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Original Article

A randomized, open-label, standard controlled, parallel group study of efficacy and safety of baclofen, and chlordiazepoxide in uncomplicated alcohol withdrawal syndrome

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ABSTRACT

Background: Alcohol withdrawal syndrome (AWS) is a distressing condition, generally controlled by benzodiazepines (BZD's). Baclofen, a gamma-aminobutyric acid-B ($GABA_B$) agonist, has also shown promising results in controlling AWS. As there are few studies comparing the efficacy and tolerability of chlordiazepoxide with baclofen, the present study was taken up. The objective of this study was to compare efficacy and tolerability of baclofen with chlordiazepoxide in uncomplicated AWS.

Methods: Sixty subjects with uncomplicated AWS were randomized into two groups of 30 each, to receive baclofen (30 mg) or chlordiazepoxide (75 mg) in decremented fixed dose regime for 9 days. Clinical efficacy was assessed by Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale (CIWA-Ar) and tolerability by the nature and severity of adverse events. Lorazepam was used as rescue medication. Secondary efficacy parameters were Clinical Global Impression scores, symptom-free days, and subject satisfaction as assessed by visual analog scale. This study was registered with Clinical Trial Registry-India (CTRI/2013/04/003588), also subsequently registered with WHO's ICTRP clinical trial portal.

Results: Both baclofen and chlordiazepoxide showed a consistent reduction in the total CIWA-Ar scores. However, chlordiazepoxide showed a faster and a more effective control of anxiety and agitation requiring lesser lorazepam supplementation, and also showed a better subject satisfaction compared to baclofen. Both the drugs showed good tolerability with mild self-limiting adverse events.

Conclusion: The present study demonstrates that baclofen is not as good as chlordiazepoxide in the treatment of uncomplicated AWS. However, baclofen might be considered as an alternative.

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At a glance commentary

Scientific background on the subject

The pathophysiology of alcohol withdrawal syndrome (AWS) has been largely implicated toward gamma-aminobutyric acid-B ($GABA_B$) disturbance among other neurotransmitters, which is also presently targeted in the pharmacological intervention of AWS management. Chlordiazepoxide and other benzodiazepines (BZDs) which are allosteric agonists of $GABA_A$ are equally efficacious in controlling the AWS, also provides smoother withdrawal; however has the risk of over-sedation and abuse liability. Baclofen a $GABA_B$ receptor agonist has demonstrated the ability to rapidly control the manifestations of AWS without producing significant side effects such as over-sedation, euphoria, abuse liability, systemic toxicity, and are safe in hepatic dysfunction.

What this study adds to the field

The baclofen in a dose of 30 mg/day is inferior to chlordiazepoxide in controlling the AWS, However baclofen may be considered as an alternative option when BZD's cannot be used, which necessitates further studies.

Alcohol dependence is a major and a multifaceted problem throughout the world, the incidence and prevalence of which varies from country to country, and alcohol consumption is the third largest risk factor for disease and disability in the world, especially with a greater risk in middle-income countries. It accounts for about 4% of all deaths worldwide [1]. In developing countries like India, which has seen a tremendous rise in alcohol consumption among younger generation which is aided by swift sprouting of nightclubs, lately the people are quickly detaching from the inhibitions about alcohol as a lifestyle choice.

It is estimated that 10–15% of the alcohol users in India, develop dependence and become chronic alcoholics who are accounted as one million [2]. The ideal objective in the management of alcohol dependence is to achieve complete abstinence which may not always be practicable, can be accomplished by various behavioral and pharmacological approaches.

Treatment of alcoholism starts only when the alcoholic is motivated; it includes detoxification, rehabilitation, and maintenance of abstinence. Abrupt discontinuation of alcohol in alcohol dependents may result in withdrawal symptoms referred to as alcohol withdrawal syndrome (AWS), a distressing and life-threatening condition, where it is estimated that about 8% of hospitalizations are due to the alcohol withdrawal manifestations. The manifestations of AWS includes mild to moderate symptoms characterized by anxiety, depression, tremors, restlessness, insomnia, sweating, vivid dreams, diarrhea, tachycardia, and headache, which are mostly self-limiting and resolve spontaneously within a day or two and medical intervention is necessitated only if symptoms persist. Severe withdrawal symptoms are characterized by seizures, hallucinations (auditory, visual, and tactile), agitation, tremulousness, and delirium tremens, where prompt pharmacological interventions are necessary to control the symptoms and prevent complications. The long-term consumption of alcohol causes increase in brain gamma-aminobutyric acid (GABA) levels and decrease in N-methyl-D-aspartate levels, which on abrupt withdrawal of alcohol, unmasks the adapted defense responses to persistent chronic alcoholism, resulting in nervous system hyperactivity, producing AWS, and hence treatment is aimed at enhancing the GABA activity by GABA receptor agonists or sensitizers [3].

The withdrawal manifestations are well controlled by benzodiazepines (BZDs) like chlordiazepoxide, and all BZDs are equally efficacious in controlling the signs and symptoms of alcohol withdrawal and aids in smoother withdrawal of alcohol, however with the risk of over-sedation and abuse liability, hence it must be used with care [4].

Baclofen a $GABA_B$ receptor agonist has demonstrated the ability to rapidly control the manifestations of AWS without producing significant side effects such as over-sedation, euphoria, abuse liability, systemic toxicity, and are safe in hepatic dysfunction. Baclofen is considered as an off-label agent in the management of AWS and as there are few studies with inconsistent data and presently there is no data regarding the usefulness of baclofen in Indian population for AWS. Moreover, there are no studies on the comparative efficacy and tolerability with that of BZDs, the present study was taken up [5,6].

Methods

Study subjects

Inclusion criteria

1. Subjects of either gender aged between 18 and 65 years
2. Subjects who fulfill Diagnostic and Statistical Manual of Mental Disorders IV Revised Criteria for AWS and or alcohol dependence
3. Last alcohol intake within 24–48 h preceding the initiation of therapy
4. Willingness to give written informed consent.

Exclusion criteria

1. Subjects with complicated AWS comprising any one or all of the following delirium tremens, withdrawal seizures, and cognitive impairment (Wernicke–Korsakoff syndrome)
2. Subjects with known psychiatric disorders
3. Subjects with multi-drug abuse (except nicotine)
4. Subjects with advanced hepatic, renal, and cardiovascular diseases
5. Subjects with known allergy to any of the study medications
6. Subjects with recent use of drugs which lower the seizure threshold
7. Subjects with conditions which can mask or affect the clinical parameters of AWS such as use of β-blockers (propranolol), thyrotoxicosis, meningitis, and hemorrhage/head injury.

Study design

This study was a randomized, open-label, standard controlled, parallel group study of baclofen, and chlordiazepoxide in AWS. This study was registered with Clinical Trial Registry, India (CTRI/2013/04/003588), also subsequently in WHO's ICTRP clinical trial registry portal.

Methodology

After obtaining approval and clearance from the Institutional Ethics Committee, 60 subjects who met the inclusion and exclusion criteria were included in the study. Anonymity, confidentiality, and professional secrecy were maintained for all the study subjects. This study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the revised declaration of Helsinki. The study was conducted in a Tertiary Care Hospital, Bengaluru between February and December 2012.

The subjects were assigned either to the baclofen ($n = 30$) or to the chlordiazepoxide group ($n = 30$) based on the 1:1 randomization table. Detailed history of alcoholism was obtained, subjects were clinically evaluated and baseline scores of Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale, revised were assessed. The flow diagram depicting the progress of the study is provided in Fig. 1.

A 9-day decremental fixed dose regimen was designed for the study using equivalent doses of baclofen 10 mg and chlordiazepoxide 25 mg, which were calculated from the previous studies [5,7]. After nine day study duration, the study subjects were observed for a period of three days before the discharge.

Lorazepam (injection lorazepam 2 mg [IM]) was supplemented if the withdrawal symptoms did not improve with any of the study medication or if the subjects had any one of the following: Anxiety, tremors, irritability, and insomnia to a maximum dose of 10 mg/day.

All subjects received vitamin injection (IM) containing thiamine hydrochloride 100 mg, riboflavin sodium phosphate 5 mg, pyridoxine hydrochloride 100 mg, cyanocobalamin 1 mg, nicotinamide 100 mg, and D-panthenol 50 mg. Pantoprazole 40 mg was also administered daily before food for 5 days (continued if required).

Withdrawal symptoms were monitored and assessed daily by Clinical Institute Withdrawal Assessment for Alcohol-Revised scale (CIWA-Ar) scores before the administration of morning dose. Vital signs such as pulse, blood pressure, respiration rate, and body temperature were assessed and recorded daily along with CIWA-Ar scores.

If the withdrawal symptoms did not subside completely by the end of the study period (CIWA-Ar scores of >5), the same regimen was continued till the withdrawal symptoms abated.

Counseling and cognitive behavioral therapy

Cognitive behavioral therapy and daily counseling for both patients and their caretakers were provided throughout the

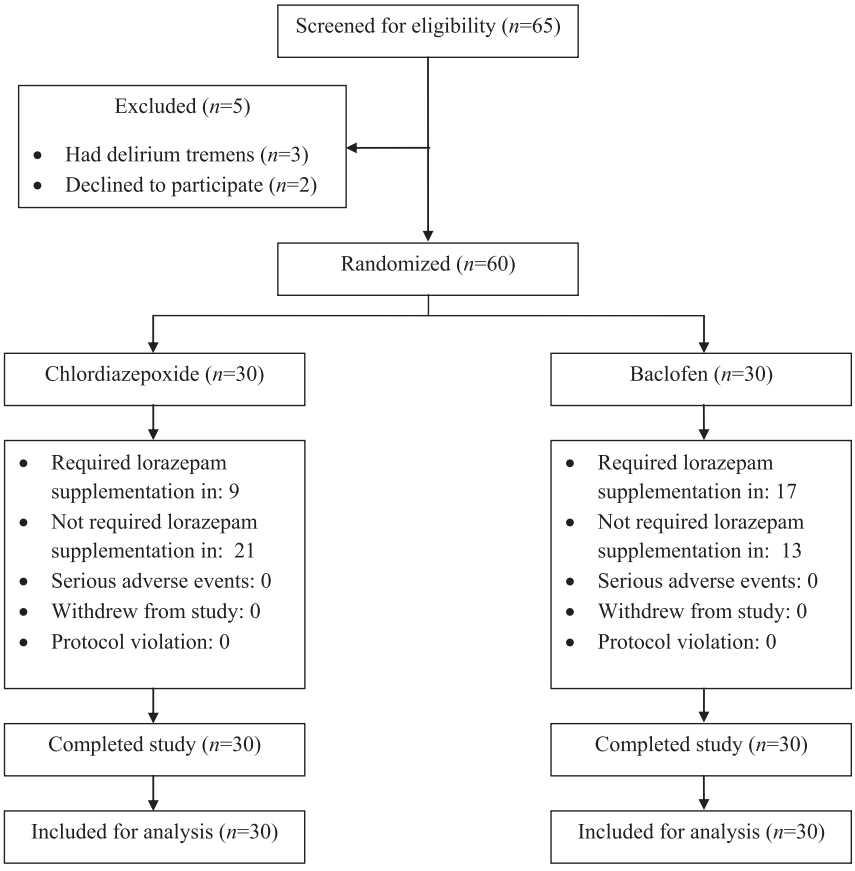

Fig. 1 – Consort flow diagram.

study period. Subjects were observed for any study drug withdrawal or rebound symptoms during the therapy. Following rescue protocol measures were available for the treatment of the same.

Chlordiazepoxide withdrawal symptoms were to be managed by substitution of an equivalent dose of diazepam (25 mg of chlordiazepoxide is equivalent to 10 mg of diazepam). The dose of diazepam was to be tapered down gradually until the abatement of withdrawal symptoms [8].

Withdrawal symptoms induced by baclofen was to be managed by re-institution of a higher dose of baclofen and gradually tapering off till withdrawal symptoms disappear, diazepam 10 mg was to be used to control seizures and spasticity [9,10].

Mild rebound symptoms like metallic taste, perceptual disturbances were to be managed conservatively and moderate to severe rebound symptoms of the study drugs such as insomnia, anxiety, and depression were to be managed by re-instillation of the respective drugs and gradually tapering off [11].

Subjects who had persistence of any AWS symptoms were followed up additional 3 days, and symptomatic treatment was to be provided whenever required.

All reported adverse events were analyzed for causality by WHO causality assessment scale. Adverse events were reported to the Institutional Pharmacovigilance Unit.

Primary objective parameters

The mean reduction of CIWA-Ar scores from the baseline. Total amount of lorazepam administered as a supplement medication.

Secondary objective parameters

Number of symptom-free days, that is, the number of days with the CIWA-Ar scores of <1 during the 9-day treatment period.

Improvement in Clinical Global Impression-Severity scale (CGI-S) and CGI-improvement scale (CGI-I). Safety parameters: Incidence and severity of adverse events. Subject's satisfaction of the AWS management to study medications. Primary parameters were considered as vital markers for the analysis of noninferiority outcome.

Laboratory investigations at baseline

The following laboratory investigations were carried out at baseline and were repeated later if necessary, the investigations were: Hematological investigations – complete blood count, biochemical investigations – liver function tests and renal function tests and radiological investigations – ultrasonography abdomen.

Statistical analysis

Evaluation of age, living status, years of alcohol consumption, laboratory parameters, lorazepam requirement, symptom-free days, and subject satisfaction was performed by Student's *t*-test or Mann–Whitney U-test whenever the data were not normally distributed. Chi-square test or Z-test was used to analyze categorical data like adverse events. Analysis of day to day effects of baclofen and chlordiazepoxide on CIWA-Ar scores and its subscales and improvement in CGI scores was performed by repeated measures analysis of variance (RM-ANOVA). One-way RM-ANOVA was used to assess day to day improvement within groups and two-way RM-ANOVA for between groups analysis. Statistical software, SPSS version 20 IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp was used for the analysis of data.

Sample size

This was an exploratory pilot study. As there were no data available on the efficacy and safety of baclofen in AWS in Indian Population, we derived at the sample size based on the results obtained by Addolorato et al. and Kumar et al. [7,12] The expected percentage response in baclofen Group was taken as 85% and for chlordiazepoxide Group as 95% and the noninferiority criteria is set to be an absolute value of 10%. Considering the annual admission of AWS patients at the study site and to achieve 80% power for demonstrating noninferiority, it was estimated that 27 subjects per group were required. With a withdrawal/nonevaluable subject rate of 10%, a total of 30 per group subjects were recruited leading to a total recruited sample size of 60 subjects. At any given time, the average uncomplicated AWS cases in the study site were 70 per year.

Results

All the study subjects were males, the other demographic and clinical characteristics are provided in Table 1.

Primary efficacy parameters

Total Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale scores

Tables 2 and 3, and Fig. 2A–E summarizes the total scores of CIWA-Ar by two-way RM-ANOVA between the study groups. The total scores of CIWA-Ar showed no significant difference ($p = 0.475$) between the study groups with a mean of 23.60 ± 6.483 with a 95% confidence interval (CI) of 21.179–26.021 on day 1 (baseline) with a decrease in a mean of 1.133 ± 0.730 with 95% CI of 0.861–1.406 for baclofen group. Whereas for the chlordiazepoxide group the mean 23.90 ± 7.038 with a 95% CI of 21.272–26.528 with a reduction in the mean of 0.133 ± 0.434 with a 95% CI of −0.029 to 0.295, respectively.

Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale sub score: anxiety scores

Fig. 2D summarizes the effects of study medications on CIWA-Ar anxiety scores. RM-ANOVA analysis between the groups for anxiety scores showed a significant reduction with time ($p = 0.014$), a mean of 2.933 ± 1.201 with a 95% confidence interval of 2.485–3.382 for baclofen group on day 1 (baseline) which reduced to 0.633 ± 0.490 with 95% CI of 0.450–0.816 on day 9, indicating persistence of anxiety in baclofen group to the last day of the study (day 9). The mean anxiety scores for chlordiazepoxide group was 2.833 ± 1.085 with a 95% confidence

Table 1 – Baseline characteristics.

Characteristics	Baclofen	Chlordiazepoxide	*p*
Age (mean ± SD)	36.7 ± 8.8	40.0 ± 10.1	0.190
Living status (%)			
Urban	24 (80)	22 (73.3)	0.545
Rural	6 (20)	8 (26.6)	
Duration of hazardous consumption of alcohol in years (mean ± SD)	16.5 ± 8.2	16.9 ± 7.7	0.743
Tobacco smoking in years (mean ± SD) (%)	23 (76)	28 (93)	0.362
CAGE scores for alcohol dependence (%)			
Subjects with CAGE score 3	8 (26.7)	5 (16.7)	0.347
Subjects with CAGE score 4	22 (73.3)	25 (83.3)	
Baseline investigations (mean ± SD)			
SGOT	89.8 ± 61.0	76.0 ± 64.1	0.176
SGPT	62.1 ± 33.2	45.0 ± 37.5	0.022*
Albumin	4.1 ± 0.4	4.0 ± 0.6	0.865
Total bilrubin	1.0 ± 0.9	0.8 ± 0.7	0.130
Direct bilrubin	0.6 ± 0.5	0.3 ± 0.4	0.004*
GGT	199.2 ± 329.8	198.6 ± 236.8	0.460
ALP	95.2 ± 28.7	104.8 ± 72.7	0.836
Total proteins	7.3 ± 0.6	7.2 ± 0.6	0.370

Abbreviations: SD: Standard deviation; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase.

interval of 2.428–3.239 on day 1 (baseline) which reduced to 0.000 ± 0.000 with 95% CI of 0.000–0.000 on day 9 respectively indicating resolution of anxiety by the last day of the study.

Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale sub score: agitation scores

Fig. 2E summarizes the effects of study medications on CIWA-Ar agitation scores. RM-ANOVA analysis between the groups for agitation scores showed a significant reduction with time ($p = 0.014$) with a mean of 2.533 ± 1.105 with a 95% confidence interval of 2.120–2.946 for baclofen group on day 1 (baseline) which reduced to 0.067 ± 0.253 with 95% CI of 0.000–0.161 on day 9, indicating persistence of agitation in baclofen group to the last day of the study (day 9). The mean agitation scores for chlordiazepoxide group were 2.500 ± 1.525 with a 95% confidence interval of 1.930–3.070 on day 1 (baseline) which reduced to 0.000 ± 0.000 with 95% CI of 0.000–0.000 on day 9 respectively, indicating resolution of agitation by the last day of the study.

Effect of lorazepam supplementation on total Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale scores in both the groups

There was no significant difference in the proportion of patients who needed lorazepam supplement to control AWS in the baclofen group and chlordiazepoxide group ($n = 17$ vs. 10; $p = 0.067$). The median dose (95% CI) in each group was 6.0 mg (2.0–4.8 mg) and 4.0 mg (0.6–3.2 mg) ($p = 0.384$).

Table 2 – Individual CIWA-Ar scores (RM-ANOVA).

Individual scores	Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	*p*	
											Within group[d]	Between group[e]
Nausea and vomiting	Group B[a] (mean ± SD)	2.83 ± 1.39	2.03 ± 0.80	1.56 ± 0.72	0.83 ± 0.64	0.43 ± 0.56	0.13 ± 0.34	0.06 ± 0.36	0.03 ± 0.18	0 ± 0	0.000	0.827
Nausea and vomiting	Group C[b] (mean ± SD)	2.66 ± 1.37	2.00 ± 1.14	1.33 ± 1.09	0.80 ± 0.96	0.50 ± 0.68	0.26 ± 0.44	0.06 ± 0.25	0.06 ± 0.25	0 ± 0	0.000	
Tremors score	Group B (mean ± SD)	4.73 ± 1.17	3.70 ± 1.11	3.03 ± 1.18	2.46 ± 1.10	1.90 ± 1.12	1.16 ± 0.94	0.80 ± 0.76	0.53 ± 0.57	0.40 ± 0.62	0.000	0.492
Tremors score	Group C (mean ± SD)	4.86 ± 1.30	3.83 ± 1.17	2.96 ± 1.32	2.00 ± 1.31	1.43 ± 1.07	0.96 ± 1.09	0.66 ± 1.02	0.36 ± 0.92	0.13 ± 0.43	0.000	
Paroxysmal sweats	Group B (mean ± SD)	2.93 ± 1.22	2.03 ± 0.96	1.26 ± 0.86	0.73 ± 0.73	0.33 ± 0.60	0.06 ± 0.25	0.03 ± 0.18	0 ± 0	0 ± 0	0.000	0.773
Paroxysmal sweats	Group C (mean ± SD)	2.53 ± 1.07	1.90 ± 0.84	1.26 ± 0.86	0.76 ± 0.77	0.50 ± 0.73	0.16 ± 0.37	0.03 ± 0.18	0 ± 0	0 ± 0	0.000	
Anxiety score	Group B (mean ± SD)	2.93 ± 1.20	2.13 ± 0.89	1.76 ± 0.67	1.33 ± 0.60	1.03 ± 0.55	0.76 ± 0.43	0.76 ± 0.43	0.73 ± 0.44	0.63 ± 0.49	0.000	0.014[c]
Anxiety score	Group C (mean ± SD)	2.83 ± 1.08	2.20 ± 0.88	1.50 ± 0.77	1.03 ± 0.76	0.66 ± 0.75	0.50 ± 0.62	0.36 ± 0.61	0.20 ± 0.40	0 ± 0	0.000	
Agitation score	Group B (mean ± SD)	2.53 ± 1.10	1.76 ± 0.67	1.53 ± 0.97	0.86 ± 0.77	0.63 ± 0.71	0.43 ± 0.56	0.36 ± 0.55	0.13 ± 0.34	0.06 ± 0.25	0.000	0.014[c]
Agitation score	Group C (mean ± SD)	2.50 ± 1.52	1.96 ± 1.12	1.33 ± 0.88	0.83 ± 0.74	0.53 ± 0.68	0.46 ± 0.62	0.26 ± 0.52	0.16 ± 0.37	0 ± 0	0.000	

Abbreviations: SD: Standard deviation; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised scale; RM-ANOVA: Repeated measures analysis of variance.

[a] B: Baclofen.

[b] C: Chlordiazepoxide.

[c] *p*: Significant (<0.05).

[d] One-way RM-ANOVA.

[e] Two-way RM-ANOVA.

Table 3 – Individual CIWA-Ar scores (RM-ANOVA) (continued).

Individual scores	Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	*p*	
											Within group[a]	Between group[b]
Tactile disturbance	Group B (mean ± SD)	2.46 ± 0.81	1.86 ± 0.77	1.46 ± 0.68	1.0 ± 0.64	0.56 ± 0.62	0.30 ± 0.46	0.06 ± 0.25	0 ± 0	0 ± 0	0.000	0.793
Tactile disturbance	Group C (mean ± SD)	2.5 ± 1.04	1.86 ± 0.93	1.26 ± 0.94	0.83 ± 0.83	0.50 ± 0.73	0.30 ± 0.46	0.13 ± 0.34	0.06 ± 0.25	0 ± 0	0.000	
Auditory disturbance	Group B (mean ± SD)	1.1 ± 1.42	0.70 ± 0.91	0.30 ± 0.53	0.13 ± 0.34	0.03 ± 0.18	0.03 ± 0.18	0 ± 0	0 ± 0	0 ± 0	0.000	0.257
Auditory disturbance	Group C (mean ± SD)	1.36 ± 1.24	1.00 ± 0.94	0.53 ± 0.68	0.20 ± 0.40	0.13 ± 0.34	0.03 ± 0.18	0 ± 0	0 ± 0	0 ± 0	0.000	
Visual disturbance	Group B (mean ± SD)	0.96 ± 1.32	0.70 ± 1.02	0.33 ± 0.66	0.16 ± 0.37	0.03 ± 0.18	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.000	0.389
Visual disturbance	Group C (mean ± SD)	1.4 ± 1.11	0.86 ± 0.89	0.40 ± 0.56	0.20 ± 0.40	0.10 ± 0.30	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.000	
Headache score	Group B (mean ± SD)	2.66 ± 0.71	2.1 ± 0.54	1.63 ± 0.66	1.03 ± 0.66	0.63 ± 0.55	0.40 ± 0.49	0.10 ± 0.30	0.03 ± 0.18	0 ± 0	0.000	0.128
Headache score	Group C (mean ± SD)	2.36 ± 0.88	1.76 ± 0.72	1.13 ± 0.86	0.70 ± 0.83	0.50 ± 0.68	0.33 ± 0.54	0.13 ± 0.34	0.06 ± 0.25	0 ± 0	0.000	
Orientation and clouding	Group B (mean ± SD)	0.36 ± 0.92	0.13 ± 0.43	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.000	0.062
Orientation and clouding	Group C (mean ± SD)	0.86 ± 1.04	0.36 ± 0.71	0.13 ± 0.34	0.10 ± 0.30	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.000	
Total CIWA-Ar score	Group B (mean ± SD)	23.6 ± 6.48	17.1 ± 3.70	12.8 ± 3.21	8.56 ± 2.62	5.63 ± 2.38	3.30 ± 1.78	2.23 ± 0.85	1.50 ± 0.68	1.13 ± 0.73	0.000	0.475
Total CIWA-Ar score	Group C (mean ± SD)	23.9 ± 7.03	17.7 ± 4.81	11.8 ± 4.21	7.80 ± 4.24	4.86 ± 3.10	3.00 ± 2.01	1.63 ± 1.71	0.86 ± 1.47	0.13 ± 0.43	0.000	

Abbreviations: SD: Standard deviation; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised scale; RM-ANOVA: Repeated measures analysis of variance.

[a] One-way RM-ANOVA.

[b] Two-way RM-ANOVA.

However, lorazepam supplementation posed a significant impact on the improvement of CIWA-Ar scores in the baclofen group but not in chlordiazepoxide group [Table 4, Fig. 3].

The supplementation of lorazepam in baclofen group had a significant effect on the reduction of CIWA-Ar scores over time ($p = 0.009$) indicating that the reduction of CIWA-Ar scores in baclofen group was dependent upon lorazepam and it also indicates that the subjects ($n = 13$, 43.33%) with lesser baseline CIWA-Ar scores who did not require lorazepam supplementation, demonstrated a steady reduction of scores. Whereas the subjects ($n = 17$, 56.66%) who required lorazepam supplementation had a fluctuating reduction in CIWA-Ar scores, it also indicates that the reduction of CIWA-Ar scores was smoother on supplementation of lorazepam as compared to days without supplementation.

In chlordiazepoxide group the lorazepam supplementation had no significant effect on the reduction of CIWA-Ar scores over time ($p = 0.363$) and that it indicates, irrespective of lorazepam supplementation the subjects had a steady and smoother reduction in CIWA-Ar scores.

Secondary efficacy parameters

There was neither study drug related withdrawal symptoms nor study drug related rebound symptoms in the present study [Table 5].

Symptom-free days in study groups

Indicated that all the subjects of chlordiazepoxide group were free from symptoms by an additional day as compared to baclofen group [Table 5].

Clinical Global Impression – improvement scores in study groups

The CGI-I scores showed no significant difference between the study groups (two-way RM-ANOVA, $p = 0.527$) indicating a much improvement in symptoms [Table 5].

Clinical Global Impression – severity scores of symptoms in study groups

The CGI-S scores showed no significant difference between the groups (two-way RM-ANOVA, $p = 0.662$) it also explains that the severity of symptoms is absent in chlordiazepoxide group at the end of study period while in baclofen group the severity of symptoms disappeared on day 8 and reoccurred on day 9 with a very mild severity, probably due to persistence of anxiety and agitation [Table 5].

Subject satisfaction of alcohol withdrawal syndrome management in both groups at day 9

Subject satisfaction was rated on a visual analog scale, indicated that the subject satisfaction was more with chlordiazepoxide group (median = 82%) as compared to baclofen group (median = 75%) [Table 5].

Discussion

In the present study the efficacy and tolerability of Baclofen - a $GABA_B$ agonist was compared with chlordiazepoxide – an allosteric modulator of $GABA_A$ receptor and a gold standard,

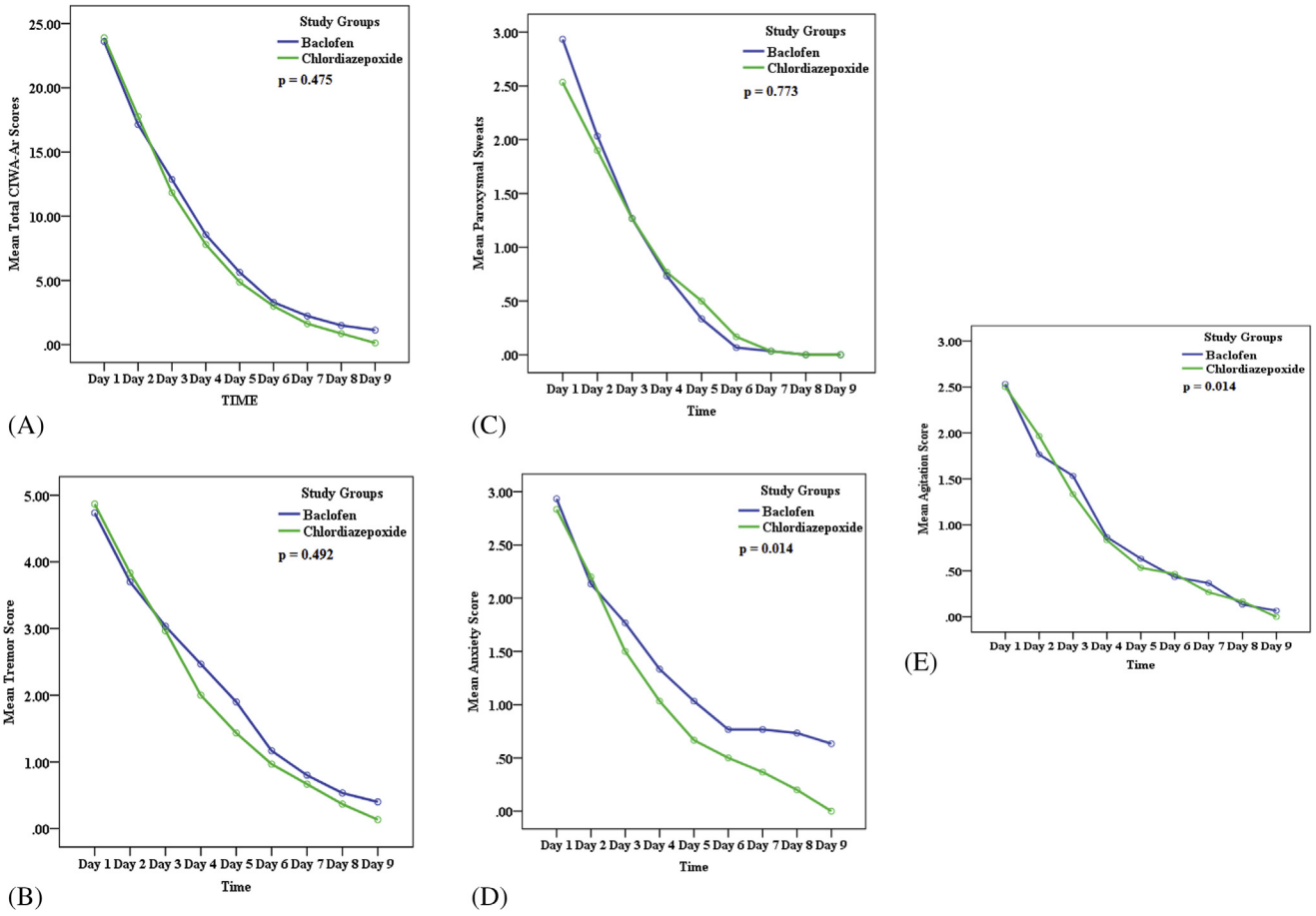

Fig. 2 – (A) Total scores. (B) Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale sub score – tumors. (C) Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale sub score – sweating. (D) Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale sub score – anxiety. (E) Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale sub score – agitation.

in uncomplicated AWS. Although baclofen is not approved for the management of AWS, because of its reported efficacy and tolerability which compared well with BZD's, it was evaluated in the present study for its noninferiority to chlordiazepoxide [5]. Most of the subjects were from urban vicinity indicating the impact of lifestyle on the incidence of alcoholism and a majority belonged to lower middle socio-economic class where alcoholism is high. The majority had already undergone detoxification earlier or restarted consuming alcohol within one month of their detoxification, indicating the craving for alcohol. Most of the subjects were tobacco smokers or chewers which may point to the fact that

Table 4 – Effect of lorazepam supplementation on total CIWA-Ar scores.

Tests of within-subjects effects and between subject factor (RM-ANOVA)

Study group	Parameters	Correction	df	F	Significant (*p*)
Baclofen	Lorazepam supplementation (X)	Greenhouse–Geisser	13.2	2.523	0.009[a]
	Total CIWA-Ar scores		50.8		
Chlordiazepoxide	Lorazepam supplementation (X)	Greenhouse–Geisser	9.8	1.127	0.363[b]
	Total CIWA-Ar scores		47.5		

Abbreviation: CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale; RM-ANOVA: Repeated measures analysis of variance.

[a] *p*: Significant ($p < 0.05$); the supplementation of lorazepam in baclofen group had a significant effect on the reduction of CIWA-Ar scores over time.

[b] *p*: Not significant ($p > 0.05$); the supplementation of lorazepam in chlordiazepoxide group did not have a significant effect on the reduction of CIWA-Ar scores over time.

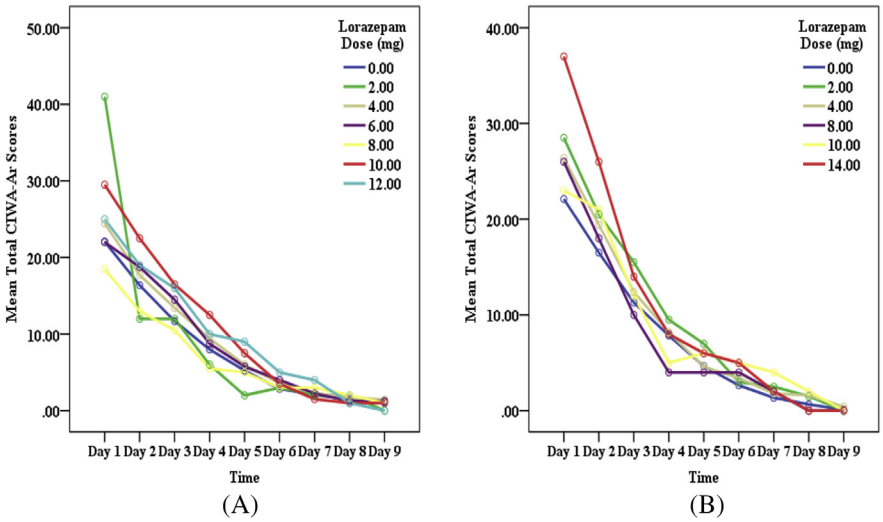

Fig. 3 – Effect of lorazepam supplementation on total Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale scores (mean dose of lorazepam supplementation for entire study duration is plotted against the periodic reduction of Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale scores, colored lines indicate Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale scores) (A) baclofen group, (B) chlordiazepoxide group.

habitual alcohol use is often associated with other substance abuse [13].

The primary efficacy parameter, the reduction of CIWA-Ar scores was consistently similar between the groups with no significant difference excepting agitation and anxiety scores.

The mean anxiety scores of chlordiazepoxide showed a smooth resolution of anxiety, with a complete abatement by the 9th day, while anxiety persisted in baclofen group till the 9th day of study. There was a rapid reduction of anxiety scores from day 3 in chlordiazepoxide group contrary to baclofen group, which lacked the faster reduction as compared with chlordiazepoxide group. The resolution of anxiety achieved by chlordiazepoxide group at day 5, could not be achieved by baclofen group even at the end of a 9th day of study. Other studies observed that baclofen could effectively control anxiety which was even equated to diazepam in contrast with the present study [5].

The reduction in mean agitation scores of chlordiazepoxide had a smooth resolution with a complete abatement of agitation by the 9th day of study, which persisted till the 9th day of study in baclofen group. There was a rapid reduction of agitation scores from day 4 in chlordiazepoxide group contrary to baclofen group which lacked the faster reduction. Complete reduction in total CIWA-Ar scores was not seen in either of the study groups due to some persistence in symptoms. It also shows that baclofen is slightly slower in reducing the total CIWA-Ar scores, even though chlordiazepoxide produced near normal reduction in total scores, which was neither statistically nor clinically significant.

In terms of lorazepam supplementation for a smoother control of AWS symptoms, though more number of subjects in baclofen group required a higher amount of lorazepam supplementation as compared to chlordiazepoxide group.

The effect of lorazepam supplementation on reduction of total CIWA-Ar scores for a better control of AWS symptoms in

Table 5 – Secondary efficacy parameters.

Parameter	Baclofen	Chlordiazepoxide	*p*
Residual symptoms, *n* (%)			
Insomnia	3 (10)	5 (16)	0.448
Anxiety	7 (23.3)	1 (3.3)	0.023*
Symptom-free days	1.7 ± 1.6 (1.1–2.2)	2.6 ± 1.4 (2.1–3.1)	0.022*
CGI scores, day 1 versus day 9, score (95% CI)			
Improvement	1.1 ± 0.3 (1.0–1.2)	1.0 ± 0.2 (1.0–1.1)	0.527
Severity	1.0 ± 0.2 (1.0–1.1)	1.0 ± 0.0 (1.0–1.0)	0.662
Subject satisfaction (%)	73.7 ± 13.1	80.3 ± 13.8	0.018*
Adverse events, *n* (%)	10 (33.3)	4 (13.3)	>0.05

Abbreviation: CGI: Clinical Global Impression; CI: Confidence interval.
* $p < 0.05$.

both the groups with Greenhouse–Geisser correction showed that, in baclofen group the reduction of CIWA-Ar scores was dependent on the lorazepam supplementation (in milligrams) as compared to chlordiazepoxide group indicating that the lorazepam supplementation was significantly essential to the baclofen group for a better and smoother control of AWS symptoms as compared to that of chlordiazepoxide group.

Though the study drugs were identical in controlling the symptoms of AWS, it was observed that there was a significantly better subject satisfaction with chlordiazepoxide at the end of the study.

The adverse events were analyzed as per the WHO Causality Assessment Scale. Low back muscle pain was observed only in baclofen group which was probably due to the drug, whereas other adverse events like loose stools, drowsiness, fever and discoloration of urine were unlikely or possibly caused by the study drugs [14].

Thus in the present study, it was observed that baclofen was less effective than chlordiazepoxide in controlling the anxiety and agitation and required more lorazepam supplementation, and chlordiazepoxide showed a better subject satisfaction compared to baclofen. This may be probably because, the $GABA_B$ receptors may play less important role in the pathogenesis of AWS, and also the recommended dose of baclofen (30 mg) might not have been adequate to produce a comparable effect. Indian population may require a higher dose. This may need further confirmation.

Both the drugs showed similar tolerability. The present study failed to demonstrate the noninferiority of baclofen to chlordiazepoxide in uncomplicated AWS, However baclofen might be an alternative.

Limitations of the present study are that it was an open-label study with sample size being small and hence not enough to identify the minute differences in efficacy parameters between the study groups. The dose of baclofen was based on previous European studies, which may not be optimum for Indian population as the response may vary in different racial groups.

Scope for further research

More number of randomized double-blind, parallel group, controlled, and multicentric studies with large sample size may be warranted. Further studies with dose titration or higher doses of baclofen (50 mg) may be required to assess the efficacy in AWS.

As baclofen acts through a different GABA-sub type ($GABA_B$) receptor, it can be used in combination with other BZD's ($GABA_A$ allosteric modulators), which may be useful to provide a synergistic effect in controlling the symptoms and to hasten resolution of AWS.

Source of support

Nil.

Conflicts of interest

None declared.

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