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Original Article

A Study on Comparison of Two Benzodiazepines in Treatment of Alcohol Dependence Syndrome in Nepal

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Abstract

Background

Benzodiazepines are regularly prescribed to treat patients in alcoholic withdrawal. After analyzing pharmacology of benzodiazepines, diazepam is faster metabolized and concentrated in the liver, as an active metabolite whereas lorazepam is metabolized in liver by conjugation and excreted in urine. lorazepam being a drug of choice used in patients with deranged liver functions is needed to be compared with that of diazepam. The objective of the study is the comparison of two benzodiazepines in treatment of alcohol dependence syndrome in Nepal.

Materials and Methods

This was a prospective, open label study carried out in department of Psychiatry, Nobel Medical College and Teaching Hospital, Biratnagar. 50 patients (25 in each) aged between 25 to 65 years diagnosed as alcohol dependent admitted and grouped in either diazepam or lorazepam alternatively. The doses prescribed to the diazepam group and lorazepam group are 30 mg/day and 8 mg/day respectively in divided doses. For both the treatment groups, the dose was tapered every alternate day for 10 days. The Clinical Institute Withdrawal Assessment Alcohol Scale Revised (CIWA-Ar) scale was used for withdrawal symptoms scoring on the baseline and day 10. Lab Investigations were performed but were not a part of the study.

Results

Out of the Fifty patients included in the study, at day 0, the mean CIWA-Ar scores were similar in both the treatment groups: 24.38±5.03 in the diazepam group and 24.79±6.42 in the lorazepam group. There was a significant intra group decrease in the CIWA-Ar scores measured from Day 0 to the end of 10 days ($p<0.0001$) in both treatment groups; there was no significant difference between the two groups.

Conclusion

Diazepam and lorazepam are equally effective in alcohol withdrawal detoxification.

Keywords: *Benzodiazepines, Lorazepam, Diazepam*

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Introduction

Alcohol is an important risk factor for morbidity and mortality, worldwide. It is estimated that globally, around two billion people consume alcoholic beverages, of whom nearly 76.3 million are likely to suffer from at least one alcohol use disorder [1]. Alcohol is responsible for almost 3.2% of all deaths and loss of 4% of total Disability adjusted life years (DALYs) [2]. Edwards described the "alcohol dependence syndrome" that included cognitive, behavioral, and physiological changes associated with alcohol use [3]. Individuals with alcohol dependence syndrome can develop alcohol withdrawal symptoms, which include physical and psychological symptoms that they experience on sudden reduction of quantity of alcohol consumed.

For the treatment of alcohol dependence syndrome, it is required to discontinue the use of alcohol. This leads to the development of withdrawal syndrome [4]. This syndrome is characterized by some or all of the symptoms like delirium, seizures, tremors, lack of sleep, tachycardia, hypertension, agitation, and in certain serious cases by death [4]. Benzodiazepines have the property of cross-tolerance with alcohol which makes them the first line of treatment for such cases. Some benzodiazepines used commonly are chlordiazepoxide, diazepam, and lorazepam [3]. Diazepam and Chlordiazepoxide are metabolism is by hepatic oxidation and later glucuronidation. Whereas Lorazepam metabolism is by hepatic glucuronidation. Alcoholic liver disease; patients have decrease of benzodiazepineoxidation.this leads to sedation and respiratory depression. The metabolism of lorazepam does not get effected by liver disease [3].

The current study is aimed at studying the efficacy by head on comparison of two benzodiazepines namely diazepam and lorazepam in the treatment of the patients admitted for detoxification from mental and behavioral disorder due to use of alcohol currently dependent [4] So that if validated, lorazepam can also be used in place of diazepam for detoxification from alcohol. This will be helpful for patients with alcoholic liver disease and old age patients.

Materials and Methods

This was an open label interventional study. The study was conducted at Nobel Medical College and Teaching Hospital, Biratnagar from 1st February 2018 to 2nd December 2018.The first consecutive fifty patients attending the Psychiatry outpatient's department, who were diagnosed as alcohol dependence syndrome by the on-duty Consultant Psychiatrist were included in the study. Following which they were screened by inclusion and exclusion criteria and later enrolled alternatively in Group1 (diazepam group) or Group 2 (lorazepam group). They were then asked to proceed to residential ward of department of psychiatry, Nobel Medical College and Teaching Hospital, Biratnagar, Nepal. The inclusion criteria included patients of 25-65 years, diagnosed with alcohol dependence syndrome, medically stable, having no comorbidity and not taking any medication. The exclusion criteria included patients with a history of psychoactive substance and alcohol use, history of loss of consciousness, known cases of hypersensitivity or contraindications to the medications under study, and pregnant or nursing females. The study was conducted after the ethical clearance from the institutional review committee, wide ref no 612/2018. The patients were enrolled for the study after detailed explanation of the study and an informed consent was taken from the patient and the informants before the commencement of the study.

Group 1 was treated with diazepam 30 mg/day in divided doses. The dose was reduced by 5 mg every alternate day. Group 2 was treated with lorazepam tablets 8 mg/day in divided doses. The dose was reduced by 1 mg every alternate day. Apart from this all patients received thiamine 100 mg orally and injection of multivitamins daily. It has been noted that the people consuming alcohol in dependence levels usually have deficiency of thiamine and other vitamins. So it was decided to give all patients one ampoule of optineuron (thiamine 100mg, Pyridoxine 100mg, cyanocobalamin 1000mcg, vitamin B2 5mg, nicotinamide 100mg, d-panthenol 50mg)intramuscularly for 5 days and tablets of thiamine 300 mg daily orally, in divided doses. The Clinical Institute Withdrawal Assessment Alcohol Scale Revised (CIWA-Ar)was used for recording improvement of symptoms of withdrawal [5]. Liver function tests and ultra-sonography of abdomen were performed at admission but were not part of study.

The data so collected was tabulated and analyzed using descriptive analytical tools. Statistical analysis was done using the SPSS statistics for windows version 16 (SPSS Inc., Chicago, Ill., U.S.A.). The data collected was compared between the groups using student t-test.

Results

A total of 50 patients were divided into two groups equally to receive either diazepam or lorazepam alternatively (25 each). Mean age group was

41.68±8.07 in Group 1 and 40.20±5.83 in Group 2. A ll our patients were male in both groups (Table 1).

Table 1: Table depicting Socio Demographic Profile in Group 1(diazepam) & Group 2 (lorazepam)

		Group 1 N=25	Group 2 N=25
Sex (% age)	male	100	100
	female	0	0
Age in years	mean ± sd	41.68±8.07	40.20±5.83
Marital status (% age)	married/divorced/ widower	88	96
	unmarried	12	4
Residence (% age)	rural	76	84
	urban	24	16
occupation (% age)	employed	28	40
	unemployed/irregularly employed	72	60

The average dose consumed was 860 ±7.44 ml in diazepam, 892 ± 3.22 ml in the lorazepam group. Average last intake before admission was 95.63 ± 4.21ml, 94.89 ± 3.11ml in both groups respectively before admission. Average use was 13.34 ± 4.69, 15.58 ± 5.32 years respectively.

Table 2: Table depicting the intake of alcohol in ml in Group 1(Diazepam) & Group 2 (Lorazepam)

	Group1 (25)	Group 2 (25)
Avg (ml)	860 ±7.44	892 ± 3.22
Max (ml)	963 ±3.45	1082 ±5.56
Min (ml)	238 ±7.43	320 ±6.67
Last Dose (ml)	95.36±4.21	94.89 ±3.11
Avg Years ± SD	13.3 ±4.69	15.58 ±5.32

The CIWA-Ar scores at baseline was 24.38 ± 5.03 in Group 1 and 24.79 ± 6.42 in group 2. At the end of 10 days the scores were 2.02 ± 1.32 and 1.92 ± 2.12; (Table-2). There was significant intragroup difference in the CIWA-Ar scores measured at baseline and at day 10 (≤0.0001) in both groups. However, there was no significant difference noted of the CIWA-Ar scores in between the diazepam and lorazepam groups (≤0.318) (Table-3).

Table 3: Table showing the change in the CIWA-Ar scores from baseline to the end of study.

Day of assessment	Diazepam Group			Lorazepam Group		
	CIWA-Arscore	difference of CIWA-Arscore	p-value	CIWA-Arscore	difference of CIWA-Arscore	p-value
baseline	24.38±5.03	-	-	24.79±6.42	-	-
day 10	2.02±1.32	22.36±4.51	<0.0001	1.92±2.12	22.87±4:21	<0.0001

Discussion

This study was conducted, comparing diazepam and lorazepam in the patients having withdrawal of alcohol to check the efficacy of this therapy.

A study of two hundreds and seventy six subjects was conducted with the CIWA-Ar. Scale and were found to improve the quality of patient care, safety of patient during therapy and effectiveness of therapy for alcohol withdrawal in an in-hospital study [6]. CIWA-Ar scale was used in the current study to assess the improvement in the withdrawal symptoms as the study progressed frombaseline, the mean CIWA-Ar scores were similar in both the treatment groups: 24.38 ±5.83 in Group1 and 24.79 ±6.42 in Group 2. There was a significant intragroup decrease in the CIWA-Ar scores measured from beginning to 10 the day (p<0.0001) in both treatment groups; however, there was no significant noticeable difference between the two groups (Table 2). Alcohol dependence syndrome is gradual and involves multiple sub processes. The person's drinking habits were a weight and balance between the positive reinforcement of alcohol on one hand and on the other hand the negative effects on the other. These factors and the innate qualities, environment play a role in strengthening the behavior of initiation and continuation of drinking [7]. Many people drink large volumes of alcohol but they do not meet the criteria of dependence. But such behavior for a very long time can lead to dependence. Lots of neuroadaptive changes occur in the stress and reward center of the brain. The dependence was a system for maintaining stability through change of state of the brain. It tries to restore normalcy of functions during the presence of continuous alcohol. Brain is not able to restore normal levels of functioning. There was abnormal regulation of the reward centerin the brain and stress center in the brain. This happens in the dependent individuals [8].

When a person dependent on alcohol all of a sudden either stops or decreases the quantity of alcohol intake, the person starts to suffer from alcoholic withdrawal symptoms. The withdrawal syndrome is composed of physical symptoms, psychological symptoms and emotional changes that lead to distress [8]. The preferred drugs of choice are benzodiazepines, which are cross tolerant with alcohol and provide anxiolysis by stimulating GABA receptors. They were affordable, safe, effective and preferred treatment. The basic principle was to start benzodiazepines to prevent the distressing symptoms from occurring, and then gradually decreasing the doses The other drugs that can be used were anticonvulsants, baclofen, barbiturates [10]. Diazepam

was a drug of choice for the withdrawal syndrome as its half-life was more thus preventing serious withdrawal symptoms. Shorter acting benzodiazepine lorazepam was metabolized by conjugation in the liver and no active metabolites were concentrated in the liver. This makes it ideal for use in patients who have a deranged function of liver [3]. Lorazepam, (3-hydroxy, 1, 4-benzodiazepine) was immediately absorbed, the peak levels reached in the human blood in nearly 2 hours after oral intake, in proportion to the dosage taken. Blood levels gradually decreased, the half-life was nearly 12 hrs. Steady state blood levels directly proportional to the daily dose occur within 2--3 days in case if divided or multiple doses were taken and were maintained. The inactive metabolite was lorazepam glucuronide. It was made by a process of conjugation in the liver, with glucuronic acid. 75% of the drug was excretion from the kidney. The glucuronide conjugate in the urine was its excreted form. It takes one week for the complete excretion process to finish after the last intake [9]. Diazepam had a large interindividual variation (up to 30-fold) in dose/blood level ratios in short-term treatments. The half-life is prolonged in the newborn, elderly and liver disease. Its half-life was 20 – 50 hours and transformed into many active metabolites. In long term treatment there was accumulation of N-demethylated metabolite. Research has found that a single dose of diazepam at night should be adequate for hypnotic and anxiolytic effects. There was no direct relationship between the plasma levels of diazepam and its effects. Thus, here was no need to monitor the blood concentrations [10].

Kumar et al in a study of 2009 found that lorazepam was as effective as chlordiazepoxide in treating uncomplicated withdrawal cases by comparing the CIWA-Ar scores. he concluded that as previously practiced higher doses of lorazepam were not required and it was a better choice of drug in cases where liver function could not be done or was deranged [14]. In another study Kumar et al., found CIWA-Ar scores in the two groups were similar (Diazepam group: Baseline score of 12.0 ±5.6 and day 12 score 0.3 ±0.9; lorazepam group: The initial score was of 11.7 ±4.6 and last day (12) score was 0.3Â±1.6) [11]. Miller and Mc Curdy, in their study in a a five-day double-blind trial in alcoholic patients. The daily doses of lorazepam and diazepam were tapered down gradually, respectively, Drug efficacy was measured by Total Severity Assessment Scores (TSAS), There was no difference in the two groups results. Their physical conditions with lorazepam (57%) and diazepam (59%) improved. No clinically significant differences in vital signs or laboratory values were noted. Their results indicated lorazepam and diazepam as equally effective for management of alcohol withdrawal. lorazepam may have therapeutic advantages over diazepam in their pharmacokinetics [12].

Solomon et.al, in their results found that lorazepam was as effective as chlordiazepoxide in improving the acute alcohol withdrawal. It has a predictable metabolic pathway and plasma accumulation during multiple-dose therapy, lorazepam may be the drug of choice [13]. Bird and Makela in a review of current available literature on drugs of choice for alcohol withdrawal treatment, that lorazepam is the drug of choice due to its pharmacokinetics. It is considered superior in older adults and liver disease cases. But they caution that a drug with a longer half-life like diazepam will give smoother withdrawal [14]. The Rajmohan and Mohandas in a study of 2013 in 108 subjects who were kept in IPD. The admitted patients were divided into two groups of chlordiazepoxide and lorazepam randomly. Results indicated that there was a difference in the improvement which was assessed by CIWA-AR scale. The duration of withdrawal was less in the lorazepam group i.e 5.6 days as compared to 6.7 days of the chlordiazepoxide group. The p value was 0.001. whereas the improvement was quantified in 48 hours at p value of 0.000 where in lorazepam group had 70.4% improvement and 54.8% was see in Chlordiazepoxide group. They concluded that lorazepam was more effective and it shortened the time and severity of withdrawal [15].

The current study has some shortcomings like it is an open label study and the sample size is small. There is no placebo control group. It will be better if studies are carried out on a bigger sample size and a double-blind study is conducted on this topic. It is recommended to use lorazepam in cases of deranged liver function common in alcoholic liver disease, due to its metabolism and shorter half-life.

Conclusion

This current study had madea conclusion that lorazepam was not inferior to diazepam in managing the patients in withdrawal of alcohol. So, it can be used interchangeably for regular detoxification regimens.

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Conflict of interest: None

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