

ORIGINAL ARTICLE

Conscious Awareness-Based Breathing Method on Perceived Stress, Salivary Cortisol Level and Alcohol Craving

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Main Points

- Cortisol level is an indicator of the desire to drink alcohol and the course of treatment.
- Managing stress can prevent addiction by reducing the desire to drink alcohol.
- Applying stress-relief methods during addiction treatment has a supportive effect on the treatment and increases treatment success.
- Conscious awareness-based breathing method has a positive effect on the perceived stress level.

Abstract

Alcohol abuse has emerged as a significant contributor to mortality rates in recent years. In the literature, it implies that individuals feeling under a lot of stress tend to consume more alcohol, and that stress can set off cravings during the treatment period of alcohol use disorder, leading to relapse and having a detrimental impact on the treatment. This study aims to introduce and evaluate a mindfulness-based breathing method to facilitate stress management and bolster the treatment of alcohol use disorder. The study was designed to examine patients who were admitted to an Alcohol and Substance Addiction Treatment Center for treatment of alcohol use disorder. These individuals were free from any mental or chronic illnesses and had abstained from drug use for the preceding 3 months. As part of the pre-test/post-test, the perceived stress scale and the Penn alcohol craving scale were administered to the experimental and control groups, and the cortisol levels in the saliva samples were assessed. Results indicate that the mindfulness-based breathing method exhibits favorable and statistically significant effects on perceived stress, salivary cortisol levels, and alcohol craving. This suggests its potential utility as a supportive intervention in alcohol treatment centers.

Keywords: Addictions to alcohol, breathing method, conscious awareness

Introduction

According to the statement of the World Health Organization, 3 million deaths occur worldwide every year due to alcohol abuse, and this represents 5.3% of all deaths (World Health Organization [WHO], 2018). Studies indicate that perceived stress has a role in individuals' tendency to alcohol and increases alcohol consumption (Streeter et al., 2012; Stephens & Wand, 2012; Chen et al., 2020). Studies conducted on alcohol-dependent individuals show

high levels of cortisol, a marker of stress (Sinha et al., 2009; Chen et al., 2020), and saliva samples are also used in the analysis (Sinha et al., 2009; Lee et al., 2015).

It has been reported that craving in alcohol use disorder can be induced by stress, leading to relapse, highlighting the significance of reducing craving in alcohol treatment (Vieten et al., 2010; Witkiewitz et al., 2013; Wemm et al., 2019). Additionally, there are studies indicating that cortisol responses

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measured during the treatment process can be used as an indicator of relapse (Stephens & Wand, 2012).

Breathing practices are recommended and applied in alcohol treatment; mindfulness-based breathing techniques are promising for reducing craving (Shuai et al., 2020), breathing and mindfulness practices can relieve emotional stress (Vieten et al., 2010; Busch et al., 2012; Witkiewitz et al., 2013; Hemenway et al., 2020).

Research Questions

1. Is there a statistically significant effect of the Mindfulness-Based Breathing Method on perceived stress levels?
2. Is there a statistically significant effect of the Mindfulness-Based Breathing Method on salivary cortisol level?
3. Is there a statistically significant effect of the Mindfulness-Based Breathing Method on alcohol craving?

Material and Methods

Participants

The inclusion criteria for the study were determined as male individuals aged between 25 and 65 years, who had been admitted to a University's Faculty of Medicine Alcohol and Substance Dependency Research, Treatment, and Education Center (AMATEM) for the treatment of alcohol use disorder, had no history of certain mental or chronic illnesses, and had not used any substances in the past 3 months.

The inclusion criteria encompassed a range of conditions and factors that could potentially confound cortisol level evaluations, including post-traumatic stress disorder (Stephens & Wand, 2012), depression, bipolar disorder, schizophrenia, psychotic disorders, dementia, delirium, alcohol withdrawal symptoms, alcohol and non-nicotine substance use disorder, Addison's disease, Nelson syndrome, Cushing's syndrome, pituitary tumor, active flu infections, and the use of certain medications such as prednisone, dexamethasone, oral steroids, and glucocorticoids. These factors were screened for through the Personal Information Form. Additionally, male participants aged 25-65 were specifically included, while women were excluded due to their potential hormonal fluctuations and the prevalence of male participants seeking treatment at the clinic. The presence of any conditions or medication use affecting the study was assessed by a mental and neuropsychiatry specialist in accordance with DSM-5 criteria. The study commenced with 30 participants, evenly divided between the control group and the experimental group. However, it concluded with 28 participants, as two individuals were removed from the control group during the study.

The application was applied to the control and experimental groups at separate times, and randomization was not deemed necessary since the first 15 people who applied to the clinic and met the inclusion criteria were included in the control group, and the 15 people who applied after the sessions of the first group were completed and met the research inclusion criteria were included in the experimental group. Additionally, the research was conducted in a single-blind manner.

In addition to alcohol use disorder treatment, the TAT (Thematic Apperception Test) was applied to the control group, which was formed with the first 15 people who applied to the clinic and met

the inclusion criteria for the study. After the 15-day application period was completed with the control group participants, the Conscious Awareness-Based Breathing Method was applied to the second group, the experimental group, in addition to alcohol use disorder treatment. The applications were carried out individually with the participants of both groups in four sessions, and all sessions were completed with each participant within 15 days.

In the first session, the experimental group underwent a 15-minute training session detailing the stages of the method, the key elements to focus on, the timing and technique for independent application, and the importance of repetition. This was followed by a 20-minute practical application and a 15-minute feedback session. After the feedback, participants completed a survey, and samples were collected. The subsequent sessions—second, third, and fourth—each lasted 50 minutes. They began with a 10-minute segment where participants reported on their usage frequency and the impact of the application, and this information was recorded. Each session then continued with 25 minutes of applying the method and concluded with a 15-minute feedback period, after which surveys were filled out and samples were taken.

Ethical Approval

For the research to be carried out at the Ege University, Faculty of Medicine, Alcohol and Substance Dependency Research, an application was also made to the Rectorate, and permission was received on 5 March 2021. An application was also made to the Ege University Ethics Committee to conduct the research, and after the necessary corrections, the ethics committee approval was received on 6 May 2021 with the approval number: 21-5T/82. The research was conducted with volunteer participants. We provided explanations about the study to the participants, an informed consent form was read to all participants, and their approval and signatures were obtained. To protect confidentiality, the identity information of the participants was kept confidential, and a case number was assigned.

Statistical Analysis

In this study, the Python programming language and its various libraries were utilized for statistical analysis. Descriptive statistics were presented using the number of units (n), percentage (%), mean, standard deviation (SD), median (M), minimum (min), and maximum (max) values, as appropriate. Furthermore, the Wilcoxon Signed Rank Test was applied to compare the medians of paired samples.

Perceived Stress Scale

Originally developed by Cohen, Kamarck, and Mermelstein in 1983 (Cohen et al., 1983), the Perceived Stress Scale (PSS) exhibits strong internal consistency, with a Cronbach Alpha value of 0.86. This scale aims to assess an individual's perception of stress regarding various life situations experienced within the past month. The PSS is available in three forms: PSS-14 items, PSS-10 items, and PSS-4 items. Participants rate each item on a 5-point Likert-type scale ranging from "Never (0)" to "Very often (4)." Notably, seven items featuring positive statements (questions 4, 5, 6, 7, 9, 10, 13) are reverse scored. PSS-14 scores range from 0 to 56, with higher scores indicating greater perceived stress levels.

To categorize stress levels, total scores are divided into three ranges: 0-13 indicating a low stress level, 14-26 indicating a medium stress level, and scores ≥ 26 indicating a high stress level.

The Turkish adaptation of the PSS underwent a validity and reliability study conducted by Eskin et al. in 2013.

Penn Alcohol Craving Scale

The validity and reliability of the Penn Alcohol Craving Scale (PACS) were initially established by Flannery, Volpicelli, and Pettinati in 1999. Subsequently, the Turkish adaptation underwent a validity and reliability study conducted by Evren et al. in 2008.

In the original validation, Cronbach's alpha coefficient was calculated to be 0.88 for the first measurement and increased to 0.94 for the second measurement. These coefficients indicate a high internal consistency of the scale. The Turkish version of PACS demonstrated validity and reliability specifically for assessing alcohol use disorder.

PACS is a 5-item self-report scale designed to gauge the severity of alcohol craving experienced in the previous week. It assesses various aspects including the frequency and intensity of thoughts about alcohol, the time spent dwelling on these thoughts, the difficulty of resisting opportunities for alcohol use, and the overall severity of craving. Each item is scored between 0 and 6 points, with a maximum total craving score of 30.

Cortisol Analysis in Saliva

To measure cortisol levels in saliva, samples were collected using the Sarstedt Salivette (salivary cortisol tube) instrument. Participants were instructed to remove the cotton roll from the inner tube, lightly chew it for approximately 2 minutes to saturate it with saliva, then place the cotton roll back into the inner tube and seal it.

Next, the saliva samples collected with the Sarstedt Salivette device underwent centrifugation at 1000 rpm for 2 minutes. This process separated the saliva from the inner tube and transferred it to the outer tube. The centrifuged samples remain stable for different durations depending on storage conditions: 24 hours at 20–25°C, 4 days at 2–8°C, and up to 12 months at –20°C (± 5°C), with the condition that samples are frozen only once.

Subsequently, to conduct the Elecsys Cortisol II Test, an immunological assay for the quantitative determination of cortisol in saliva samples, a Biological Material Transfer Form was completed and sent to the relevant unit at Private Izmir Ege Laboratory. The samples were then analyzed using the Cobas E411 Elecsys Device, employing the electrochemiluminescence immunoassay (ECLIA) method. The test results were subsequently transferred to the data system for further analysis.

It's worth noting that approximately 95% of cortisol in the bloodstream is bound to globulin albumin proteins, with only a small fraction circulating freely as unbound, biologically active cortisol. The Elecsys Cortisol II Test utilizes a competitive testing principle, employing a monoclonal antibody specifically targeting cortisol. Endogenous cortisol from the sample competes with a ruthenium complex-labeled exogenous cortisol derivative for binding sites in a biotinylated antibody, allowing for precise measurement (Cobas application, Elecsys Cortisol II 06687733500 V6.0, 2020-06, V 6.0).

Conscious Awareness-Based Breathing Method

Conscious awareness meditation, a practice of conscious awareness, involves an individual sitting in a comfortable position and focusing their attention on their breathing. The individual monitors the physical sensations occurring in their body, as well as their current emotions and thoughts, from an open, non-judgmental field of awareness. As the practice continues, the individual becomes more aware of the present moment and their feelings at that time (Schonert-Reichl & Lawlor, 2010). Research suggests that the silence and calmness provided by mindful breathing exercises foster confidence and help alleviate existing fears and concerns (Geuter et al., 2010; Vural, 2017). Breath awareness and control contribute to individuals being more physically, emotionally, and mentally balanced, enhancing both individual and social awareness and fostering more conscious living (Vural, 2017).

In addition to breath awareness, learning to activate the diaphragm effectively during breathing exercises is important (Vural, 2017). Diaphragmatic breathing exercises strengthen the diaphragm and abdominal muscles, ensuring that the chest muscles, which assist in breathing, are used more passively and become less fatigued. Diaphragmatic breathing enables more efficient use of the lungs, reduces respiratory frequency, and increases the volume of blood gases through more effective inhalation and exhalation. When a person breathes slowly and deeply through the nose, the diaphragm moves downward as the abdomen expands. As the individual exhales through the nose, the abdomen contracts and the diaphragm moves upward, thus activating the diaphragm (Gündoğdu, 2019).

Use of Conscious Awareness and Breathing Exercises in the Treatment of Addiction and Alcohol Use Disorder

The use of mindfulness-based therapies in addiction treatment is on the rise, with reports highlighting their positive effects (Alterman et al., 2004; Witkiewitz et al., 2005). These therapies have been noted for their role in preventing relapse (Bowen et al., 2009). Conscious awareness practices help individuals confront uncomfortable emotions that may lead to substance addiction and enhance their capacity to tolerate such situations (Silvia, 2002). Research describes mindfulness as a crucial emotion regulation skill (Goldin & Gross, 2010), emphasizing the significance of emotion regulation in maintaining psychological and physical well-being (Kring & Werner, 2004). Inadequate emotion regulation, the process of assessing and modifying responses to emotions, has been linked to various mental disorders including mood disorders, anxiety, post-traumatic stress disorder, major depression, and substance use (Thompson, 1994; Linehan, 1993; Hartzell, 2009).

Owing to its effects in reducing anxiety and depression, mindfulness practices are increasingly utilized in the treatment of substance addiction (Kara, 2020; Ögel, 2012). Tırışkan and colleagues reported that through mindfulness practices, individuals could manage their negative emotions by developing emotion regulation skills, thereby improving their mood, reducing distress and pain, and enhancing overall well-being (Tırışkan et al., 2015).

Results

Table 1 displays the descriptive statistics of the participants. For example, mean ages, which were 45.31 for the control group

Table 1.
Demographic Characteristics of the Participants

	Control Group (n = 13)	Experimental Group (n = 15)	p
Age			
Mean ± SD	45.31 ± 14.65	48.20 ± 10.52	.5498
Married			
Yes	7 (53.85%)	3 (20.00%)	.1419
No	6 (46.15%)	12 (80.00%)	
Employment Status			
Employed	6 (46.15%)	10 (66.67%)	.4771
Unemployed	7 (53.85%)	5 (33.33%)	
Living Alone			
Yes	2 (15.38%)	5 (33.33%)	.5116
No	11 (84.62%)	10 (66.67%)	
Hobby			
Yes	11 (84.62%)	10 (66.67%)	.5116
No	2 (15.38%)	5 (33.33%)	
Perceived Stress			
Yes	8 (61.54%)	10 (66.67%)	1.0
No	5 (38.46%)	5 (33.33%)	
Previous Experience			
Yes	3 (23.08%)	5 (33.33%)	.8574
No	10 (76.92%)	10 (66.67%)	
Major Illness			
Yes	9 (69.23%)	7 (46.67%)	.412
No	4 (30.77%)	8 (53.33%)	
Ongoing Illness			
Yes	6 (46.15%)	5 (33.33%)	.7605
No	7 (53.85%)	10 (66.67%)	
Received Treatment			
Yes	5 (38.46%)	5 (33.33%)	1.0
No	8 (61.54%)	10 (66.67%)	
Regular Medication Use			
Yes	9 (69.23%)	10 (66.67%)	1.0
No	4 (30.77%)	5 (33.33%)	
Doctor-Diagnosed Psychological Disorder			
Yes	6 (46.15%)	5 (33.33%)	.7605
No	7 (53.85%)	10 (66.67%)	
Psychological Therapy			
Yes	7 (53.85%)	5 (33.33%)	.4771
No	6 (46.15%)	10 (66.67%)	
Ongoing Psychological Disorder			
Yes	6 (46.15%)	4 (26.67%)	.4979
No	7 (53.85%)	11 (73.33%)	
Serious Childhood Trauma			
Yes	5 (38.46%)	8 (53.33%)	.684
No	8 (61.54%)	7 (46.67%)	

and 48.20 for the experimental group, 7 (53.33%) were married, 6 (46.15%) were not married for the control group and 3 (20.00%) were married, 12 (80.00%) were not married for the experimental group. Whether there was a difference in demographic characteristics between the participants in the control and experimental groups was assessed through hypothesis tests. The *p*-values resulting from the independent two-sample *t*-test for the age variable and the chi-square test for other variables are summarized in Table 1. As all *p*-values exceeded the threshold $\alpha = .05$, indicating statistical non-significance, no notable difference was observed between the two groups.

Wilcoxon signed rank test results conducted for the Perceived Stress Scale are given in Table 2. This scale was administered to the participants both before the treatment initiation and after four sessions, the Wilcoxon signed rank test was employed for both the control and experimental groups to examine whether there existed a statistically significant difference between the pre-test (session 0) and subsequent sessions.

For the control group, except for the first session in question 10 on the scale, all calculated *p*-values between sessions were found to be greater than .05, indicating no statistically significant difference. Conversely, for the experimental group, it was observed that *p*-values were less than .05 across all questions and sessions, except for the first session in the first, sixth, and 12th questions. This suggests a statistically significant difference for the experimental group in these instances.

The Perceived Stress Scale is used to assess Hypothesis 1. Since the *p*-values exceeded $\alpha = .05$, indicating no statistically significant difference, it can be concluded that the TAT test administered to the control group did not have a discernible effect. Conversely, in the experimental group, the *p*-values were $< \alpha = .05$, indicating a statistically significant difference in the median value due to the Conscious Awareness-Based Breathing Method intervention. Consequently, it can be inferred that the applied method had a beneficial impact on the participants.

Table 3 presents the *p*-values obtained from the Wilcoxon Signed Rank Test conducted for the five questions in the Penn Alcohol Craving Scale. This scale was administered to the participants both before the treatment initiation and after four sessions. The Wilcoxon signed rank test was employed for both the control and experimental groups to examine whether there existed a statistically significant difference between the pre-test (session 0) and subsequent sessions.

For the control group, except for the second session in the fourth question on the scale, all calculated *p*-values between sessions were found to be greater than .05, indicating no statistically significant difference. Conversely, for the experimental group, it was observed that *p*-values were less than .05 across various questions and sessions, except for the conclusion of the first session in the second question. This suggests a statistically significant difference for the experimental group in these instances.

The Penn-Alcohol Craving Scale is used to assess Hypothesis 3. When comparing the pre-tests of session 0 with subsequent sessions within each group, no statistically significant difference was found among the sessions for the control group (*p*-values $>$

Table 2.
p-Values Obtained from Wilcoxon Signed Rank Test for Perceived Stress Scale

Question	Group	Between Sessions			
		0 – 1	0 – 2	0 – 3	0 – 4
Q1	Control	.317	.180	.852	.516
	Experimental	.083	.001*	.001*	.001*
Q2	Control	1.000	.599	.737	.709
	Experimental	.046*	.002*	.001*	.001*
Q3	Control	1.000	.280	.626	.883
	Experimental	.003*	.002*	.001*	.001*
Q4	Control	.317	.157	.374	.626
	Experimental	.025*	.001*	.001*	.001*
Q5	Control	.414	1.000	.665	.770
	Experimental	.008*	.001*	.001*	.001*
Q6	Control	.414	.056	.257	1.000
	Experimental	.083	.001*	.001*	.001*
Q7	Control	.626	.240	.908	.628
	Experimental	.046*	.001*	.001*	.001*
Q8	Control	.102	.908	.597	.180
	Experimental	.008*	.001*	.001*	.001*
Q9	Control	.626	.822	1.000	1.000
	Experimental	.025*	.001*	.001*	.001*
Q10	Control	.046*	.157	.336	.538
	Experimental	.008*	.001*	.001*	.001*
Q11	Control	1.000	1.000	.257	.534
	Experimental	.046*	.001*	.001*	.001*
Q12	Control	.655	.822	.124	.195
	Experimental	.083	.033*	.004*	.006*
Q13	Control	.737	.772	.737	.795
	Experimental	.026*	.002*	.001*	.001*
Q14	Control	.705	.626	.473	.200
	Experimental	.008*	.001*	.001*	.001*

Note: *Statistically significant.

$\alpha = .05$). In the experimental group, no statistically significant difference was obtained when comparing the pre-test data with the first session. However, there is a statistically significant difference between the pre-test and the second, third, and fourth sessions, p -values were $< \alpha = .05$, which is introduced by the Conscious Awareness-Based Breathing Method.

Moreover, for the fifth question, which assesses the general average alcohol craving over the last week, p -values were $< \alpha = .05$ for the comparison between the pre-test and all sessions. This suggests that the Conscious Awareness-Based Breathing Method had a statistically significant impact on reducing alcohol cravings throughout the sessions, indicating a positive effect on the participants.

To evaluate cortisol levels, normality tests were first performed using the Shapiro – Wilk Test. Hypothesis test results, including

Table 3.
p-values for Wilcoxon Hypothesis Test for Penn Alcohol Craving Scale

Question	Group	Between Sessions			
		0 – 1	0 – 2	0 – 3	0 – 4
Q1	Control	.365*	.195	.911	.144
	Experimental	.046*	.008*	.001*	.001*
Q2	Control	.799	.775	.913	.204
	Experimental	.157	.003*	.001*	.001*
Q3	Control	.599	.969	.249	.444
	Experimental	.046*	.001*	.001*	.001*
Q4	Control	.084	.009*	.545	.066
	Experimental	.025*	.002*	.001*	.002*
Q5	Control	.313	.249	.971	.279
	Experimental	.008*	.005*	.001*	.001*

Note: *Statistically significant.

p -values, are presented in Table 4. The p -value for the control group was found to be less than .05, as was the p -value for the experimental group. This indicates that the cortisol values in both groups did not follow a normal distribution, as determined by the test.

Table 5 presents the p -values resulting from the Wilcoxon hypothesis test conducted between the first session and subsequent sessions (up to the last session) for both the control and experimental groups. For the control group, p -values exceeded .05, indicating the absence of any statistically significant difference. Conversely, in the experimental group, p -values were less than .05, signifying a statistically significant distinction.

Cortisol levels are used to evaluate hypothesis 2. Upon examination of the p -values from the Wilcoxon signed rank test, a statistically significant difference was found between the cortisol medians of each session and the subsequent session for the experimental group. Hence, it can be concluded that the Conscious Awareness-Based Breathing Method exerted a positive influence on the participants.

Table 4.
p-values for Normality Test

Group	Test Statistics	p
Control	0.87	.001*
Experimental	0.90	.001*

Note: *Statistically significant.

Table 5.
p-values for Wilcoxon Hypothesis Test for Cortisol Values

Group	Between Sessions			
	0-1	0-2	0-3	0-4
Control	.155	.787	.273	.588
Experimental	.001*	.001*	.001*	.001*

Note: *Statistically significant.

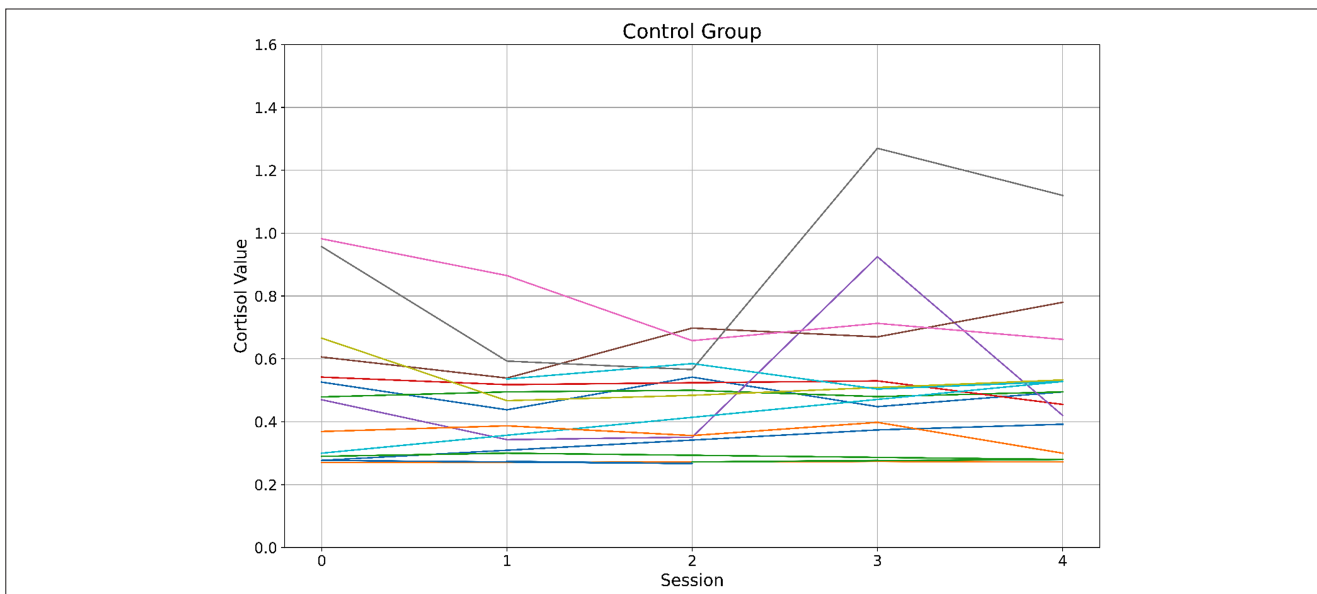


Figure 1. Cortisol Levels Among Participants in Control Group.

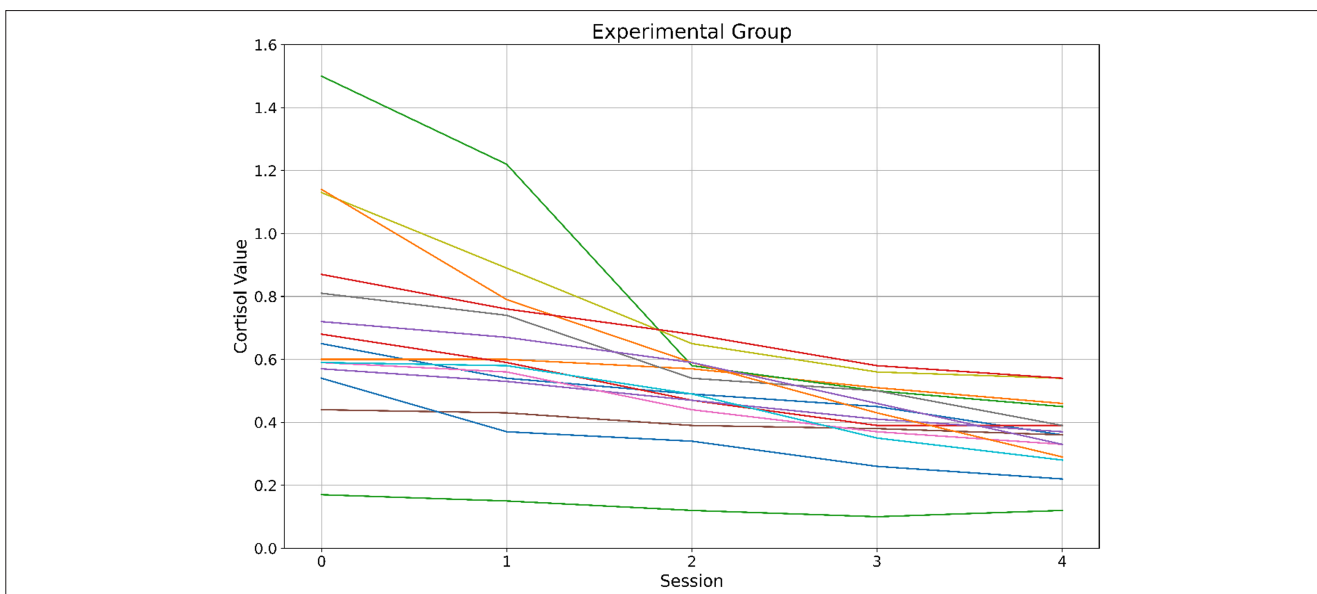


Figure 2. Cortisol Levels Among Participants in Experimental Group.

Figures 1 and 2 depict the graph illustrating the fluctuation in forehead cortisol levels among participants in both the control and experimental groups across five sessions. In the control group, random variations in cortisol levels among patients are evident between sessions, with no discernible significant increase or decrease observed. Conversely, in the experimental group, a noticeable overall decline in cortisol levels is observed following the initial session.

Discussion

The treatment process of alcohol use disorder is a very difficult and complex process, and the data collected from the participants regarding the practices performed within the pharmacological treatment in this process also includes the effect of the

pharmacological treatment. For example, considering the results of alcohol craving, the participants were included in the study after withdrawal treatment because they were not able to participate in the study while in the abstinence process. Therefore, the method was applied after their cravings were largely suppressed with pharmacological treatment. It can be said that the effect of the method on craving may have been suppressed.

Although the withdrawal process that occurs when alcohol is not consumed as addiction develops is both a physiological and psychological stressor, this situation further reinforces the addiction. In addition to pharmacological treatments, it is also important to provide individuals with stress coping skills during the treatment process. It has been stated that with conscious awareness, individuals can get rid of the effects of thoughts about craving by

developing the ability to direct attention (Tapper, 2018; Garland & Howard, 2013) and that mindfulness-based therapies are effective in preventing relapse in individuals receiving treatment (Bowen et al., 2009). It is important to acquire these skills to prevent relapse after treatment and for the treatment to be permanent. In summary, the lack of ability to cope with stress is a major factor in the onset and development of addiction and the return to addictive behavior in the post-treatment period. That is why the Conscious Aware Breathing Method can be recommended as a method that can be applied in AMATEM units to people who have completed the treatment process after alcohol treatment, both to support them in a healthier process and to prevent relapse. Again, by adding the training and implementation of this method to the awareness programs carried out by AMATEM units to prevent addictions before they occur, society can be supported in helping individuals gain skills in managing stress, which is one of the reasons for turning to alcohol.

The ability to cope with stress is the ability to consciously use attention for a purpose, and as the level of consciousness increases, the ability to produce solutions, maintain personal balance, see the positive side of a stressful situation, and turn it into an opportunity also develops (Csikszentmihalyi, 1990; Csikszentmihalyi, 2005; Aydın, 2005). In light of all the research done on this subject, it can be said that breathing exercises done with conscious awareness will contribute to healing and strengthening both the individual and society.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ege University (approval number: 21-5T/82; date: 06/05/2021).

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.S., W.S.; Design – G.S., S.Ç., W.S.; - Materials – G.S.; Data Collection and/or Processing – G.S., S.Ç.; Analysis and/or Interpretation – G.S., S.Ç.; Literature Search – G.S.; Writing – G.S., S.Ç., W.S.; Critical Review – W.S.

Declaration of Interests: The authors have no conflict of interest to declare.

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