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RESEARCH ARTICLE

The Relationship of Acamprosate and Small Intestine in Alcoholic Rats*

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Abstract

Acamprosate, which is used to reduce alcohol use relapse in alcohol use disorder; It was aimed to evaluate its side effects and its effectiveness in the small intestine.

The related study was carried out on 20.9.2021-25.10.2021. In the study, 32 Wistar Albino female rats were used. Saline at a concentration of 10 mg/kg/g was given to the control group. The alcohol group received 10 mg/kg/g ethanol diluted with 10 mg/kg/g saline. Acamprosate group received 200 mg/kg/g acamprosate diluted with 10 mg/kg/g saline. In the total group, 10 mg/kg/g ethanol was diluted with 10 mg/kg/g saline before being combined with 200 mg/kg/g acamprosate. Alcohol withdrawal symptoms on the 21st day were studied. The small intestinal tissues were hung in the isolated organ wash on the 22nd day.

Alcohol withdrawal syndrome results from both the alcohol and total groups were significant ($p<0.001$). Small intestine contractions in the alcohol, acamprosate, and total groups were substantially lower than in the control group ($p<0.001$). When the total group's small intestinal contractions were compared to the alcohol group's, a significant reduction ($p<0.001$) was detected.

It was understood that acamprosate affects the functioning of smooth muscles due to its activity on calcium channels. Acamprosate has been shown to reduce small intestinal contractions and motility. It was also discovered that this impact is stronger than alcohol's contraction-reducing effect.

Keywords: Alcohol, Alcoholism, Alcohol Use Disorder, Acamprosate, Small Intestine

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1. Introduction

Alcohol consumption disorder, occurs in humans as a result of frequent and long-term alcohol usage. Individuals suffer from alcohol withdrawal syndrome as a result of an alcohol use problem (Varol, 2011). Alcohol withdrawal syndrome raises the likelihood of relapse and shortens the length of abstinence over time (Varol, 2011).

Clinically, alcohol consumption disorder is fairly common. According to World Health Organization figures, nearly 3 million individuals die each year as a result of alcohol consumption disorder (Poznyak & Rekve, 2018). As in many cultures and belief systems, alcohol consumption is not considered appropriate in Islam.

As a result of alcohol use disorder, various disorders occur in many systems and organs. One of the organs negatively affected by alcohol use disorder is the small intestine (Varol, 2011; Köker, Şahintürk & Çekin, 2015; Poznyak & Rekve, 2018). In the small intestine as a result of alcohol use disorder; Pathological growths occur in tissue cells, oxidative stress increases, absorption disorders occur, intestinal motility decreases, and infection occurs (Preedy & Peters, 1990; Persson, Berg, Jölund & et al.,1990; Persson, 1991; Bhonchal, Nain, Prasad & et al., 2008; Bagyázanski, Krecsmarik, Winter & et al.,2010).

With the rise in alcohol use disorder in recent years, medications that minimize alcohol use relapse are becoming increasingly significant. In the treatment of patients with alcohol consumption disorder, both psychosocial and pharmacological therapy methods are used together. Acamprosate is the most recent medication used to treat alcoholism (Alcohol use disorder) (Boothby & Doering, 2015).

Acamprosate; It is a pharmacological drug available in oral tablet form, used 3 times a day, and then absorbed from the small intestines and added to the blood circulation (Kennedy, Leloux, Kutscher & et al., 2010; Witkiewitz, Saville & Hamreus, 2012; Polsker, 2015).

Individuals with alcohol consumption disorder may only abstain from alcohol for a short period of time (max: 4-8 hours) (Varol, 2011). As a result, it is critical that the medications being utilized have no interaction with alcohol (Evren, 2012). There is no interaction between acamprosate and alcohol (Evren, 2012). As a result, acamprosate can be used safely in a variety of conditions, including the consumption of alcohol (Evren, 2012). In humans, the typical duration of acamprosate usage for alcohol consumption disorder has been observed to be one year (Mann, Kiefer, Spanagel & et al.,2008). Acamprosate, like any other medication, has a number of negative effects. Severe stomach discomfort, diarrhea, nausea, vomiting, gas complaints, and sexual reluctance are all common adverse effects of acamprosate (Mann and et al., 2008; Boothby & Doering, 2015).

The bulk of the adverse effects linked with acamprosate usage; although it is connected with digestive system diseases, no physiopathological study in this area has been discovered. Acamprosate is known that it inhibits the entry of calcium into cells while also reducing calcium release in the cell (Mann and et al., 2008; Shwartz, Siddiqui, Roza & et al., 2010; Boothby & Doering, 2015).

Calcium has a major effect on smooth muscle contractions. It is also known that smooth muscle contractions are impaired as a result of disruptions in the calcium system. Given the drug's effectiveness on calcium mechanisms and the side effects that occur as a result of its use, it is believed that the drug disrupts the motility of the small intestine, which contains smooth muscle tissue, and thus causes various side effects such as diarrhea and severe abdominal pain.

As a result of determining the exact source of the side effects of acamprosate and the disorders it creates; important clues will be obtained to improve its use. For this reason, in our current study; the effect of acamprosate use on small intestine contractions was investigated.

2. Materials and Methods

For the associated research, an ethics committee permission numbered 2021-050 was acquired. Our experiment was conducted between September 20 and October 25, 2021. This work adheres to the World Medical Association's Helsinki Declaration on the ethical conduct of animal research.

In our research, we employed the alcoholism model developed by the intragastric intubation method in the literature, which was tailored to the usage of acamprosate. 32 Wistar Albino female rats weighing 300-350 grams were used in our investigation. The rats were first put into four equal groups at random. The groups were labeled as follows: control, alcohol, acamprosate, and total. The drug application time is 21 days, according to the modeling utilized. The oral gavage approach was used for all drug delivery operations. During the experiment, rats in the same group received fixed treatments every day at the same time interval. The control group (n=8) received 10 mg/kg/g saline. The alcohol group (n=8) received 10 mg/kg/g ethanol (99.8%) diluted with 10 mg/kg/g saline. Acamprosate group (n=8) received 200 mg/kg/g ground acamprosate (Sigma-Aldrich) following reconstitution with 10 mg/kg/g saline. In the total group (n=8), 10 mg/kg/g ethanol (99.8%) was diluted with 10 mg/kg/g saline and delivered with 200 mg/kg/g pulverized acamprosate.

Although the length of alcohol consumption disorder varies depending on the amount of alcohol used in the study, it develops in rats between 9 and 21 days. The emergence of alcohol withdrawal syndrome in rats coincides with the occurrence of alcohol use disorder. The symptoms of alcohol withdrawal syndrome in rats have been well characterized in the literature. In rats with alcohol withdrawal syndrome, withdrawal symptoms become more and more severe in parallel with the time elapsed after the last alcohol intake. Various scoring systems are used to evaluate alcohol withdrawal syndrome in rats. Alcohol withdrawal syndrome score was used in our study to assess alcohol withdrawal syndrome (EWS Score Test). On the 21st day of the experiment, the applicable scoring method was implemented following the completion of the modeling processes. The scoring method is carried out in three groups: the alcohol group, the total group, and the control group. Rats were used in the grading procedure. In observation cages, a clear plexiglass cylinder with a diameter of 25 cm and a height of 65 cm was inserted. An independent researcher rated the rats' alcohol withdrawal syndrome symptoms during the ten-minute follow-up session (Related groups were observed for 10 minutes after 30 minutes, 10 minutes after 120 minutes, 10 minutes after 240 minutes, and 10 minutes after 360 minutes, and scoring was performed 4 times for each rat). The video recording equipment was also used to record relevant observation and scoring operations. Relevant scores; time-dependent (30.-120.-240.-360.minute) changes and group comparative changes were analyzed in detail. The relevant item application phase of the modeling has been finished as of the experiment's 21st day.

On the morning of the 22nd day (08:00-8.20), a mixture of ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg) was delivered intraperitoneally to rats that had fasted since the night of the 21st experiment day. Following the anesthetic effect, cervical dislocation was done, and roughly 2 cm long pieces of the rats' small intestines were extracted. Tissues were collected and put in Krebs solution before being sent to the laboratory for examination. The lumen sections of the tissues were not covered in the laboratory; a cotton rope ring was linked to one end and a 10 cm long silk yarn ring was knotted to the other end, making it suitable for hanging. The upper end of the prepared small intestinal tissue is placed on the strain gauge of the isolated organ bath, and the lower end is placed on the hook section, completing the hanging procedure. The optimal circumstances (37 C temperature, Krebs solution, continually introduced 95 percent O2- 5 percent CO2 gas) for the survival of the tissues suspended in the isolated organ bath were given, and the tension was set to 1 g and contraction data were collected. Contraction recordings that are relevant; physiologic power transducer (FDT05, Commat Ltd.) and MP150WS Windows (Biopac Systems Inc.) system. After hanging the small intestinal tissues in the isolated organ bath for approximately an hour, they were cleaned for about an hour to minimize the potency of the existing anesthetic agents. At the end of one hour, a 75-minute recording session was initiated for each tissue. Spontaneous strain values of small intestinal tissues were obtained throughout the first 30 minutes of the registration procedure. After 30 minutes, 106 acetylcholine was placed into the isolated organ bath chambers to stimulate contraction increase, and the ensuing tension values were measured

for 15 minutes. The small intestinal tissues were cleaned with Krebs solution at the 45th minute, the Krebs solution in the chamber was replaced, and the tissues were anticipated to revert to their spontaneous tension levels. At 60 minutes, 0.001 M adrenaline was given to the isolated organ bath chambers to promote contraction reduction, and the ensuing tension values were measured. At the 75th minute, the recording procedures were completely terminated and the tissues were removed from the isolated organ bath.

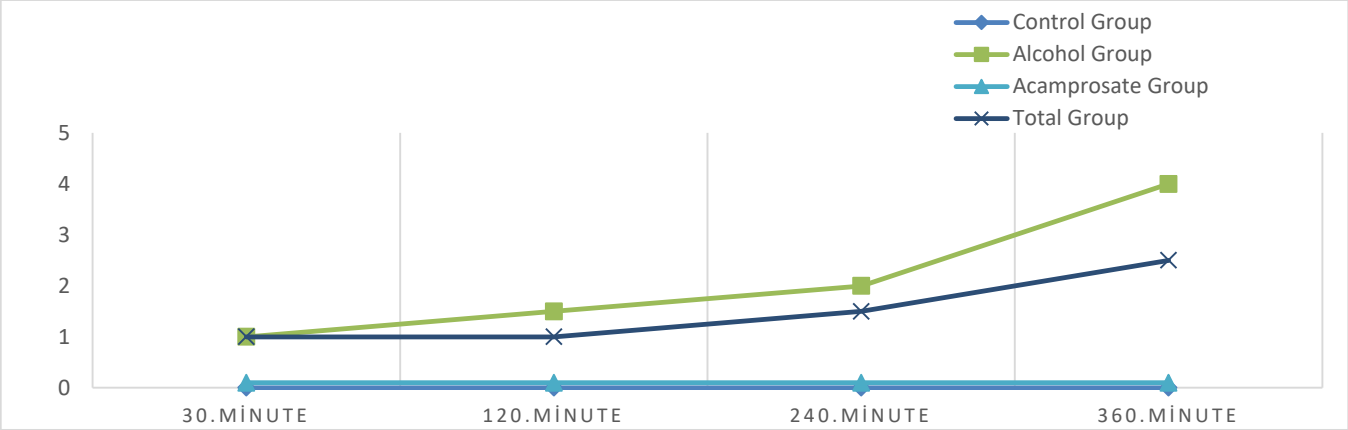
2.1. Statistical Method

Jamovi Version 2.0 and R. Core Team Version 4.0 applications were utilized for statistical analysis of the data received. For numerical data, the mean standard deviation is given; for categorical variables, the frequency and percentage values are supplied. The data was analyzed using the generalized linear mixed effects model. The statistical data collected from the analyses with $p<0.05$ were deemed significant.

3. Results

3.1. Alcohol Withdrawal Syndrome Findings

The scoring procedure of alcohol withdrawal syndrome was applied to three groups: control, alcohol, and total. Alcohol withdrawal syndrome scores of the control group were found to be statistically insignificant in all time periods (30.min-120.min-240.min-360.min) and it was understood that there was no withdrawal syndrome. ($p>0.05$). It was found that the alcohol withdrawal syndrome scores of the alcohol group and the total group showed a statistically significant increase in all time periods (120.min, 240.min and 360.min) except the 30th minute ($p<0.001$).



Figures 1: Time-dependent alcohol withdrawal syndrome behavioral scores of rats.

Alcohol withdrawal syndrome data of the alcohol group and total group were found to have statistically significant differences compared to the data of the control group ($p<0.001$). As a result of the related analyzes, it was understood that the alcohol group and the total group experienced alcohol withdrawal sendrom. Detection of alcohol withdrawal syndrome in the alcohol group and the total group indicates that alcohol use disorder developed in these rats.

Table 1: Results of time-group comparative analysis of alcohol withdrawal syndrome data evaluated using the rats-specific alcohol withdrawal syndrome behavioral scoring test (EWS Score Test)

Moderator Levels	**95% Confidence Interval**		
Time	**Contrast Groups**	**z**	**p**
30. Minute	Alcohol Group- Control Group	38 161	<.001
	Total Group- Control Group	9 813	<.001
120. Minute	Alcohol Group-Control Group	28 126	<.001
	Total Group-Control Group	27,989	<.001
240. Minute	Alcohol Group-Control Group	30 643	<.001
	Total Group-Control Group	30 754	<.001
360. Minute	Alcohol Group-Control Group	30 613	<.001
	Total Group-Control Group	29,826	<.001

3.2. Isolated Organ Bath Findings

Isolated organ bath measurements were performed to measure small intestinal contractions and evaluate intestinal motility. As a result of the comparison of the contraction data of the experimental groups at the 30th and 60th minutes, it was found that there was no significant difference and it was understood that spontaneous contractions were recorded in both time periods ($p>0.05$). As a result of the analysis of the contraction data obtained after the application, the contraction data of all experimental groups at the 45th (Acetylcholine applied) and 75th (Adrenaline applied) minutes were found to be statistically significant; It was understood that their excitability continued ($p<0.001$).

Table 2: Statistical analysis results of temporal changes of small intestine contraction data of experimental groups

Moderator Levels	**95% Confidence Interval**		
Groups	**Contrast Minute**	**t**	**p**
Control Group	30-15	-0.128	0.898
	45-15	4.345	<.001
	60-15	-1.659	0.100
	75-15	-10.309	<.001
Alcohol Group	30-15	-1.034	0.303
	45-15	2.212	<.001
	60-15	-0.015	0.988
	75-15	-8.634	<.001
Acamprosate Group	30-15	1.586	0.116
	45-15	6.019	<.001
	60-15	2.395	0.018
	75-15	-5.727	<.001
Total Group	30-15	-0.347	0.729
	45-15	4.849	<.001
	60-15	1.289	0.200
	75-15	-5.174	<.001

Small intestine contraction values of alcohol, acamprosate and total groups; significantly decreased compared to the control group ($p<0.001$). When the contraction data of the total group was compared to the contraction data of the alcohol group, it was concluded that there was a significant decrease ($p<0.001$). As a result of statistical analysis, it was understood that acamprosate reduced small intestine contractions and motility. It has also been determined that this effect is stronger than the contraction-reducing effect of alcohol.

Table 3: Group comparison analysis results of contraction data obtained from isolated organ bath measurements of small intestine tissues

	95% Confidence Interval	
Contrast Groups	t	p
Alcohol Group- Control Group	-4,658	<.001
Acamprosate Group- Control Group	-8,469	<.001
Total Group- Control Group	-9,330	<.001
Total Group- Alcohol Group	-5,472	<.001

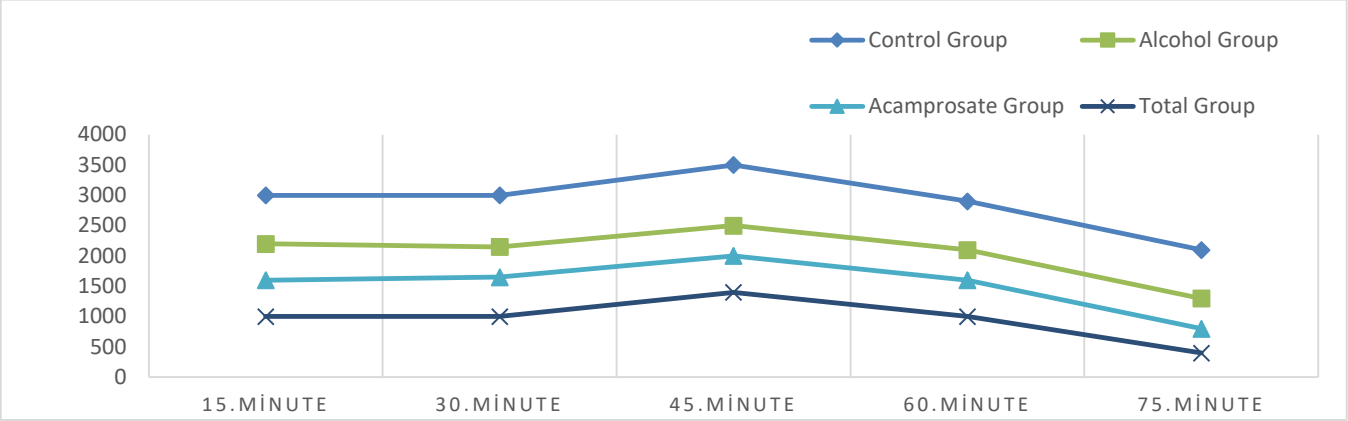
4. Discussion

It is well recognized that alcohol use disorder makes the small intestine more susceptible to infection, and that it also causes a variety of difficulties such as malabsorption (Persson, 1991; Wang, Chen, Chen & et al.,2020). According to a careful analysis of absorption issues, there is a reduction in the absorption of glucose, fatty acids, B12, water, electrolytes, and folic acid (Saivin, Hulot, Chabac & et al., 1998; Köker and et al., 2015). It has been observed that the villi heights of the small intestines are lowered as a consequence of morphological investigations in alcohol use disorder, and there are pathological enlargements between the cells (Persson and et al.,1990; Bhonchal and et al., 2008; Bagyázanski and et al.,2010; Yılmaz & Altındiş, 2019). It has also been observed that alcohol use disorder causes a reduction in small intestinal contraction levels, which increases the occurrence of diarrhea in persons (Preedy & Peters, 1990; Persson, 1991; Bode, 1997; Bagyázanski and et al.,2010; Yılmaz & Altındiş, 2019). As a result of the data analysis in our study, it was found that the small intestine tension values of the alcohol group fell considerably ($p<0.001$) when compared to the data of the control group, and it was understood that the findings obtained were consistent with the literature.

Alcohol use disorder is a broad category of mental disease (Özpoyraz, Taman & Şentürk, 1998). As a result, both psychological and physiological disorders caused by alcohol use disorder should be treated (Karakuş and et al.,2021). While various treatment approaches such as psychotherapy and group therapy are used for the treatment of psychological disorders, pharmacological drugs are used for the treatment of physiological disorders (Özpoyraz and et al., 1998; Eşel & Dinç, 2017). Before starting the pharmaceutical treatment of alcohol use disorder, physical examination data, neurological examination data, and laboratory data should be thoroughly examined (Özpoyraz and et al., 1998; Yenigün, 2006; Varol, 2011).

Acamprosate is a pharmacological substance that comes in 333 mg oral tablets and should be taken three times per day. The use of acamprosate is very important for the holistic and sustainable treatment of alcohol use disorder. Acamprosate is absorbed in the body by passive diffusion from the small intestines (Serrano, Granero, Algarra & et al.,2000). Acamprosate, which is absorbed by passive diffusion, is directly involved in blood circulation (Serrano and et al.,2000). Acamprosate is an NMDA (N-methyl-D-aspartate) receptor antagonist (Uğurlu, Şengül & Şengül, 2012). The medicine also works against the actions of stimulating components like glutamate while boosting the function of gamma aminobutyric acid (Evren, 2012; Chau, 2018; Pan, Jin, Shen & et al., 2018). At the same time, it has been shown that acamprosate inhibits the functioning of voltage-gated calcium channels in the brain and lowers calcium release in the cell (Mann and et al., 2008). Because of its calcium-binding properties, acamprosate is known to lessen the relapse of alcohol intake (Mann and et al., 2008). Alcohol has no effect on acamprosate. As a result, it

is thought to be more trustworthy in alcohol consumption disorder than other medications (Evren, 2012; Uğurlu and et al., 2012). However, acamprosate, like any other medicine, has a variety of negative effects. Acamprosate commonly causes diarrhea, severe stomach discomfort, nausea, vomiting, and gas problems (Yenigün, 2006). The bulk of the adverse effects linked with acamprosate usage; although it is connected with digestive system diseases, no physiopathological study in this area has been discovered. Acamprosate is known to inhibit calcium entrance into cells while also reducing calcium release in the cell. Calcium, as is well known, plays an important role in smooth muscle movement. Given the drug's effectiveness on calcium mechanisms and the side effects that occur as a result of its use, it is believed that the drug disrupts the motility of the small intestine, which contains smooth muscle tissue, and thus causes various side effects such as diarrhea and severe abdominal pain. In our study, small intestine contraction data of the acamprosate group and the total group showed a significant decrease compared to the control group ($p<0,001$). Our findings support the effectiveness of acamprosate on calcium channels in the literature. Our data reveal important clues about the possible source and cause of the drug's current side effects.



Figures 2: Time-Varying Small Intestine Contraction Data of Rat Groups

Various problems in the system and organs arise as a result of alcohol use disorder. For this reason, it is very important that the pharmacological agent to be used for treatment does not worsen the existing contraction decrease. In line with the data we obtained in our study, it was determined that the small intestine contraction data of the total group decreased significantly compared to the contraction data of the alcohol group ($p<0,001$). As a result of the analysis of the available data, it was understood that the use of acamprosate had a negative effect on the decrease in small intestine contraction caused by the current alcohol use disorder and deepened the problem even more.

As a result of the detailed analysis of the data obtained, it was understood that the use of acamprosate may be risky for small intestine health. Due to the negative effect of the use of acamprosate on the small intestines; It is thought that acamprosate treatment should be scrutinize very carefully.

4. Conclusion

It has been reported as a result of scientific research and clinical studies that alcohol consumption impairs human health. As in many cultures and belief systems, alcohol consumption is not considered appropriate in Islam. Unfortunately, alcohol use disorders are on the rise worldwide. Due to the increase in alcohol use disorders, the treatment of the existing problem becomes more important. Acamprosate is used in the treatment of alcohol use disorder. For this reason, it is very important to determine the efficacy of acamprosate on the small intestines and to continue the treatment in line with this information.

As a result of our research ıt has been understood that acamprosate negatively affects the mobility of smooth muscles due to its activity on calcium channels. Acamprosate has been shown to reduce small intestinal contractions and motility. It was also discovered that this impact is stronger than alcohol's contraction-reducing effect.

It is known that acamprosate should be used for a long time to reduce relapse and eliminate alcohol use disorder. It is very risky for a drug that requires long-term use to adversely affect the small intestine contractions that have already decreased due to alcohol use disorder. In the case of long-term acamprosate usage while disregarding its present activity in the small intestine, several difficulties such as digestion, absorption, and contraction abnormalities may occur. As a result, it is assumed that it is critical to monitor the health of the small intestine during certain times of acamprosate usage. Based on the findings of the study, it is believed that the usage of acamprosate may be harmful for those who have a variety of small intestinal health concerns.

New research is required to lessen acamprosate's existing adverse effects and to enhance the treatment method.

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