

## A study of the effect of Baclofen on blood glucose level in alcohol dependence syndrome(ADS) patients at a tertiary care hospital

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### Abstract

**Background:** Alcohol dependence syndrome affects an individual at physiological, behavioral, and cognitive level and include symptoms like withdrawal, tolerance, and craving. Heavy alcohol intake is often associated with many health related and social problems which poses a threat to the society. Recently Baclofen has been used to reduce the symptoms of ADS, and is shown to affect the level of blood glucose in patients receiving it.

**Objective:** The main objective of the study is to find out the effect of baclofen on blood glucose levels in ADS patients during therapy.

**Methodology:** A Prospective interventional study was designed and conducted in patients attending Psychiatry Department 30 patients aged between 18 years and 60 years diagnosed with alcohol dependence syndrome (ADS) per ICD-10 criteria are enrolled in the study.

Blood glucose levels are checked at baseline, 10<sup>th</sup> day and at 20<sup>th</sup> day.

**Results:** Mean fasting blood glucose levels in patients was 87.1 mg/dl on day 0, 103.23mg/dl on day 1, 98.63 mg/dl on day 10 and 95.30 mg/dl on day 20.

Mean post prandial blood glucose was 125.5 mg/dl on day 0, 144.57mg/dl on day 1, 137.2 mg/dl on day 10 and 136.6 mg/dl on day 20.

**Conclusion:** Our study shows that Baclofen has a definite role in the levels of glucose, but the mechanism of action of depression in blood glucose levels is still unknown. Further studies are needed to confirm the long term effect of Baclofen on the blood glucose levels.

**Keywords:** Baclofen, Alcohol withdrawal syndrome, FBS, PPBS.

### Introduction

Alcohol is the most frequently used intoxicating substance and contributes to considerable morbidity and mortality. An estimated 3.8% of all global deaths and 4.6% of global disability-adjusted life-years are attributable to alcohol.<sup>(1)</sup>

Chronic dependence on alcohol is clinically termed as 'Alcohol dependence syndrome' which is defined by a cluster of physiological, behavioral, and cognitive phenomena in which the use of alcohol is on a much higher priority for a given individual than other behaviors that once had greater value.<sup>(2)</sup> This can include symptoms like withdrawal, tolerance, and craving.<sup>(3)</sup>

Heavy alcohol intake is often associated with nutritional deficiencies, impaired mental and physical status, neurological afflictions and multiple organ damage. So treating ADS is essential and is normally treated with benzodiazepines, naltrexone, acamprostate or disulfiram.<sup>(4)</sup>

With proper counseling these drugs are found to be useful but a new line of treatment has come into practice which includes drugs like GABA<sub>B</sub> receptor agonist baclofen.<sup>(5)</sup>

Animal studies investigated the effect of the baclofen on the acquisition of alcohol drinking behavior in bred Sardinian alcohol-preferring rats and baclofen

had been proven to reduce this alcohol drinking behaviour.<sup>(6)</sup>

In order to gather some more evidences human trials have been conducted which have demonstrated that Baclofen was associated with reductions in withdrawal-related anxiety and alcohol craving. Hence it represents a promising treatment for alcohol dependence. Clinical studies have also indicated that baclofen is able to suppress withdrawal symptoms in alcohol-dependent patients affected by the alcohol withdrawal syndrome. Moreover, baclofen has shown efficacy and safety in promoting alcohol abstinence in alcohol dependent patients and even with the association of liver cirrhosis.<sup>(7)</sup>

However observations of increased blood sugar concentrations on Baclofen administration have been made which might suggest its contraindication in diabetic patient.<sup>(8)</sup> The substantiation of which forms the main objective of this study.

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. When unqualified, 'alcohol' refers to ethyl alcohol or ethanol. Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history), alcoholism and for alcohol intoxication, rather than as a medicinal substance. Alcohol is manufactured by fermentation of sugar.<sup>(9)</sup>

The use of alcoholic beverages has been documented since at least 10,000 BC.<sup>(10)</sup> By about 3000 BC, the Greeks, Romans, and inhabitants of Babylon continued to incorporate ethanol into religious festivals, while also using these beverages for pleasure, to facilitate socialization, as a source of nutrition, and as part of medicinal practices. The role of ethanol in society continued through biblical times, with beverage alcohol incorporated into most religions, and occupying a central role in daily life. Over the last 2000 years, alcoholic beverages have been identified in most cultures, including pre-Columbian America in ~200 AD, and the Islamic world in the 700s. Whiskey was invented in ~1400 in Ireland and rapidly increased in popularity; champagne was developed in France in 1670. In 1690, the English government enacted a law encouraging the consumption of distilled spirits, and the production of gin subsequently increased from about 0.5 million gallons in 1685 to 5 million by 1727 and 18 million gallons by the early 1800s. The dangers of heavy consumption of beverage alcohol have been recognized by almost all cultures, with most stressing the importance of moderation. Despite these warnings, problems with ethanol are as ancient as the pattern of use of this beverage itself, and were noted early on in India, Greece, and Rome. The increase in use of ethanol in the 1800s, along with industrialization and need for a more dependable work force, contributed to the development of more widespread organized efforts to discourage drunkenness. The subsequent temperance movements set the stage for the prohibition against drinking instituted in the U.S. in 1920. In 1933, the long tradition of the use of alcohol, as well as the large minority of the population who favored the availability of alcoholic beverages, resulted in the repeal of the constitutional amendment enacting prohibition. Beverage alcohol has widespread use in today's society, with an average age of first use of ~15 years in most Western countries. Almost two-thirds of women and as many as 80% of men in these countries have consumed alcoholic beverages, with one-half to two thirds reporting alcohol consumption within the past year.<sup>(10)</sup> The highest quantities and frequencies of drinking are usually observed in the late teens to early 20s, and in the U.S., the average adult consumes alcoholic beverages containing the equivalent of 2.2 gallons (8.3 L) of absolute alcohol per year. Among drinkers, as many as half have had a temporary alcohol-related problem such as missing school or work, alcohol-related amnesia (blackouts), or operating a motor vehicle after consuming alcohol. More severe repetitive problems with alcohol (known as abuse and dependence) have a lifetime risk in men of almost 20% and in women of 10-15%.<sup>(11)</sup> The annual costs associated with heavy drinking and associated problems have been estimated to be \$185 billion in the U.S. in recent years, and this drug contributes to 100,000 deaths per year in the U.S. alone, including as many as

20,000 alcohol-related fatal car accidents annually.<sup>(12)</sup> Thus, the delivery of optimal medical care in modern times is greatly affected by the use of beverage alcohol, with this drug adversely affecting many body systems, interacting with medications and other drugs, and responsible for a great deal of the healthcare dollar.

Bartsch AJ, Homola G, Biller A and others showed in their study that chronic heavy drinking reportedly increases the probability of developing a more permanent cognitive deficit often referred to as alcoholic dementia. However, the signs of cognitive deficits and brain atrophy observed soon after a heavy drinking period often reverse over the subsequent several weeks to months following abstinence.<sup>(13)</sup>

It is also proved that Ethanol intake greater than three standard drinks per day elevates the risk for heart attacks and bleeding-related strokes as per the study conducted by Hvidtfeldt et al.<sup>(14)</sup> It has bad effect on liver as it produces a constellation of dose-related deleterious effects in the liver shown by Fickert and Zatloukal.<sup>(15)</sup> The primary effects are fatty infiltration of the liver, hepatitis, and cirrhosis. Because of its intrinsic toxicity, alcohol can injure the liver in the absence of dietary deficiencies according Lieber's study.<sup>(16)</sup>

ICD-10 by World Health organization gave guidelines for diagnosing harmful alcohol use. It defined chronic dependence of alcohol as "a cluster of physiological, behavioral, and cognitive phenomena in which the use of alcohol is on a much higher priority for a given individual than other behaviors that once had greater value is called as alcohol dependence syndrome (ADS)."

According to ICD-10, three or more of the following manifestations should have occurred together for at least 1 month or, if persisting for periods of less than 1 month, should have occurred together repeatedly within a 12month period:

- A strong desire or sense of compulsion to take the alcohol.
- Impaired capacity to control alcohol-taking behavior in terms of its onset, termination, or levels of use, as evidenced by: the alcohol being often taken in larger amounts or over a longer period than intended; or by a persistent desire or unsuccessful efforts to reduce or control substance use;
- A physiological withdrawal state when alcohol use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the alcohol, or by use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms
- Evidence of tolerance to the effects of the alcohol, such that there is a need for significantly increased amounts of the alcohol to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the alcohol;

- Preoccupation with alcohol use, as manifested by important alternative pleasures or interests being given up or reduced because of alcohol use; or a great deal of time being spent in activities necessary to obtain, take, or recover from the effects of the it;
- Persistent alcohol use despite clear evidence of harmful consequences as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.<sup>(17)</sup>

The core of care is a process of interventions and sessions that help enhance changes in how the person views their problem, along with efforts to help them alter the problematic behaviors according to Schuckit.<sup>(18)</sup> Along with this, three drugs are approved in the U.S. for treatment of alcoholism: disulfiram (ANTABUSE), naltrexone (REVIA), and acamprosate. Disulfiram has a long history of use but has fallen into disfavor because of its side effects and problems with patient adherence to therapy. Naltrexone and acamprosate were introduced more recently. Ondansetron, a 5-HT<sub>3</sub>-receptor antagonist and antiemetic drug, reduces alcohol consumption in laboratory animals and currently is being tested in humans. Preliminary findings suggest that ondansetron is effective in the treatment of early-onset alcoholics.<sup>(19)</sup> A new line of treatment has come into practice which includes drugs like GABA<sub>B</sub> receptor agonist baclofen.<sup>(20)</sup>

The overall findings from studies performed by Lorenzo Leggio James C. Garbutt and Giovanni Addolorato indicate that baclofen represents a promising new pharmacotherapy for the treatment of alcohol dependence. First, baclofen represents an interesting medication because of its role in reducing withdrawal symptoms as well as in reducing alcohol drinking and craving, thus promoting alcohol abstinence. Second, baclofen has displayed a very safe profile, with the lack of serious or severe side-effects. Third, baclofen has also been shown to be a manageable drug, without any potential of abuse, a feature of paramount importance when administering a medication to an addicted population. Future studies involving larger number of patients should be conducted to confirm the present findings, as well as to identify the best subpopulation of alcoholics which is more likely to respond to treatment with baclofen.<sup>(21)</sup> However observations of increased blood sugar concentrations on Baclofen administration have been made which formed the base of this study.<sup>(22)</sup>

### Objective

The main objective of the study is to find out the effect of baclofen on blood glucose levels in ADS patients during the course of therapy.

### Methodology

**Study Design:** Prospective interventional study.

**Source of data:** Patients attending Psychiatry Department OPD of our hospital.

**Sample size- N=30**

**Enrolment:** Patients aged between 18 years and 60 years diagnosed with alcohol dependence syndrome (ADS) according to ICD-10 criteria.

**Data collection:**

- Demographic data
- Disease data
- Treatment data
- Investigations

**Inclusion criteria:**

- Patients aged between diagnosed with alcohol dependence syndrome (ADS) according to ICD-10 criteria.

**Exclusion criteria:**

- Patients already diagnosed with type-1 diabetes mellitus & type-2 diabetes mellitus.
- Patients on oral hypoglycaemic drugs.
- Patients on insulin.
- Patients on GABA antagonist drugs.
- Patients with hepatic and renal disorders.
- Pregnant woman.
- Epilepsy patients.

**Methods of data collection:** Data was collected in specially designed case record format. Thirty patients were enrolled for the study after obtaining their consent and eight blood samples were collected each patient. Blood samples were drawn under full aseptic precautions.

Eight venous blood samples of 2ml each are drawn from the subjects over 20 days of study period for blood glucose level analysis in the Fluoride-EDTA vacuum evacuated tubes. On day 0 fasting and post prandial blood samples were collected (T<sub>0</sub>). Treatment of ADS is started with the administration of baclofen in the dosage of 60 mg/ day (20 mg TDS). Again on day one fasting and post prandial blood samples were collected (T<sub>1</sub>). The Baclofen therapy with same dosage is continued for 10 days and on day 10 fasting and post prandial blood samples are collected for blood glucose analysis (T<sub>10</sub>). From day 10 the Baclofen dosage is stepped down to 20-40mg/day maintenance dose. On 20<sup>th</sup> day again fasting blood samples and post prandial blood samples were collected for analysis of fasting and post prandial blood Glucose respectively (T<sub>20</sub>).

Estimation of fasting and post prandial blood Glucose respectively were done by glucose oxidase-peroxidase method. The statistical analysis done using anova test.

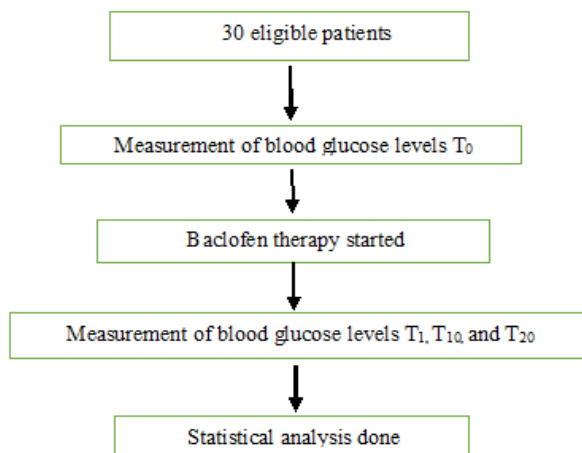


Fig. 1: Flow chart of methodology

**Observation & Result**

A total of 30 male patients were enrolled in the study. All 30 patients were able to complete the study. Mean age of the patients was 34.67±10.12 years.

Mean fasting blood glucose levels in patients was 87.1 mg/dl on day 0, 103.23mg/dl on day 1, 98.63 mg/dl on day 10 and 95.30 mg/dl on day 20 at 95% confidence interval for mean and a range of 61 to 125 mg/dl.

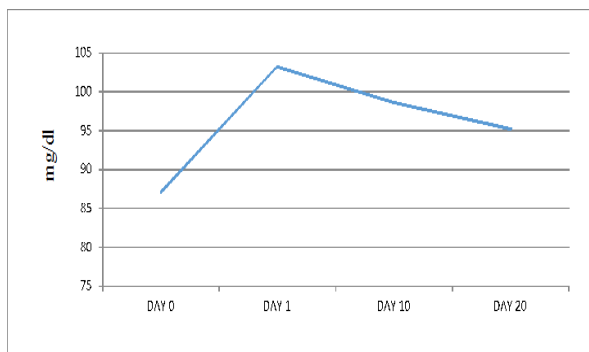


Fig. 2: Mean fasting Blood Glucose levels

The mean FBS values increased in day 1 when compared to day 0 and in gradually decreased in day 10 and day 20.

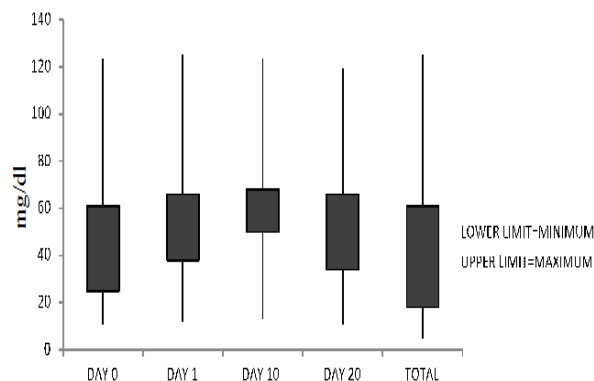


Fig. 3: Minimum and Maximum Blood glucose levels

ANOVA was used to measure the significant difference (p value) between the groups for means OD FBS levels. The calculated p value was observed to be significant (0.001) at a 95% confidence level.(Table 2)

Multiple comparison was done to calculate the repeated measures. There was a significant difference found between the day 0 and day 1 values for FBS.(Table 3)

Table 1: Fasting Blood Glucose levels

Descriptive								
FBS								
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Day 0	30	87.10	15.126	2.762	81.45	92.75	61	123
Day 1	30	103.23	16.831	3.073	96.95	109.52	66	125
Day 10	30	98.63	13.994	2.555	93.41	103.86	68	123
Day 20	30	95.30	13.752	2.511	90.16	100.44	66	119
Total	120	96.07	15.926	1.454	93.19	98.95	61	125

**Table 2: ANOVA test for FBS**

	Sum of Squares	Mean Square	F	Sig.
Between Groups	4168.133	1389.378	6.196	0.001
Within Groups	26013.333	224.253		
Total	30181.467			

**Table 3: Multiple comparison between different visits(FBS)**

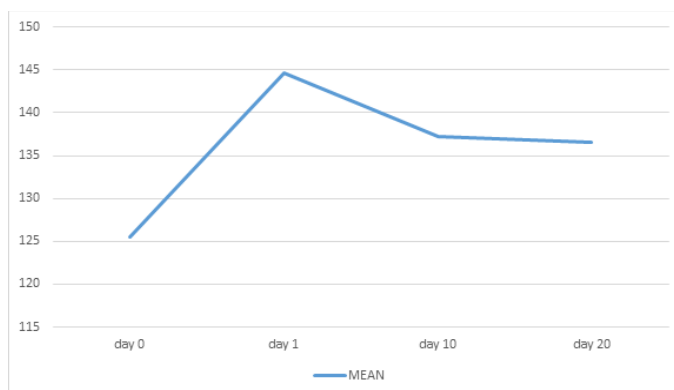
Multiple Comparisons						
Dependent Variable: FBS						
Tukey HSD						
(I) Baclofen Day	(J) Baclofen Day	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Day 0	Day 1	-16.133*	3.867	.000	-26.21	-6.05
	Day 10	-11.533*	3.867	.018	-21.61	-1.45
	Day 20	-8.200	3.867	.153	-18.28	1.88
Day 1	Day 0	16.133*	3.867	.000	6.05	26.21
	Day 10	4.600	3.867	.635	-5.48	14.68
	Day 20	7.933	3.867	.175	-2.15	18.01
Day 10	Day 0	11.533*	3.867	.018	1.45	21.61
	Day 1	-4.600	3.867	.635	-14.68	5.48
	Day 20	3.333	3.867	.824	-6.75	13.41
Day 20	Day 0	8.200	3.867	.153	-1.88	18.28
	Day 1	-7.933	3.867	.175	-18.01	2.15
	Day 10	-3.333	3.867	.824	-13.41	6.75

\*. The mean difference is significant at the 0.05 level.

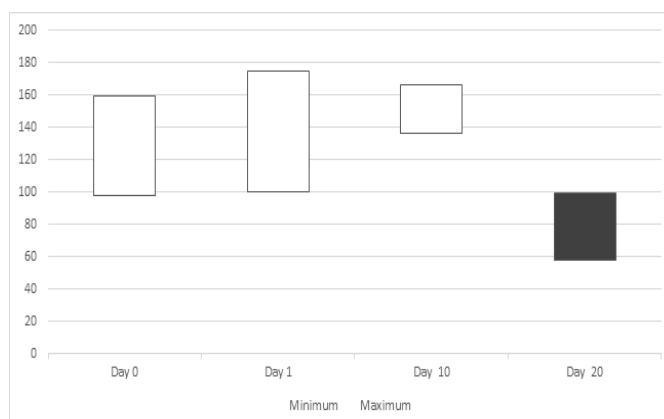
**Table 4: Post prandial Blood Glucose levels**

Descriptive								
PPBS								
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Day 0	30	125.50	14.748	2.693	119.99	131.01	98	159
Day 1	30	144.57	18.137	3.311	137.79	151.34	100	175
Day 10	30	137.20	23.959	4.374	128.25	146.15	136	166
Day 20	30	136.60	12.176	2.223	132.05	141.15	99	157
Total	120	135.97	18.866	1.722	132.56	139.38	136	175

**Post Prandial Blood Glucose:** Mean post prandial blood glucose was 125.5 md/dl on day 0, 144.57mg/dl on day 1, 137.2 mg/dl on day 10 and 136.6 mg/dl on day 20. The range was between 136 and 175 mg/dl. (Table 4)

**Fig. 4: Mean post prandial blood glucose levels**

The mean PPBS values increased in day 1 when compared to day 0 and in gradually decreased in day 10 and day 20.



**Fig. 5: Range of Post prandial blood glucose**

ANOVA was done to compare the values between different days of follow up. This showed a significant difference of p value (0.001) (Table 5).

**Table 5: ANOVA test for FBS**

ANOVA					
PPBS					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5563.000	3	1854.333	5.846	0.001
Within Groups	36792.867	116	317.180		
Total	42355.867	119			

**Table 6: Multiple comparison between different visits(PPBS)**

Multiple Comparisons						
Dependent Variable: PPBS						
Tukey HSD						
(I) Baclofen Day	(J) Baclofen Day	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Day 0	Day 1	-19.067*	4.598	.000	-31.05	-7.08
	Day 10	-11.700	4.598	.058	-23.69	.29
	Day 20	-11.100	4.598	.080	-23.09	.89
Day 1	Day 0	19.067*	4.598	.000	7.08	31.05
	Day 10	7.367	4.598	.382	-4.62	19.35
	Day 20	7.967	4.598	.312	-4.02	19.95
Day 10	Day 0	11.700	4.598	.058	-.29	23.69
	Day 1	-7.367	4.598	.382	-19.35	4.62
	Day 20	.600	4.598	.999	-11.39	12.59
Day 20	Day 0	11.100	4.598	.080	-.89	23.09
	Day 1	-7.967	4.598	.312	-19.95	4.02
	Day 10	-.600	4.598	.999	-12.59	11.39

\*. The mean difference is significant at the 0.05 level.

## Discussion

The baclofen is widely used now in Psychiatric clinics to treat alcohol dependence syndrome patients. Previous studies shown correlation between GABA receptors and blood glucose levels. The studies showed

that Baclofen (a GABA<sub>B</sub> receptor agonist or bicuculline (a GABA<sub>A</sub> receptor antagonist) caused an elevation of the blood glucose level in a dose-dependent manner in ICR mice.<sup>(23)</sup> However not much human study done regarding this, this study was carried out.

The study showed that baclofen increased both FBS and PPBS on day 1 which was statistically significant, and showed a significant reduction in glucose levels on day 10 with the dose of baclofen remaining unchanged. The dosage of Baclofen was reduced after day 10. The glucose levels decreased more as seen on day 20, although the reduction was not significant.

Hence our study shows that Baclofen has a definite role in the levels of glucose, but the mechanism of action of depression in blood glucose levels is still unknown. Further studies are needed to confirm the long term effect of Baclofen on the blood glucose levels. Based on the findings of our study the usage of baclofen should be done carefully especially in patients suffering from diabetes mellitus to avoid any complications related to uncontrolled blood glucose levels.

### Conclusion

The main purpose of the study was to determine the effect of effect of baclofen on blood glucose levels in ADS patients. As there are a lot of controversies regarding this, a detailed research was carried out to find answers regarding the question as to whether baclofen increases the blood glucose levels or not. This study was conducted to assess the effect of baclofen on blood glucose levels in ADS patients. Baclofen could significantly increase blood glucose levels. This would be of paramount importance in diabetic patients.

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