RESEARCH ARTICLE

Efficacy, Safety and Tolerability of Clonazepam 0.25 mg and Propranolol 10/20 mg Fixed-dose Combination among Anxiety Disorder Patients: A Randomized, Double-blind, Multicentric, Active-controlled, Phase IV Study

Anu Kant Mital[1], Manushree Gupta[2], Nilesh Shah[3], Rajesh Kumar[4], Sathianathan R[5], SVB Gupta[6], Manjula S[7], Krishna Kumar M[8]

Received on: 05 April 2024; *Accepted on*: 29 April 2024; *Published on*: 19 February 2025

Abstract

Background and aim: Although monotherapy of anti-anxiety drugs is effective in controlling anxiety, due to the progressive nature of the disease, it is often associated with a lack of effectiveness over time. So, this study was carried out to assess the efficacy, safety, and tolerability of clonazepam 0.25 mg and propranolol 10/20 mg fixed-dose combination among anxiety disorder patients.

Materials and methods: This was a randomized, double-blind, multicenter, actively-controlled, phase IV study conducted among individuals having established diagnosis of anxiety, total Hamilton Rating Scale for Anxiety (HAM-A) score ≥17, Clinical Global Impressions Severity (CGI-S) score >4 in the week prior to inclusion. The study participants were randomized to receive either the test or the reference drug once daily for 8 weeks. At the last study visit, the degree of a patient's anxiety was assessed by using the HAM-A and CGI-S scores.

Results: At week 8, it was observed that there was a decrease in HAM-A score in all the groups. Between the group analysis, at visit 3, there was a reduction in the HAM-A score compared with the randomization visit. The investigator-rated scale and patient-rated global improvement were highest in group B followed by group C compared with group A. Also, there was a notable reduction in group A at week 8 in the CGI-S score as compared with baseline in group B.

Conclusion: The combination of clonazepam and propranolol was effective, safe, and well-tolerated. Hence, it can be a significant armamentarium in anxiety disorder management.

Clinical significance: The clonazepam 0.25 mg and propranolol 10/20 mg fixed-dose combination showed a significant decrease in the HAM-A score across patients with anxiety disorders and was found to be clinically effective, safe, and well-tolerated.

Keywords: Additive effects, Anxiety, Clonazepam, Fixed-dose combination, Propranolol.

Indian Journal of Private Psychiatry (2025): 10.5005/jp-journals-10067-0177

Introduction

Anxiety disorders are the most pervasive mental health conditions and can be just as incapacitating despite being less obvious than schizophrenia, depression, and bipolar illness.[1,2] As per the World Health Organization (WHO), nearly 264 million people suffer from anxiety disorders worldwide, demonstrating a 15% rise from the year 2005.[3] Specifically, phobia is more frequent with a 12.1% of 12-month prevalence rate. Anxiety disorders occur more commonly in women compared with men with an approximate 2:1 ratio.[3] In 2017, 197.3 million individuals suffered from psychiatric disorders in India inclusive of 44.9 million (41.2–48.9) anxiety disorder individuals.[4]

Anxiety is associated with agitation and is revealed as a future-oriented mood state which consists of severe cognitive, physiological, affective, and behavioral response networks linked with arrangement for the predicted events or conditions considered as minatorial. When there is an exaggerated perception of threat or an incorrect assessment of the risk in a scenario, pathological anxiety is set off, leading to excessive and inappropriate behaviors.[1,2] The management of chronic anxiety involves psychological therapy,

[1]Department of Psychiatry, Rajiv Gandhi Medical College and Chhatrapati Shivaji Maharaj Hospital, Thane, Maharashtra, India

[2]Department of Psychiatry, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

[3]Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai, Maharashtra, India

[4]Department of Psychiatry, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

[5]Department of Psychiatry, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India

[6]Department of Psychiatry, Rajiv Gandhi Institute of Medical Sciences and Government General Hospital, Srikakulam, Andhra Pradesh, India

[7,8]Department of Medical Services, Micro Labs Limited, Bengaluru, Karnataka, India

Corresponding Author: Manjula S, Department of Medical Services, Micro Labs Limited, Bengaluru, Karnataka, India, Phone: +91 9845122853, e-mail: drmanjulas@gmail.com

How to cite this article: Mital AK, Gupta M, Shah N, *et al*. Efficacy, Safety and Tolerability of Clonazepam 0.25 mg and Propranolol 10/20 mg Fixed-dose Combination among Anxiety Disorder Patients:

pharmacological therapy, or a combination of both are required. Pharmacological therapy includes serotonin–norepinephrine reuptake inhibitors (SNRIs), benzodiazepines (BZDs), selective serotonin reuptake inhibitors (SSRIs), mild tranquilizers, tricyclic antidepressants (TCAs), and beta-adrenergic blocking agents.

Monotherapy of anti-anxiety drugs is effective in controlling anxiety, but due to the progressive nature of the disease, monotherapy is often associated with a lack of effectiveness over time. Combining anti-anxiety drugs with different mechanisms of action produces additive effects, allowing the use of submaximal doses of the agents, thereby reducing the side effects and increasing the complementary benefits of risk factors.[5] Propranolol, a competitive beta-blocker acts by exerting its action by aggressively inhibiting beta-1 and beta-2 adrenergic excitation in the heart, which was consistently induced by epinephrine and norepinephrine.[6] As an optimistic allosteric modulator on GABA-A receptors, clonazepam is an effective, long-acting benzodiazepine that provides pharmacological effects. It facilitates the action of GABA-A by enhancing the occurrence of chloride channel opening and then depolarization of the neurons and lowered firing, producing relaxing effects on the brain by lowering the excitability of neurons.[7] Therefore, this study was conducted to compare the efficacy and safety of clonazepam 0.25 mg and propranolol 10/20 mg fixed-dose combination among anxiety disorder patients.

Materials and Methods

A randomized, double-blind, multicenter, active controlled, phase IV study was conducted from January 2018 to July 2019 across 6 centers in India among patients with anxiety disorders aged between 18 and 65 years and with an established diagnosis of anxiety, total Hamilton rating scale for anxiety (HAM-A) score ≥17, clinical global impressions severity (CGI-S) score greater than 4 in the week before inclusion of the study, and who have a willingness and able to give informed consent and comply with requirements for participation in the study. Ethical clearance was received from the Institute Ethics Committee (IEC) of partner institutions in each state and the registration of the Trial was done with the Clinical Trial Registry of India before commencing the study (CTRI/2017/12/010962).

Subjects were randomized to receive either the test or the reference drug once daily for a period for 8 weeks from the randomization visit. A total of 50 individuals (group A) got clonazepam 0.25 mg, 50 subjects (group B) got clonazepam 0.25 mg + propranolol 10 mg, and 49 subjects (group C) received clonazepam 0.25 mg + propranolol 20 mg as described in Figure 1. Group A was the reference arm while group B and C were test arms. There was no treatment for anxiety disorder other than study medication which was allowed during the study period and no specific titration procedures were done. If rescue medications were required during the study, paracetamol and other NSAIDS were the drugs of choice administered.

Schedule of visits: visit 1: screening, day 3; visit 2: baseline/randomization; week 0; visit 3: follow-up visit 1, week 4 ± 3 days; visit 4: follow-up visit 2/end of study visit, week 8 ± 3 days.

The primary efficacy endpoint was a change in the score on the HAM-A at the end of treatment (week 8) as compared with baseline, between groups receiving test and reference product. The degree of a patient's anxiety was evaluated by the HAM-A. It consisted of 14 parameters and every parameter has a 5-point rating system, where 0 represents not existent and 4 represents severe.

Secondary efficacy endpoints included the percentage of patients having a 50% reduction in the HAM-A total score at the end of the study (week 8) as compared with baseline and the degree of improvement in the mean CGI-S (global severity of the CGI scale) score at the end of study (8th week) as compared with baseline.

Tolerability assessment was done by the investigator at the end of the study visit (Visit 4, week 8). Excellent = No adverse event reported; Good = Mild adverse event(s) reported which subsided with or without medication and did not necessitate stoppage of study medication; Fair = Moderate-to-severe adverse event(s) reported which subsided with or without medication and did not necessitate stoppage of study medication; Poor = Severe or serious adverse event(s), which necessitated stoppage of study medication.

A Randomized, Double-blind, Multicentric, Active-controlled, Phase IV Study. Ind J Priv Psychiatry 2025;19(1):11–16.

Source of support: Nil

Conflict of interest: Dr Anu Kant Mital is associated as the National Advisory Board member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and his research group.

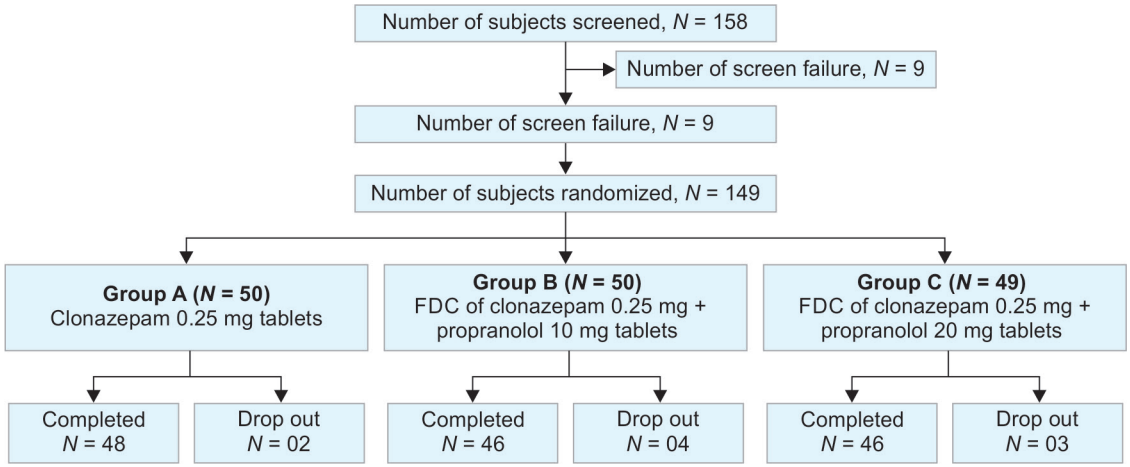

Fig. 1: Flowchart of the study participants

Global Improvement Scale was scored at the end of the study visit (Visit 4, week 8) by both the investigator and patient on a 4-point scale (1 = Poor; 2 = Moderate; 3 = Good; 4 = Excellent).

The safety endpoints between the clonazepam 0.25 mg tablets, FDC of clonazepam 0.25 mg + propranolol 10 mg tablets, and FDC of clonazepam 0.25 mg + propranolol 20 mg tablets were assessed by comparing the ECG at every visit and laboratory investigation (Hematology, serum chemistry, LFT, RFT, lipid profile) during visit 1 and visit 4 of the treatment period. The adverse event profile of each treatment arm was recorded to compare between the three groups. Adverse events were recorded as volunteered by patients and evaluated by the investigator during all the study visits.

The data analysis was carried out by using Statistical Package for Social Sciences (SPSS) software and R software. To analyze the hypotheses of the study, descriptive statistics such as mean and standard deviation, SD, and inferential statistics including analysis of variance, ANOVA, and Bonferroni test were used. Whenever $p < 0.05$, the results were marked statistically significant.

Table 2: HAM-A score in group A, group B, and group C – general linear model

	HAM-A	*Mean*	*SD*	*F-value*	*p-value*
Group A	Visit 1	28.54	7.41	674.786	<0.001
	Visit 2	28.69	7.36		
	Visit 3	20.56	6.50		
	Visit 4	18.77	8.06		
Group B	Visit 1	26.78	7.20	567.778	<0.001
	Visit 2	26.64	6.95		
	Visit 3	17.11	5.05		
	Visit 4	10.64	6.41		
Group C	Visit 1	25.46	6.41	772.479	<0.001
	Visit 2	25.52	6.30		
	Visit 3	16.59	5.47		
	Visit 4	8.28	4.94		

Results

About 149 participants were enrolled in the study, about 71 participants were females and 78 were males. The mean study population age was 35.32 ± 8.79 years. The mean of male subjects' age was 35.01 ± 8.48 years and of female subjects' age was 35.66 ± 9.05 years. The mean height and weight of the male subjects were 160.99 ± 13.63 cm and 65.38 ± 11.54 kg while in female subjects, it was 156.63 ± 7.49 cm and 59.90 ± 9.83 kg respectively. Female participants of childbearing potential underwent a urine pregnancy test.

The HAM-A score at baseline was 28.69 ± 7.36 (95% CI: 26.55–30.83) in group A. The HAM-A in group B was 26.64 ± 6.94 (95% CI: 24.56–28.73) and group C was 25.52 ± 6.30 (95% CI: 23.65–27.39), respectively (Table 1). At week 8, the HAM-A score in group A was 18.77 ± 8.06 where there was a statistically significant decrease as compared with the baseline in group B from 26.78 ± 7.20 to 10.64 ± 6.41 ($p < 0.001$) (Table 2).

Between the group analysis, at screening visit 1, the HAM-A scores were 28.54 ± 7.41 (95% CI: 26.39–30.69), 27.15 ± 7.56 (95% CI: 24.91–29.40), and 25.46 ± 6.14 (95% CI: 23.63–27.28) in group A, B and C with no discernible statistical difference ($p = 0.110$), respectively. Similarly, at the randomization/baseline visit (visit 2), there were no discernible statistical differences between these three groups. The HAM-A scores were as follows: group A: 28.69 ± 7.36 (95% CI: 26.55–30.83), group B: 26.64 ± 6.95 (95% CI: 24.56–28.73) and group C: 25.52 ± 6.30 (95% CI: 23.65–27.39). At visit 3, (follow-up visit/week 4), there was a reduction in the HAM-A score compared with the randomization visit. The group A HAM-A score was 20.56 ± 6.50 (95% CI: 18.68–22.45). The HAM-A score in group B was 17.37 ± 5.29 (95% CI: 15.80–18.94) and 16.59 ± 5.47 (95% CI: 14.96–18.21) in group C, respectively.

Table 1: HAM-A at baseline in group A, group B, and group C

					95% Confidence interval (CI) for mean	
Group	*N*	*Mean*	*SD*	*Std. error*	*Lower bound*	*Upper bound*
Group A	48	28.69	7.36	1.06	26.55	30.83
Group B	46	26.64	6.94	1.03	24.56	28.73
Group C	46	25.52	6.30	0.92	23.65	27.39
Total	140	26.98	6.96	0.59	25.81	28.15

The one-way ANOVA test for between the group analysis was done and found to be significant ($p < 0.003$). Also, there were statistically significant results ($p < 0.001$) among group A, B, and C at visit 4 (week 8). The HAM-A scores in the three groups were 18.77 ± 8.06 (95% CI: 16.43–21.11), 10.70 ± 6.35 (95% CI: 8.81–12.58), and 8.28 ± 4.94 (95% CI: 6.81–9.75) in group A, group B, and group C, respectively. For multiple comparisons, the Bonferroni test, a *post hoc* test for between the group analysis also showed that the HAM-A reductions in group B and group C at visit 3 (at week 4) and visit 4 (at week 8) were statistically significant as compared with group A (Fig. 2, Table 3).

The mean baseline CGI-S score in group A was 4.79 ± 0.71 (95% CI: 4.58–5.00), in group B, it was 4.67 ± 0.87 (95% CI: 4.42–4.93), and in group C, it was 4.61 ± 0.80 (95% CI: 4.37–4.85) (Table 4). At visit 4 (week 8), the CGI-S score in group A was 2.69 ± 0.88 where there was a statistically significant decrease as compared with the baseline in group B from 4.67 ± 0.87 to 2.13 ± 0.93 ($p < 0.001$). In group C, the baseline CGI-S score was 4.61 ± 0.80 at visit 2 and reduced to 3.09 ± 1.01 at visit 3 (week 4) and further reduced to 1.57 ± 0.72 at week 8 (visit 4) where the reduction from baseline to follow-up visits was clinically and statistically significant (Table 5).

Between the group analysis, at screening visit 1, the CGI-S scores were 4.73 ± 0.68 (95% CI: 4.53–4.93), 4.72 ± 0.86 (95% CI: 4.46–4.97), and 4.65 ± 0.82 (95% CI: 4.41–4.90) in group A, B, and C respectively with no discernible statistical difference ($p = 0.879$). Similarly, at visit 2, there were no discernible statistical differences between these three groups. The CGI-S scores were as follows: group A: 4.79 ± 0.71 (95% CI: 4.58–5.00); group B: 4.67 ± 0.87 (95% CI: 4.42–4.93); and group C: 4.61 ± 0.80 (95% CI: 4.37–4.85). At visit 3, the between the group analysis was found to be significant ($p < 0.003$) and there was a reduction in CGI-S score compared with the randomization visit. The group A CGI-S core was 3.33 ± 0.72 (95% CI: 3.12–3.54). The CGI-S score in group B was 3.24 ± 0.95 (95% CI: 2.96–3.52) and 3.09 ± 1.01 (95% CI: 2.79–3.39) in group C, respectively.

There were also statistically significant results ($p < 0.001$) between groups A, B, and C at visit 4 (week 8). The CGI-S scores in the three groups were 2.69 ± 0.88 (95% CI: 2.43–2.94), 2.13 ± 0.93 (95% CI: 1.85–2.41), and 1.57 ± 0.72 (95% CI: 1.35–1.78) in group A, B, and C, respectively (Fig. 3). For multiple comparisons, the Bonferroni

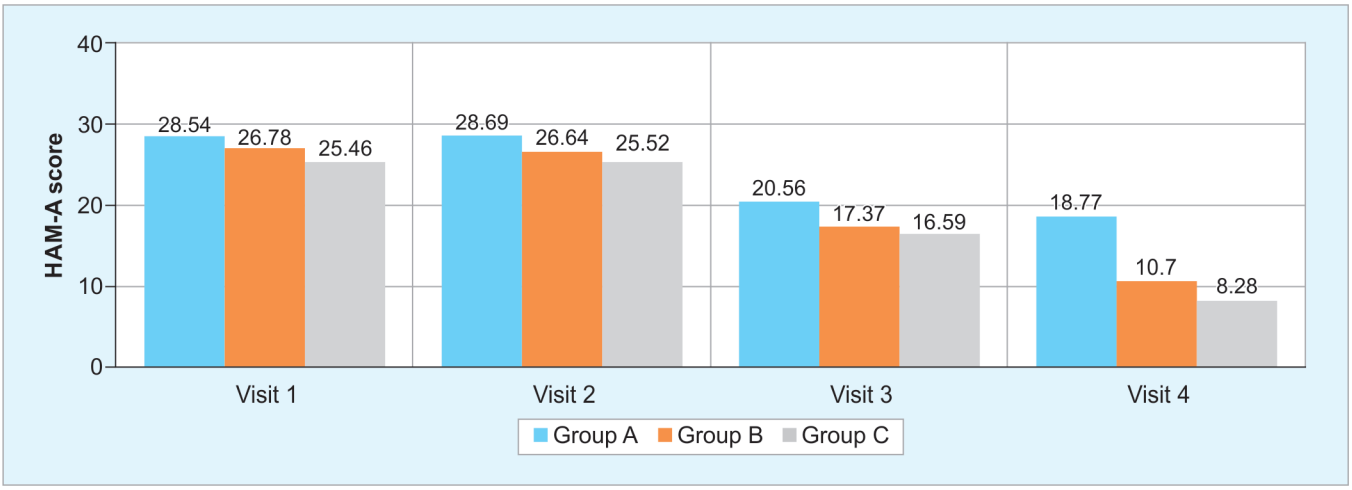

Fig. 2: HAM-A score comparison between groups A, B and C

Table 3: Bonferroni test for HAM-A score at visit 3 and visit 4 for groups A, B, and C

Post hoc tests – multiple comparisons					
			95% CI		
Bonferroni test	*Mean difference (I–J)*	*Std. error*	*Lower bound*	*Upper bound*	*p-value*
HAM-A score – Visit 3					
Group A and group B	3.193*	1.195	0.298	6.088	0.025
Group A and group C	3.976*	1.195	1.080	6.871	0.003
Group B and group C	0.783	1.207	–2.143	3.708	1.000
HAM-A score – Visit 4					
Group A and group B	8.075*	1.362	4.775	11.375	0.000
Group A and group C	10.488*	1.362	7.188	13.788	0.000
Group B and group C	2.413	1.376	–0.922	5.748	0.245

*The mean difference is significant at the 0.05 level

Table 4: CGI-S score at baseline

					95% CI for mean	
CGI-S baseline	*N*	*Mean*	*Std. deviation*	*Std. error*	*Lower bound*	*Upper bound*
Group A	48	4.79	0.71	0.10	4.58	5.00
Group B	46	4.67	0.87	0.12	4.42	4.93
Group C	46	4.61	0.80	0.11	4.37	4.85
Total	140	4.69	0.79	0.06	4.56	4.83

test, a *post hoc* test for between the group analysis also showed that the CGI-S reductions in group C were more significant than group B and group A. Furthermore, CGI-S for group B was more significant than for group A.

Table 5: CGI-S score in group A, group B and group C – general linear model

	CGI-S	*Mean*	*SD*	*F value*	*p-value*
Group A	Visit 1	4.73	0.68	2349.645	<0.001
	Visit 2	4.79	0.71		
	Visit 3	3.33	0.72		
	Visit 4	2.69	0.88		
Group B	Visit 1	4.72	0.86	1115.362	<0.001
	Visit 2	4.67	0.87		
	Visit 3	3.24	0.95		
	Visit 4	2.13	0.93		
Group C	Visit 1	4.65	0.82	1422.661	<0.001
	Visit 2	4.61	0.80		
	Visit 3	3.09	1.01		
	Visit 4	1.57	0.72		

The other secondary efficacy endpoint included the proportion of patients having a 50% decrease in the HAM-A score. At the conclusion of the study (week 8), an overall score was compared with the baseline score. Over 11 subjects (22.9%) in group A had more than 50% decrease in HAM-A score at visit 4 (week 8) as compared with visit 2 (baseline/randomization visit). While 36 subjects (78.3%) in group B and 38 subjects (82.6%) in group C had >50% reduction in HAM-A.

The mean investigator-rated global improvement scale in group A was 3.2 ± 0.71 (95% CI: 3.00–3.41), group B was 3.37 ± 0.67 (95% CI: 3.16–3.57), and group C was 3.47 ± 0.62 (95% CI: 3.29–3.66). The investigator-rated scale was increased in group B and C compared with group A. The mean patient-rated global improvement scale in group A was 3.18 ± 0.70 (95% CI: 2.98–3.39), group B was 3.23 ± 0.79 (95% CI: 3.00–3.47), and group C was 3.32 ± 0.70 (95% CI: 3.11–3.53). Similar to the investigator-rated scale, even the patient-rated global improvement was more in group B and C than in group A. Since the global improvement scale was scored by both the investigator and the study subjects, there was no discernible statistical difference between the investigator score

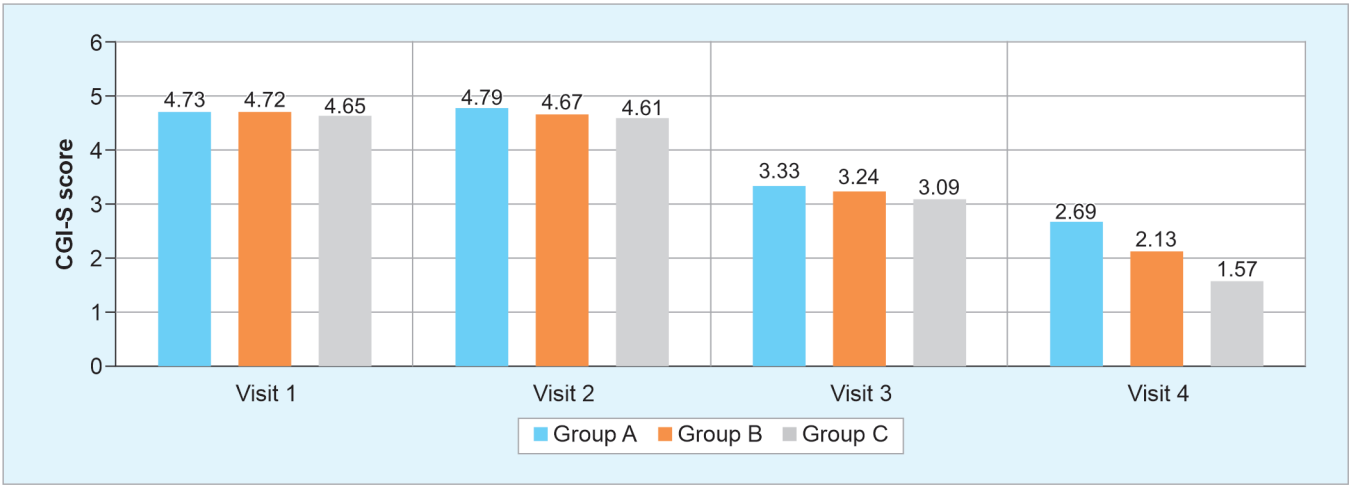

Fig. 3: CGI-S score comparison between groups

and participants scores in group A ($p = 0.443$), group B ($p = 0.199$), and group C ($p = 0.137$), respectively.

Although the study medication was well-tolerated in all the study participants, there were 9 subjects who highlighted mild adverse events which recovered with or without taking medicines and did not necessitate the cessation of the study drug. The most frequent adverse event was headache by 4 participants (2.68%), and fever by 3 subjects (2.01%) reporting it. One subject each reported acidity (0.67%) and vomiting (0.67%), respectively.

Discussion

The present study showed that HAM-A score reductions in clonazepam 0.25 mg + propranolol 10 mg FDC tablets group and clonazepam 0.25 mg + propranolol 20 mg FDC tablets group at week 4 and week 8 which were statistically significant as compared with clonazepam 0.25 mg tablets group. Similarly, the percentage of patients having >50% reduction in CGI-S score was also analyzed. About 38 (82.6%) study subjects in clonazepam 0.25 mg + propranolol 20 mg FDC tablets group had more than 50% reduction as compared with 28 (60.9%) study subjects in clonazepam 0.25 mg + propranolol 10 mg tablets FDC group and only 14 subjects (29.2%) in clonazepam 0.25 mg tablets group.

According to Nardi AE and Perna G, clonazepam can limit CO_2-induced panic and improve some aspects of PD patients' quality of life further validating the drug's efficacy in treating PD. Clonazepam has also highlighted superior effectiveness in social phobia. Clonazepam's two primary qualities—its longer half-life and greater potency—give it a distinct and possibly special value among BZDs because they make preventing the drug easier and cause fewer withdrawal symptoms than other BZDs.[8] When clonazepam was used to treat panic disorder, the therapeutic benefit was attained and maintained that was comparable to that of other pharmaceutical treatments, without tolerance developing and showing symptoms of worsening clinical status or dose escalation.[9] Clonazepam was as effective as other BZDs for different anxiety disorders management. Moreover, the clonazepam safety profile was better than other BZDs and was the most frequently prescribed benzodiazepine for anxiety.[10,11]

According to Laverdure B and Boulenger JP, beta-blockers specifically propranolol, should be deemed as powerful therapeutic agents in the treatment of anxiety disorders besides BZDs, antidepressants, and the newer azapirones.[12] In one case report, it was observed that the addition of propranolol 10 mg twice daily over 2 weeks decreased the HAM-A score significantly.[13] Hallstrom C et al. conducted a placebo-controlled crossover study with 24 chronically anxious outpatients to evaluate the therapeutic value of combining propranolol with benzodiazepine. The combination was generally more efficacious than benzodiazepine alone. While benzodiazepine was more effective than placebo or propranolol, both propranolol alone and in combination produced a better therapeutic response when it decreased the resting pulse rate by greater than 7.5 beats per minute. Smaller degrees of pathology responded better to the treatment. Psychological factors in management described themselves to be a significant barrier in regulating pharmacological response. Chronic anxious patients generally achieved minimal benefit from continued anti-anxiety treatment.[14] Shehi M and Patterson WM described the successful management of 16 patients with panic attacks. The alprazolam and propranolol combination permitted doses of each drug were notably lesser compared with the normally needed dose to manage the panic disorder. This clinical study suggested a probable additive effect with this composition.[15]

To the best of the authors' understanding, this was the first study that assessed the fixed-dose combination of clonazepam with propranolol among anxiety patients in various centers. Notwithstanding the rigorous inclusion and exclusion criteria and robust methodology employed in this study, there were few limitations that could be considered when evaluating the observations. The study's sample size was small. Because the study had a smaller follow-up period and a sample of patients with comparable racial and cultural backgrounds, attention should be taken when extrapolating the findings. So, it should be proved in a larger sample with different races and ethnicities to provide more specific results.

Conclusion

This study confirmed that clonazepam 0.25 mg + propranolol 10/20 mg combination tablets were effective, safe, and well-tolerated. The FDC of clonazepam 0.25 mg + propranolol 10/20 mg tablets can be an effective option for anxiety disorder management.

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