

## Chlordiazepoxide Vs Lorazepam- A Study of Comparison of Clinical Outcome and Cost of Alcohol Detoxification

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### Original Research Article

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#### Article History

Received: 11.10.2017

Accepted: 16.10.2017

Published: 30.10.2017



**Abstract:** Alcohol withdrawal is treated by cross tolerant benzodiazepines like Chlordiazepoxide, Diazepam and Lorazepam. The most frequently used Drugs Diazepam and Chlordiazepoxide have a long duration of action and are converted to active metabolites in the liver, while Lorazepam is metabolized by conjugation, which is less effected than the microsomal liver enzyme pathway in liver disease and it is short acting, with no active metabolites. The objective is to compare the clinical outcome and cost in treating uncomplicated alcohol withdrawal state using Chlordiazepoxide and Lorazepam. 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. There was no significant difference observed between the two groups in the liver function tests done at baseline and at the end of study. The cost of treating moderate alcohol withdrawal with Chlordiazepoxide and Lorazepam was Rs 9.00 and Rs 5.00 per person for the duration of treatment respectively. Lorazepam is as good option as Chlordiazepoxide in reducing alcohol withdrawal symptoms.

**Keywords:** Chlordiazepoxide, Lorazepam, Alcohol detoxification, Alcohol de-addiction, Chlordiazepoxide vs lorazepam

### INTRODUCTION

Alcohol is a psychoactive substance with dependence producing properties that has been widely used in many cultures for centuries. In 2012 about 3.3 million deaths, or 5.9% of all global deaths, 139 million DALYs, or 5.1% of the global burden of disease and injury were attributable to alcohol consumption. (WHO -Global status report on alcohol and health [1]. Stoppage or reduction in alcohol consumption by a dependent person results in withdrawal symptoms ranging from milder symptoms like insomnia, shakiness, sweating, anxiety to more severe and life threatening complications like delirium tremens and withdrawal seizures

Medically assisted alcohol withdrawal (alcohol detoxification) aims to relieve the symptoms of withdrawal, prevent delirium and other life-threatening complications. Benzodiazepines are the safest and most effective drugs in this regard and have been used for decades in alcohol detoxification programs [2], Shucked [3], Ntais [4], Petrakis [5]. There are few head to head comparisons between the benzodiazepines to determine their efficacy [6], Kumar *et al.*, [7]; and cost of Alcohol detoxification. This study attempts to conduct a double blind comparison of Chlordiazepoxide and Lorazepam in terms of clinical outcome and cost of Alcohol detoxification.

## MATERIALS AND METHODS

### Study design

Randomized double blind comparative, prospective and interventional study

### Place of study

De-addiction ward, Institute of Mental Health, Erragadda, Hyderabad.

### Sample size

30 Patients each for Chlordiazepoxide and Lorazepam. Institutional ethical committee approval.

### INCLUSION CRITERIA

- Subjects who have given written informed consent
- Subjects meeting the criteria for alcohol dependence as per (WHO) ICD-10 Clinical descriptions and Diagnostic guidelines [12]
- Patients admitted to De-addiction ward of Institute of Mental Health
- Dependence severity – Moderate to severe on SADQ(13)(20 and above)
- CIWA-Ar(30) between 10-15
- Age between 18 years and 65 years
- Patients who are clinically stable

### EXCLUSION CRITERIA

- Patients who were abstinent and treated with counter tolerant drugs just prior to admission
- Patients being treated on an outpatient basis
- Patients with dependence on other substances except nicotine and caffeine
- Patients with clinically significant psychiatric comorbidity (Eg: Major depression, Psychosis)
- Subjects having contraindications and sensitivity to either of the study medications
- Patients already experienced a complication related to alcohol withdrawal of this episode
- Pregnant and Lactating women

### Materials

- Semi Structured Intake proforma for patient's demographic data specifically prepared by investigator.
- Written informed consent (English, Telugu, Hindi, Urdu) or consent taken after having explained to the patient in their own language.
- Kuppaswamy Classification for Education, Employment and Socio-economic Status[11].
- ICD\_10 Clinical Descriptions and diagnostic guidelines for diagnosis of alcohol dependence (WHO) [12].

- Liver function tests.
- Severity of Alcohol dependence Questionnaire - Created by Stockwell *et al* [13].

Clinical Institute withdrawal assessment scale – Alcohol revised was developed by Sullivan *et al*, in 1989[14].

### PROCEDURE

This is a prospective, randomised, 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.

The severity of alcohol dependence assessed using the Severity of Alcohol Dependence Questionnaire (SADQ). Severity of Alcohol withdrawal is assessed using Clinical Institute withdrawal assessment-Alcohol revised Scale. Those with moderate to severe dependence on SADQ (20 and above) and moderate withdrawal on CIWA-Ar (10-15) were included in the study. Written informed consent was taken from the patient after having explained them in their own language.

Depending upon the random number, they were assigned to either of the treatment groups by my Guide and fixed treatment schedule was followed till the end of the study.

The study drugs were removed from strips and filled in a opaque, empty bottles of the same size and colour by our Institution Pharmacist, those bottles were given coding (Eg: A or B) by my Guide. Required number of tablets were administered to the patients according to the treatment group they were in, by the staff nurse in our De-addiction ward. Hence all the participants and the outcome assessor (Investigator) were unaware of treatment allocation.

Thirty patients were treated with Lorazepam tablets 8mg/day (2mg in the morning, 2mg in the afternoon, 4mg in the night).The dose was reduced by 2mg per day at every 2 days, and at the end of 8 days of treatment, the patient was drug free. Another thirty patients were treated with Chlordiazepoxide 100mg/day (25mg in the morning, 25 mg in the afternoon, 50 mg in the night). The dose was reduced by 25mg per day at every two days, and at the end of eight days of treatment, the patient was drug free. The dose titration schedule was fixed. For convenience sake equivalent doses of Lorazepam to Chlordiazepoxide was taken as 1:12.5mg. Most other recent studies Kumar *et al.* [7], Rajani Ramanujam *et al.* [10] took equivalent doses of study drugs as 1:10 ratio. All patients received a B-

complex injection daily for 5 days, along with oral thiamine supplementation till the end of the study.

**Safety measures:** All unwanted effects reported by the patient spontaneously and on enquiry by the investigator during the 10 days study period was recorded in the case sheet and analyzed. **Efficacy:** Measured by CIWA-Ar scores, assessed daily by the investigator till the end of the study i.e. 10 days. Liver function tests were performed at baseline, at the end of the study.

**Cost of treatment:** Cost of treatment with Lorazepam and Chlordiazepoxide was calculated by considering the price of each drug as purchased by Telangana Medical and Health Infrastructure Corporation.

After statistical analysis drug coding was revealed by Guide.

**Statistical Analyses**

The data were analyzed and results were recorded as means and proportions. Statistical tests like t-test, Analysis of variance (ANOVA), chi-square test were done to analyze the different variables. The analysis of statistical data was done using SPSS v 22.0 program for Windows (Statistical Package for the Social Services).

**RESULTS**

The study consisted of 45 Males and 15 Females constituting 75% and 25% respectively. The mean weight of the sample was 59.48kgs(CDZ vs. LOR = 59.37kgs vs.59.60kgs). There were no drop-outs in either arm as the study was of a short duration. The mean age of the sample was 38.90 years. The sample consisted mostly of people with low socio economic status (61.7%) and the rest belonged to upper lower socioeconomic status (38.3%).

With respect to marital status, 78.33% were married, 11.67% were unmarried; and 10% were divorced or separated. The average years of dependent use was found to be 11.52 years (CDZ vs. LOR = 12.33y vs.10.70y). The average daily alcohol consumption expressed as number of drinks was 11.25 (CDZ vs. LOR = 11.27 vs.11.23). Of the patients 8(13.4%) were unemployed, 11(18.3%) were unskilled workers, 17(28.4%) 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 45(75%) and Urban were 15 (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, 9 patients underwent prior detoxification once and 4 patients twice. None of the demographic variables were statistically significant for variation among the two groups

**Safety and tolerability**

In the total sample, 86.7% did not suffer from any side effects. Of the complications that were seen, Giddiness was found in 3 patients of Lorazepam group, Lassitude complained by one patient of Lorazepam group. Whereas Day time drowsiness complained by 3 and Headache by 1 Chlordiazepoxide group patients.

**Table-1: liver function tests at baseline and end of the study**

Liver function tests	Chlordiazepoxide		Lorazepam	
	Baseline	End of study	baseline	End of study
Total bilirubin	0.9333	0.9233	0.9167	0.9033
Direct bilirubin	0.2350	0.2313	0.2470	0.2463
Total proteins	5.44	5.46	5.53	5.536
Serum albumin	3.66	3.68	3.78	3.793
Serum globulin	1.7833	1.78	1.7467	1.7433
SGPT	36.8	36.73	35.86	35.80
SGOT	34.2	34.03	34.6	34.50
ALP	55.2667	55.20	57.3	57.

**ANOVA analysis for liver function tests between the groups at baseline and end of the study were not statistically significant**

Paired t-test was done for Total bilirubin, Direct bilirubin, Total protein, Serum albumin, serum globulin, SGPT, SGOT, Alkaline phosphatase. The paired t-test was statistically significant for total

bilirubin. ( $t=2.791$ ,  $p=0.007$ ), total protein ( $t=-2.187$ ,  $p=0.033$ ), serum albumin ( $t=-2.206$ ,  $p=0.031$ ), SGPT ( $t=2.053$ ,  $p=0.045$ ), SGOT ( $t=3.013$ ,  $p=0.04$ ).

**Table-2: CIWA-Ar scores at baseline through day10**

CIWA-Ar score	Chlordiazepoxide(A) (n=30) MEAN(SD)	Lorazepam(B) (n=30) MEAN(SD)
DAY 1	12.60(1.380)	12.70(1.466)
DAY 2	4.40(2.191)	3.90(1.423)
DAY 3	2.37(1.752)	2.13(1.167)
DAY 4	1.33(1.561)	1.20(0.847)
DAY 5	0.67(0.959)	0.53(0.629)
DAY 6	0.47(0.776)	0.40(0.563)
DAY 7	0.30(0.535)	0.30(0.466)
DAY 8	0.23(0.430)	0.20(0.407)
DAY 9	0.20(0.407)	0.17(0.379)
DAY 10	0.20(0.407)	0.13(0.346)

**Ciwa-Ar- Clinical Institute withdrawal assessment-Alcohol revised Scale.  
The groups did not differ significantly on any of the days of assessment.**

### COST

The cost of Alcohol detoxification (moderately severe withdrawal) using a fixed dose regimen for a period of 8 days in a tapering course accounted for 20 tablets each group. Each Chlordiazepoxide tablet (25mg) provided to the institution at 45 np/tab. Lorazepam tablet (2mg) was provided at the cost of 25 np/tab. The cost of detoxification with Chlordiazepoxide was 9 rupees/patient whereas treating with Lorazepam was 5 rupees/patient.

### DISCUSSION

The randomised double blind study of comparison of Chlordiazepoxide and Lorazepam in moderately severe alcohol was done with an aim to evaluate safety, efficacy and cost of treating alcohol withdrawal. The sample consisted of 60 patients. They were randomised to either Chlordiazepoxide (A) or Lorazepam group (B), based on the random number they received. There were no drop outs.

The sample consisted of 75% male patients and 25% female patients. In Chlordiazepoxide group 73.4% were males and 26.6% were females. In Lorazepam group 76.6% were males and 23.4% were females. It was 50 patients and the whole sample were males (100%) in a study by Solmon [6], It was 100 patients and all are male in a study by Kumar *et al.* [7]. The sample consisted of male to female ratio of 3:1, while it was 9:1 in a study by Rajani Ramanujam *et al.* [10]. With respect to marital status 78.3% were married, 11.7% were unmarried and 10% were separated. In Rajmohan *et al.* [9] study 85.4% were married, 8.7 were unmarried and 5.8% were separated.

The sample consisted mostly of people with low socio-economic status (61.7%) and the rest belongs to upper lower class (38.3%), this is in keeping with the

socio economic pattern of population attending hospital. In a study by Rajmohan *et al.* [8], 70.9% belongs to lower socio economic class and rest belongs to middle class (29.1%). Another study by Rajmohan *et al.* [9], 71.8% were of lower socio economic class and 28.2% were of middle class.

The mean amount of alcohol use in the study was 112.5gms with the standard deviation of 29.67. It was 116.9gms with a standard deviation of 28.91 in males and 99.3gms with a standard deviation of 28.9 in females. In Chlordiazepoxide group it was 112.7gms with a standard deviation of 29.7 and in Lorazepam group it was 112.3gms with a standard deviation of 30.1. The amount of alcohol use was high In a study by Kumar *et al.* [7], mean amount of alcohol use was 248.6gms with a standard deviation of 55.3 in Chlordiazepoxide group and 250.6gms with a standard deviation of 55.2 in Lorazepam group, and In studies done by Rajmohan *et al.* [8, 29], mean amount of alcohol use was 237.9gms. In Chlordiazepoxide group it was 195.3gms and in Lorazepam group 267.4gms.

In the study, the most common drink in males was Whisky while in females it was Toddy. Most common type of drink in both the study groups was Whisky. In a study by Rajani Ramanujam *et al.* [10], most common drink in Chlordiazepoxide group was Whisky while in Lorazepam group it was Brandy.

In the study, mean years of alcohol use were 11.52 with a standard deviation of 3.838. In males it was 11.16 years with a standard deviation of 4.05 while in females, it was 12.60 years with a standard deviation of 2.94. In Chlordiazepoxide group it was 12.33years with a standard deviation of 3.772 while in lorazepam group it was 10.70 years with a standard deviation of 3.789. In a study by Kumar *et al.* [7], the mean years of

alcohol use was 12.5 years with a standard deviation of 6.2 in Chlordiazepoxide group and 10.0 years with a standard deviation of 4.9 in Lorazepam group. In studies done by Rajmohan *et al.* [8] the mean years of alcohol use were 16.4. In Chlordiazepoxide group it was 13.3 years and in Lorazepam group it was 18.4 years.

In the study, among 60 patients 13 patients underwent prior detoxification. Among them 10 were male and 3 were female patients.

Prior detoxification	once	twice
Male	7	3
Female	2	1
Chlordiazepoxide	5	2
Lorazepam	4	2

In a study by Kumar *et al.* [7], among 100 patients 47 patients underwent prior detoxification. In studies done by Rajmohan *et al.* [8, 9], 64.1% undergone prior detoxification.

Of the total sample 86.7% did not suffer from any side effects. Of the complications that were seen, Giddiness was found in 3 patients of Lorazepam group, Lassitude complained by one patient of Lorazepam group. Whereas Day time drowsiness complained by 3 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.

All the laboratory parameters of the liver function tests, showed improvement with medication, though no variability was seen between the two groups. This finding also confirmed in a study by Kumar *et al.* [7], and also by Rajani Ramanujam *et al.* [10]. After the treatment schedule was completed, in-patient admission was continued for further two days. During this two days no withdrawal symptoms or complications were noted in both the groups. Similar findings were seen in Kumar *et al.*[7] and in a study by Rajani Ramanujam *et al.*[10].

The base line for CIWA-Ar in the study in Chlordiazepoxide group was  $12.60 \pm 1.380$  and in Lorazepam group it was  $12.65 \pm 1.466$ . In a study by Kumar *et al.* [7], mean baseline CIWA-Ar score in Chlordiazepoxide group was  $12.0 \pm 5.6$  and in Lorazepam group it was  $11.7 \pm 4.6$ . While in study by Rajani Ramanujam *et al.* [10], in Chlordiazepoxide group mean base line CIWA-Ar score was  $24.77 \pm 5.98$  and in Lorazepam group it was  $24.73 \pm 5.10$ .

The mean for day-2 CIWA-Ar score in Chlordiazepoxide group was  $4.20 \pm 2.191$  and in Lorazepam group it was  $3.90 \pm 1.423$ . The fall in CIWA-Ar scores is rather gradual than rapid as In a study by Kumar *et al.* [7], (Chlordiazepoxide  $1.5 \pm 1.2$ , Lorazepam  $1.5 \pm 1.8$ ).

Liver function tests were done for all patients at baseline as well as at the end of the study period to assess the safety of the two study drugs. The laboratory investigations at the end of the study were significant for changes in paired t-test were, total bilirubin ( $t= 2.791$ ,  $p= 0.007$ ), total protein ( $t= -2.187$ ,  $p= 0.033$ ), serum albumin ( $t=-2.206$ ,  $p= 0.031$ ), SGPT ( $t= 2.053$ ,  $p= 0.045$ ) and SGOT ( $t= 3.013$ ,  $p= 0.004$ ). None of the laboratory investigations were significant for variance between the two groups.

The cost of treating moderate alcohol withdrawal with Chlordiazepoxide was Rs 9.00 per person for the duration of treatment. While it was Rs 5.00 per person, for duration of treatment in Lorazepam group. As there was no difference in treatment efficacy of both Chlordiazepoxide and Lorazepam and lower cost of treatment with Lorazepam. It appears that Lorazepam is as good option as Chlordiazepoxide for alcohol detoxification.

#### LIMITATIONS

The limitations of the study were

- Small sample size.
- No placebo control group was included in the study for ethical reasons
- Only moderate withdrawal cases were considered which is insufficient to accurately comment on drug cost and efficacy.
- As the duration of stay is short, the improvement in liver functions cannot be attributed to drug.
- Cost cannot be accurately assessed, as only moderate withdrawal cases were considered and fixed dose regimen was followed.

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