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An Observational Comparative Study of Clinical Efficacy and Safety of Chlordiazepoxide and Lorazepam in Alcohol Withdrawal Syndrome

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Abstract: ***Introduction:*** *Currently, Benzodiazepines like chlordiazepoxide, diazepam and lorazepam are the preferred drugs in the management of Alcohol withdrawal syndrome (AWS). These drugs of similar class are different in their pharmacokinetic profile which differently affect in AWS. Chlordiazepoxide is longer acting and converted to active metabolites in the liver, while lorazepam is shorter acting, with no active metabolites.*
Aim:*To compare and evaluate the safety and efficacy of lorazepam and chlordiazepoxide in patients with alcohol dependence syndrome with symptoms of alcohol withdrawal.*
Methods & Results: *After obtaining approval from the IEC and valid informed consent, the participants were recruited into the study. This is a prospective, randomized, double blind, interventional study. Sixty patients with alcohol dependence syndrome with moderate withdrawal symptoms were allocated to receive either Chlordiazepoxide or Lorazepam, by means of a computer generated random sequence at a ratio of 1:1.Those with moderate to severe dependence on SADQ (20 and above) and moderate withdrawal on CIWA-Ar (10-15) were included in the study Thirty patients each were started with lorazepam tablets 8 mg/day and chlordiazepoxide 100 mg/day. For both treatment groups, the dose was tapered and at the end of 8 days, the patients were drug-free. At baseline, the mean CIWA-Ar scores were similar in both the treatment groups: 12.60±1.380 in the chlordiazepoxide group and 12.70±1.466 in the lorazepam group. There was a significant intragroup decrease in the CIWA-Ar scores measured from baseline to the end of 10days in both treatment groups; however, there was no significant difference between the two groups*.
Conclusion: *Lorazepam is as good option as Chlordiazepoxide in reducing alcohol withdrawal symptoms.*
Keywords: *Chlordiazepoxide, Lorazepam, Alcohol detoxification.*

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I. Introduction

Alcohol is a psychoactive substance with dependence producing properties that has been widely used in many cultures for centuries. The harmful use of alcohol is a causal factor in more than 200 diseases & injury conditions [1]. According to World Health Organization Global status report on alcohol and health 2014, in 2010 47.7% males and 28.9% females globally were current drinkers among total population of aged 15 years and older [2]. As per WHO ¼ to ⅓ of male population drink alcohol in India and neighboring south Asian countries and also the use amongst women in increasing [3].

Alcohol Withdrawal Syndrome (AWS) is a potentially life threatening condition that can occur in people who have been drinking heavily for weeks, months or years and then either stop or significantly reduce their alcohol consumption [4]. The symptoms range from minor ones such as insomnia and tremulousness to severe complications such as withdrawal seizures and delirium tremens [5]. Because alcohol withdrawal symptoms can rapidly worsen it is important to seek medical attention even if symptoms are seemingly mild [4]. The effective management of AWS includes a combination of supportive and pharmacological measures.

Currently, benzodiazepines like chlordiazepoxide, diazepam and lorazepam are the preferred drugs in the management of alcohol withdrawal symptoms. While the first two drugs are long-acting, lorazepam is intermediate-acting. Both chlordiazepoxide and diazepam are time-tested choices to treat alcohol withdrawal. However, they are metabolized by the hepatic enzymes, and also form active metabolites that accumulate in the liver. On the contrary, lorazepam is less likely to accumulate in the liver, because it is metabolized by

conjugation, a pathway that is less affected than the hepatic microsomal pathways in liver dysfunction. Additionally, lorazepam has no active metabolites. It is preferred in the management of alcohol withdrawal, especially in those with alcoholic liver disease [6].

Currently, searching the literature we find very few head-to-head trials comparing chlordiazepoxide with lorazepam [6, 7, 8, 9] Therefore, the current study was undertaken to compare the safety and efficacy of chlordiazepoxide and lorazepam in individuals with alcohol withdrawal symptoms.

II. Aims And Objectives

To compare and evaluate the safety and efficacy of lorazepam and chlordiazepoxide in patients with alcohol dependence syndrome with symptoms of alcohol withdrawal.

III. Materials And Methods

Study Design: prospective, randomized, double-blind, interventional study
Study period: Feb 2017- Jan 2018

Study population

Patients above the age of 18 years with alcohol dependence syndrome admitted to in-patient wards, Departments of Psychiatry and Medicine at Government Hospital for Mental Health , and King George Hospital , Visakhapatnam with mild-to-moderate alcohol withdrawal symptoms were included in the study. Informed consent was obtained from all the patients. Ethical clearance was obtained from the Institutional Ethics Committee.

Eligibility criteria

Inclusion criteria

1. Age ≥18 years
2. Meet criteria for alcohol dependence (DSM-IV) and mild-to-moderate alcohol withdrawal.
3. Must be medically stable (not likely to require hospitalization for medical complication within 15 days).
4. Have a clinical withdrawal assessment prior to study.
5. Must be medically acceptable for study treatment. Considerations include no past or present physical disorder that is likely to deteriorate during participation.
6. Not have any other psychiatric condition or psychotropic medication prior to entering the study.

Exclusion criteria

1. Are dependent on any substance other than nicotine
2. Have a history of alcohol withdrawal seizures, epilepsy or delirium tremens
3. Have a history of hepatic encephalopathy, ascites, diabetes, or renal disease
4. Used a drug known to lower the seizure threshold during the past 14 days
5. Already received medication that could influence the clinical picture of alcohol withdrawal or the outcome assessments
6. Have clinically significant psychiatric comorbidity
7. Have contraindications for the use of either of the study medications
8. Already experienced a complication related to alcohol withdrawal at the time of screening
9. Females who are pregnant or nursing

Methodology

This was a prospective, randomized, double-blind, interventional study carried out between November 2011 and October 2012. Sixty patients with alcohol dependence syndrome with mild-to-moderate withdrawal symptoms were allocated to receive either lorazepam or chlordiazepoxide, by means of a computer-generated random sequence using a concealed envelop at a ratio of 1:1. The study drugs were powdered and filled in opaque, empty capsules of the same size and color and the required number of capsules were administered to the patients according to the randomization number mentioned in the envelop, by the pharmacist in our department. All the participants and the outcome assessor (dissertation author) were unaware of the treatment allocation. Thirty patients were treated with lorazepam tablets 8 mg/day (2 mg in the morning, 2 mg in the afternoon, 4 mg in the night). The dose was reduced by 2 mg per day every 2 days, and at the end of 8 days of treatment, the patient was drug free. Another thirty patients were treated 51 chlordiazepoxide 80 mg/day (20 mg in the morning, 20 mg in the afternoon and 40 mg in the night). The dose was reduced by 20 mg per day every 2 days, and at the end of 8 days of treatment, the patient was drug free. This dose titration schedule was fixed. All patients received a multivitamin injection daily, because malnutrition from dietary deficiency and vitamin deficiencies due to malabsorption are common in alcoholism; additionally, malabsorption of water-soluble vitamins is especially severe.

The severity of alcohol dependence was assessed using the Severity of Alcohol Dependence Questionnaire. The CIWA-Ar90 was used for quantification of withdrawal symptoms.
Liver function tests were performed at baseline and at the end of the study.

IV. Results

There were no drop-outs in either arm as the study was of a short duration. The mean age of the sample was 36.90 years. The sample consisted mostly of people with low socio economic status (60.7%) and the rest belonged to upper lower socioeconomic status (39.3%). The average daily alcohol consumption expressed as number of drinks was 11.25 (CDZ vs. LOR = 11.27 vs.11.23). Of the patients 6(10.4%) were unemployed, 11(18.3%) were unskilled workers, 15(25.4%) were semiskilled workers, 9(15%) were skilled workers and 15(25%) were farmers. Among the 60 patients 20 (33.3%) were illiterates, 20(33.3%) people studied up to primary school, 15(25%) patients studied up to middle school and 5(8.4%) patients up to higher school, Rural population were 46(75%) and Urban were 14 (25%). The Mean SADQ score of the sample was 29.28 with a standard deviation of 4.415. In Chlordiazepoxide group mean SADQ score was 29.63 with a standard deviation of 4.657 and in Lorazepam group mean SADQ score was 28.93 with a standard deviation of 4.209. As can be seen in table-7, ANOVA analysis for SADQ scores between groups revealed no statistical significant ($F=0.373$, $p=0.544$). In the study, 6 patients underwent prior detoxification once and 4 patients twice. None of the demographic variables were statistically significant for variation among the two groups.

In the total sample, 86.7% did not suffer from any side effects. Of the complications that were seen, Giddiness was found in 4 patients of Lorazepam group, Lassitude complained by one patient of Lorazepam group. Whereas Day time drowsiness complained by 2 and Headache by 1 Chlordiazepoxide group patients.

V. Discussion

The sample consisted mostly of people with low socio-economic status (60.7%) and the rest belongs to upper lower class (39.3%), this is in keeping with the socio economic pattern of population attending hospital. In a study by Rajmohan *et al.* [9], 70.9% belongs to lower socio economic class and rest belongs to middle class (29.1%). Another study by Rajmohan *et al.* [10], 71.8% were of lower socio economic class and 28.2% were of middle class. In the study, among 60 patients 06 patients underwent prior detoxification. Among them 4 were male and 2 were female patients. Of the total sample 86.7% did not suffer from any side effects. Of the complications that were seen, Giddiness was found in 4 patients of Lorazepam group, Lassitude complained by one patient of Lorazepam group. Whereas Day time drowsiness complained by 2 and Headache by 1 Chlordiazepoxide group patients. In a study by Solomon *et al.* there were no drug related adverse events noted. In Kumar et al., study, one Chlordiazepoxide patient developed delirium and one complained giddiness while in Lorazepam group one patient developed lassitude. In a study by Rajani ramanujam *et al*. [10] there were no adverse events associated with any of the study drugs. The base line for CIWA-Ar in the study in Chlordiazepoxide group was 12.60 ± 1.380 and in Lorazepam group it was 12.65 ± 1.466. In a study by Kumar *et al*. [11], mean baseline CIWA-Ar score in Chlordiazepoxide group was 12.0 ± 5.6 and in Lorazepam group it was 11.7 ± 4.6.While in study by Rajani Ramanujam *et al*. [10], in Chlordiazepoxide group mean base line CIWA-Ar score was 24.77 ± 5.98 and in Lorazepam group it was 24.73 ± 5.10. The mean for day-2 CIWA-Ar score in Chlordiazepoxide group was 4.20 ± 2.191 and in Lorazepam group it was 3.90 ± 1.423. The fall in CIWA-Ar scores is rather gradual than rapid as In a
study by Kumar *et al.* [11], (Chlordiazepoxide 1.5 ± 1.2 , Lorazepam 1.5 ± 1.8). It appears that Lorazepam is as good option as Chlordiazepoxide for alcohol detoxification.

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