Study samples were randomly assigned to the studied groups using random numbers by a statistical consultant. In this random block method, a block of 25 including block size = 4 and one block (block size = 2) were selected, and individuals from

MAIN POINTS

- Insomnia is a common psychological problem in hemodialysis patients.
- Insomnia in hemodialysis patients can lead to increased fatigue.
- The effect of Noma syrup is equal to the effect of clonazepam tablets in improving the severity of insomnia.

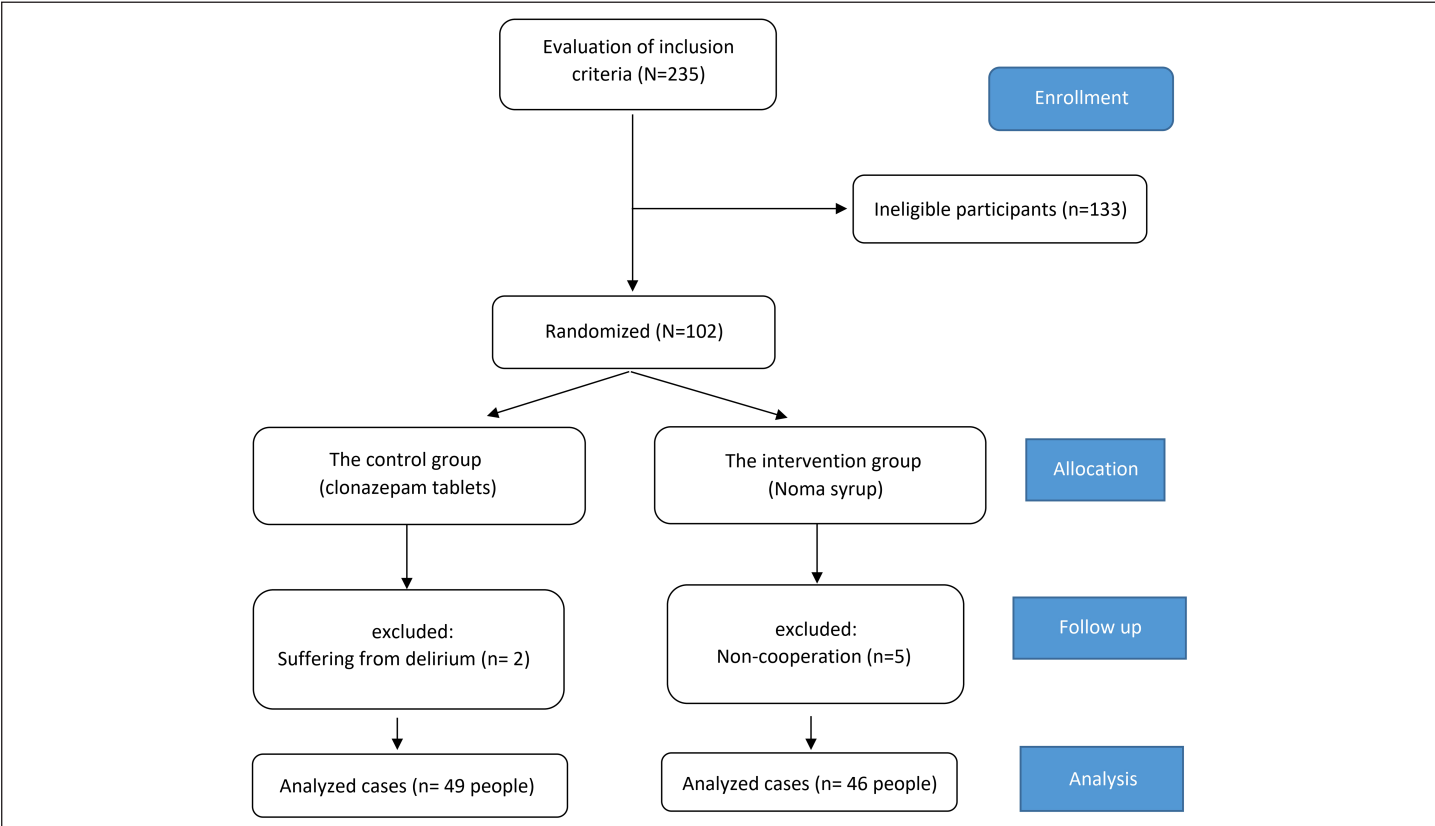


Figure 1. Study flow diagram.

the intervention and control groups (n = 2 per group) were placed in the block size = 4, and in the block size = 2; 2 persons from the Noma and clonazepam groups were selected respectively. Selecting participants by using 102 envelopes from one to 120 based on computer program to letter A (Intervention) and letter B (Control). Accordingly, the first patient who met the inclusion criteria participated in the study, and the process continued until the whole study population was covered (Figure 1).

Absence of cognitive problems and delirium were among the eligible criteria. For this purpose, the Nursing Delirium Screening Scale (NE-DESC) was used to identify delirium, and the Mini-Mental State Examination (MMSE) was applied in order to check the mental and understanding awareness of the subjects at baseline. The Nursing Delirium Screening Scale has 85.7% sensitivity and 86.8% specificity and assesses delirium that is ranked 0-2 (0 = asymptomatic, 1 = moderate, and 2 = severe). This tool is finished by the nurse within 2 minutes, and the patient can be evaluated for delirium symptoms twice a day by using this tool. Lack of insight, inappropriate behavior, inappropriate communication, delirium, and motor delay are among the studied variables. This range was evaluated every day before the intervention, and the participants were eliminated from the study when a score ≥ 2 indicated delirium.²¹

The Mini-Mental State Examination is completed in the form of an interview and evaluates 5 criteria, including orientation,

information recording, attention and calculation, recalling, and language. Orientation consists of 2 questions (each with 5 parts), and a person receives a score by answering each part. The information recording dimension consists of a 3-part question and has 3 scores. The attention and calculation dimension has 5 scores, and the ability of a person to pay attention is measured by practicing subtracting numbers. Remembering and language have 3 and 9 grades, respectively. The upper and lower MMSE score is 30 and 0, respectively. When the participant received 25 of a 30 total score, it showed the normal range. The scores of 21-24, 10-20, and <9 indicate mild, moderate, and severe cognitive impairment, respectively. The same cutoff point was used in this study.²²

In order to identify insomnia patients, the Diagnostic and Statistical Manual of Mental Disorders (DSM5) diagnostic criteria were used. According to DSM5, insomnia is detected if the patient has one or more symptoms of insomnia, including difficulty falling asleep, difficulty staying asleep (frequent nighttime awakenings, or difficulty falling asleep after waking up during the night), or wakes up early in the morning and is not able to fall asleep again. Insomnia causes mental stress and impaired social, occupational, educational and behavioral functions, and this problem occurs at least 3 times a week for at least during 3 months. It should also be kept in mind that insomnia persists although the person has enough time and opportunity to fall asleep.²³

Then the insomnia severity index (ISI) was measured between eligible patients. This index includes 7 self-reported items that evaluate the nature, severity, and effects of insomnia. This questionnaire examines the person’s history during the past 2 weeks and evaluates falling asleep, staying asleep, waking up early in the morning, sleep dissatisfaction, and problems related to daily performance due to daytime sleepiness. The questions are scored based on a 5-point Likert scale ranging from “I have no problems” (0) to “I have very severe problems.”³ The possible score range is also 0-28.²⁴ ISI scores 0 -7, 8-14, 15-21, and 22-28 indicate no insomnia, mild, moderate, and severe insomnia, respectively.²⁵

According to eligible criteria, 235 patients were investigated, and 133 patients did not enter the study due to hearing and vision problems and subsequent communication problems (n = 6), drug addiction (n = 20), using sleeping pills (n = 68), having delirium (n = 10), having cognitive impairment (n = 12), and unwillingness to participate in the study (n = 7) (Figure 1). Out of 102 patients, 2 clonazepam tablet recipients were excluded from the study due to suffering from delirium at the time of the intervention. Also, 5 Noma syrup recipients were excluded from the study due to medication non-adherence.

Statistical Analysis

Finally, data were processed using the Statistical Package for the Social Sciences Statistics software, version 19 (IBM SPSS Corp.; Armonk, NY, USA). The normality was checked using kurtosis and skewness. Considering the normality, the independent *t*-test, paired *t*-test, and analysis of covariance (ANCOVA) were used for data analysis and to adjust the effect of the initial difference between the 2 groups.

RESULTS

Most of the participants were male and married. There were not any statistically significant differences between the studied groups in terms of demographic and clinical variables (gender, marital status, employment status, education level, body mass index, history of underlying diseases, frequency and duration of hemodialysis per week), and age ($P > 0.05$) (Table 1).

The mean of ISI in the Noma and clonazepam groups before the intervention was $.8 \pm 1.77$ and 20.81 ± 1.86 , respectively, which showed a significant difference ($P = .009$). After the intervention, the grade of ISI in the Noma and control groups was 17.45 ± 4.13 and 16.46 ± 3.007 , respectively, which showed no significant difference ($P = .184$). Furthermore, the findings

Table 1. Comparison of Demographic Characteristics of Patients in Intervention and Control Groups				
Characteristics		Intervention Group (Noma syrup) Frequency (%)	Control Group (Clonazepam Tablets) Frequency (%)	P
Gender	Female	14 (30.43)	24 (48.98)	.065
	Male	32 (69.57)	25 (51.02)	
Marital status	Married	44 (95.65)	43 (87.76)	.166
	Divorced/widowed	2 (4.35)	6 (24.12)	
Job	Employed	13 (28.26)	14 (28.17)	.973
	Unemployed	33 (71.74)	35 (71.43)	
Level of education	Illiterate	8 (17.39)	8 (33.16)	.095
	High school	13 (28.26)	24 (98.48)	
	Diploma and above	25 (54.35)	17 (69.34)	
History of underlying disease	Yes	46 (100)	48 (97.96)	.330
	No	0 (0)	1 (1.05)	
Duration of hemodialysis (years)	≤less than 1	14 (30.43)	9 (37.18)	.276
	2-3	9 (19.57)	15 (61.30)	
	> More than	23 (50)	25 (51.02)	
Age (years)	Mean (± SD)	61 (± 12)	60.14 (± 10)	.710
Body mass index (kg/m²)	18-24.9	18 (39.13)	12 (49.24)	.151
	25-29.9	22 (48.98)	24 (98.48)	
	30≥	6 (13.04)	13 (56.26)	
Frequency of hemodialysis (per week)	2 times	8 (17.39)	9 (37.18)	.901
	3 times	38 (82.61)	40 (81.63)	

Table 2. Comparison of the Mean Insomnia Severity Scores in the Intervention and Control Groups Before and After the Intervention				
Time	Groups			Result of Independent t-Test
	Intervention (Noma Syrup)	Control (Clonazepam Tablets)	Difference in Means	
	Mean (± SD)	Mean (± SD)	Mean	
Before the intervention	21.8 (± 1.77)	20.81 (± 1.86)	0.99	$P = .009^*$
After the intervention	17.45 (± 4.13)	16.46 (± 3.00)	0.99	$P = .184$
Difference in means	4.35	4.35		
Result of paired t-test	$P < .001^{\#}$	$P < .001^{\#}$		
[*] Significant difference (independent t-test). [#] Significant difference (paired t-test).				

showed an equal mean difference between the 2 groups before and after the intervention (0.99).

214 Based on the paired *t*-test, the score of insomnia severity decreased and was significant ($P < 0.001$ $P < .001$). Also, the test indicated the mean scores of insomnia severity in the clonazepam group before and after the intervention were significant ($P < .001$) (Table 2).

Since a significant difference between Noma syrup and clonazepam tablet recipients was observed in terms of insomnia severity before the intervention. Afterwards, according to ANCOVA analysis, 2 groups had any difference in terms of insomnia severity ($F = 0.802$, $P = .372$), and indicated that Noma syrup and clonazepam tablets are equally effective on reducing the insomnia severity symptoms in hemodialysis patients (Table 3).

DISCUSSION

Our findings demonstrated that ISI decreased significantly from 21.8 to 17.45 in the Noma Syrup recipients, The observed drop in insomnia severity ofthe intervention group can be the impact of Noma Syrup on enhancing the sleep quality of this patient group. Results of the Yektoo study (2011)²⁰ on the effect of lettuce seed extract on improving sleep problem symptoms in the Egyptian elderly revealed that the mean sleeping difficulty score in the lettuce seed extract recipients decreased in the intervention group and had a significant difference. Their results are the same as the present study. Although the scale in the mentioned study (the sleeping difficulty score) is different from the scale of the present study (ISI), the significant decrease in the sleeping difficulty score in this study (which study ?? the reference or the current one) indicates the effectiveness of lettuce seed extract in improving sleep disorder symptoms.

Safari Pour and colleagues (2018)¹⁹ findings on the effectiveness of lettuce seed extract on pregnancy-related insomnia showed that the mean Pittsburgh sleep quality index (PSQI) score of the lettuce seed extract was declined in the intervention group, which indicated an improvement in sleep quality. Therefore, these results are consistent with ours and confirm the effect of lettuce seed extract on improving insomnia symptoms.

Also, the mean of pre- and post-intervention ISI in the clonazepam group showed a significant improvement in the insomnia severity of hemodialysis patients. Results of a Tehran study (2011)¹⁸ on the impact of clonazepam with zolpidem on the sleep quality of hemodialysis patients showed that the mean PSQI score in the clonazepam group decreased, which was similar to the present study. Also, the mean sleep quality index of the zolpidem group decreased, which was consistent with the findings of our study.

Because of the reported side effects of clonazepam (1 mg/d), it was decided to prescribe clonazepam (0.5 mg/d) in the present study. Considering that the effectiveness of clonazepam in the present study was statistically significant and only 2 cases were excluded from the study due to delirium, it can be concluded that the prescribed amount of clonazepam, while having the desired effectiveness, was able to prevent further side effects.

The result of the impact of melatonin on the sleep quality of hemodialysis patients in Gorgan revealed that the PSQI in the melatonin group decreased and had the same results as our study, which is the effect of clonazepam on enhancing the insomnia severity in hemodialysis patients.²⁶

Table 3. Results of Covariance Analysis of Insomnia Severity Scores in Intervention and Control Groups After the Intervention						
Sources/Indices	Sum of Squares	df	Mean Square	Variance	P	Partial Square Root
The dependent variable (insomnia severity)	29.452	1	29.452	2.308	.132	0.024
The independent variable (group)	10.262	1	10.262	0.802	.372	0.009
Error	1174.165	92	12.763			

Limitation

The socioeconomic factors of the participants, sleeping and waking habits, their mental conditions, and the way they were treated by medical staff, which affected the insomnia severity, were beyond our control and hence not measured.

Taking into account the effectiveness of drugs on insomnia and also the number of drugs' side effects observed in the studied groups, it can be concluded that the Noma syrup is as effective as clonazepam on treating the insomnia severity in patients and has no reported side effects, which suggests the priority of using this syrup to improve insomnia symptoms in hemodialysis patients.

Further studies of herbal products with hypnotic actions on sleep quality of hemodialysis patients is required to suggest their use in daily practice.

Ethics Committee Approval: This study was approved by Ethical Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC. date: 2021/6/2) and obtained permission from the responsible authorities (IRCT20110906007494N37).

Link IRCT: <https://www.irct.ir/search/result?query=IRCT20110906007494N37>

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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