e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(1); 149-175

Original Research Article

A Double- Blind Randomised Study of Parenteral Thiamine in Patients of Alcohol Dependence Syndrome

S. Kiran Kumar[1], P. Lokeswara Reddy[2], K.Srilakshmi[3], T. Suryanarayana Raju[4], Meghana S[5]

[1]Associate Professor of Psychiatry, Andhra Medical College, Visakhapatnam
[2]Professor of Psychiatry, Andhra Medical College, Visakhapatnam
[3]Associate Professor of Psychiatry, Government Medical College, Markapuram
[4]Associate Professor of Psychiatry, Government Medical College, Paderu
[5]Senior Resident, Siddhartha Medical College, Vijayawada

Received: 25-10-2023 / Revised: 23-11-2023 / Accepted: 26-12-2023
Corresponding Author: Dr. T. Suryanarayana Raju
Conflict of interest: Nil

Abstract:

Introduction: In emerging countries like India, alcohol use disorders (AUD) are on the rise. Apart from tobacco, alcohol (21.4 percent) was the most commonly used substance in the National Household Survey. [1] Between 17 and 26 percent of alcohol users met the ICD-10 criteria for dependency, resulting in an average prevalence of 4%. [1] In numerous ways, alcohol consumption has been connected to the development of cognitive impairment and dementia. . [2] Thiamine insufficiency, which can lead to Wernicke Encephalopathy and Wernicke-Korsakoff Syndrome, is one of the most well- known causes of alcohol-related brain injury. Thiamine deficiency (vitamin B1) is frequent in people who are addicted to alcohol. Early on, thiamine deficiency can cause cognitive issues. [3] Long-term alcohol usage causes adaptive changes in the brain, which induce alcohol withdrawal syndrome. It has been linked to changes in neurotransmitter, neuropeptide, and hormone systems. [4] Due to low food intake, reduced gastrointestinal absorption, and decreased hepatic storage, thiamine deficiency is more common in patients with alcoholism. Wernicke's encephalopathy is caused by a combination of reduced dietary thiamine consumption, poor thiamine transport through the intestinal mucosa, and impaired conversion of thiamine to thiamine pyrophosphate.

Because the metabolism of alcohol increases the demand for thiamine, ADS patients have a higher thiamine need, resulting in thiamine deficit.

Aims and Objectives of the Study: To compare the clinical outcome in the 2 groups of patients receiving 100mg and 500mg of parenteral thiamine respectively.

Methodology: A Double-blind Randomized Comparative study was conducted at Government Hospital for Mental Care, Visakhapatnam In-Patients diagnosed with Alcohol Dependence Syndrome from October 2020 – September 2021.Two Thiamine treatment regimens were designed containing either 100mg or 500mg per day for 5 days, labelled as Regime A and B respectively. Thiamine was administered parentally through intravenous route mixed in 100ml of Normal Saline in a slow IV drip. In-patients diagnosed with Alcohol Dependence Syndrome were randomly assigned a treatment plan using simple randomization. Neither the patient nor the examiner had knowledge as to which treatment regimen they have been assigned. Patients were assessed on Day-0 using the SADQ, CGI, CIWA-AR, scales. Patients were again being assessed with CGI, CIWA-AR, scales at the end of the treatment i.e on Day 5.

Results: A total of 74 patients diagnosed with Alcohol Dependence Syndrome who met the inclusion criteria were taken into the study after obtaining a written informed consent to participate in the study.Group 1 included 38 participants who received a regimen of 500mg of thiamine for 5 days. Group 2 included 36 participants who received 100 mg of thiamine for 5 days.

The sample population were assessed for improvement of illness using the Clinical Global Impressions-global improvement.15.8%(n=6) in group 1 and 13.9%(n=5) in group 2 were very much improved ; 50.0%(n=19) in group 1 and 41.7%(n=15) in group 2 were much improved ;31.6%9n=12) in group 1 and 44.4%(n=16) in group 2 were minimally improved ; 2.6%(n=1) in group 1 and nil in group 2 showed no change.Majority of the sample population were much improved. P-value (p=0.556) was not significant with chi-square test between the two groups according to the improvement of illness.

Conclusion: The findings of this study have no found no significant difference in the supplementation of a higher of thiamine in ADS patients to reduce withdrawal; hence the current recommendations can be followed. There was no difference in the reduction of AWS and severity of illness with both doses of thiamine given. Probable risk factors for developing severe withdrawal identified were severe alcohol dependence and previous history of complicated withdrawal.

Keywords: Parenteral Thiamine, Alcohol Dependence Syndrome.

Introduction

In emerging countries like India, alcohol use disorders (AUD) are on the rise. Apart from tobacco, alcohol (21.4 percent) was the most commonly used substance in the National Household Survey. [1] Between 17 and 26 percent of alcohol users met the ICD-10 criteria for dependency, resulting in an average prevalence of 4%. [1] In numerous ways, alcohol consumption has been connected to the development of cognitive impairment and dementia. . [2] Thiamine insufficiency, which can lead to Wernicke Encephalopathy and Wernicke-Korsakoff Syndrome, is one of the most well- known causes of alcohol-related brain injury.

Thiamine deficiency (vitamin B1) is frequent in people who are addicted to alcohol. Early on, thiamine deficiency can cause cognitive issues. [3] Long-term alcohol usage causes adaptive changes in the brain, which induce alcohol withdrawal syndrome. It has been linked to changes in neurotransmitter, neuropeptide, and hormone systems. . [4] AWS is a clinical syndrome that affects persons who have been drinking regularly for a long time and then cut back or quit drinking totally.

AWS is a clinical condition marked by agitation, tremors, irritability, anxiety, hyperreflexia, confusion, hypertension, tachycardia, fever, and diaphoresis, all of which are indications of autonomic hyperactivity. In alcohol-dependent patients, AWS usually appears 6–24 hours after abruptly ceasing or reducing alcohol usage. Symptoms range from mild/moderate tremors, nausea, anxiety, and depression to severe hallucinations, seizures, delirium tremens, and coma. Long-term ethanol consumption causes an imbalance in excitatory (particularly glutamate, a major excitatory amino acid) and inhibitory (mainly GABA, a key inhibitory amino acid) neurotransmitter systems. [4] A decrease in GABA receptor function and an increase in NMDA receptor function generate alcohol withdrawal symptoms. [4]

Due to low food intake, reduced gastrointestinal absorption, and decreased hepatic storage, thiamine deficiency is more common in patients with alcoholism. Wernicke's encephalopathy is caused by a combination of reduced dietary thiamine consumption, poor thiamine transport through the intestinal mucosa, and impaired conversion of thiamine to thiamine pyrophosphate. Because the metabolism of alcohol increases the demand for thiamine, ADS patients have a higher thiamine need, resulting in thiamine deficit. Thiamine is an essential cofactor for glycolysis and the citric acid cycle. These metabolic cycles control the amounts of neurotransmitters in the brain such glutamate, gamma amino butyric acid, and aspartate, which are hypothesised to play a role in AUD patients' Alcohol Withdrawal Symptoms (AWS). [5]

The three principal thiamine-dependent enzyme systems are pyruvate dehydrogenase, transketolase, and 2-oxo-glutarate dehydrogenase. Pyruvate Dehydrogenase is an enzyme that aids in carbohydrate digestion. Pyruvate is converted to acetyl coenzyme A, which participates in the Krebs cycle and, as a result, in energy production. Transketolase is an enzyme involved in carbohydrate metabolism, the maintenance of the pentose phosphate pathway, myelin sheaths, lipids, and myelin branched chain amino acids in the nervous system, and glucose metabolism. The tricarboxylic acid cycle neurotransmitter production of acetylcholine, -aminobutyric acid (GABA), and y-aminobutyric acid (GABA)] is aided by 2- oxoglutarate dehydrogenase. .

Thiamine deficiency is caused by the suppression of oral thiamine hydrochloride absorption in humans, which can be caused by malnutrition in alcoholics or by the direct effects of ethanol on intestinal transport. [6] The inability to cure Wernicke's encephalopathy with massive oral doses of thiamine hydrochloride highlights the importance of appropriate and rapid replenishment of decreased brain thiamine levels through repeated parenteral therapy in adequate dosages. [6]

Because there is now no clear information on how to use thiamine in people who are alcoholics, it is recommended that a thiamine prescription be started gradually. [8] In people with AUD or suspected Wernicke encephalopathy, there is still no evidence-based consensus on thiamine dosage and treatment method. [7]

Aims and Objectives of the Study

To compare the clinical outcome in the 2 groups of patients receiving 100mg and 500mg of parenteral thiamine respectively.

Hypothesis:

Group receiving 500 mg of thiamine will have a better clinical outcome than the group receiving 100 mg of thiamine.

Review of Literature

Dushad Ram (2015)5 in their study titled "Whole Blood Thiamine Levels and its Relationship with Severity of Alcohol Withdrawal and Neurological Soft Signs in Patients with Alcohol Use Disorder" assessed 60 patients with alcohol use disorder with Clinical Institute Withdrawal Assessment for Alcohol scale and extended standard Neurological Assessment Instrument. Whole blood thiamine levels were measured using High Performance Liquid Chromatography. The mean thiamine level in whole blood was 8.7 (SD 12.9) g/l. Symptoms of withdrawal were experienced by 70% of patients. The total blood thiamine level was not substantially predicted by the withdrawal score. These findings back up the current Th replacement dose recommendation (100 mg IV/PO daily).

M.Ceccanti et al. (2005) [15] in their study titled "Erythrocyte Thiamine (Th) esters : A Major factor of the Alcohol Withdrawal Syndrome or a candidate marker for Alcoholism itself ?" The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-ar) test, erythrocyte levels of Th and its esters, Th monophosphate (TMP), and Th diphosphate (TDP) were measured to see if they had any relationship — if any — with AWS severity levels, in order to establish a less empirical indication for Th treatment in AWS. Although there was no link between the severity of AWS and Th and its esters, thiamine diphosphate (TDP) and Th had a high diagnostic power. Supplementing with thiamine is still a crucial aspect of AWS treatment. All heavy drinkers should seek treatment at this time. M. Nordentoft et al. (1993)16 in their study titled "Thiamine pyrophosphate effect and erythrocyte transketolase activity during severe alcohol

withdrawal syndrome" In a group 5of 28 patients who were admitted to a psychiatric emergency ward with severe alcohol withdrawal symptoms, the effects of thiamine pyrophosphate (TPP) and erythrocyte transketolase activity (ETKA) were compared to the effects of TPP and ETKA in a control group of 20 healthy non-alcoholic volunteers.

After one and four days of treatment, the patients were given 300 mg thiamine intramuscularly three times a day, and the TPP effect and ETKA were measured. There was no difference in TPP effect or ETKA between the patient and control groups, and after 4 days of intensive thiamine treatment, there was no reduction in TPP effect in the patient group. ETKA levels rose in response to thiamine administration, indicating that ETKA is a sensitive thiamine indicator.

Benjamin Rolland et al. (2015) [8] in their paper titled "Pharmacotherapy for Alcohol Dependence: The 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies" where an 18-member multi-professional working group was tasked with answering questions posed by a four-member European steering committee (WG). The WG created the Group Practice Recommendations after conducting a systematic, hierarchical, and structured literature analysis and submitting the document to two review procedures consisted of 37 French members from various disciplines and 5 non-French EUFAS members. Wernicke's encephalopathy is treated with thiamine (vitamin B1) as a preventive and therapeutic drug. It can develop at any stage of a AUD, even during abstinence from alcohol. Because there is currently no clear evidence on how to use thiamine in people who are addicted to alcohol, it is recommended that a thiamine prescription be started on a regular basis, though the treatment dose and duration should be adapted to the individual's nutritional needs.

R. Galvin et al. (2010) [29] in their article titled "EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy" Their purpose was to create useful guidelines for disease diagnosis, treatment, and prevention. The clinical diagnosis of WE must consider the disease's multiple presentations, as well as clinical signs in alcoholics and non-alcoholics. Despite the fact that WE is more common among drinkers, it should be suspected in any clinical scenario that could lead to thiamine shortage. WE is treated with thiamine, whether the condition is suspected or proven. It should be administered three times a day, ideally intravenously, and before any carbohydrate. Thiamine is extremely safe in general.

Ambrose et al. (2001) [44] in their study titled "Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings" As the primary working memory outcome measure, the results of the delayed alternation test were used. They compared five doses of injectable thiamine hydrochloride (5, 20, 50, 100, and 200 mg) given once daily for two days. On the third day of therapy, a psychologist who was blind to treatment allocation administered the delayed alternation test to each participant. Their blood alcohol content was revealed to be 0%. They discovered that

The number of trials necessary to meet requirements on a delayed alternation test differed significantly between dosage groups. The 200 mg/day dose outperformed the 5 mg/day dose by a significant margin in the number of trials necessary to meet criteria on a delayed alternation test. When the various doses were evaluated, it was found that M. Baines et al. (1988) [39] in their study titled "Tissue thiamin levels of hospitalised alcoholics before and after oral or parenteral vitamins"

Using a novel high-performance liquid chromatographic approach, erythrocyte levels of the physiologically active form of thiamin, thiamin diphosphate (ETDP), were examined in 25 alcoholics admitted to a hospital for detoxification and rehabilitation. On a controlled basis, measurements were performed before, during, and after multivitamin treatment, either orally or parenterally. Only one incidence of thiamin insufficiency has been documented prior to treatment. Both treated groups demonstrated an increase in mean ETDP levels within 24 hours of receiving 250 mg of thiamin, although only the parenterally treated group's was significantly higher (P less than 0.05) than the pre-treatment mean. Both treatment groups, however, revealed a significant (P less than 0.05) and nearly similar increase in mean ETDP levels (90 nmol/l. and 91 nmol/l. for the oral and intravenous treatments, respectively). Prior to treatment, only one case of thiamin deficiency was documented. Within 24 hours of receiving 250 mg of thiamin, both treated groups showed an increase in mean ETDP levels, although only the parenterally treated group's was substantially higher (P less than 0.05) than the pre-treatment mean. However, both treatment groups showed a significant (P less than 0.05) and virtually identical increase in mean ETDP levels (90 nmol/l. and 91 nmol/l. for the oral and intravenous treatments, respectively).

N.Latt (2014)11 in their article titled “Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders” Despite the fact that thiamine is the cornerstone of Wernicke encephalopathy treatment, there are no universally accepted dose, mode of administration, frequency of administration, or treatment duration requirements, according to the authors. Dosing recommendations are currently being provided in a variety of ways.

Thiamine is commonly administered intramuscularly or intravenously over the course of five days. The three-times-daily dosing schedule is based on the short half-life of thiamine. The following are their recommendations: Patients with a confirmed diagnosis of WKS should receive at least 200–500 mg t.d.s. I/V for 5–7 days, then 100 mg t.d.s. oral thiamine for 1–2 weeks, and then 100 mg daily after that (if I/V is not practicable).

Patients with Wernicke encephalopathy/Wernicke Korsakoff syndrome who are suspected or at risk should get prophylactic therapy. At the very least For 3–5 days, take 100–200 mg t.d.s. IM or IV, then 100 mg t.d.s. oral thiamine for 1–2 weeks, then 100 mg daily after that.

Alain Dervaux et al. (2017)3 in their article titled “Thiamine (vitamin B1) treatment in patients with alcohol dependence” have proposed Individuals with Wernicke's encephalopathy should get parenteral thiamine 200-500mg three times a day for 3-5 days, then oral thiamine 250-1000mg/day.

For 3-5 days, patients with suspected Wernicke's encephalopathy should receive parenteral thiamine 250-300mg two times a day, followed by oral thiamine 250-300mg/day. Parenteral thiamine 250-500mg/day should be given for 3-5 days in those at high risk of thiamine deficiency, followed by oral thiamine 250-300mg/day. Oral thiamine 250-500mg/day should be given for 3-5 days to patients at low risk (with uncomplicated alcohol dependence), followed by oral thiamine 100-250mg/day. In a paper by Nathalie pruckner et al. (2019)2 where they conducted a review of current treatment guidelines for AUD in order to identify recommendations for the use of thiamine. In total, 14 guidelines were included.

The American Psychiatric Association advises thiamine for individuals experiencing "moderate to severe" alcohol withdrawal symptoms, without specifying the type or dosage. Parenteral thiamine administration (50–100 mg i.v or i.m. per die) is advised for the onset of symptoms associated with WE ("ophthalmoplegia, ataxia, and confusion"). In patients with WE, long-term vitamin B complex medication (up to a year) is recommended; however, dosage and duration are not specified.

The American Psychiatric Association advises thiamine for individuals experiencing "moderate to severe" alcohol withdrawal symptoms, without specifying the type or dosage. Parenteral thiamine administration (50–100 mg i.v. or i.m. per die) is advised for the onset of symptoms associated with WE ("ophthalmoplegia, ataxia, and confusion"). In patients with WE, long-term vitamin B complex medication (up to a year) is recommended; however, dosage and duration are not specified.

In its 2013 Consensus Statement, the Austrian Society for Neuropsychopharmacology and Biological Psychiatry advises thiamine parenteral treatment during withdrawal, albeit dosage and duration are not mentioned. Furthermore, there is no recommendation for the use of thiamine in the treatment of AUD.

The British Association for Psychopharmacology is a professional organisation dedicated to the study of psychopharmac Early detection and treatment of WE are emphasised in the 2012 updated "Guidelines for the Pharmacological Management of Substance Abuse." During detoxification, oral thiamine (>300 mg/die) is suggested for "healthy uncomplicated heavy drinkers." Thiamine should be given i.v. or i.m. for 3–5 days or until no further improvement is noticed in patients at high risk of developing WE.

The French Alcohol Society recommends that thiamine be administered during detoxification with "adaptation to nutritional status," with no further details on application form, dose, or duration in its 2015 recommendation on pharmacological treatment of alcohol dependence. It also recommends that WE should be prevented and treated in a systematic manner.

Alcoholic Society of Italy Parenteral thiamine delivery is suggested for all patients in this position paper on recommendations for the management of alcohol withdrawal (2018). The recommended dose is 200 mg per day for 3–5 days.

During alcohol withdrawal, the German Association for Psychiatry, Psychotherapy, and Psychosomatics recommends thiamine treatment. A dose of 100 mg twice a day should be taken orally for 7–14 days.

All individuals suffering alcohol withdrawal should be treated with thiamine, according to the Australian Government Department of Health and Ageing. "Healthy individuals with adequate dietary consumption" should be given 300 mg of oral thiamine daily for 3–5 days, then 100 mg for another 4–9 days. Parenteral thiamine (300 mg/day for 3 to 5 days) is recommended for "chronic drinkers with poor food intake and general poor nutritional condition," followed by oral doses of 300 mg per day for "several weeks."

Methodology

Study Design: A Double-blind Randomized Comparative study.

Study Setting: Government Hospital for Mental Care, Visakhapatnam.

Study population: In-Patients diagnosed with Alcohol Dependence Syndrome at Government Hospital for Mental Care, Visakhapatnam.

Study Period: October 2020 – September 2021.

Inclusion Criteria:

- Age group: from 18 to 60 years.
- Patients diagnosed with Alcohol Dependence Syndrome, according to ICD 10 diagnostic criteria.
- Patients who gave valid written, informed consent.

Exclusion Criteria:

- Patients who do not give a valid written consent.
- Patients with intellectual disability, developmental disorders.
- Patients with comorbid psychiatric disorders.
- Patients with comorbid medical conditions.

Operational Procedure:

The study was conducted after obtaining institutional ethics committee clearance. Patients who fulfill the criteria for Alcohol Dependence Syndrome according to ICD-10 DR are taken up for the study.

Demographic data, including age, sex, education, occupation, socioeconomic status, marital status, the residence is taken. Illness variables like age of onset of alcohol intake, duration of alcohol intake, duration of regular use and dependence, previous history of treatment for ADS, history of complicated withdrawal, hospitalizations were obtained during the interview. Two Thiamine treatment regimens were designed containing either 100mg or 500mg per day for 5 days, labelled as Regime A and B respectively. Thiamine was administered parentally through intravenous route mixed in 100ml of Normal Saline in a slow IV drip.

In-patients diagnosed with Alcohol Dependence Syndrome were randomly assigned a treatment plan using simple randomization. Neither the patient nor the examiner had knowledge as to which treatment regimen they have been assigned. Patients were assessed on Day-0 using the SADQ, CGI, CIWA-AR, scales. Patients were again being assessed with CGI, CIWA-AR, scales at the end of the treatment i.e on Day 5. The administered scales and clinical outcome were compared between the two groups.

Sample Size:

A total of 74 participants were taken into the study. 38 were assigned to group 1 and 36 to group 2 by simple randomization.

Study Tools:

Consent form

- General information sheet to collect sociodemographic details and illness variables.
- Severity of Alcohol Dependence Questionnaire (SADQ).
- Clinical Institute Withdrawal Assessment of Alcohol scale, Revised (CIWA-AR)
- Clinical Global Impression (CGI).

Informed consent form:

A self - designed informed consent form, which explained the nature of the study, the contents of which were in vernacular language, was read out to the subjects and for those who are willing to participate in the study, signature was obtained.

General Information Sheet:

A self-designed form to collect personal and sociodemographic details of the subject has been used. This contains details regarding demographic data, including age, sex, education, occupation, socioeconomic status, marital status, the residence is taken. Illness variables like age of onset of

alcohol intake, duration of alcohol intake, duration of regular use and dependence, previous history of treatment for ADS, history of complicated withdrawal, hospitalizations.

Severity of Alcohol Dependence Questionnaire Scale:

The SADQ is a 20-item self-administered, quick, easy-to-complete questionnaire developed by Edwards & Gross (1976) to assess the severity of alcohol dependence (1978). There are five subscales with four items in each: Physical Withdrawal, Affective Withdrawal, Withdrawal Relief Drinking, Alcohol Consumption, and Rapidity of Reinstatement. Each item is scored on a 4-point scale, ranging from "Almost Never" to "Nearly Always," resulting in a corresponding score of 0 to 3. As a result, the maximum possible score is 60, and the lowest possible score is 0. Clinical Institute Withdrawal Assessment for Alcohol Revised version scale: This is a revised version of the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) which was derived from scales devised by Gross and associates. This is a validated scoring system that has high inter-rater reliability.

The CIWA-Ar is not copyrighted and may be reproduced freely. This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. It consists of the following 10 items: nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache and clouding of sensorium. Each item on the scale is scored independently, and the summation of the scores yields an aggregate value that correlates to the severity of alcohol withdrawal. All items are scored from 0–7, with the exception of the orientation category, scored from 0–4.

Mild alcohol withdrawal is defined with a score less than or equal to 10, moderate with scores 11 to 15, and severe with any score equal to or greater than 16.The maximum score is 67. Patients scoring less than 10 do not usually need additional medication for withdrawal.

Clinical Global Impressions:

The Clinical Global Impression (CGI) rating scales are measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders. It is a brief 3-item observer-rated scale that can be used in clinical practice as well as in researches to track symptom changes.

It was developed by Early Clinical Drug Evaluation Program (ECDEU) team of researchers for use in NIMH-led clinical trials that could provide clinical judgment based assessment for determining the severity of symptoms and the treatment progress. This was meant to assess the patient's functioning prior to and after initiating medication in trials which is an important part of study process. Its 3 items assess, 1) Severity of Illness (CGI-S), 2) Global Improvement (CGI-I), and 3) Efficacy Index (CGI-E, which is a measure of treatment effect and side effects specific to drugs that were administered). The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Clinicians ask: "Considering your total clinical experience with this particular population, how ill is the patient at this time?" Possible ratings are:

1.Normal, not at all ill 2.Borderline mentally ill 3.Mildly ill 4.Moderately ill 5.Markedly ill 7.Severely ill 7.Among the most extremely ill patients

The Clinical Global Impression – Improvement scale (CGI-I) is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. Clinicians ask: "Compared to the patient's condition at baseline, this patient's [average] condition has...?" and rated as: 1.Very much improved 2.Much improved

3. Minimally improved 4.No change 5.Minimally worse 6.Much worse 7.Very much worse. Descriptive statistics were used for socio-demographic details. The Chi-square test was used to compare categorical data.

Independent t-test and Paired t-test were used to compare continuous variables between the groups. A p-value of <0.05 was considered significant.

Results and Observations

A total of 74 patients diagnosed with Alcohol Dependence Syndrome who met the inclusion criteria were taken into the study after obtaining a written informed consent to participate in the study.

Group 1 included 38 participants who received a regimen of 500mg of thiamine for 5 days. Group 2 included 36 participants who received 100 mg of thiamine for 5 days.

Socio-Demographic Details:

All the participants included in the study were males.

Age Distribution: Number of subjects in the age group of 18-29 were 5.3%(n=2) in group 1 and 16.7%(n=6) in group 2 ; 44.7%(n=17) in group 1 and 41.7%(n=15) in group 2 were in the age group of 30-39 ; 44.7%(n=17) in group 1 and 25.0%(n=9)

in group 2 were in the age group of 40-49 ; 5.3%(n=2) in group 1 and 16.7%(n=6) in group 2 were in the age group of 50-60. Majority of the sample belonged to the 30-39 age group.

P-value (p=0.088) is not significant with chi-square test between the two groups according to age.

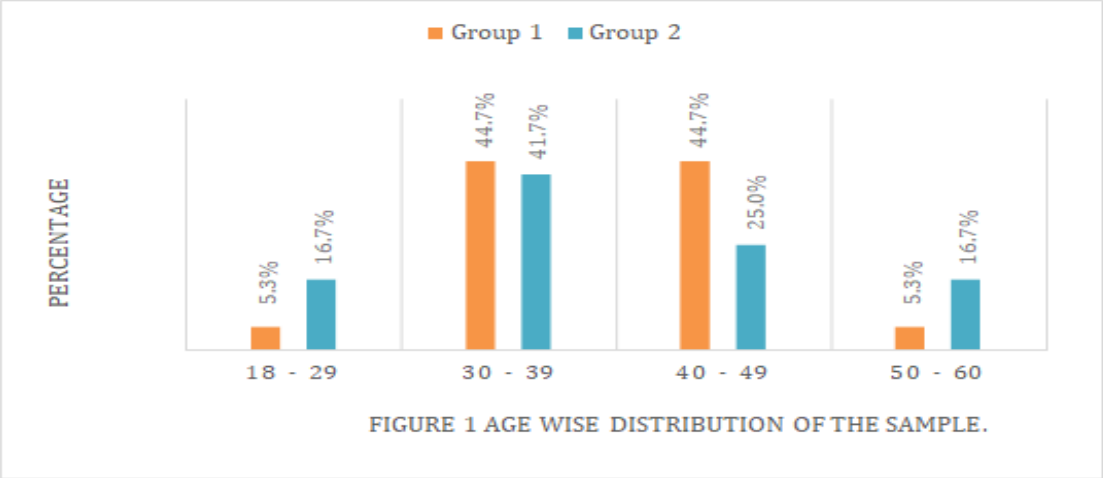

Figure 1: Age Wise Distribution of the Sample

Table 1: comparison of age wise distribution of the sample in the two groups

Age	Group 1		Group 2	
	Count	%	Count	%
18 - 29	2	5.3%	6	16.7%
30 - 39	17	44.7%	15	41.7%
40 - 49	17	44.7%	9	25.0%
50 - 60	2	5.3%	6	16.7%
Total	38	100.0%	36	100.0%
p-value = 0.088				

Table 1 showing the comparison of age wise distribution of the sample in the two groups using chi-square test.

Literacy:

Number of participants who were illiterate in group 1 included 28.9%(n=11) and 22.2%(n=8) in group 2 ; 31.6%(n=12) in group 1 and 27.8%(n=10) in group 2 studied up to primary school ; 23.7%(n=9) in group 1 and 30.6%(n=11) in group 2 studied up to secondary school ; 5.3%(n=2) in group 1 and 8.3%(n=3) in group 2 studied up to intermediate ; 10.5% (n=4) in group 1 and 11.1%(n-4) in group 2 were graduates.

Majority of the sample completed primary schooling.

P-value (p=0.909) was not significant with chi-square test between the groups according to their education level.

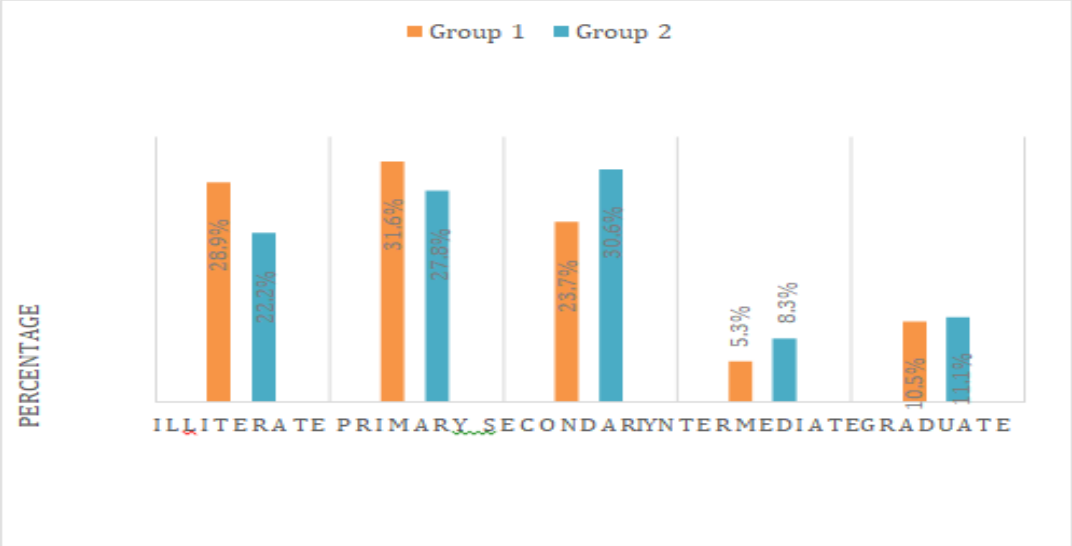

Figure 2: Literacy status of the sample.

Table 2: comparison of literacy status of the sample in the two groups

Education	Group 1		Group 2	
	Count	%	Count	%
Illiterate	11	28.9%	8	22.2%
Primary	12	31.6%	10	27.8%
Secondary	9	23.7%	11	30.6%
Intermediate	2	5.3%	3	8.3%
Graduate	4	10.5%	4	11.1%
Total	38	100.0%	36	100.0%
p-value = 0.909				

Table 2 showing the comparison of literacy status of the sample in the two groups using chi-square test.

Occupation:

Number of participants in group 1 who were employed include 84.2%(n=32) and 91.7%(n=33) in group 2 ; 2.6%(n=1) in group 1 and 0 participants in group 2 were retired ; 13.2%(n=5) in group 1 and 8.3%(n=3) in group 2 were unemployed. Majority of the sample were employed. p-value (p=0.481) was not significant with chi-square test between the groups according to their employment status.

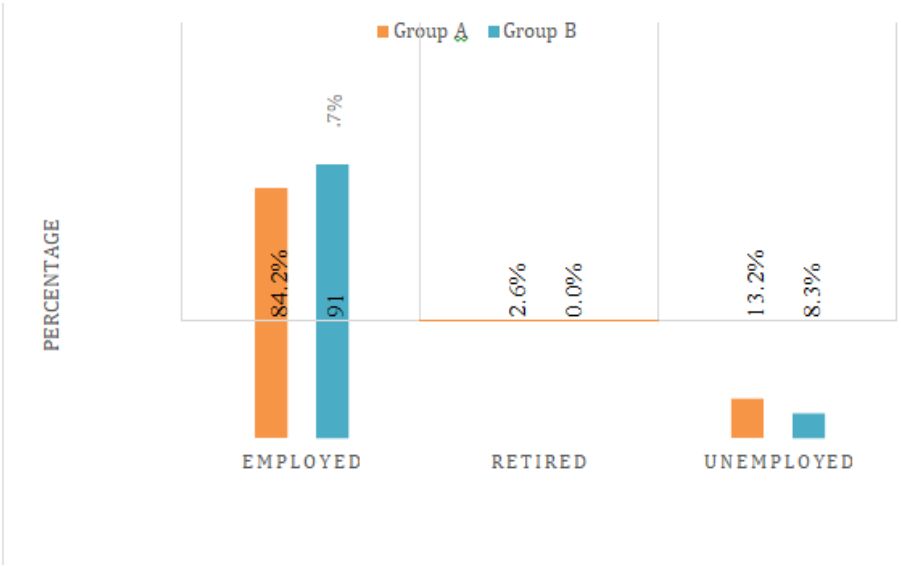

Figure 3: Employment status of the sample.

Table 3: comparison of employment status of the sample in the two groups

Occupation	Group 1		Group 2	
	Count	%	Count	%
Employed	32	84.2%	33	91.7%
Retired	1	2.6%	0	0.0%
Unemployed	5	13.2%	3	8.3%
Total	38	100.0%	36	100.0%
p-value = 0.481				

Table 3 showing the comparison of employment status of the sample in the two groups using chi-square test.

Socioeconomic status:

Number of participants belonging to lower socio-economic status were 7.9%(n=3) in group 1 and 16.7%(n=6) in group 2 ; 18.4%(n=7) in group 1 and 11.1%(n=4) in group 2 belong to lower middle socioeconomic status ; 63.2%(n=24) in group 1 and 61.1%(n=22) in group 2 belong to upper lower socioeconomic status ; 10.5%(n=4) in group 1 and 11.1%(n4) in group 2 belong to upper middle socioeconomic status. Majority of the sample belongs to upper lower socioeconomic status. P-value (p=0.210) was not significant with chi-square test between the two groups according to their socioeconomic status.

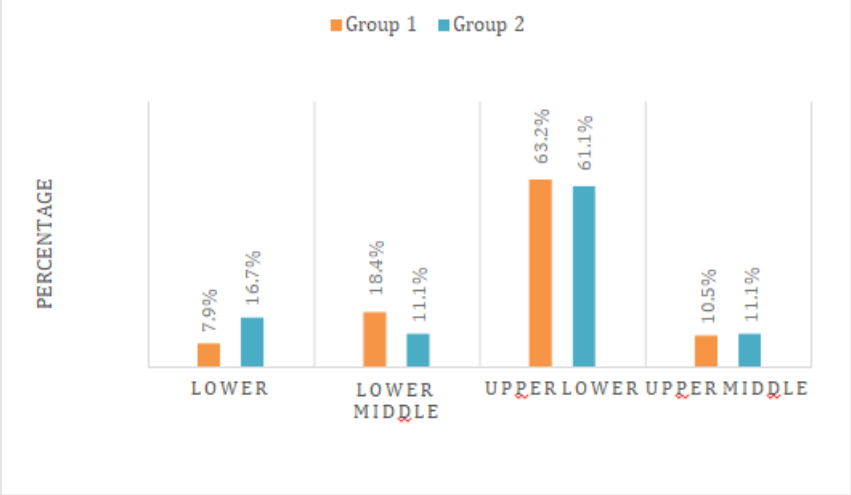

Figure 4: socioeconomic status of the sample.

Table 4: comparison of socioeconomic status of the sample in the two groups

SES	Group 1		Group 2	
	Count	%	Count	%
Lower	3	7.9%	6	16.7%
Lower Middle	7	18.4%	4	11.1%
Upper lower	24	63.2%	22	61.1%
Upper Middle	4	10.5%	4	11.1%
Total	38	100.0%	36	100.0%
p-value = 0.210				

Table 4 showing the comparison of socioeconomic status of the sample in the two groups using chi-square test.

Marital status: Number of participants who were married in group 1 were 76.3%(n=29) and 86.1%(n=31) in group 2 ; 23.7%(n=9) in group 1 and 13.9%(n=5) in group 2 were unmarried. Majority of the sample were married. P-value (p=0.219) was not significant with chi-square test between the two groups according to their marital status.

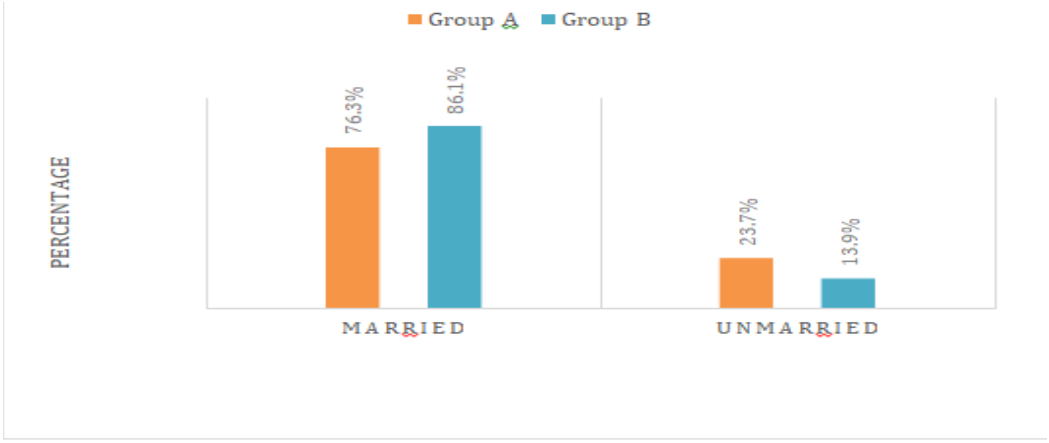

Figure 5: Marital status of the sample.

Table 5: comparison of marital status of the sample in the two groups

Marital status	Group 1		Group 2	
	Count	%	Count	%
Married	29	76.3%	31	86.1%
Unmarried	9	23.7%	5	13.9%
Total	38	100.0%	36	100.0%
p-value = 0.219				

Table 5 showing the comparison of marital status of the sample in the two groups using chi-square test.

Domicile: Number of participants belonging to rural background were 50.0%(n=19) in group 1 and 44.4%(n=16) in group 2 ; 50.0%(n=19) in group 1 and 55.6%(n=20) in group 2 belong to urban background. Majority of the sample population belonged to urban background. p-value (p=0.403) was not significant using chi-square test between the two groups according to domicile.

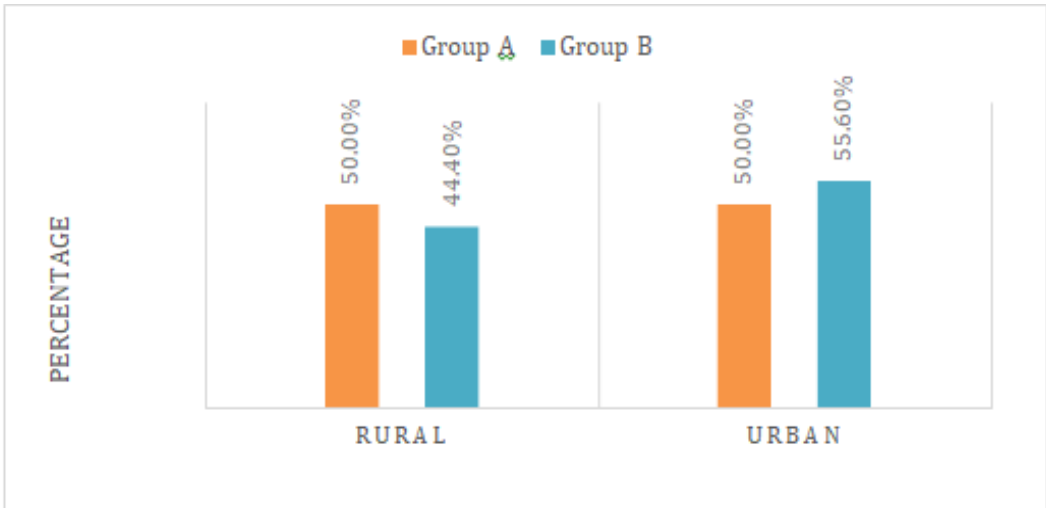

Figure 6: domicile of the sample

Table 6: Comparison of domicile of the sample in the two groups

Domicile	Group 1		Group 2	
	Count	%	Count	%
Rural	19	50.0%	16	44.4%
Urban	19	50.0%	20	55.6%
Total	38	100.0%	36	100.0%
p-value = 0.403				

Table 6 showing the comparison of domicile of the sample in the two groups using chi-square test.

Religion:

Number of sample population who were Christians was 15.8%(n=6) in group 1 and nil in group 2 ; 84.2%(n=32) in group 1 and 97.2%(n=35) in group 2 were Hindus ; nil in group 1 and 2.8%(n=1) in group 2 was a Muslim.

Majority of the sample were Hindus.

P-value (p=0.029*) was significant using the chi-square test between the two groups according to their religion.

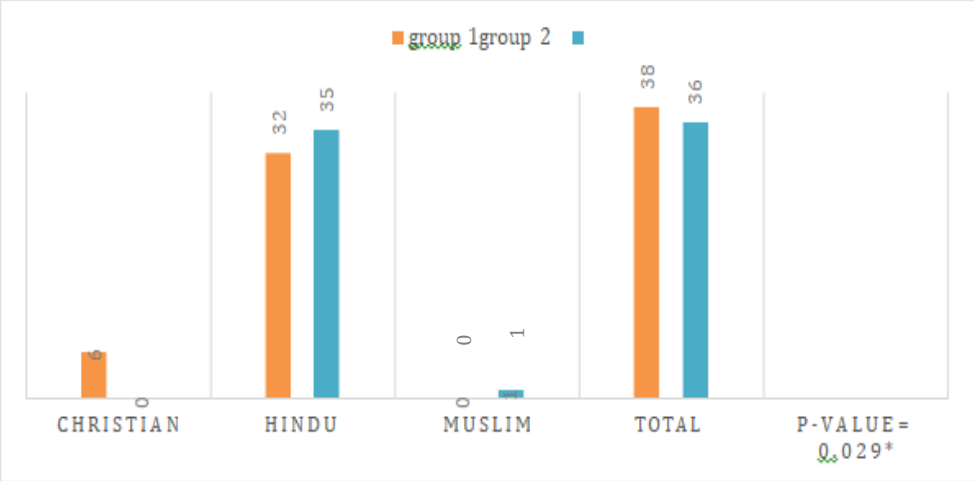

Figure 7: Religion of the sample

Table 7: Comparison of religion of the sample in the two groups

Religion	Group 1		Group 2	
	Count	%	Count	%
Christian	6	15.8%	0	0.0%
Hindu	32	84.2%	35	97.2%
Muslim	0	0.0%	1	2.8%
Total	38	100.0%	36	100.0%
p-value = 0.029*				

Table 7 showing the comparison of religion of the sample in the two groups using chi-square test.

Illness Variables:

Age of onset of alcohol intake:

31.6%(n=12) in group 1 and 5.6%(n=2) in group 2 were in the age group of 10-15 years ; 65.8%(n=25) in group 1 and 69.4%(n=25) in group 2 were in the age group of 16-25 years ; 2.6%(n=1) in group 1 and 19.4%(n=7) in group 2 were in the age group of 26-35 years ; nil from group1 and 5.6%(n=2) in group 2 were in the age group of 36-45 years. Majority of the sample were in the age group of 16-25 years. P-value (p=0.004*) was significant using the chi-square test between the two groups according to the age of onset of alcohol intake.

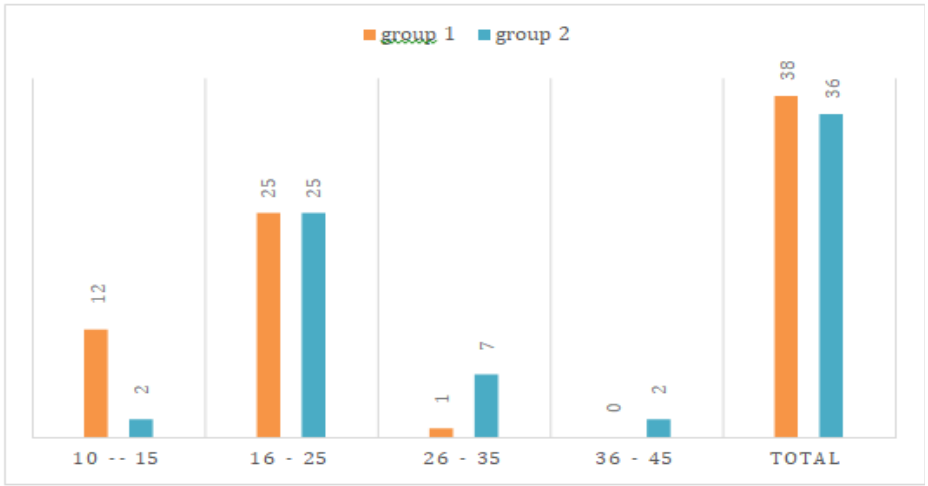

Figure 8 Age of onset of Alcohol intake

Table 8: Comparison of sample according to the age of onset of alcohol intake in two groups

Age of Onset of Drinking Alcohol	Group 1		Group 2	
	Count	%	Count	%
10 -- 15	12	31.6%	2	5.6%
16 - 25	25	65.8%	25	69.4%
26 - 35	1	2.6%	7	19.4%
36 - 45	0	0.0%	2	5.6%
Total	38	100.0%	36	100.0%
p-value = 0.004*				

Table 8 shows the comparison of sample according to the age of onset of alcohol intake in two groups using chi-square test.

Duration of alcohol intake:

2.6%(n=1) in group 1 and 5.6%(n=2) in group 2 had a duration of alcohol intake between 0-5 years ; 10.5%(n=4) in group 1 and 41.7%(n=15) in group 2 had a duration of alcohol intake between 6-10 years ; 60.5%(n=23) in group 1 and 36.1%(n=13) in group 2 had a duration of alcohol intake between 11-20 years ; 18.4%(n=7) in group 1 and 8.3%(n=3) in group 2 had a duration of alcohol intake between 21-30 years ; 7.9%(n=3) in group 1 and 8.3%(n=3)in group 2 had a duration of alcohol intake between 31-40 years.

Majority of the sample had a duration of alcohol intake between 11-20 years.

P-value (p=0.026*) was significant using the chi-square test between the two groups according to the duration of alcohol intake.

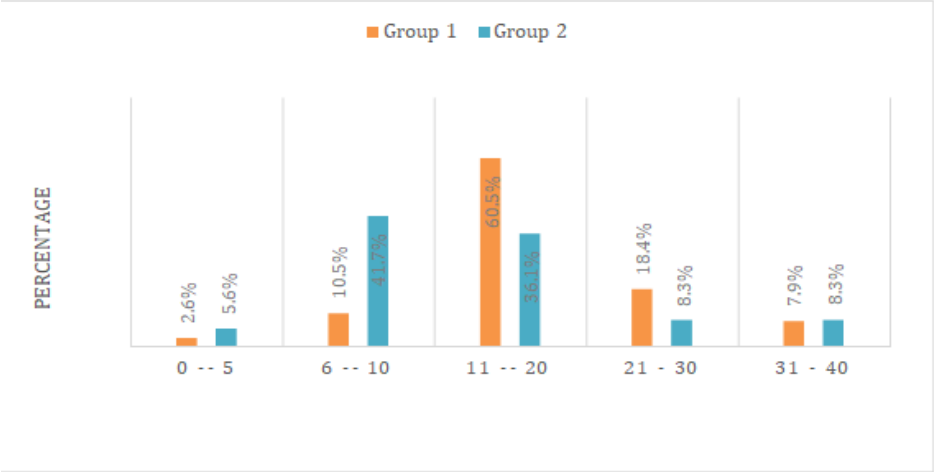

Figure 9: Duration of History of Alcohol Intake (yrs)

Table 9: Comparison of sample according to the age duration of history of alcohol intake in two groups

Duration of History of Alcohol Intake (yrs)	Group 1		Group 2	
	Count	%	Count	%
0 – 5	1	2.6%	2	5.6%
6 – 10	4	10.5%	15	41.7%
11 – 20	23	60.5%	13	36.1%
21 – 30	7	18.4%	3	8.3%
31 – 40	3	7.9%	3	8.3%
Total	38	100.0%	36	100.0%
P-value = 0.026*				

Table 9 shows the comparison of sample according to the age duration of history of alcohol intake in two groups using chi-square test.

Duration of regular usage of alcohol:

23.7%(n=9) in group 1 and 52.8%(n=19) in group 2 had a duration of regular use between 0-5 years ; 44.7%(n=17) in group 1 and 27.8%(n=10) in group 2 had a duration of regular use between 6-10 years ; 26.3%(n=10) in group 1 and 16.7%(n=6) in group 2 had a duration of regular use between 11-15 years ; 5.3%(n=2) in group 1 and 2.8%(n=1) in group 2 had a duration of regular use between 16-20 years. Majority of the sample population had duration of

regular usage of alcohol between 6-10 years. P-value (p=0.083) was not significant using the chi-square test between the two groups according to the duration of regular usage of alcohol.

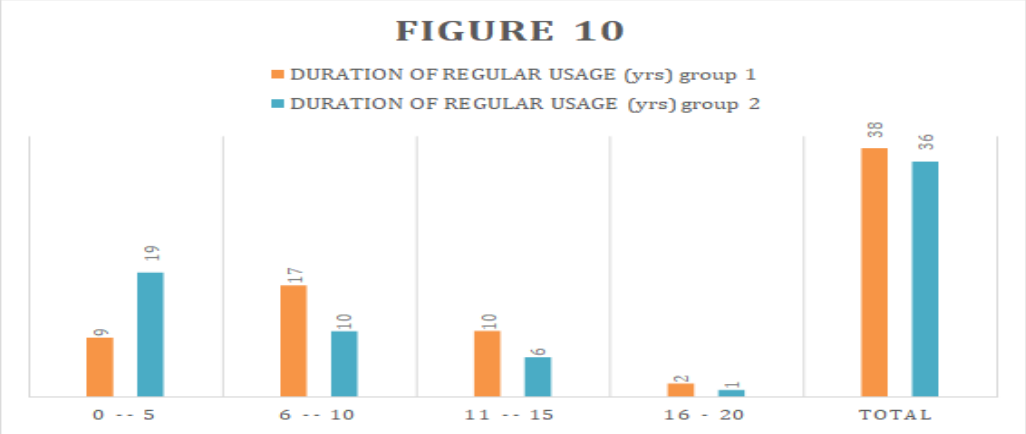

Figure 10: shows distribution of sample population according to duration of regular usage of alcohol.

Table 10: distribution of sample population according to duration of regular usage of alcohol

Duration of Regular Usage (Yrs)	Group 1		Group 2	
	Count	%	Count	%
0 -- 5	9	23.7%	19	52.8%
6 -- 10	17	44.7%	10	27.8%
11 -- 15	10	26.3%	6	16.7%
16 - 20	2	5.3%	1	2.8%
Total	38	100.0%	36	100.0%
P-value = 0.083				

Table 10 shows distribution of sample population according to duration of regular usage of alcohol.

Duration of dependence:

68.4%(n=26) in group 1 and 72.2%(n=26) in group 2 had a duration of dependence between 0-5 years; 26.3%(n=10) in group 1 and 25.0%(n=9) in group 2 had a duration of dependence between 6-10 years ; 5.3%(n=2) in group 1 and 2.8%(n=1) in group 2 had a duration of dependence between 11-15 years.

Majority of the sample population had duration of dependence between 0-5 years.

P-value (p=0.847) was not significant using the chi-square test between the two groups according to the duration of dependence.

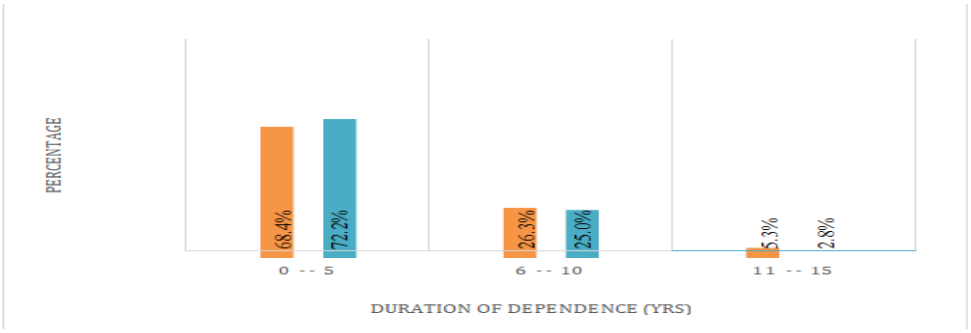

Figure 11: shows distribution of sample population according to duration of dependence.

Table 11: distribution of sample population according to duration of dependence

Duration of Dependence (Yrs)	Group 1		Group 2	
	Count	%	Count	%
0 -- 5	26	68.4%	26	72.2%
6 -- 10	10	26.3%	9	25.0%
11 -- 15	2	5.3%	1	2.8%
Total	38	100.0%	36	100.0%
P-value = 0.847				

Table 11 shows distribution of sample population according to duration of dependence.

Treatment history for alcohol dependence:

55.3%(n=21) in group 1 and 58.3%(n=21) in group 2 had no previous history of treatment for alcohol dependence ; 44.7%(n=17) in group 1 and 41.7%(n=15) in group 2 had a history of treatment for alcohol dependence. Majority of the sample population didn't have any history of treatment for alcohol dependence. P-value (p=0.487) was not significant using the chi-square test between the two groups according to the treatment history for alcohol dependence.

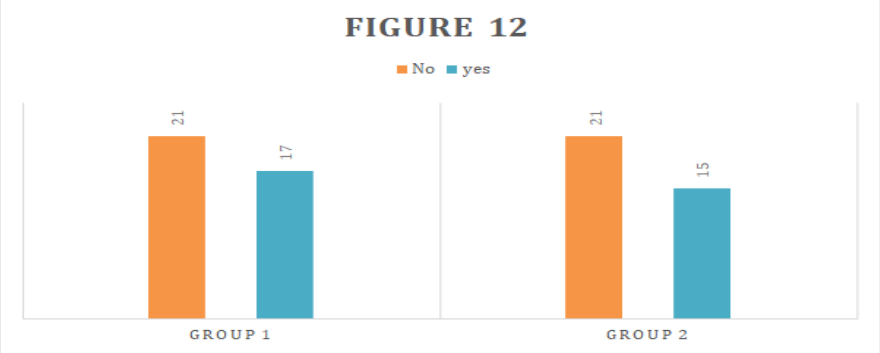

Figure 12: distribution of sample population based on treatment history for alcohol dependence.

Table 12:

Treatment history for alcohol dependence	Group 1		Group 2	
	Count	%	Count	%
No	21	55.3%	21	58.3%
yes	17	44.7%	15	41.7%
Total	38	100.0%	36	100.0%

Table 12 shows distribution of sample population based on treatment history for alcohol dependence.

History of complicated withdrawal: 86.8%(n=33) in group 1 and 72.2%(n=26) in group 2 have no history of complicated withdrawal ; 13.2%(n=5) in group 1 and 27.8%(n=10) in group 2 have a history of complicated withdrawal.

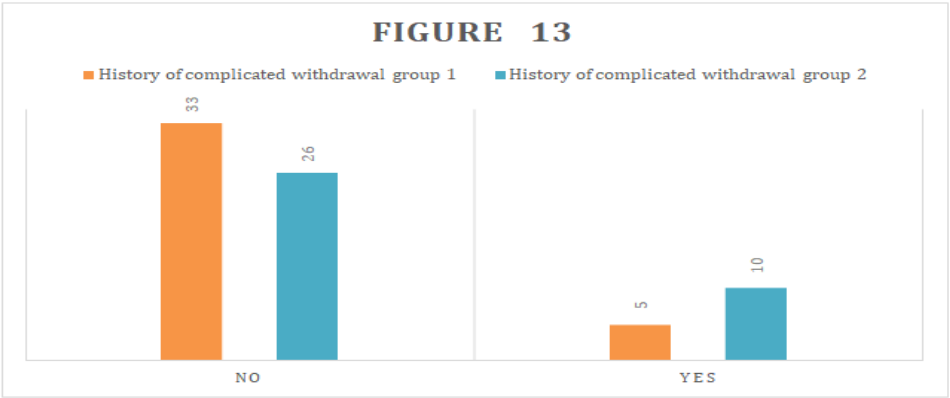

Figure 13: shows distribution of sample population based on history of complicated withdrawal

Table 13:

History of complicated withdrawal	Group 1		Group 2	
	Count	%	Count	%
No	33	86.8%	26	72.2%
yes	5	13.2%	10	27.8%
Total	38	100.0%	36	100.0%

Table 13 shows distribution of sample population based on history of complicated withdrawal.

Number of hospitalizations:

52.6%(n=20) in group 1 and 55.6%(n=20) in group

2 had nil hospitalizations ; 15.8%(n=6) in group 1 and 11.1%(n=4) in group 2 had 1 episode of hospitalization ; 15.8%(n=6) in group 1 and 25.0%(n=9) in

group 2 had 2 episodes of hospitalization ; 10.5%(n=4) in group 1 and 8.3%(n=3) in group 2 had 3 episodes of hospitalization ; 2.6%(n=1) in group 1 and nil in group 2 had 4 episodes of hospitalization ; ; 2.6%(n=1) in group 1 and nil in group 2 had 5 episodes of hospitalization. Majority of the sample population were not previously hospitalized.

P-value (p=0.686) was not significant using the chi-square test between the two groups according to number of hospitalizations.

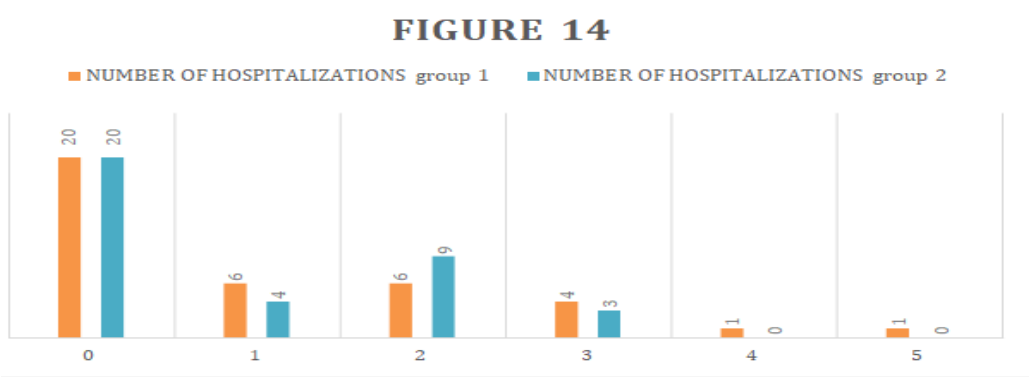

Figure 14: shows distribution of sample population based on number of hospitalizations.

Table 14:

Number of Hospitalizations	Group 1		Group 2	
	Count	%	Count	%
0	20	52.6%	20	55.6%
1	6	15.8%	4	11.1%
2	6	15.8%	9	25.0%
3	4	10.5%	3	8.3%
4	1	2.6%	0	0.0%
5	1	2.6%	0	0.0%
Total	38	100.0%	36	100.0%
P-value = 0.686				

Table 14 shows distribution of sample population based on number of hospitalizations

Severity of Alcohol Dependence:

The severity of alcohol dependence in the sample population was evaluated using the Severity of Alcohol Dependence Questionnaire. Based on the score, the dependence was classified into mild, moderate and severe. 13.2%(n=5) in group 1 and 27.8%(n=10) in group 2 had mild dependence ; 39.5%(n=15) in group 1 and 44.4%(n=16) in group 2 had moderate dependence ; 47.4%(n=18) in group 1 and 27.8%(n=10) in group 2 had severe dependence.

Majority of the patients in both groups had moderate dependence.

P-value (p=0.140) was not significant using the chi-square test between the two groups.

Mean score of the SADQ scale was 29.00(±8.111) in group 1 and 25.17(±8.157) in group 2 with a p-value (0.046*) which was significant using the independent t-test between the two groups.

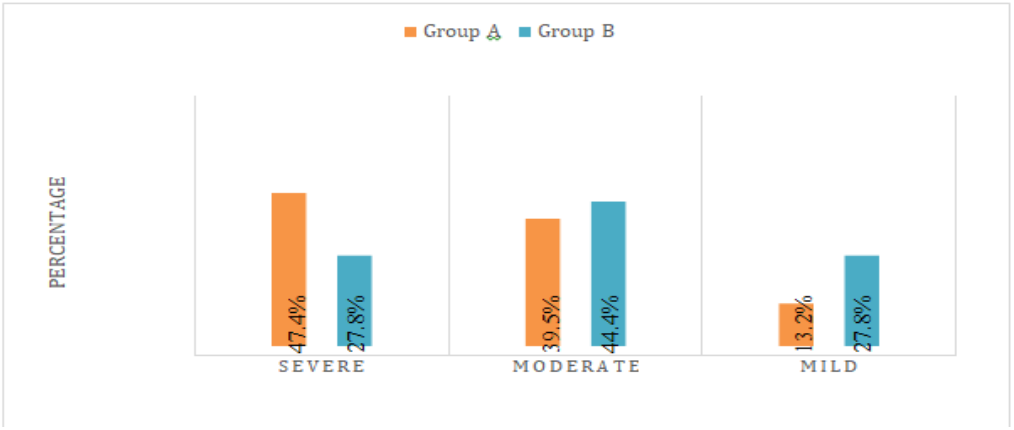

Figure 15: shows the mean scores of SADQ Scale in both groups.

Table 15:

Group	SDAQ Score		P-value
	Mean	SD	
Group 1	29.00	8.111	0.046*
Group 2	25.17	8.157	

Table 15 shows the mean scores of SADQ Scale in both groups.

Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar):

Alcohol withdrawal symptoms were assessed in both groups on the day of admission (DOA) and on day 5 using the CIWA-Ar scale.

Based on the score they were classified as having no withdrawal, minimal withdrawal, mild withdrawal, moderate withdrawal and severe withdrawal.

Severity of withdrawal on DOA:

10.5%(n=4) in group 1 and 5.6%(n=2) in group 2 had minimal withdrawal; 36.8%(n=14) in group 1 and 33.3%(n=12) in group 2 had mild withdrawal; 31.6%(n=12) in group 1 and 30.6%(n=11) had moderate withdrawal; 21.1%(n=8) in group 1 and 30.6%(n=11) in group 2 had severe withdrawal.

Majority of the sample population had moderate withdrawal. P-value (p=0.733) was not significant using the chi-square test between the two groups according to the severity of withdrawal.

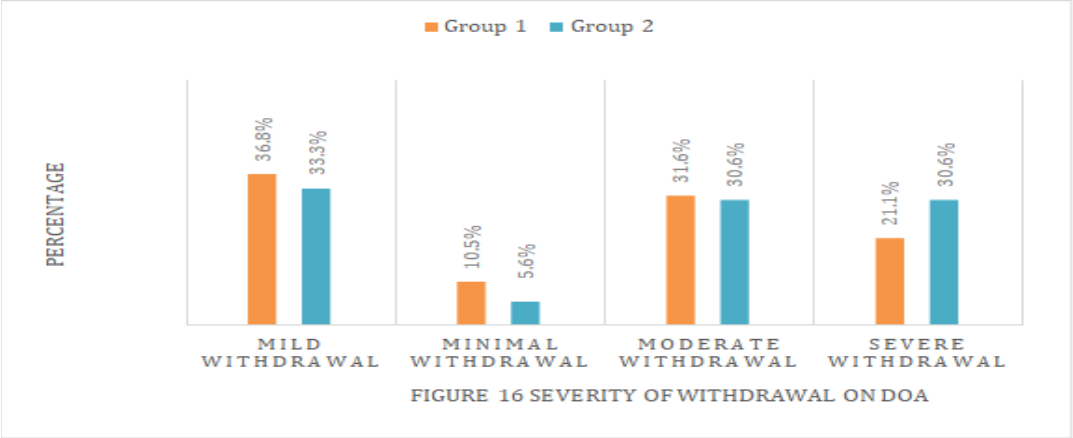

Figure 16: shows the severity of withdrawal on the DOA between the two groups.

Table 16:

Interpretation	Group 1		Group 2	
	Count	%	Count	%
Mild withdrawal	14	36.8%	12	33.3%
Minimal withdrawal	4	10.5%	2	5.6%
Moderate withdrawal	12	31.6%	11	30.6%
Severe withdrawal	8	21.1%	11	30.6%
Total	38	100.0%	36	100.0%
P-value = 0.733				

Table 16 shows the severity of withdrawal on the DOA between the two groups.

Severity of withdrawal on day 5 : 15.8%(n=6) in group 1 and 22.2%(n=8) in group 2 had no withdrawal ; 73.7%(n=28) in group 1 and 52.8%(n=19) in group 2 had minimal withdrawal ; 10.5%(n=4) in group.

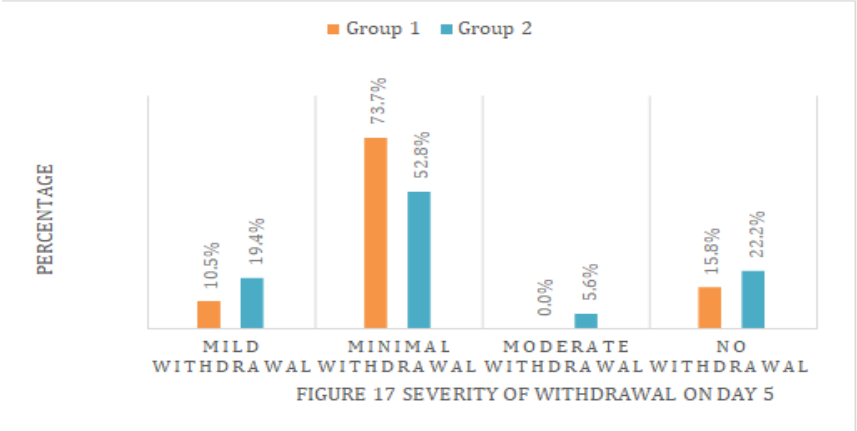

Figure 17: shows the severity of withdrawal on the Day 5 between the two groups.

Table 17:

Interpretation	Group 1		Group 2	
	Count	%	Count	%
Mild withdrawal	4	10.5%	7	19.4%
Minimal withdrawal	28	73.7%	19	52.8%
moderate withdrawal	0	0.0%	2	5.6%
No withdrawal	6	15.8%	8	22.2%
Total	38	100.0%	36	100.0%
P-value = 0.189				

Table 17 shows the severity of withdrawal on the Day 5 between the two groups

Paired test of CIWA-Ar scores in group 1: The mean score and Standard deviation on DOA is 15.71±4.472 ; the mean score and standard deviation on Day 5 is 3.47±3.18. Paired correlation in group 1 was significant with p=0.001.

Table 18:

Mean		N	Std. Deviation	Std. Error Mean
CIWA Score On DOA	15.71	38	4.472	0.725
Score on D5	3.47	38	3.186	0.517

Paired Samples Correlations

N			Correlation	Sig.
Pair 1	CIWA Score On DOA & Score on D5	38	0.516	0.001

a. Group =

Table 18 shows paired t-test of CIWA-Ar scores in group 1.

Paired test of CIWA-Ar scores in group 2: The mean and standard deviation on DOA is 16.28±4.651 ; the mean and standard deviation on Day 5 is 5.06±4.745. Paired correlation in group 2 was significant with p=0.000

Paired Samples Statistics[a]

Mean			N	Std. Deviation	Std. Error Mean
Pair 1	CIWA Score On DOA	16.28	36	4.651	0.775
Score on D5		5.06	36	4.745	0.791

a. Group =

Paired Samples Correlations[a]

Table 19:

N			Correlation	Sig.
Pair 1	CIWA Score On DOA & Score on D5	36	0.715	0.000

a. Group =

Table 19 shows the paired t-test of CIWA-Ar scores in group 2.

Independent sample t- test comparing CIWA-Ar scores between both groups on DOA and Day 5: Levene's test for equality of variances was used and the p-value was greater than 0.05 in the CIWA-Ar scores on both DOA and Day 5 hence variance is equal across both groups.

Table 20:

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
CIWA Score On DOA	Equal variances assumed	.009	.923	-.535	72	.594	-.567	1.061	- 2.681	1.547
	Equal vari-ances not assumed			-.534	71.367	.595	-.567	1.062	- 2.684	1.549
Score on D5	Equal vari-ances assumed	7.597	.007	- 1.692	72	.095	-1.582	.935	- 3.446	.282
	Equal vari-ances not assumed			- 1.675	60.790	.099	-1.582	.945	- 3.471	.307

Table 20 shows independent t-test of CIWA-Ar scores between two groups.

Severity of illness on DOA:

Severity of illness of the sample population was assessed using the Clinical Global Impressions scale - severity of illness. 21.1%(n=8) in group 1 and 30.6%(n=11) in group 2 were markedly ill; 31.6%(n=12) in group 1 and 30.6%(n=11) in group 2 were moderately ill; 36.8%(n=14) in group 1 and 33.3%(n=12) in group 2 were borderline; 10.5%(n=4) in group 1 and 5.6%(n=2) in group 2 were normal. Majority of the sample population in both groups were borderline.

P-value (p=0.733) was not significant using the chi-square test between the two groups according to their CGI-S score on DOA.

Figure 17 showing the distribution of sample population according to CGI-S Score on DOA.

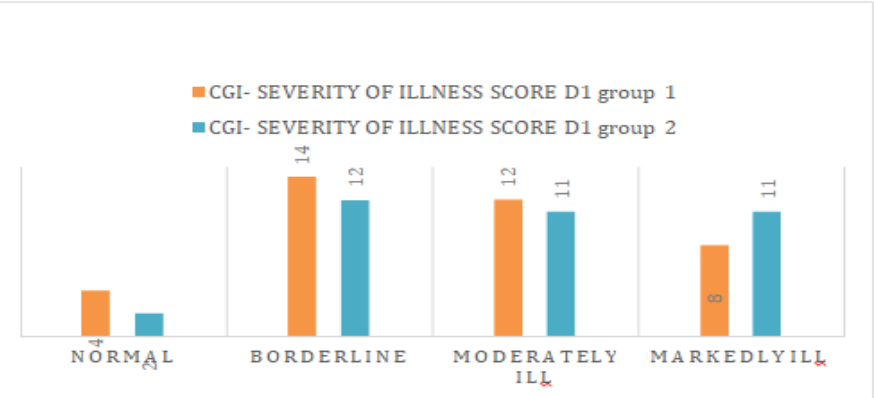

Figure 18: showing the distribution of sample population according to CGI-S Score on DOA.

Table 21:

CGI- Severity pf Illness Score D1	Group 1		Group 2	
	Count	%	Count	%
Normal	4	10.5%	2	5.6%
borderline	14	36.8%	12	33.3%
Moderately ill	12	31.6%	11	30.6%
Markedly ill	8	21.1%	11	30.6%
Total	38	100.0%	36	100.0%
P-value = 0.733				

Table 21 showing the distribution of sample population according to CGI-S Score on DOA.

Severity of illness on Day 5: 89.5%(n=34) in group 1 and 75.0%(n=27) in group 2 had CGI-S scores indicating they were normal; 10.5%(n=4) in group 1 and 19.4%(n=7) in group 2 had CGI-S scores indicating that they were borderline ill; nil from group 1 and 5.6%(n=2) in group 2 had CGI-S scores indicating that they were moderately ill.

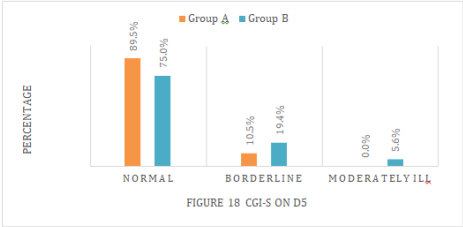

Figure 19: shows the severity of illness between the two groups on day 5.

Table 22:

CGI-S on D5	Group 1		Group 2	
	Count	%	Count	%
Normal	34	89.5%	27	75.0%
Borderline	4	10.5%	7	19.4%
Moderately ill	0	0.0%	2	5.6%
Total	38	100.0%	36	100.0%
P-value = 0.168				

Table 22 shows the severity of illness between the two groups on day 5.

Improvement of illness:

The sample population was assessed for improvement of illness using the Clinical Global Impressions-global improvement.

15.8%(n=6) in group 1 and 13.9%(n=5) in group 2 were very much improved; 50.0%(n=19) in group 1 and 41.7%(n=15) in group 2 were much improved; 31.6%9n=12) in group 1 and 44.4%(n=16) in group 2 were minimally improved ; 2.6%(n=1) in group 1 and nil in group 2 showed no change.

Majority of the sample population were much improved.

P-value (p=0.556) was not significant with chi-square test between the two groups according to the improvement of illness.

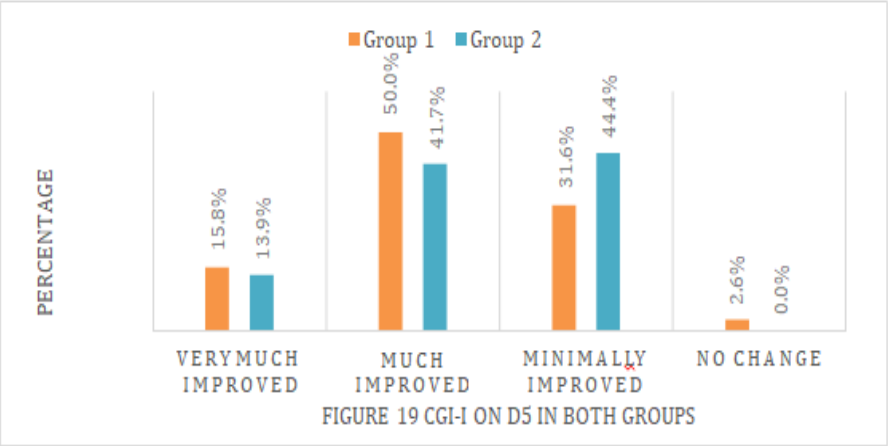

Figure 20: CGI-I on D5 in both groups.

Table 23:

CGI-I on D5	Group 1		Group 2	
	Count	%	Count	%
Very much improved	6	15.8%	5	13.9%
Much improved	19	50.0%	15	41.7%
Minimally improved	12	31.6%	16	44.4%
No change	1	2.6%	0	0.0%
Total	38	100.0%	36	100.0%
P-value = 0.556				

Table 23 shows the improvement of illness (CGI-I) between the two groups on day 5.

Correlation between Severity of Alcohol Dependence and AWS Severity:

The highest CIWA-Ar score is taken into consideration and correlated with the SADQ score. Out of the 28 participants who had severe dependence 68.4%(n=13) of the population had severe withdrawal; 39.1%(n=9) of the population had moderate withdrawal ; 19.2%(n=5) had mild withdrawal and 16.7%(n=1) had minimal withdrawal. Majority of the population with severe dependence had severe withdrawal. Severity of dependence was found to increase the severity of withdrawal, this was evident in the correlation between the SADQ Score and CIWA-Ar score on DOA and this correlation was found to be significant(p=0.000).

Table 24:

		SADQ Score- Severe dependence	Percentage
CIWA on DOA	Minimal withdrawal	1	16.7%
	Mild withdrawal	5	19.2%
	Moderate withdrawal	9	39.1%
	Severe withdrawal	13	68.4%
Total		28	37.8%

Table 24 distribution of population who had severe dependence

Table 25:

Spearman's rho	SADQ TOTAL SCORE	CIWA Score On DOA
	Correlation Coefficient	.527**
	Sig. (2-tailed)	.000
	N	74

**. Correlation is significant at the 0.01 level (2-tailed). Table 25 Correlation between Total SADQ Score and CIWA-AR Score on DOA

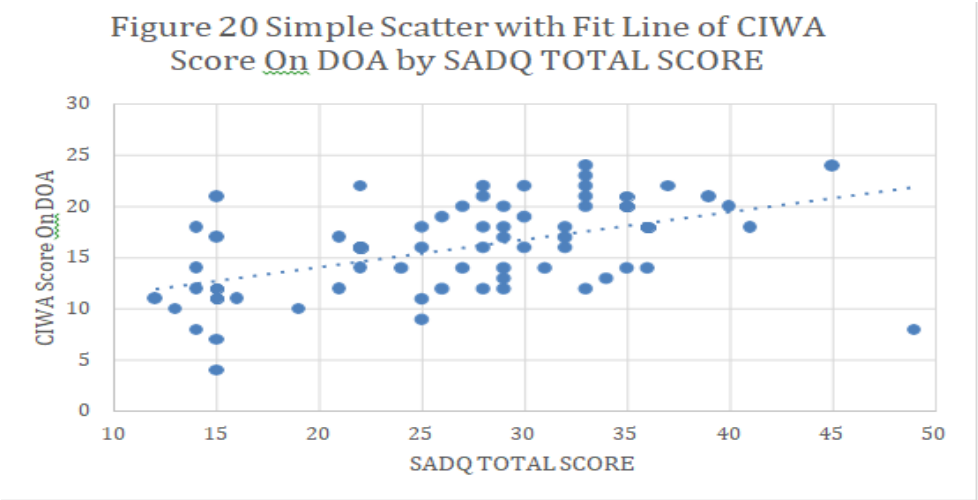

Figure 21: Simple Scatter with Fit Line of CIWA Score on DOA by SADQ total score.

Correlation between CIWA-Ar Score on DOA and CGI-Severity of illness Score on Day 1: The severity of alcohol withdrawal symptoms was found to increase the CGI-S Score on Day 1, this was evident by the correlation in the CIWA-Ar score and CGI-S score on DOA and this correlation was found to be significant(p=0.000*) 2 tailed.

Table 26:

			CGI-S Score on DOA
Spearman's rho	CIWA-Ar on DOA	Correlation coefficient	.955**
		Sig. (2-tailed)	.000
		N	74
**correlation is significant at the 0.01 level(2-tailed).			

Table 26 Correlation between CIWA-Ar Score on DOA and CGI-Severity of illness Score on Day 1.

Discussion

Alcohol dependence Syndrome is a serious medical and societal issue that is a huge public health concern. When the amount of alcohol consumption is abruptly stopped or significantly decreased, the onset of symptoms linked with the alcohol withdrawal syndrome is a major consequence of dependency.

Signs of central nervous system hyperexcitability, heightened autonomic nervous system activation, and a constellation of symptoms contributing to psychologic discomfort and negative affect are all clinical hallmarks of alcohol withdrawal. Chronic alcohol exposure causes changes in a variety of neurochemical systems, including glutamate, -aminobutyric acid, monoamines, a variety of neur peptide systems, and numerous ion channels, all of which damage the brain's functional integrity. These neuroadaptations not only lead to the genesis and manifestation of numerous alcohol withdrawal symptoms, but also to increased relapse vulnerability and the continuation of drinking.

Chronic alcohol use alone doesn't result in Wernicke's encephalopathy but along with low dietary thiamine consumption, decreased transport of thiamine across the intestinal mucosa and impaired conversion of thiamine to thiamine pyrophosphate. The metabolism of alcohol raises the demand for thiamine so ADS patients have an increased requirement of thiamine leading to thiamine deficiency.

Age

In this study majority of the sample belonged to the 30-39 age group. Number of subjects in the age group of 18-29 were 5.3%(n=2) in group 1 and 16.7%(n=6) in group 2 ; 44.7%(n=17) in group 1 and 41.7%(n=15) in group 2 were in the age group of 30- 39 ; 44.7%(n=17) in group 1 and 25.0%(n=9) in group 2 were in the age group of 40- 49 ; 5.3%(n=2) in group 1 and 16.7%(n=6) in group 2 were in the age group of 50-60.

In a study done by Dushad ram (2015), majority of the sample belonged to the age group between 30-55 and this finding was consistent with this study. [3] In a study done by B S Chavan et al (2007)majority of the sample belonged to the age group of 15-24 years, this finding is inconsistent with this study. [12]

In a study done by M.Ceccanti et al. (2005) the majority of the population belonged to middle age and this finding is consistent with this study. [15] In a study done by Ghulam et al. (1996) the majority of population belonged to the age group between 20-29 and then 30-39, and this finding is consistent with regard to the age group. [13] This could be because

majority of the sample population in this study had an age of onset of alcohol consumption at around 16-25 years and duration of dependence was between 0-10 years hence most of the patients recruited belonged to middle age group.

Literacy

In this study majority of the sample completed primary schooling and very few of them completed their graduation i.e around 8 of the total sample population.

Number of participants who were illiterate in group 1 included 28.9%(n=11) and 22.2%(n=8) in group 2 ; 31.6%(n=12) in group 1 and 27.8%(n=10) in group 2 studied up to primary school ; 23.7%(n=9) in group 1 and 30.6%(n=11) in group 2 studied up to secondary school ; 5.3%(n=2) in group 1 and 8.3%(n=3) in group 2 studied up to intermediate ; 10.5%(n=4) in group 1 and 11.1%(n-4) in group 2 were graduates.

In a study done by B S Chavan et al. (2007) majority of the sample were illiterate and completed only secondary, this finding is consistent with this study.12

In a study done by Dushad ram (2015), majority of the sample were educated, this finding is inconsistent with this study. [3] In a study done by Ghulam et al.(1996) the majority of population had studied up to secondary [13], and this finding is consistent with our study. This could be due to the fact that India is still a developing country and the sample mainly consisted of people hailing from a rural background, upper lower socioeconomic status they probably couldn't afford to complete their education. The study setting was done in the Government Hospital for Mental care Visakhapatnam, while it is easily accessible by the people hailing from lower socioeconomic statuses.

Occupation

In this study majority of the sample were employed. Number of participants in group 1 who were employed include 84.2%(n=32) and 91.7%(n=33) in group 2 ; 2.6%(n=1) in group 1 and 0 participants in group 2 were retired ; 13.2%(n=5) in group 1 and 8.3%(n=3) in group 2 were unemployed.

This finding is consistent with two studies done by Dushad ram (2015) and B S Chavan et al. (2007) and Ghulam et al.(1996) where majority of the sample were employed. [3,12,13] As the study population had almost equal number of patients hailing from rural background and belonging to upper lower socioeconomic status the men are expected to be the bread winners and are employed far more commonly than women. Especially since the study population age group was middle aged and married due to these reasons majority of them are required to hold a job for the sustainment of their families.

Socioeconomic Status

In this study majority of the sample belongs to upper lower socioeconomic status and very few belong to upper middle SES. Number of participants belonging to lower socioeconomic status were 7.9%(n=3) in group 1 and 16.7%(n=6) in group 2 ; 18.4%(n=7) in group 1 and 11.1%(n=4) in group2 belong to lower middle socioeconomic status ; 63.2%(n=24) in group 1 and 61.1%(n=22) in group 2 belong to upper lower socioeconomic status ; 10.5%(n=4) in group 1 and 11.1%(n4) in group 2 belong to upper middle socioeconomic status. People from lower socioeconomic classes do not have buying power when compared to those in upper lower and middle classes.

As the study was done in the Government Hospital for Mental care Visakhapatnam, it is easily accessible by the people hailing from lower socioeconomic statuses; as most of them cannot to get treatment in a private setting. Hence probably the reasons for this finding in this study.

Marital status

In this study majority of the sample were married. Number of participants who were married in group 1 were 76.3%(n=29) and 86.1%(n=31) in group 2 ; 23.7%(n=9) in group 1 and 13.9%(n=5) in group 2 were unmarried.

This finding is consistent with two studies done by Dushad ram (2015) and B S Chavan et al.(2007) where majority of the sample were married. [3,12]

Probably due to the fact that majority of the sample belonged to middle age group, belonging to upper lower socioeconomic status the majority of the population are to be expected. In India it is mostly customary to get married at a young age especially in the lower social classes and rural areas; hence probably the reason for this finding. Domicile:

In this study majority of the sample population belonged to urban background. Number of participants belonging to rural background were 50.0%(n=19) in group 1 and 44.4%(n=16) in group 2 ; 50.0%(n=19) in group 1 and 55.6%(n=20) in group 2 belong to urban background.

This finding is inconsistent with the findings in studies done by Dushad ram (2015) and B S Chavan et al.(2007) where majority of the sample were from rural and slum areas. [3,12]

This discrepancy could be that although patients hailing from rural areas most frequent government tertiary facilities such as the study setting in this study, many people are now migrating from rural areas but staying in urban areas for any daily wage work that is easy available in cities. And since the

study setting is located in an urban area more people from nearby localities will attend the hospital. These could be reasons for the study comprises a majority of population from urban areas.

Religion

In this study majority of the sample were Hindus. Number of sample population who were Christians was 15.8%(n=6) in group 1 and nil in group 2 ; 84.2%(n=32) in group 1 and 97.2%(n=35) in group 2 were Hindus ; nil in group 1 and 2.8%(n=1) in group 2 was a Muslim. Owing to the study setting and state in which this study was conducted majority of the general population are Hindus which is reflected in the sample. Also there are many practices in Muslims which prohibit them from consuming alcohol or any other psychoactive substances.

Illness Variables:

Age of onset of alcohol intake:

In this study majority of the sample were in the age group of 16-25 years. 31.6%(n=12) in group 1 and 5.6%(n=2) in group 2 were in the age group of 10-15 years ; 65.8%(n=25) in group 1 and 69.4%(n=25) were in the age group of 16-25 years ; 2.6%(n=1) in group 1 and 19.4%(n=7) in group 2 were in the age group of 26-35 years; nil from group1 and 5.6%(n=2) in group 2 were in the age group of 36-45 years. Mean age of first use was between 19-20 years in studies done by B S Chavan et al.(2007), Ghulam et al.(1996) this finding is consistent with the current study. [12,13]

In a study done by M.Ceccanti et al. (2005) the majority of the population had an age of onset of alcohol intake as above 21 years. [15] Most teenagers are introduced to alcohol either by their peers or encouraged to drink by some family members and become influenced by alcohol use or other substance use by watching movies, celebrities etc. Hence probably the reason for the age of onset of drinking being at a young age. As majority of the sample population are in the age group of 30-39, they probably started drinking when they were teenagers; hence this finding is justified.

Duration of alcohol intake:

In this study majority of the sample had duration of alcohol intake between 11-20 years. 2.6%(n=1) in group 1 and 5.6%(n=2) in group 2 had a duration of alcohol intake between 0-5 years ; 10.5%(n=4) in group 1 and 41.7%(n=15) in group 2 had a duration of alcohol intake between 6-10 years ; 60.5%(n=23) in group 1 and 36.1%(n=13) in group 2 had a duration of alcohol intake between 11-20 years ; 18.4%(n=7) in group 1 and 8.3%(n=3) in group 2 had a duration of alcohol intake between 21-30 years ; 7.9%(n=3) in group 1 and 8.3%(n=3)in group 2 had a duration of alcohol intake between 31-40 years. Most of the patients in this study were in the middle age group and majority of them had their age of onset of drinking alcohol at younger age, hence the duration of alcohol intake came out to be between 11-20 years.

Duration of dependence:

In this study majority of the sample population had duration of dependence between 0-5 years. 68.4%(n=26) in group 1 and 72.2%(n=26) in group 2 had a duration of dependence between 0-5 years; 26.3%(n=10) in group 1 and 25.0%(n=9) in group 2 had a duration of dependence between 6-10 years; 5.3%(n=2) in group 1 and 2.8%(n=1) in group 2 had a duration of dependence between 11-15 years.

Accounting the age group, age of onset of regular alcohol intake majority of the population had duration dependence between 0-5 years.

Treatment history for alcohol dependence:

In this study majority of the sample population didn't have any history of treatment for alcohol dependence. 55.3%(n=21) in group 1 and 58.3%(n=21) in group 2 had no previous history of treatment for alcohol dependence ; 44.7%(n=17) in group 1 and 41.7%(n=15) in group 2 had a history of treatment for alcohol dependence. Although the difference is not very high a majority of the sample population didn't have any prior treatment for alcohol dependence. This finding could be due to the fact that majority of the sample were of the age group 30-39 with a duration of dependence between 0-5 years.

History of complicated withdrawal:

In this study majority of the sample population did not have any history of complicated withdrawal. 86.8%(n=33) in group 1 and 72.2%(n=26) in group 2 have no history of complicated withdrawal ; 13.2%(n=5) in group 1 and 27.8%(n=10) in group 2 have a history of complicated withdrawal. As complicated withdrawal is a medical emergency and occurs in around 5% of ADS patients probably why majority of the sample did not have a history of complicated withdrawal.

Number of hospitalizations:

In this study majority of the sample population were not previously hospitalized. 52.6%(n=20) in group 1 and 55.6%(n=20) in group 2 had nil hospitalizations ; 15.8%(n=6) in group 1 and 11.1%(n=4) in group 2 had 1 episode of hospitalization ; 15.8%(n=6) in group 1 and 25.0%(n=9) in group 2 had 2 episodes of hospitalization ; 10.5%(n=4) in group 1 and 8.3%(n=3) in group 2 had 3 episodes of hospitalization ; 2.6%(n=1) in group 1 and nil in group 2 had 4 episodes of hospitalization ; 2.6%(n=1) in group 1 and nil in group 2 had 5 episodes of hospitalization.

As majority of the patients didn't have any prior history of treatment for alcohol dependence and complicated withdrawal, these probably could be the reason for the majority of the population not having any history of hospitalization.

Severity of Alcohol Dependence:

In this study majority of the patients in both groups had moderate dependence.13.2% (n=5) in group 1 and 27.8%(n=10) in group 2 had mild dependence; 39.5%(n=15) in group 1 and 44.4%(n=16) in group 2 had moderate dependence ; 47.4%(n=18) in group 1 and 27.8% (n=10) in group 2 had severe dependence. This finding is consistent with the study by Dushad ram (2015) where they had taken moderate to severe dependent patients were included into the study. [1] In another study done by M.BAINES et al. (2004) the majority of the population had severe dependence. [39] Since the study population were hospitalized patients it is likely the reason for this finding as ADS patients with moderate to severe dependence are usually admitted for deaddiction treatment.

Severity of withdrawal on DOA:

In this study majority of the sample population had moderate withdrawal. 10.5%(n=4) in group 1 and 5.6%(n=2) in group 2 had minimal withdrawal ; 36.8%(n=14) in group 1 and 33.3%(n=12) in group 2 had mild withdrawal ; 31.6%(n=12) in group 1 and 30.6%(n=11) in group 2 had moderate withdrawal ; 21.1%(n=8) in group 1 and 30.6%(n=11) in group 2 had severe withdrawal.

Severity of withdrawal on day 5:

15.8%(n=6) in group 1 and 22.2%(n=8) in group 2 had no withdrawal; 73.7%(n=28) in group 1 and 52.8%(n=19) in group 2 had minimal withdrawal; 10.5%(n=4) in group 1 and 19.4%(n=7) in group 2 had mild withdrawal ; nil in group 1 and 5.6%(n=2) in group 2 had moderate withdrawal. No patients in both groups had severe withdrawal. Paired sample correlations in group 1&2:

The paired correlation in CIWA-Ar scores on DOA and Day 5 in both groups was statistically significant. This could be explained as a significant reduction in the AWS in both groups on Day 5. But as there no difference in both groups it cannot be concluded that the reduction is due to thiamine supplementation. Also because majority of the patients had moderate to severe withdrawal they were started on a Benzodiazepine (BZD) regimen for alcohol withdrawal. The type, dosage and duration of BZD's used were not accounted for and not standardized. This confounding variable was not accounted for in the outcome. This finding is consistent with a study done by Dushad ram(2015) they found that thiamine concentrations had no correlation with AWS.3

This finding is also consistent with a study by M.Ceccanti et al.(2005) where they have found that though alcoholics have a thiamine deficiency; levels of thiamine and its esters had no positive or significant correlation with the CIWA-Ar values.15

Severity of illness on DOA:

In this study majority of the sample population in both groups were borderline. 21.1%(n=8) in group 1 and 30.6%(n=11) in group 2 were markedly ill ; 31.6%(n=12) in group 1 and 30.6%(n=11) in group 2 were moderately ill; 36.8%(n=14) in group 1 and 33.3%(n=12) in group 2 were borderline ; 10.5%(n=4) in group 1 and 5.6%(n=2) in group 2 were normal. As majority of the patients had moderate to severe dependence and moderate withdrawal on the DOA the CGI-S scores on DOA reflect the same in that majority of the population were borderline ill.

Severity of illness on Day 5:

In this study majority of the sample population were normal on day 5 and a very small quantity of patients still experiencing a disease severity of borderline and moderately ill. 89.5%(n=34) in group 1 and 75.0%(n=27) in group 2 had CGI-S scores indicating they were normal; 10.5%(n=4) in group 1 and 19.4%(n=7) in group 2 had CGI-S scores indicating that they were borderline ill ; nil from group 1 and 5.6%(n=2) in group 2 had CGI-S scores indicating that they were moderately ill.

This finding is reflected in the observation that the difference in the pre and post treatment CIWA-Ar scores was not statistically significant, that is not conclusive to say that the improvement is due to the treatment being administered.

Improvement of illness:

The sample population were assessed for improvement of illness using the Clinical Global Impressions-global improvement.

Majority of the sample population were much improved. 15.8%(n=6) in group 1 and 13.9%(n=5) in group 2 were very much improved; 50.0%(n=19) in group 1 and 41.7%(n=15) in group 2 were much improved; 31.6%9n=12) in group 1 and 44.4%(n=16) in group 2 were minimally improved; 2.6%(n=1) in group 1 and nil in group 2 showed no change. This finding is in line with the reduction of withdrawal symptoms and also severity of illness.

Correlation between Severity of Alcohol Dependence and AWS Severity:

The highest CIWA-Ar score is taken into consideration and correlated with the SADQ score. There was a significant correlation between the SADQ Score and CIWA-Ar score on DOA. This proves that the severity of dependence was found to increase the severity of withdrawal. In a study done

by Evan wood et al. they have identified excess of alcohol intake and severe dependence as risk factors to develop severe withdrawal. This is consistent with the finding in this study. [11]

Strengths:

1. As this was a double blind study patient and examiner were both blind to the treatment being given and hence reduced bias.
2. This is one of the few studies assessing the correlation between thiamine and Alcohol withdrawal symptoms.
3. In this study thiamine supplementation at different doses was correlated with withdrawal and clinical outcome.
4. The scales used in this study were all valid and reliable.
5. Various risk factors and associations were found for the development of severe withdrawal.

Limitations:

1. The study size was small.
2. As the patients were selected using an inclusion criteria and didn't include those with any medical or psychiatric comorbidity the results cannot be generalized.
3. The nutritional status of the patient was not assessed in this study and hence patients' thiamine deficiency couldn't have been identified in early stages
4. The study didn't take into consideration the other medication given to the patient during detoxification.
5. The follow-up period was limited to the end of treatment.

Future Recommendations:

1. A study with a larger sample size could be more helpful in assessing the hypothesis of this study.
2. A study including patients with medical comorbidities could be done to generalize the results and may recommend for a dose change in special population.
3. Levels of Whole blood thiamine and its esters and enzymes like Thiamine pyrophosphate (TPP) and erythrocyte transketolase could be assessed along with thiamine supplementation.
4. Various confounding factors like nutritional status of the patients and other treatments could be assessed.

Conclusion

The findings of this study have no found no significant difference in the supplementation of a higher of thiamine in ADS patients to reduce withdrawal; hence the current recommendations can be followed.

There was no difference in the reduction of AWS and severity of illness with both doses of thiamine given.

Probable risk factors for developing severe withdrawal identified were severe alcohol dependence and previous history of complicated withdrawal.

References

1. Dalal PK, Basu D. Substance use disorders. Indian J Psychiatry. 2001 Oct 1; 43:381.
2. Pruckner N, Baumgartner J, Hinterbuchinger B, Glahn A, Vyssoki S, Vyssoki B. Thiamine substitution in alcohol use disorder: a narrative review of medical guidelines. European addiction research. 2019; 25(3):103-10.
3. Dervaux A, Laqueille X. Thiamine (vitamin B1) treatment in patients with alcohol dependence. Presse medicale (Paris, France: 1983). 2017 Mar; 46(2 Pt 1):165.
4. Eşel E. Neurobiology of alcohol withdrawal inhibitory and excitatory neurotransmitters. Turk psikiyatri dergisi Turkish journal of psychiatry. 2006 Jan 1; 17(2):129-37.
5. Ram D. Whole blood thiamine levels and its relationship with severity of alcohol withdrawal and neurological soft signs in patients with alcohol use disorder. Journal of Neuropsychiatry. 2016 Jan; 1:1-5.
6. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. Alcohol and Alcoholism. 2000 May 1; 35(Supplement_1):2-1.
7. Latt N, Dore G. Thiamine in the treatment of W ernicke encephalopathy in patients with alcohol use disorders. Internal medicine journal. 2014 Sep; 44(9):911-5.
8. Rolland B, Paille F, Gillet C, Rigaud A, Moirand R, Dano C, Dematteis M, Mann K, Aubin HJ. Pharmacotherapy for alcohol dependence: the 2015 recommendations of the French Alcohol Society, issued in partnership with the European Federation of Addiction Societies. CNS neuroscience & therapeutics. 2016 Jan; 22(1):25-37.
9. Cook CC, Hallwood PM, Thomson AD. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. Alcohol and Alcoholism. 1998 Jul 1; 33(4):317-36.
10. Latt N, Dore G. Thiamine in the treatment of W ernicke encephalopathy in patients with alcohol use disorders. Internal medicine journal. 2014 Sep; 44(9):911-5.
11. Wood E, Albarqouni L, Nolan S, Mclean M, Klimas J, Director BC. Will this adult patient develop severe alcohol withdrawal? The Rational Clinical Examination Systematic Review.
12. Chavan BS, Arun P, Bhargava R, Singh GP. Prevalence of alcohol and drug dependence in rural and slum population of Chandigarh: A community survey. Indian journal of Psychiatry. 2007 Jan; 49(1):44.

13. Ghulam R, Rahman I, Naqvi S, Gupta SR. An epidemiological study of drug abuse in urban population of Madhya Pradesh. Indian journal of psychiatry. 1996 Jul; 38(3):160.
14. Saitz R. Introduction to alcohol withdrawal. Alcohol health and research world. 1998; 22(1):5.
15. Ceccanti M, Mancinelli R, Sasso GF, Allen JP, Binetti R, Mellini A, Attilia F, Toppo L, Attilia ML. Erythrocyte thiamine (Th) esters: a major factor of the alcohol withdrawal syndrome or a candidate marker for alcoholism itself?. Alcohol and Alcoholism. 2005 Jul 1; 40(4):283-90.
16. Nordentoft M, Timm S, Hasselbalch E, Roesen A, Gammeltoft S, Hemmingsen R. Thiamine pyrophosphate effect and erythrocyte transketolase activity during severe alcohol withdrawal syndrome. Acta Psychiatrica Scandinavica. 1993 Aug; 88(2):80-4.
17. Becker HC, Mulholland PJ. Neurochemical mechanisms of alcohol withdrawal. Handbook of clinical neurology. 2014 Jan 1; 125:133-56.
18. Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked?. Addiction biology. 2010 Apr; 15(2):169-84.
19. Keenan E, O'Donnell C, Sinanan K, O'Callaghan E. Severity of alcohol dependence and its relationship to neurological soft signs, neuropsychological impairment and family history. Acta Psychiatrica Scandinavica. 1997 Apr; 95(4):272-6.
20. Sgouros X, Baines M, Bloor RN, McAuley R, Ogundipe LO, Willmott S. Evaluation of a clinical screening instrument to identify states of thiamine deficiency in in patients with severe alcohol dependence syndrome. Alcohol and Alcoholism. 2004 May 1; 39(3):227-32.
21. Wood B, Breen KJ, Penington DG. Thiamine status in alcoholism. Australian and New Zealand journal of medicine. 1977 Oct; 7(5):475-84.
22. Heap LC, Pratt OE, Ward RJ, Waller S, Thomson AD, Shaw GK, Peters TJ. Individual susceptibility to Wernicke–Korsakoff syndrome and alcoholism- induced cognitive deficit: impaired thiamine utilization found in alcoholics and alcohol abusers. Psychiatric Genetics. 2002 Dec 1; 12(4):217-24.
23. Mancinelli R, Barlocci E, Ciprotti M, Senofonte O, Fidente RM, Draisci R, Attilia ML, Vitali M, Fiore M, Ceccanti M. Blood thiamine, zinc, selenium, lead and oxidative stress in a population of male and female alcoholics: clinical evidence and gender differences. Annali dell'Istituto superiore di sanità. 2013; 49:65-72.
24. Herve C, Beyne P, Letteron PH, Delacoux E. Comparison of erythrocyte transketolase activity with thiamine and thiamine phosphate ester levels in chronic alcoholic patients. Clinica chimica acta. 1995 Jan 31; 234(1-2):91-100.
25. Brinkman DJ, Bekema JK, Kuijenhoven MA, Wijnia JW, Dekker MJ, van Agtmael MA. Thiamine in patients with alcohol use disorder and Wernicke's encephalopathy. Nederlands tijdschrift voor geneeskunde. 2017 Jan 1; 161:D931-.
26. Rees E, Gowing LR. Supplementary thiamine is still important in alcohol dependence. Alcohol and alcoholism. 2013 Jan 1; 48(1):88-92.
27. Praharaj SK, Munoli RN, Shenoy S, Udupa ST, Thomas LS. High-dose thiamine strategy in Wernicke–Korsakoff syndrome and related thiamine deficiency conditions associated with alcohol use disorder. Indian Journal of Psychiatry. 2021 Mar 1; 63(2):121.
28. Thomson AD, Marshall EJ. The natural history and pathophysiology of Wernicke's encephalopathy and Korsakoff's psychosis. Alcohol and Alcoholism. 2006 Mar 1; 41(2):151-8.
29. Galvin R, Bråthen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. European Journal of Neurology. 2010 Dec; 17(12):1408-18.
30. Hinze-Selch D, Weber MM, Zimmermann U, Pollmächer T. Thiamine treatment in psychiatry and neurology. Fortschritte der Neurologie-psychiatrie. 2000 Mar 1; 68(3):113-20.
31. Rossouw JE, Labadarios D, Krasner N, Davis M, Williams R. Red blood cell transketolase activity and the effect of thiamine supplementation in patients with chronic liver disease. Scandinavian journal of gastroenterology. 1978 Feb 1; 13(2):133-8.
32. Kraemer KL, Mayo-Smith MF, Calkins DR. Independent clinical correlates of severe alcohol withdrawal. Substance Abuse. 2003 Dec 1; 24(4):197-209.
33. Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. Journal of Psychopharmacology. 2012 Jul; 26(7):899-952.
34. Thomson AD, Marshall EJ, Bell D. Time to act on the inadequate management of Wernicke's encephalopathy in the UK. Alcohol and alcoholism. 2013 Jan 1; 48(1):4-8.
35. Chataway JE, Hardman EL. Thiamine in Wernicke's syndrome--how much and how long?. Postgraduate medical journal. 1995 Apr; 71(834):249.
36. Markowitz JS, McRae AL, Sonne SC. Oral nutritional supplementation for the alcoholic patient: a brief overview. Annals of clinical psychiatry. 2000 Sep; 12(3):153-8.

37. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. Alcohol and Alcoholism. 2000 May 1; 35(Supplement_1):2-1.
38. ThomsonBSC AD, Jeyasingham MD, Pratt OE, Shaw GK. Nutrition and alcoholic encephalopathies. Acta Medica Scandinavica. 1987 Jan 12; 221(S717):55-65.
39. Baines M, Bligh JG, Madden JS. Tissue thiamin levels of hospitalised alcoholics before and after oral or parenteral vitamins. Alcohol and Alcoholism. 1988 Jan 1; 23(1):49-52.
40. Day E, Bentham PW, Callaghan R, Kuruvilla T, George S. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database of Systematic Reviews. 2013(7).
41. Wood B, Currie J. Presentation of acute Wernicke's encephalopathy and treatment with thiamine. Metabolic brain disease. 1995 Mar; 10(1):57-72.
42. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. The Lancet Neurology. 2007 May 1; 6(5):442-55.
43. Delaffon V, Naik S, Mann R, Vahabzadeh A, Millward T, Majeed A, Taylor A, Pant A. Diagnosis and treatment of Wernicke's encephalopathy in an in-patient alcohol detoxification unit: a completed audit cycle. The Psychiatrist. 2013 Dec; 37(12):384-8.
44. Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. Alcoholism: Clinical and Experimental Research. 2001 Jan; 25(1):112-6.
45. Rolland B, Paille F, Gillet C, Rigaud A, Moirand R, Dano C, Dematteis M, Mann K, Aubin HJ. Pharmacotherapy for alcohol dependence: the 2015 recommendations of the French Alcohol Society, issued in partnership with the European Federation of Addiction Societies. CNS neuroscience & therapeutics. 2016 Jan; 22(1):25-37.
46. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization; 1992.
47. Edition F. Diagnostic and statistical manual of mental disorders. Am Psychiatric Assoc. 2013;21