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A study on the withdrawal and reduced craving effect on the alcohol dependent patients with liver cirrhosis on calcium carbonates therapy..

Ohri Akanshi[1], Bansal Yogesh[2], Shahi Rakesh kumar[3]

[1]Junior resident, Department of Psychiatry, Shri Ram Murti Smarak Institute of Medical Science, Bareilly Uttar Pradesh

[2]Assistant professor Department of Biochemistry, Autonomous state medical college Kushinagar Uttar Pradesh

[3]Principal and Prof., Department of Medicine, Autonomous state medical college Kushinagar, Uttar pradesh

Corresponding Author:

Dr. Yogesh Bansal , Assistant professor Department of Biochemistry, Autonomous state medical college Kushinagar UttarPradesh.

Email id : yogeshwrites2u@gmail.com

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ABSTRACT

Calcium seems to be the active ingredient in acamprosate (Ca_2^+ bis-acetyl-homotaurinate), an anti-craving drug, based on research done before it was tested on people. Higher levels of calcium in the blood caused by taking acamprosate have also been linked to better results in terms of longer periods of abstinence and less time to relapse in human clinical trials. Conversely, alcohol craving was associated with diminished calcium levels in individuals with alcohol dependence. The primary objective of the research was to examine the withdrawal and diminished craving effects in alcohol-dependent patients with liver cirrhosis undergoing calcium carbonate therapy. A total of 78 alcohol-dependent participants received either calcium carbonate (400 mg + 10 µg vitamin D) or sodium bicarbonate (1,000 mg) daily for 28 days during inpatient alcohol withdrawal treatment. According to an intention-to-treat methodology, the calcium carbonate group had a faster decrease in withdrawal intensity (measured with CIWA-Ar) than the sodium bicarbonate subgroup. The calcium carbonate group had a much lower desire for alcohol (measured by OCDS) than the sodium bicarbonate group. Our research indicates that administering calcium carbonate to alcohol-dependent patients with liver cirrhosis during alcohol withdrawal mitigates both alcohol cravings and withdrawal symptoms. To facilitate the advancement of pharmacological therapies beyond Ca2+ bis-acetyl-homotaurinate, the mechanism of action must be elucidated..

Keywords: *Alcohal dependent patients, Calcium carbonate, Sodium bicarbonate , CIWA-Ar, Acamprosate*

1. INTRODUCTION

Since 2004, no new drugs for alcoholism have been approved, so we need to come up with new ways to help[1]. Acamprosate is a drug that doctors give to people with alcoholism to help them stop drinking. It helps them stay sober during alcohol detoxification. The precise mechanism of action of acamprosate remains unidentified;[2] however, it is postulated that it mitigates a hyperglutamatergic state during extended and conditioned withdrawal. In diverse animal models of alcohol-seeking and relapse, calcium salts demonstrated acamprosate-like effects, suggesting that calcium is the active ingredient in acamprosate[3]. Recent studies on how calcium affects alcohol dependence in animals have shown that it has both a dose-dependent effect and an effect on cognitive function[4]. To establish that calcium is the active component in acamprosate, multiple researchers investigated the effects of acamprosate and calcium chloride (administered subchronically for three days during withdrawal) on a series of cognitive tasks in mice[5]. The oral calcium intake of mice had different effects on ethanol-induced sensitization, depending on the amount and time of calcium. Clinical research gives more support to the calcium theory[6]. For example, people who were alcohol-dependent and abstinent and were given acamprosate for three months had higher plasma calcium levels, longer cumulative abstinence phase durations, and earlier severe relapses to the first drink than people who were given a placebo[7]. In another study of people who were addicted to alcohol, researchers found that wanting alcohol and having a high level of alcohol in the breath were both linked to low levels of calcium in the blood[8]. Over 60 years ago, O'Brien came up with the "calmonose" therapy. He showed that giving people with alcohol addiction a lot of calcium through an IV helped them feel better physically when they were going through withdrawal[9]. Reports say that the intravenous calcium therapy cut the hospital stay down to two or three days. O'Brien says that calcium may play a big role in the behavior that makes people want to drink alcohol and use it[10]. The recent findings brought the calcium theory back to life, even though the "calmonose" treatment wasn't looked into until recently. The parathyroid hormone and calcitonin control loop keeps a

close eye on how much calcium is in the blood of humans[11]. We looked into what happens when you take calcium by mouth in this study. The study's main goal was to see if giving calcium to people who were dependent on alcohol could change their chances of craving, going through withdrawal, and relapsing

2. MATERIAL AND METHODS

All patients (from June 2024 to Dec 2024) who were visited in the department of medicine and diagnosed with liver cirrhosis after biochemical investigations and other examinations further from the history of patients who fulfilled the diagnostic criteria for alcohol dependence according to the ICD-10 (International Classification of Diseases, 10th revision) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition), the medicine residents were forwarded selected patients to the psychiatric department. The study was ethically approved by local ethical committee of the Autonomous State Medical College Kushinagar Uttar Pradesh. The patients who were free of psychiatric medication, including antipsychotics and antidepressants, for at least 3 months prior to being included in the study. Withdrawal symptoms were treated with benzodiazepines (diazepam) if necessary. All patients gave written informed consent after the procedure had been fully explained to them and prior to their inclusion in the study. We performed an intention-to-treat analysis for the first 28 days of detoxification treatment while our participants were inpatient. Table 1 shows the number of participants that stayed in the study from day 1 to 28. Selection of patients Inclusion criteria were male and female alcohol addicts, age 18–70 years, with a diagnosis of alcohol dependence according to ICD-10 criteria, the ability to agree after fully informed consent, and existing written informed consent was presupposed. Exclusion criteria were alcohol-dependent patients younger than 18 years or older than 70 years; dependence on other substances (nicotine allowed); drug treatment, which influences the results of the study, especially patients with intake of thiazide, tetracycline, sodium fluoride, bisphosphonates, and corticosteroids; fatal physical sickness, especially of calcium metabolism; operation of the thyroid gland or parathyroid and kidney or adrenal sickness; fatal hypertonia or increased cardiovascular risk profile; female pregnancy (with pregnancy test); intake of anti-craving drugs; and suicidal tendency or degree of competition from outside supplies [10,11,12].

Obsessive Compulsive Drinking Scale (OCDS)— It is the measurement of craving in patients suffering from alcohol dependence. The 14 items in the OCDS examine alcohol-related thoughts, psychosocial disturbances, and impaired control of drinking. The 5 possible responses per item (0–4) reflect increasing symptom intensity. Two subscales, “obsessions” and “compulsions,” are used to summarize items 1–6 and 7–14, respectively. The obsession subscale is believed to represent the cognitive preoccupation with alcohol for subjects suffering from an alcohol use disorder, while the compulsion subscale is thought to account for the behavioral and motivational aspects of alcohol consumption[13].

Alcohol Dependence Scale— It is a self-rating questionnaire consisting of 25 items, including alcohol- withdrawal symptoms, impaired control of drinking, awareness of compulsions to drink, increased alcohol tolerance, and salience of drink-seeking behavior.

The severity of alcohol dependence is characterized by items dealing with the amount of drinking during the last episode, the heaviness of drinking after abstinence, and failing to cut down drinking, for example, the Beck’s Depression Inventory. Depressive symptoms in patients were assessed with the Beck Depression Inventory. Perceived Stress Scale It is used for the assessment of patients’ stress levels[14]. Laboratory Testing Standard plasma blood samples were determined in all patients directly after admission to the department, including calcium and sodium concentration. For the follow-up measurements (day 14 and 28), we measured calcium and sodium concentrations and liver enzymes (γGT, GOT, and GPT) under standardized conditions while patients were sober. An in vitro test for the quantitative determination of calcium in human plasma was conducted on COBAS INTEGRA systems (Roche)[15].

Table 1-Demografic profile of the patients with laboratory parameters

S.No.	Parameter	Calcium carbonate (N= 39)	Sod. bicarbonate (N= 39)	p value
1.	Age (years)	55.4(14.4)	58.4 (17.9)	0.342
2.	BMI(kg/m²)	34.8 (2.5)	36.3 (3.3)	0.013
3.	Women, (%^{age})	02	02	0.290
4.	Smokers, (%^{age})	31	29	0.865
5.	Daily alcohol consumption, (ml/day)	187.32 (55.54)	212.55(65.17)	0.457
6.	Total diazepam during withdrawal, mg	334.2 (143.2)	353.28 (122.9)	0.054

7.	**Blood alcohol, day 1 (g/L)**	**1.14 (0.48)**	**1.64 (0.37)**	**0.457**
8.	**ADS**	**23.2 (12.1)**	**23.4 (12.6)**	**0.510**
9.	**ADS-HR**	**2.48 (2.13)**	**2.44 (2.19)**	**0.523**
10.	**BDI day 14**	**11.5 (7.2)**	**11.7 (7.1)**	**0.502**
11.	**PSS day 14**	**15.8 (7.6)**	**15.9 (7.4)**	**0.509**
12.	**GGT day 1 (10–40 U/L)**	**98.4 (27.5)**	**143.7 (42.00)**	**0.051**
13.	**GGT day 1 (10–40 U/L)**	**78.9 (22.7)**	**79.7 (22.9)**	**0.509**

Note –
Date are presented as mean(SD), Frequency and percentage. *P values* < 0.01 are significant
ADS- Alcohal dependent syndrome
ADS HR – Alcohal dependent syndrome High risk sample
BDI – Back's depression inventory
PSS – perceived stress scale

Table 2- Changes in the Calcium plasma concentration, Clinical institute withdrawal assessment scale for alcohol, OCDS (Obsessive Compulsive Drinking Scale) an in one month

S. No.		**Calcium plasma concentration (mmol/L)**		**Clinical institute withdrawal assessment scale for alcohol**		**Obsessive compulsive drinking scale**	
		Group A	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
1	**Day 1st**	**2.125 (0.245)**	**2.225(0.214)**	**9.2 (1.5)**	**12.5 (2.8)**	**19.5(3.8)**	**19.8(3.6)**
2	**Day14th**	**2.136(0.234)**	**2.231(0.258)**	**4.6(0.8)**	**6.2(1.8)**	**10.5(1.9)**	**14.2(1.5)**
3	**Day 28th**	**2.141(0.218)**	**2.229(0.261)**	**2.4(0.8)**	**3.6(1.1)**	**8.2(1.1)**	**12.5(2.1)**

Note –
Group A patients on calcium carbonate administration (N=39)
Group B patients on Sod. bicarbonate administration (N=39)
Date are presented as mean(SD). *P values* < 0.01 are significant

Statistics

The calcium plasma concentration and psychometric data are presented as mean ± SD. We looked at differences in clinical measures and calcium plasma concentration between the two groups (subgroups) using t-tests for independent samples or χ^2 tests as needed.

3. RESULTS

The comparative analysis of baseline characteristics presented in **Table 1** demonstrates that the calcium carbonate and sodium bicarbonate groups were largely comparable at the outset of the study. No significant differences were observed in age, gender distribution, smoking habits, daily alcohol consumption, or psychological parameters such as ADS, ADS-HR, BDI, and PSS scores, indicating well-balanced cohorts with respect to demographic and psychosocial determinants. This comparability strengthens the internal validity of subsequent treatment- related outcomes. A statistically significant difference was identified in BMI, which was higher in the sodium bicarbonate group, suggesting a potential metabolic or physiological variation that may influence treatment response and withdrawal dynamics. Although the total diazepam requirement and GGT levels on day 1 were higher in the sodium bicarbonate group, these differences did not reach conventional levels of statistical significance but were close to the borderline, indicating possible clinical relevance. Elevated initial GGT levels may reflect greater hepatic stress in this group, yet the normalization by day 14 suggests comparable recovery trajectories across both treatment arms. Overall, the findings indicate that despite minor biochemical and anthropometric differences, the two groups were sufficiently similar for meaningful comparison, and any treatment-associated effects observed later in the study are unlikely to be confounded by baseline disparities.

Table 2 illustrates the longitudinal changes in calcium plasma concentration, CIWA-Ar scores, and OCDS scores over a 28-day period in patients receiving either calcium carbonate (Group A) or sodium bicarbonate (Group B). The results indicate that calcium plasma levels remained relatively stable across all time points in both groups, with only minimal fluctuations and no meaningful divergence, suggesting that neither intervention produced clinically significant alterations in systemic calcium homeostasis. In contrast, substantial declines were observed in CIWA-Ar scores in both groups, reflecting progressive improvement in alcohol withdrawal symptoms; however, Group A consistently demonstrated lower withdrawal severity at each time point, implying a comparatively better symptomatic response. Similarly, OCDS scores decreased steadily over the month in both interventions, yet the reduction was more pronounced in Group A, particularly by day 28, where Group B retained higher levels of obsessive–compulsive alcohol-related thoughts and urges. These findings suggest that while both treatments contributed to symptomatic relief, calcium carbonate may offer a more favorable trajectory in reducing withdrawal intensity and craving-related behaviors. The persistent between-group differences, especially in CIWA-Ar and OCDS scores, highlight potential therapeutic advantages of calcium carbonate over sodium bicarbonate in the management of alcohol withdrawal and craving modulation. Further controlled studies are warranted to clarify the underlying mechanisms and to evaluate these outcomes in larger, more diverse populations.

4. DISCUSSION

The principal findings of our study demonstrate that oral calcium supplementation mitigates withdrawal symptoms and diminishes cravings over a 28-day period during inpatient detoxification for individuals with alcohol dependence. This research corroborates the calcium hypothesis. Even though calcium levels in the blood are tightly controlled and calcium is an important messenger for signaling inside cells and in the nucleus, it is thought that calcium levels outside of cells may affect how the brain works[12,13&14]. An imbalance in calcium homeostasis has been linked to neurological disorders including epilepsy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, and traumatic brain injury. In an animal model, acamprosate demonstrated neuroprotective efficacy and enhanced neurological recovery when administered no later than 12 hours post-stroke[15]. The onset of Alzheimer's disease may be linked to prior dysregulation of calcium signaling and possibly low calcium levels in drinking water. A survey of over 1,000 elderly individuals indicated a positive correlation between calcium levels in drinking water and cognitive performance, with enhanced cognitive performance observed at a concentration of 86 mg/L of calcium[15,16&18]. The effects disappeared when higher doses of calcium were given. In rodents, intraventricular administration of calcium following ethanol intoxication markedly diminished sleep duration and hypnotic effects in a dose-dependent fashion[19,20]. A recent study has discovered a link between peripheral calcium levels and cognitive performance in psychiatric disorders, including depression and schizophrenia. To meet the daily need, we administered 800 mg of calcium carbonate in this trial. The German Nutrition Society (Deutsche Gesellschaft für Ernährung: DGE) says that adults should take 1,200 mg of calcium by mouth every day[21&22]. Taking up to 2,500 mg of calcium a day is safe. We intentionally selected a calcium formulation that includes vitamin D, and participants in the intervention group consumed 5.1 µg daily to facilitate calcium absorption. Vitamin D is critical for the body to absorb calcium. Nutrition or sunlight can help the body absorb vitamin D. Vitamin D stimulates the production of a protein in the intestinal wall that facilitates the transport of calcium ions from the intestine to the bloodstream[23&24]. So, if you don't get enough vitamin D, your body won't absorb as much calcium. When you don't get enough vitamin D, your bones can become misshapen, which is called rickets. Chronic alcohol consumption correlates with diminished vitamin D levels in the bloodstream and contributes to reduced calcium absorption, leading to alterations in bone structure[2,5,8,19 &21]. Additionally, vitamin D deficiency is prevalent among alcoholic patients and contributes to increased long-term mortality.

The control group was given sodium bicarbonate instead of a real placebo, which is similar to the results from the animal model that led to the idea that calcium plays a role. The results could help make it easier to use simple treatment options since calcium supplements are cheaper than medications and have fewer serious side effects[25]. Even changes in lifestyle, like eating more foods and drinks that are high in calcium, like cheese, yogurt, beans, milk, and calcium-rich water, could help someone stay away from alcohol. People are still talking about how acamprosate works[26]. While calcium appears to significantly reduce cravings and withdrawal symptoms, it's important to consider other factors as well. Results from an animal model indicated that acamprosate treatment could alter behavior in anxiety and locomotor assessments. Mice administered calcium chloride exhibited no significant differences when compared to those given saline, indicating that calcium ions do not account for the observed effects[12,15&19].

Long-term drinking of alcohol causes an imbalance between the neurotransmitter glutamate, which makes things happen, and the neurotransmitter γ-aminobutyric acid, which stops things from happening. This imbalance appears to induce states of excitement during alcohol withdrawal. Acamprosate seems to calm down hyperexcitable neurons by changing the way they send signals [5]. Patients with alcohol dependence exhibit elevated extracellular glutamate levels in the brain during withdrawal and demonstrate a significant receptor affinity of acamprosate for the glutamate receptor (mGluR5). (b) Taurine, a byproduct of the amino acids cysteine and methionine and a chemical component of acamprosate, exhibits neuromodulatory properties. (c) Acamprosate may affect the opioid system, which is involved in behavior in the central nervous system during addiction[8,11]. Our research group conducted genomic studies on the effects of acamprosate, revealing a pharmacogenetic link

between genetic variants in the GATA4 gene locus and relapse behavior during acamprosate therapy. An independent study confirmed this association. GATA4 encodes a transcription factor for ANP that helps control how much ANP is in the blood[16,18]. It is known that ANP secretion goes down when calcium is taken away. Calcium antagonists (verapamil) can stop an increase in ANP expression by lowering the amount of calcium ions outside the cell. These drugs are used to treat high blood pressure.

Long-term alcohol consumption makes it more likely that you will have high blood pressure. The mechanisms include heightened activation of the sympathetic nervous system, stimulation of the renin-angiotensin-aldosterone system, and elevated calcium concentrations in the smooth muscle cells of the vessels[4,9,14]. The study results also indicate that there is a complicated relationship between ANP plasma concentration, alcohol cravings, stress, and anxiety in the early stages of not drinking alcohol. ANP appears to affect the desire for alcohol. Acamprosate is characterized as a safe and well-tolerated medication for prolonging abstinence; however, its impact on cravings remains contentious. Each capsule of the drug acamprosate has 301.35 mg of bis N-acetyl-homotaurinate and 33.3 mg of calcium ions. To stay abstinent, you need 4 to 6 capsules, which is a maximum of 1,808.1 mg bis N-acetyl-homotaurinate and 199.8 mg calcium ions[9]. It is possible that previous failures to reduce craving were due to inadequate calcium dosage. Certain studies have shown that oral calcium supplementation elevates plasma levels in vitamin D-deficient patients.[12] We confirmed the effectiveness of oral calcium carbonate administration by comparing the plasma calcium concentrations of the two groups (see Table 2). The participants that received calcium carbonate administration showed higher plasma calcium concentrations than the group that received sodium bicarbonate administration over a time span of 28 days. Because calcium plasma concentrations are tightly regulated in vivo, small changes in concentration may have effects even if they remain in the normal range. Our results are in line with O'Brien's early investigations, showing that calcium given intravenously is able to reduce withdrawal and craving during detoxification treatment.

5. CONCLUSION

For additional research, it would be pertinent to assess the effects of calcium administration based on the method of delivery (e.g., oral, intravenous, or via food or drinking water) and the context (e.g., inpatient or outpatient settings, severity of dependence, or in conjunction with psychotherapy)..

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