Original Article

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Role of anti-craving drugs baclofen and topiramate in the maintenance of abstinence in alcohol dependence syndrome

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Abstract

Background: Alcohol craving is psychological condition related to motivation. Craving is risk factor for relapse in alcohol dependence syndrome. No gold standard therapy is available; many therapeutic agents are under various evaluation stages.

Objectives: To evaluate role of anti-craving drugs baclofen and topiramate in maintenance of abstinence in alcohol dependence syndrome

Methods: From March to October 2018, an open-label interventional study with 70 sample size was conducted at Nobel Medical College, following ethical clearance. Age range for inclusion was 20-60, with no history of psychotropic use, whereas history of psychiatric illness and use of substance, excluding nicotine were excluded. After written informed consent patients were admitted for detoxification, and after detoxification, anti-craving therapy was started with topiramate and baclofen and asked for follow-up at two, four, and six weeks. Clinical withdrawal assessment scale was used for withdrawal symptoms and obsessive-compulsive drinking scale (OCDS) for progress in craving. Baclofen at 20 mgs/day, topiramate at 50 mgs/day, were prescribed and increased as required at follow-up.

Results: Maximum daily dose of baclofen was 24.29 ± 2.19 mg and topiramate 120 ± 33.21 mg. Baclofen group patients had significant improvement in second week (OCDS T score 16.41± 9.52) while topiramate group showed significant improvement (OCDS T score 17.70 ± 7.57) after four weeks. Major side effects were tremors 8.10% in topiramate group, headache was 5.40% in both groups.

Conclusion: Baclofen and topiramate were equally effective at six weeks for controlling cravings. Baclofen started to show significant improvements after two weeks of trial.

Key words: Alcohol dependence syndrome; Anti-craving; Baclofen; Topiramate.

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INTRODUCTION

Alcohol craving is uncontrollable desire to take substance, that if not satisfied, provokes suffering that maybe psychological or physical, accompanied by insomnia, anorexia, anxiety, aggressiveness, asthenia, and depression.[1] Alcohol craving or alcohol related compulsion, is a motivational condition experienced by alcohol dependent patients who are currently abstinent but may relapse.[1] Craving allows prediction of relapse and is target of treatment regimens.[2] Psychobiological mode of craving has three pathways: reward, relief, and obsessive motives.[3] These motives correspond to three addiction stages: reward craving, relief craving, and obsessive craving.[4] Studies have found that craving is risk factor for relapse. Patient suffers uncontrollable urge to consume alcohol, which if uncontrolled causes relapse.[5]

Topiramate,[6] acamprosate,[7] fluoxetine,[8] naltrexone,[9] are currently used pharmacotherapeutic agents for craving control. Alcohol intake and reinforcement is caused by

mesolimbic dopamine neurons.[10] Baclofen decreases dopamine release in shell of nucleus accumbens by modulating GABA receptors.[11] GABA receptors are present on dopaminergic neurons in ventral tegmental area.[12] Dopamine neurons maybe inhibited by GABA activation due to use of GABA receptor agonist, which cause inhibitory action of dopamine system neurons.[13] Topiramate acts by antagonising excitatory glutamate receptors at amino-3- hydroxy-5-methylisoxazole-4-propionic acid and kainate receptors. It is also known to decrease mesolimbic dopamine release.[14]

METHODOLOGY

This is an open label interventional study for the effectiveness and safety profile of topiramate and baclofen as anti-craving agent in the treatment of abstinence in alcohol dependence syndrome. This study was conducted at the psychiatry outpatient services of Nobel Medical College and Teaching Hospital, Biratnagar. The present study began on March 5, 2018 and was completed in October 2018. The determined sample size was seventy. After being diagnosed as suffering from alcohol dependence syndrome, seventy patients were enrolled for the study. The study's inclusion criteria were that the participants be between the ages of twenty to sixty, have no history of using of psychotropic medication and be willing to participate in the study. Whereas those who were barred were those with identified cases of any comorbid psychiatric illness requiring treatment, no record of use of psychotropic medication, active use of any other substance excluding nicotine, and those who did not agree to participate in the study. The patients fulfilling the criteria were admitted to the inpatient care of psychiatry unit for detoxification. They were administered tab lorazepam (4-8 mg) as determined by the psychiatrist, and tab thiamine (100 mg twice daily). After the patients were detoxified and were withdrawal free, they were discharged after detoxification and started the anti-craving therapy. A semi structured questionnaire was given to the patients for in order to learn about their socio-demographic information and to enquire about their alcohol consumption habits. They were later, serially allotted into groups 1 (baclofen) and 2 (topiramate) alternatively. and asked to be followed-up on regular basis. The data was collected at the commencement of the study, two, four and six weeks later.

The clinical withdrawal assessment scale (CIWA)[8] was applied for measuring the withdrawal symptoms, and the obsessive and compulsive drinking scale (OCDS)[9] was adopted for measuring the progress in the severity of seeking behavior. Tab baclofen was prescribed at 20 mg for the first week, followed by 10 mg increment was proposed. Tab topiramate was initiated at 50 mg/day, and after each follow-up, it was proposed to be enhanced by 50 mg. Whereas, the increment of quantity was settled by the psychiatrist as per provision and after considering the adverse drug reaction. Patients were weighed for improvement on both scales at each follow-up.

Ethical considerations were paramount in the study. The study was carried out after permission from the institutional review committee (letter no. 658/2018 dated 01/03.2018). The patient and the informants were informed in detail about the study. Those patients who were ready to enroll for the study were included in it, after giving written informed consent. No one was forced to participate in the study. They were given an option to withdraw at any point during the study.

The data so collected was tabulated and analysed using descriptive analytical tools. Statistical analysis was done using the SPSS statistics for windows version 16 (SPSS Inc., Chicago, Ill., U.S.A.). Two-tailed tests were applied. To compare the socio-demographic profiles of the groups Chi-square test was used. The Mann-Whitney test was used for the assessment of craving. The p-value <0.5 were considered significant.

RESULTS

The current study has a sample size of 70 patients, 35 in each group. The socio-demographic profile is depicted below (Table 1). The average age was nearly same of 34 ± 5.41 years in group 1 and 38 ± 6.32 years in group 2. There were no females in group 1 whereas there was one female in the group 2. Majority of the patients were of lower income group (below 20,000 NPR per month) 97.14% in group (1) and, 91.42% in group (2). In group (1) 71.42% patients were undergraduate and 65.71% in group (2) were undergraduates. More patients were un employed/irregularly employed in both the groups, 82.85% in group (1) and 85.71% in group (2). The duration of alcohol use was 16 ± 5.32 years in group (1), 18 ± 2.39 years in group (2).

While studying the alcohol usage patterns in both the groups (Table 2), in group (1) 34.28% patients and in group (2) 40% had a history of dependent drinking for sixteen or more years. There were 17.14% in group (1) and 8.57% in group (2) who had less than five years of history of dependence. The patients in both the groups had tried to leave alcohol by abstaining from drinking

alcohol which amounted to 48.57% in group (1) and 51.35% in group (2). Majority of patients were having history of tobacco use either as smoking or chewing tobacco. The percentage of tobacco users in group (1) was 82.85% and group (2) was 74.28%. Majority of the patients had a pattern of habitual alcohol use; where as in group (1) 34.28% and group (2) 31.42% had binge pattern of drinking. There was a strong history of family use of alcohol in the majority of the patients. This is also socially and culturally acceptable practice in the region.

After the analysis of the mean dose (Table 3) for group (1) baclofen group was 20 ± 0.0 at the beginning of the study and maximum dose was 24.29 ± 2.19 which was marginally lower than the dose of the patients at fourth week, due to the titration of the dose to suit the patient. On the other hand, the mean topiramate dose in group (2) was 25 ± 0.0 at the initiation of the study where as the maximum mean dose was 120 ± 33.21. Topiramate was better tolerated by the patients than baclofen.

The OCDS scale measures the craving of the patients like the obsession for alcohol and compulsions to crave for alcohol in the patients during the test period. it also gives a total score of the increase or decrease in the craving (obsessive and compulsive symptoms) for drinking of alcohol in the study group. It was noted that significant reduction in the symptoms of craving was in the baclofen group than in topiramate group (Table3). The topiramate group showed significant improvement in the second follow up at four weeks whereas the baclofen group showed significant improvement in the first follow at 2 weeks on OCDS. While comparing the total OCDS score the initial score when the patient was drug naive was 26.39 ± 4.07 in Group (1) baclofen group, 25.67 ± 5.99 in group (2) topiramate group which was similar. but after first follow up which was at second week the total OCDS score was 16.41± 9.52 in baclofen group which was significant and 22.33 ± 7.46 in topiramate group which was not significant. At the second follow up the topiramate group also showed significant improvement (Table 3) with the total OCDS score at 17.70 ± 7.57. The total OCDS score at the end of the study was 4.36 ± 9.60 and 13.15 ±9.03 in baclofen and topiramate group which was statistically significant.

The common drug adverse drug reactions noted in the study is depicted below (Table 5). In group (1) 5.40% had headache and sedation respectively. Whereas, in group (2) 10.81% had sedation, 8.10% of patients had tremors. Other adverse drug reactions seen were nausea and vomiting. All adverse drug reactions were tolerable, and no therapeutic intervention was required. The dose was adjusted to a lower tolerated dose and the adverse drug reactions subsided. The adverse drug reactions were not significant. Baclofen was better tolerated than topiramate.

Table 1: Socio-demographic data of the study group 1 (baclofen) and group 2 (topiramate)

		Group 1 (baclofen)	Group 2 (topiramate)
Age in years	Mean ± SD	34 ± 5.41	38 ± 6.32
Sex (% age)	Male	35 (100%)	34 (97.14%)
	Female	0	1 (2.85%)
Socio-economic status (% age)	≤NPR 20000	34 (97.14%)	32 (91.42%)
	≥NPR21000	1(2.85%)	3 (8.57%)
Education status (% age)	Below Graduation	25 (71.42%)	23 (65.71%)
	Graduation and above	10 (28.57%)	12 (34.28%)
Occupation (% age)	unemployed/irregularly employed	29 (82.85%)	30 (85.71%)
	Employed	6 (17.14%)	5 (14.28%)
Duration of alcohol use in years	Mean ± SD	17 ± 4.82	19 ± 5.23

Table 2: Alcohol related data of the patients in Group 1 (baclofen) and Group 2 (topiramate)

		group 1 (baclofen) % (n = 35)	group 2 (topiramate) % (n = 35)	p-value
Duration of dependence	less than 5 years	6 (17.14%)	3 (8.57%)	0.77
	6 to 10 years	8 (22.85%)	9 (25.74%)	
	11 to 15 years	9 (25.74%)	9 (25.74%)	
	above 16 years	12 (34.28%)	14 (40%)	
Tried abstinence	yes	17 (48.57%)	19 (51.35%)	0.621
	no	18(51.42%)	16(45.71%)	
Pattern of drinking	habitual	23(65.71%)	24 (68.57%)	0.712
	binge	12 (34.28%)	11 (31.42%)	
Tobacco use	yes	29 (82.85%)	26 (74.28%)	0.892
	no	6 (17.14%)	9 (25.71%)	
Family History of alcohol use	present	26 (82.85%)	27 (77.14%)	0.62
	absent	9 (25.71%)	8 (22.85%)	

Table 3: Score of obsessive compulsive drinking scale (OCDS) in Group 1 (baclofen) and Group 2 (topiramate)

		Baseline (before starting therapy)	Second week mean ± sd (First follow-up)	Fourth week mean ± sd (Second follow-up)	Sixth week mean ± sd (Third follow-up)
Dose (milligrams)	Group 1 (Baclofen)	-	20 ± 0.0	24.32 ± 4.12	24.29 ± 2.19
	group 2 Topiramate	-	25 ± 0.0	50 ±23.12	120 ±.33.21
OCDS (obsession)	Group 1 Baclofen	13.24 ± 2.62	9.52 ± 3.29#	5.29 ± 3.98$	2.83 ± 5.32@
	Group 2 Topiramate	12.46 ± 3.12	11.67 ± 4.32!	9.59 ± 6.32! $	7.34 ± 5.62! @
OCDS (compulsion)	Group 1 Baclofen	13.15 ± 1.45	6.89 ± 6.23#	3.72 ± 3.29$*	1.53 ± 4.28@*
	Group 2 Topiramate	13.21 ± 1.92	10.66 ± 3.14!	8.11 ± 7.21$	5.81± 3.41@
OCDS (total)	Group 1 Baclofen	26.39 ± 4.07	16.41± 9.52#	9.01± 7.27$	4.36 ± 9.60@
	Group 2 Topiramate	25.67 ± 5.99	22.33 ± 7.46!	17.70 ± 7.57$*	13.15 ±9.03@*

! Significant difference between baclofen and topiramate (0.05), *Significant difference between baclofen and topiramate (0.001), #Significant difference between baseline and 2nd week assessment, $Significant difference between baseline and 4th week assessment, @Significant difference between baseline and 6th week assessment, OCDS – Obsessive and compulsive drinking scale; SD – Standard deviation;

Table 4: Adverse drug reaction seen in Group 1 (baclofen) and Group 2 (topiramate)

	Group 1 (baclofen) %	Group 2 (topiramate) %
Tremors	0	3 (8.10%)
Headache	2 (5.40%)	2 (5.40%)
Sedation	2 (5.40%)	4 (10.81%)
Nausea	1 (2.70%)	1 (2.70%)
Vomiting	1 (2.70%)	1 (2.70%)
Pain abdomen	1 (2.70%)	2 (5.40%)
Constipation/diarrhea	1 (2.70%)	1 (2.70%)

DISCUSSION

Alcohol craving is an important factor in resuming drinking after detoxification in an alcohol dependent patient. It is essential to recognize this important factor and treat it in time to provide timely intervention. The alcohol dependence syndrome has multiple causative factors that interact with each other, like genetic, psychological, biological, and environmental factors. These factors are involved in the causes of relapse in patients following successful detoxification and abstinence.[4]

The current study is aimed at studying the efficacy and tolerability of baclofen and topiramate in alcohol dependence patients. It was noted at the completion of six weeks of the study that both drugs had significantly improved the craving symptoms: the OCDS total score was 4.36 ± 9.60 in the baclofen group and 13.15 ±9.03 in the topiramate group (Table 3). Baclofen had shown improvement in the first follow-up which was after two weeks and it was significant the OCDS total scale score was 16.41± 9.52. Topiramate did show significant improvement after the second follow up which was after four weeks with an OCDS total score of 13.15 ± 9.03.

The greater efficacy of baclofen initially over topiramate could be due to the suppressant effect of anti-craving. It resulted in a significant reduction in obsessive and compulsive symptoms (Table 3), as evidenced by a decrease in the mean score in the OCDS sub scales. This leads to less craving and the continuance of abstinence. Addolorato et al. observed a similar effect in their study in 2000: baclofen administration significantly reduced craving from the first week of the therapy ($p < 0.01$) and continued throughout the study period. Obsessional thinking about alcohol disappeared during the study period. None of the patients had an alcohol craving, and their tolerability was also good. The common side effects that were noted are constipation/diarrhoea, pain in the abdomen, headache, vertigo, nausea, sedation and laziness.[15] In another 2007 study of cirrhosis patients, Addolorato et al. compared baclofen with placebo: 71% had abstinence in baclofen group and 29% in the placebo group (odds ratio 6·3 [95% CI 2·4–16·1]; p = 0·0001). The patients who left the study were similar in both groups (p = 0·12). Baclofen had twice the number of patients with continued abstinence (mean 62·8 [SE 5·4] vs 30·8 [5·5] days; p=0·001). Hence, baclofen maintained two times higher anti craving properties and tolerability than placebo.[16] A similar finding was noted by Capristo's 2002 study, comparing baclofen and placebo, a similar finding was noted. Baclofen use led to the maintenance of abstinence and a decrease in the obsessive and compulsive symptoms of alcohol craving compared with placebo. There was manageable side effect so the drug was safe to use.[17] These studies mention that the baclofen dose of 20–30 mg/day is efficacious and safe dose for administration of baclofen in alcohol dependence patients.[16,17,18] At the end of our study, the mean baclofen dose was 24.29 ± 2.19 mg. Which is similar to the other studies.

Topiramate, on the other hand, in the current study did not show any significant improvement at the first follow-up which was at two weeks, but the significant improvement was noted at the second follow up at four weeks the total OCDS score was 17.70 ± 7.57 (Table 3). In our study the mean topiramate dose at four weeks was 50 ±23.12 mg with a significant improvement. Earlier studies found that doses of around 200 mg were required to produce an improvement in the anti-craving effect. In a review of literature by Olmsted & Kockler, topiramate was titrated to 300 mg per day. Decreased drinking and quality of life improvement was noted. Topiramate side effects included difficulty with memory and decreased concentration, skin sensations and pruritus, dizziness, and anorexia.[18] In a study of one hundred and eighty two patients suffering from alcohol dependence syndrome, patients in an open label study were given a trial of naltrexone and topiramate. After six months of evaluation, the topiramate group had lower OCDS scores. The vast majority of patients maintained their abstinence. 200 milligrams (mg) of topiramate were better than 50 mg of naltrexone for decreasing the cravings for alcohol.[19]

However, our study found that low doses of topiramate (50 ± 23.12 milligram) reduced alcohol craving (Table 3). Certain studies have also shown that low doses of topiramate cause improvement of craving symptoms. In an open-label, controlled study by Paparrigopoulos et al. to assess the effectiveness of topiramate in low dosages (75 milligram), in a 16-week trial. The scores of obsessive-compulsive drinking symptoms improved ($p < 0.01$). Following four months of follow-up, the topiramate group had a lower relapse rate (66.7%) than the control group (85.5%), ($p = 0.043$). it was concluded that low-dose topiramate is tolerated and effective in decreasing alcohol craving.[20]

The current study, an initial study in this domain, has a small sample size, a short duration of only six weeks, is open label, has no randomisation, and lacks control group. These are the shortfalls of our study. The current study opens the door for further research on the role of

topiramate and baclofen for regular use as an anti-craving agent in regular practice to prevent relapse in alcohol dependent patients who are detoxified. It is further recommended that new studies with randomization, larger sample sizes, and longer follow up durations be done to further enhance our knowledge in this arena. So that more data will be available in this topic for clinical implementation.

CONCLUSION

Baclofen is more efficacious and tolerable than topiramate. Baclofen at low doses showed early improvement whereas topiramate also showed improvement on low doses but after four weeks.

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