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Comparative assessment of safety and efficacy of Vortioxetine with Escitalopram in patients with MDD (Major Depressive Disorder): a randomized, comparative, parallel group, open-label study

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Abstract

Background & Objectives: SSRIs and SNRIs are the preferred treatment options for patients of Major Depressive Disorder (MDD). But nonadherence and premature discontinuation due to side effects is a problem with these agents. These agents also do not adequately address cognitive dysfunction associated with MDD. Vortioxetine is a novel agent, which is known to have good efficacy and pro-cognitive property as well as good tolerability. Since there are very few studies, we aimed to compare efficacy and safety of vortioxetine with escitalopram in patients of MDD.
Methods: 60 patients were randomized in 1:1 ratio to receive either vortioxetine 10mg or escitalopram 10mg for 8 weeks. Primary efficacy measure was mean change in MADRS score from baseline to 8 weeks. Secondary efficacy measures were mean change in HDRS and CGI scores. Cognitive improvement was measured using mean change in DSST and PDQ-5 scores. Safety was compared using mean change in the values of baseline laboratory parameters and weight at the end of 8 weeks' treatment and adverse events were also recorded in each group.
Results: Mean change in MADRS was significantly better in vortioxetine compared to escitalopram ($p<0.05$). Mean change in HDRS was numerically higher in vortioxetine but statistically not significant. Mean change in CGI-S was significantly better in vortioxetine group, but CGI-I score was similar in both groups. In terms of cognitive improvement vortioxetine was significantly better on both DSST and PDQ-5 scales.
Conclusion: Vortioxetine may be a better option in MDD patients with cognitive dysfunction.
Keywords: vortioxetine, escitalopram, depression, cognition.

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1. Introduction

In the last 20 years, new antidepressant classes have come into existence. Second generation antidepressants like selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the main therapeutic drugs employed in MDD now. [1] Although these antidepressants have several advantages over TCAs, continuous use of these drugs leads to various problems like sexual dysfunction, gastrointestinal disturbances, weight gain and somnolence. [2] It is also seen in clinical practice that 40-60% of patients with MDD do not respond significantly to the first-line treatment. [3] Nonadherence and premature discontinuation of medication because of side effects are two of the most common reasons that therapy fails in current practice. [4]

MDD patients also frequently present with cognitive symptoms which often persists even after they have recovered from their mood symptoms. [5] This typically affects the ability to concentrate, remember, plan and make decisions and may thus directly compromise work performance. [6] Therefore, only mood symptoms may not adequately address the complexity of depressive symptoms, which comprises emotional as well as cognitive and physical dimensions. [7] Thus, there is a strong need for improved therapies with better tolerability and effectiveness that can address depressive symptoms as well as cognitive symptoms.

Vortioxetine is supposed to have multimodal activity related to a combination of two pharmacological modes of action: first is direct modulation of receptor activity and second is inhibition of the 5-HT (serotonin) transporter. Vortioxetine acts as a 5-HT1A receptor agonist, 5-HT1B receptor partial agonist, 5-HT3, 5-HT7, and 5-HT1D receptor antagonist and inhibitor of the 5-HT transporter (SERT). [8] This multimodal pharmacological activity is thought to be responsible for the antidepressant effects and improvement of cognitive function of vortioxetine.

After extensive literature search using PubMed, Embase, Google scholar we could find very few studies of vortioxetine and none in Indian population. Hence this study was planned with the aim to compare its efficacy and safety with escitalopram, an established antidepressant drug, in Indian population.

2. Material and Methods

This was a randomized, open-label, parallel group, comparative study conducted in patients of depression attending Psychiatry OPD of a tertiary care teaching hospital. The study was initiated after approval of the Institutional Ethics Committee & was carried out in accordance with Good Clinical Practice guidelines & the ethical principles as mentioned in the Declaration of Helsinki. Patients' information sheet was given to all prospective participants. Written informed consent was taken from each participant before enrolment. The study was registered in Clinical Trial Registry - India (CTRI.in) with CTRI no. CTRI/2019/11/022030 prospectively before enrolling the patients.

Patients of either gender aged 18-60 years with newly diagnosed MDD having MADRS (Montgomery–Åsberg Depression Rating Scale) score ≥22 were randomized in two groups in 1:1 ratio with the help of computer-generated table of random numbers, either to receive vortioxetine 10 mg tablet once a day or escitalopram 10 mg tablet once a day for a period of 8 weeks. Patients with any other co-morbidities, patients with substance abuse, patients with two failed antidepressant treatments (of at least 6 weeks duration), patients who have made a suicide attempt in previous 6 months and patients who have received electroconvulsive therapy in the preceding 6 months were excluded from the study. Patients were called for follow-up at 2, 4, 6 and 8 weeks. In each follow-up visit patients were given tablets for next 2 weeks free of cost. The expenses were born by the principal investigator only. No external funding or sponsorship was involved.

Primary efficacy measure was comparing the efficacy of vortioxetine with escitalopram using mean change in MADRS (Montgomery–Åsberg Depression Rating Scale) score from baseline to 8 weeks in patients with MDD. Efficacy was also measured using mean change in HDRS (Hamilton Depression Rating Scale) and Clinical Global Impression (CGI) scale at the end of 8 weeks. Cognitive improvement was measured using mean change in DSST (Digit Symbol Substitution Test) score and Perceived Deficits Questionnaire-5 (PDQ-5) score after 8 weeks. Safety was compared using mean change in the values of baseline laboratory investigations and weight at the end of 8 weeks' treatment and adverse events were also recorded in each group.

Sample size was calculated using PS for Sample Size ver. 3.1.6. Software. Minimum expected difference between the two groups was taken as 0.7 with standard deviation 0.9 from previous study. With 0.05 level of significance and 80% power sample size came out to be 27 in each group. Considering 10% drop out rate final sample size in each group was taken as 30.

Statistical analysis was done using Graph pad prism version 8.4.2. Analysis was done by intention to treat basis. Missing visit data were substituted by the last observation carried forward (LOCF) strategy. For safety analysis, all randomized subjects who had received at least one dose of trial medication were considered evaluable. Descriptive statistics were reported as percentage or mean ± standard deviation. Categorical variables were reported as actual numbers and percentage. For comparison of continuous parametric variables student's t-test was used. Non-parametric variables were compared between groups by Mann-Whitney U test and within group by Friedman's ANOVA followed by post hoc Dunn test. Categorical data was compared using Chi-square or Fisher's exact test as appropriate. Value of $P \leq 0.05$ was considered statistically significant.

3. Results

92 patients were assessed for eligibility. Out of these 32 patients were excluded. 60 patients were randomized. 6 patients were lost to follow-up so 54 patients were included for statistical analysis (Figure 1). Mean age of patients was

34.6 years. 23.2% patients were males and 76.8% were females. Demographic characteristics and baseline data was comparable between the groups (Table 1).

Efficacy measures and cognitive measures were compared within the group in vortioxetine and escitalopram groups and both showed significant improvements in all parameters from baseline to 8 weeks. These parameters were also compared between the groups (Table 2). Improvement in MADRS, which was our primary efficacy parameter, was significantly better in vortioxetine compared to escitalopram. In secondary efficacy parameters, improvement in HDRS, though statistically not significant, was numerically better in vortioxetine group than escitalopram group. Improvement in CGI-S was significantly better in vortioxetine group, but CGI-I score improvements were similar in both the groups. In terms of cognitive improvement vortioxetine was significantly better than escitalopram on both DSST and PDQ-5 scales.

Safety parameters were also compared between both the groups from baseline to 8 weeks. There was no significant difference in any of the parameters. Adverse events were similar in both the groups nausea being the commonest.

Figure 1: Study flowchart

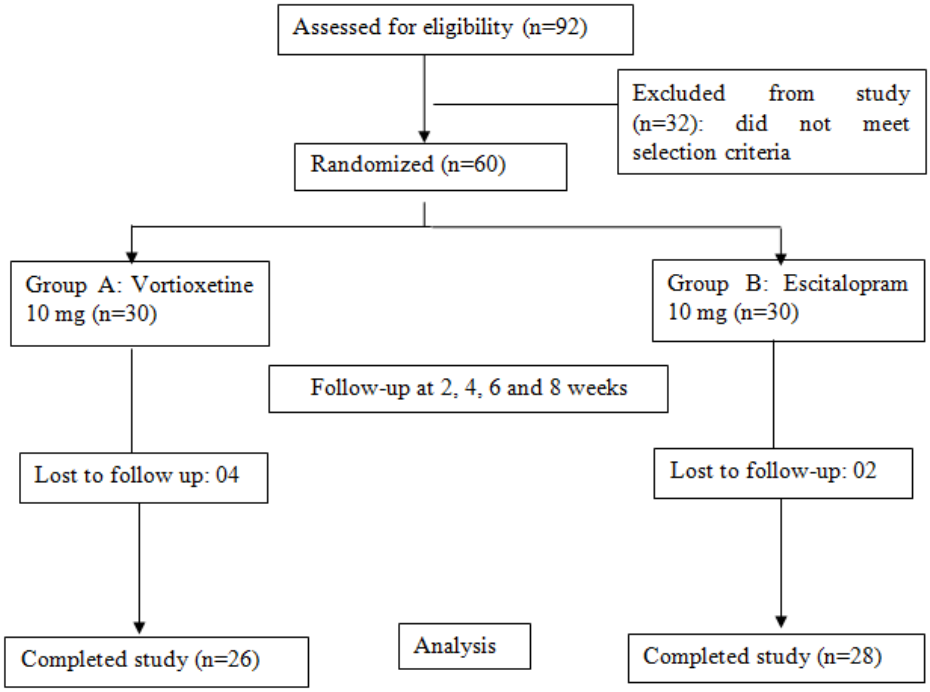

Table No.1: Baseline demographic data and clinical characteristics of MDD patients

Characteristics	Vortioxetine group (n=26)	Escitalopram group (n=28)	p-value
Age (year)	35.73 (11.27)	34.04 (10.74)	0.5740$
Males: Females	1:3	1:33	0.8688^
Weight (kilograms)	57.27 (11.09)	55.21 (10.28)	0.4828$
Alkaline phosphatase (IU/Lt)	91.38 (38.23)	95.43 (43.04)	0.6092#
SGOT (IU/Lt)	28.46 (4.868)	28.71 (5.603)	0.8607$
SGPT (IU/Lt)	24.85 (7.816)	24.86 (8.935)	0.9962$
Serum bilirubin (mg/dl)	0.6846 (0.244)	0.6571 (0.164)	0.6277$
Blood urea (mg/dl)	19.50 (3.808)	19.64 (3.861)	0.8917$
Serum creatinine (mg/dl)	0.7615 (0.129)	0.7821 (0.130)	0.5161#
MADRS	29.08 (7.766)	26.93 (5.381)	0.4003#
HDRS	17.31 (5.978)	15.29 (4.108)	0.3528#
CGI-S	4.192 (0.401)	4.107 (0.315)	0.4602#
DSST	18.65 (14.97)	21.50 (14.25)	0.2748#
PDQ-5	6.077 (4.232)	4.821 (3.926)	0.2803#

Values are expressed as mean (SD)
$ Unpaired 't' test; # Mann-Whitney test; ^ Chi-square test

Table No. 2: Comparison of mean change in efficacy and cognition parameters from baseline to 8 weeks between vortioxetine and escitalopram groups

Parameters	Vortioxetine group (n=26)	Escitalopram group (n=28)	P value
MADRS	-25.926 (7.183)*	-22.144 (4.836)	0.0337
HDRS	-15.73 (5.668)	-12.82 (3.830)	0.0657
CGI-S	-2.462 (1.104)*	-1.893 (0.956)	0.0148
CGI-I[#]	-1.192 (0.749)	-1.393 (0.628)	0.3787
DSST	6.038 (3.053)*	4.179 (1.541)	0.0169
PDQ-5	-5.769 (3.963)**	-3.036 (2.899)	0.0065

Values are expressed as mean (SD) ; Mann-Whitney test is applied
[#] mean change from 2 weeks to 8 weeks

4. Discussion

Vortioxetine 10 mg and escitalopram 10 mg both significantly improved MADRS score at the end of 8 weeks' treatment in patients with MDD. But improvement was statistically more significant with vortioxetine compared to escitalopram. Cognitive improvement was also significantly more with vortioxetine compared to escitalopram at the end of 8 weeks assessed using DSST and PDQ-5 scores. Vortioxetine and escitalopram both were well-tolerated.

Efficacy of vortioxetine has been well-established in patients with MDD in placebo-controlled randomized controlled trials (RCTs) but comparison with a first-line drug has been done in only in a few RCTs. Our results are in line with Levada *et al*, who concluded in their study comparing vortioxetine and escitalopram that vortioxetine was superior to escitalopram in improving cognition and other functioning domains in MDD patients and also well-tolerated. [9] Vieta *et al* compared vortioxetine and escitalopram in patients with inadequate response to current antidepressant monotherapy. [10] They found that vortioxetine is as efficacious as escitalopram and well-tolerated with beneficial effect on cognition in MDD patients, however in our study vortioxetine was more efficacious. Mahableshwarkar *et al*., Inoue *et al*. and Baune *et al*. all compared vortioxetine's efficacy and safety with placebo in MDD patients in different studies and reported vortioxetine as significantly more efficacious than placebo. [11-13]

Vortioxetine's multimodal mechanism of action differentiates it from currently used SNRI and SSRI antidepressants like escitalopram. Vortioxetine acts as selective blocker of serotonin reuptake (by inhibiting the serotonin transporter [SERT]) and direct modulator of 5-HT receptors activity (such as 5-HT3, 5-HT7, 5-HT1D, 5-HT1A and 5-HT1B) while escitalopram inhibits only serotonin reuptake (blockade of SERT). Due to this multimodal action, vortioxetine inhibits some negative feedback mechanisms that control neuronal activity in key areas of the brain involved in major depression, particularly dorsal and median raphe nuclei and the prefrontal cortex. [14] Moreover, vortioxetine is known for antidepressant effect at SERT occupancies as low as 50% while SSRIs and SNRIs require at least 80% occupancy for their antidepressant effects. [15] These factors may be responsible for vortioxetine's better efficacy compared to escitalopram.

Better cognitive improvement due to vortioxetine could be explained by its multimodal action, which combines effects on the monoaminergic and glutamatergic systems. [9] According to Sanchez *et al*. vortioxetine differs from the SSRIs fluoxetine and escitalopram in that it significantly increases excitatory synaptic transmission and neuroplasticity. [14] Preclinical studies using receptor-selective compounds indicate that 5-HT1A, 5-HT1B, 5-HT3 and 5-HT7 receptors can regulate cognitive functions. Vortioxetine acts on all these receptors. Vortioxetine also enhances cholinergic and histaminergic neurotransmission, which play important roles in cognition. [16] In addition, vortioxetine's multi-receptor activities may also modulate glutamate neurotransmission and affect cognition, either directly or indirectly via GABA interneurons. [17]

The strength of our study is that it's the first study in Indian population comparing vortioxetine and escitalopram assessing improvement in depressive symptoms and cognition as well as safety for both the drugs. Some of the limitations in our study are 1. It is an open-label study hence probability for bias cannot be excluded. 2. Some the patients who were recruited could not complete some follow-ups hence we have used last observation carried forward (LOCF) method for analysis.

5. Conclusion

In our study, vortioxetine was more efficacious than escitalopram in improving depression severity as MADRS and CGI-S scores and also cognitive dysfunction as DSST and PDQ-5 scores. Further clinical studies will help to establish the efficacy of vortioxetine in Indian population.

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