Original Article

Effects of Combination Therapy of Escitalopram with Magnesium Oxide versus Escitalopram Alone in Major Depressive Disorder

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Abstract

Background: *Major depressive disorder (MDD) is one of the most common mental illnesses and a leading cause of disability worldwide. Medications and psychotherapy together act well for remission of MDD. The aim of the study was to determine the efficacy of Escitalopram with MgO versus Escitalopram alone in the treatment of major depressive disorder.*

Materials and Methods: *This randomized clinical trial on major depressive disorder was conducted in the Department of Pharmacology and Therapeutics in collaboration with the outpatient department of Psychiatry, Rajshahi Medical College Hospital, Rajshahi for a period of 1 year from July 2022 to June 2023. Based on predefined eligibility criteria, a total number of 90 patients with major depressive disorder were included in this study. The study population was divided into two groups. In Group-A (study group) 45 patients were treated with Escitalopram (10 mg/day) with MgO (365 mg/day) and in Group-B (control group) 45 patients were treated with Escitalopram (10 mg/day) alone for 12 weeks.*

Results: *The mean ages of the patients were 26.31 ± 7.85 years and 24.98 ± 5.38 years in the study group and control group, respectively. Reduction of BDI-II (BV) test score from baseline to the end of 12 weeks of drug administration between the two groups was found statistically highly significant ($p < 0.001$). The mean percent of reduction of BDI-II (BV) test scores were 89.39±9.41 and 62.43±9.98 in study group and control group, respectively and it was also statistically highly significant ($p < 0.001$). On the basis of achievement of BDI-II (BV) test score ≤ 13, Escitalopram with MgO was more effective than Escitalopram alone in major depressive disorder and it was statistically highly significant ($p < 0.01$).*

Conclusions: *So, The combination of Escitalopram with Magnesium oxide (MgO) is more beneficial in MDD than Escitalopram alone.*

Key words: *Major Depressive Disorder, Beck Depression Inventory-II (BV) test score, Escitalopram and MgO.*

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Introduction

Depressive disorder is a common, debilitating and sometimes fatal disorder which limits occupational and social functioning and diminishes well-being quality of life (QOL). Depression is the leading factor in suicidal death and globally, it is the largest contributor to non-fatal health loss. In 70–80% cases, depression is a chronic recurring condition and antidepressant drugs are not always effective.[1] Escitalopram (SSRI) is a widely used antidepressant drug that selectively binds to the human serotonin transporter (SERT) and inhibits serotonin (5-HT) reuptake.[2] So, it increases the amount of serotonin in synaptic clefts which results in antidepressant action. About 30% to 50% patients do not respond to initial antidepressant and 15% of them continue to suffer from symptoms despite the completion of multiple antidepressants, in addition to facing unwanted adverse drug reactions.[3]

Magnesium (Mg2+) is a micronutrient which plays a critical role in brain function and mood. It ensure that magnesium is responsible for the correct functioning of all human cells, neurons, intracellular transmission, myelination process,

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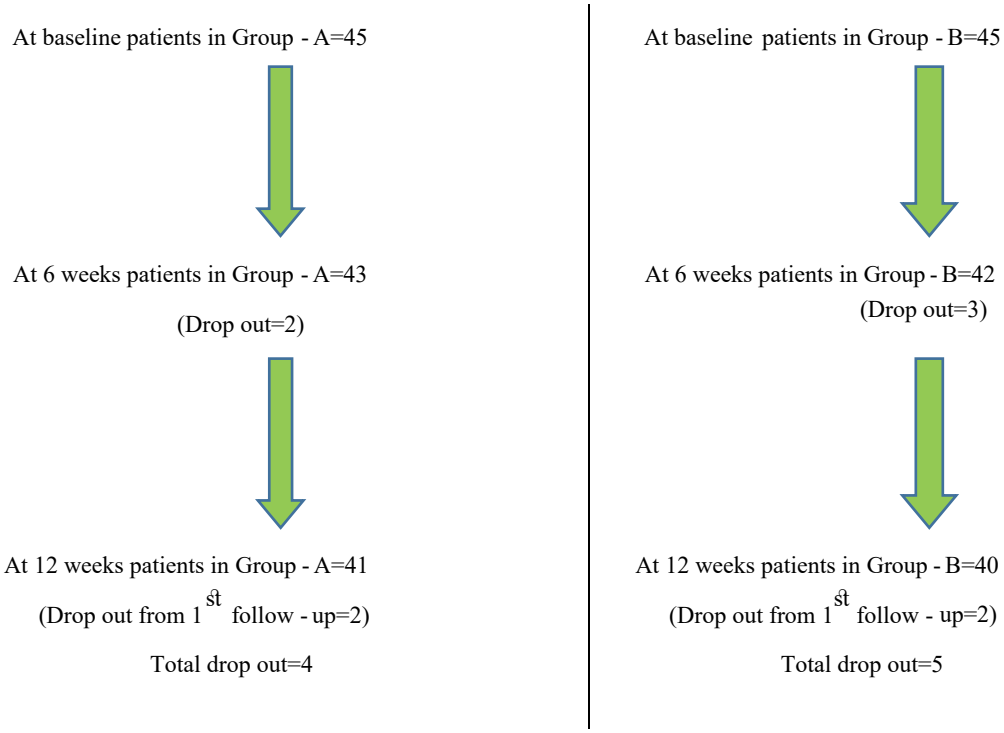
synapses formation and maintenance as well as in the regulation of serotonergic, dopaminergic and cholinergic transmission.[4,5] Several studies reported that there is an association between magnesium and depression and it is proven that magnesium works well in depression. Magnesium may be supplied in various forms in the body such as magnesium oxide, chloride, citrate, orotate etc.[6] In the study, magnesium oxide was used because MgO contributes more magnesium than any other magnesium supplement. Magnesium oxide is an over the counter drug and it can be safely used in combination with SSRI because only magnesium is not enough to reduce the symptoms properly. As there was limited data on combined effect of Escitalopram with MgO, the current study was undertaken to evaluate the combined effect of Escitalopram with MgO than Escitalopram alone in major depressive disorder.

Materials and Methods

A total ninety patients who were diagnosed as major depressive disorder by the psychiatrist and matched with the eligibility criteria were recruited in this study. All consenting patients, in the age group of 18-60 years, who were diagnosed by the psychiatrist as suffering from major depressive illness were included in the study. Patients who were pregnant, lactating and nonconsensual as well as those who had a history of taking psychotropics treatment within three months prior to baseline visit were excluded from the study. After informed written consent, the patient's history like age, sex, family history, comorbidities (diabetes mellitus, hypertension), past history of mental illness and treatments, duration of current disorder and associated disorders were obtained and recorded in the data-sheet. The patients were examined by the designated physicians and were evaluated on the basis of BDI-II (BV) test which contained 21 statement. Beck Depression Inventory-II (Bangla Version) Scale score was measured initially at baseline then again at the end of the 6 and 12 weeks of drug administration.

Patients were randomly allocated into group A and group B for allotment of the respective drug. Out of the 90 patients, 45 were received Escitalopram (10 mg/day) with MgO (365 mg/day) for 12 weeks and the other 45 were received Escitalopram (10 mg/day) for 12 weeks orally. Patient compliance was assessed by pill-count method on every visit. Patients were instructed to consult the physician immediately in case if any unusual side effects (nausea, vomiting, diarrhea, abdominal pain, appetite changes, headache and vertigo) occur before the follow-up date.

They were followed up 6 weeks later of initiation of treatment and 12 weeks later of initiation of treatment. During each visit, the scores of BDI-II (BV) test were calculated as mentioned above and recorded for statistical analysis. Any reported adverse drug reactions were also noted. The therapeutic efficacy was evaluated after completion of treatment. Patients were considered normal when there was a score of 30 or less in BDI-II (BV) test. The violation of protocol was recorded and the data were analyzed on the intent-to-treat basis. Data were analyzed by SPSS software, version-24.



Flow chart: Allocation of patients in the study

Results

Table I: Comparison of baseline variables between the two groups (n=45 in each group).

Variables	Group		p-value
	Group -A (Escitalopram with MgO) (n = 45)	Group -B (Escitalopram alone) (n = 45)	
Mean age (Years) #	26.31 ± 7.85 years	24.98 ± 5.38 years	> 0. 05
Mean BMI (Kg/m^2) #	21.71 ± 4.51 kg/m^2	23.08 ± 4.90 kg/m^2	> 0.05
Mean monthly family income (taka) *	30866.67 ± 15099.07 taka	23688.89 ± 9117.47 taka	> 0.0 5
Sex*			
Male	14 (31.10%)	23 (51.10%)	> 0. 0 5
Female	31 (68.90%)	22 (48.90%)	
Occupational status *			
Housewife	8 (17.78%)	13 (28.90%)	> 0.05
NGO worker	4 (8.89%)	6 (13.30%)	
Businessman	30 (66.67%)	22 (48.90%)	
Others	3 (6.67%)	4 (8.90%)	

*Chi-squared Test (2) was done to analyze the data and were presented as frequency (%). #Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

The mean ages of the patients in Group-A and Group-B were 26.31 ± 7.85 years and 24.98 ± 5.38 years, respectively and statistically non-significant (p > 0.05). The mean BMI of patients in Group-A and Group-B were 21.71 ± 4.51 kg/m2 and 23.08 ± 4.90 kg/m2, respectively and statistically not significant (p > 0.05). The mean monthly family income of the patients in Group-A was tk 30866.67 ± 15099.07 and in Group-B was tk 23688.89 ± 9117.47 and statistically non-significant (p > 0.05). Gender and occupational status were also statistically non-significant between the two groups (p > 0.05) in both cases (Table I).

Table II: Monitoring of BDI-II (BV) test score at different time intervals in the two groups (4 patients in Group-A and 5 patients in Group-B dropped out).

Time of evaluation	Group - A (Escitalopram with MgO) (n=45)	Group - B (Escitalopram alone) (n=45)	F, p - value #
	mean ± SD		
At baseline	30.90±5.96	32.10±9.38	
At 6 weeks	11.83±5.69	22.98±8.33	15.56, < 0.001
At 12 weeks	3.03±1.44	11.58±2.73	

(#Data were analyzed with Repeated Measure ANOVA statistics and were presented as mean ± SD.)

In Group-A, the mean BDI-II (BV) test score at baseline was 30.90±4.96 which decreased to 11.83±4.69 at the end of 6 weeks and then to 3.03±2.44 at the end of 12 weeks of drug administration. On the other hand, in Group-B, the mean score at baseline was 32.10±3.38, which decreased to 22.98±3.33 at the end of 6 weeks and then to 11.58±2.73 at the end of 12 weeks of drug administration. Reduction of BDI-II (BV) test score from baseline to the end of 12 weeks of drug administration between the two groups was found statistically highly significant ($p < 0.001$) (Table II).

Table III: Comparison of the percentage of reduction of BDI-II (BV) test score from baseline to 2nd follow-up between the two groups (4 patients in Group-A and 5 patients in Group-B dropped out).

Percent of reduction	Group - A (Escitalopram with MgO)	Group - B (Escitalopram alone)	t - value p - value #
	mean ± SD		
BDI - II (BV) test score	89.39±9.41	62.43±9.98	7.72 < 0.001

(#Data were analyzed with an Independent sample test and were presented as mean ± SD.)

Reduction of BDI-II (BV) test score between the two groups revealed that after 12 weeks of drug administration, the mean percent of reduction test scores were 89.39±9.41 and 62.43±9.98 in Group-A and Group-B, respectively and it was statistically highly significant ($p < 0.001$) (Table III).

Table IV: Efficacy of Escitalopram with MgO over Escitalopram alone based on achievement of BDI-II (BV) test score ≤ 13 (Group-A=41 and Group-B=40).

BDI - II (BV) test score	Group - A (Escitalopram with MgO) n (%)	Group - B (Escitalopram alone) n (%)	Total n (%)
≤ 13	34 (64.20%)	19 (35.80%)	53 (65.40%)
> 13	7 (25.00%)	21 (75.00%)	28 (34.60%)
Total	41 (50.60%)	40 (49.40%)	81 (100.00%)

$\chi^2 = 11.24$, df=1, $p < 0.01$

Escitalopram with MgO was more effective than Escitalopram alone in major depressive disorder on the basis of achievement of BDI-II (BV) test score ≤ 13 and it was statistically highly significant ($p < 0.01$) (Table IV).

Discussion

Depression is a chronic, recurring condition in the majority of cases and is also a significant burden on global healthcare resources. It is one of the most common reasons for visiting a general practitioner. Selective serotonin reuptake inhibitors (SSRIs) are the first developed drugs for the treatment of major depressive disorder as well as anxiety disorders. Escitalopram has been used for more than 20 years in the treatment of major depressive disorder. But recent evidence states that MgO added to Escitalopram act more effectively than only Escitalopram in major depressive disorders. The aim of this trial was to determine the effects of Magnesium administration with Escitalopram on 90 patients suffering from major depressive disorder.

In this study, the mean age of the patients in the Escitalopram with MgO group was 26.31 ± 7.85 years and in the Escitalopram alone group was 24.98 ± 5.38 years. Findings were not similar in a study done by Rajizadeh et al.[7] where the mean age was 32.20±9.54 years in the magnesium oxide group.[7] Yevtushenko et al.[8] found that mean age of the patients in Escitalopram group was 35.19±0.63 years which was also dissimilar with our study.

In the current study, gender distribution of the patients revealed that in the Escitalopram with MgO group, majority 31 (68.90%) of the patients were female and the remaining 14 (31.10%) were male. But in the Escitalopram alone group, more than half 23 (51.10%) of the patients were male and 22 (48.90%) were female. Nearly similar findings were found in a study done by Yevtushenko et al., (2007) where 66 (61.1%) were female and 42 (38.9%) were male in the Escitalopram group.[8] Rajizadeh et al.[7] found that 73.10% were female and 26.90% were male in the magnesium oxide group.[7]

In the present study, educational status of the patients revealed that in Escitalopram with MgO group, 19 (42.20%) of the patients had secondary and higher secondary, 14 (31.10%) had graduate and above, 8 (17.80%) had read & write and 4 (8.90%) had primary level of education. On the other hand, in Escitalopram alone group, 18 (40.00%) of the patients had graduate and above, 16 (35.60%) had secondary and higher secondary, 8 (17.80%) had read & write and 3 (6.70%) had primary level of education. Findings were not similar with a study done by Rajizadeh et al.7 where 15 (57.60%) had B.S., 7 (26.90%) had diploma, 2 (7.70) had elementary and 2 (7.70%) had associate degree in magnesium group.[7] There were large variations in educational parameters of the study from our study might be due to regional variations.

In this study, in Escitalopram with MgO group, majority 30 (66.67%) of the patients were businessman, 8 (17.78%) were housewife, 4 (8.89%) were NGO worker and only 3 (6.67%) were involved in others occupation. Similarly, in Escitalopram alone group, 22 (48.90%) of the patients were businessman, 13 (28.90%) were housewife, 6 (13.30%) were NGO worker and 4 (8.90%) were involved in others occupation. Findings were not similar with a study done by Rajizadeh et al.[7] where 11 (42.30%) were housewife, 9 (34.60%) were employed, 5 (19.20%) were unemployed and 1 (3.80%) were self-employed in magnesium group.[7] There were large variations in occupational parameters of the study from our study might be due to regional variations.

In the present study, the mean BMI of Escitalopram with MgO group was 21.71 ± 4.51 kg/m^2 and Escitalopram alone group was 23.08 ± 4.90 kg/m^2. Rajizadeh et al.[7] reported that mean BMI was 28.58±4.50 kg/m^2 in magnesium group.[7]

In this study, in Escitalopram with MgO group mean BDI-II (BV) test score at baseline was 30.90±4.96 which decreased to 11.83±4.69 at the end of 6 weeks and then to 3.03±2.44 at the end of 12 weeks of drug administration. On the other hand, in Escitalopram alone group, mean score at baseline was 32.10±3.38 which decreased to 22.98±3.33 at the end of 6 weeks and then to 11.58±2.73 at the end of 12 weeks of drug administration. The overall reduction of BDI-II (BV) test score from baseline to the 12 weeks of drug administration between the two groups was found statistically highly significant ($p < 0.001$). Similar findings were found in a study done by Rajizadeh et al.[7] where BDI-II (BV) test score was 26.90±7.10 at baseline which reduced to 11.26±6.90 at the end of magnesium administration and it was statistically highly significant ($p < 0.001$).[7] Yevtushenko et al.[8] reported that MADRS total score at baseline was 34.78±0.34 in Escitalopram group which reduced to -5.28 (0.51) at 1st week and -9.00 (0.94) at 4 weeks and -9.46 (0.92) at 6 weeks and the reduction was statistically highly significant ($p < 0.001$).[8] So far I explore no related scientific article on BDI-II (BV) test score between Escitalopram with MgO group and Escitalopram alone group was found.

Eby and Eby[6] also investigated the effect of magnesium supplement (125-300 mg in the form of turinate or glicinate) on three depressed individuals and observed rapid improvement of major depression in all.[6] Although in the mentioned study the status of serum magnesium was not examined in individuals at the prescribed dosage, the obtained results were in line with ours.

Daily consumption of 500 mg Magnesium oxide supplement for 8 weeks results in improvement of the status of serum magnesium and depression of depressed people suffering from hypomagnesemia. Barragán-Rodríguez et al.[9] conducted a similar study in which they investigated daily consumption of 450 mg magnesium in the form of Magnesium chloride in the treatment group versus control group. Following 12 weeks of treatment, serum magnesium increased significantly in both groups but the difference of depression status between the two groups was no significant.[9]

The mean score of BDI-II (BV) test was declined significantly and this reduction was greater in the magnesium group in comparison with the placebo group. The mean scores of changes were -15.65±8.92 and -10.40±7.90 in the magnesium and placebo group, respectively and it was also statistically significant ($p=0.02$). The mean serum magnesium at the end of the study increased significantly only in magnesium group as compared to the beginning of the study and it was also statistically significant between the two groups. Although all of the participants had hypomagnesemia, at the end of the trial 88.5%

of the patients in the magnesium group returned to normal state of magnesium while it was 48.1% in the placebo group ($p < 0.01$). Evaluation of serum magnesium level of individuals indicated that more people in the magnesium group responded to the magnesium supplement treatment (88.5% vs 48.1%) and reached the normal state.[7]

Abbasi et al.[10] examined the effect of daily consumption of 500 mg Magnesium oxide tablet for 8 weeks on the sleep status of the elderly and found that the serum magnesium level was not significantly different between the two groups. The reason of the insignificant change could be the sensitivity of serum magnesium as an index for evaluation of magnesium status.[10]

Determination of the magnesium dose and the duration of treatment for individuals suffering from hypomagnesemia are also important. Based on previous studies, the dose prescribed for treating depression has been different from 125 to 450 mg.[6,9,11] Further, the course of therapeutic supplement has also been variable from 7 to 20 months.[6,9] The prognosis of major depressive disorder is generally good if patients are under medications and counselling. Treatment and self-care can even prevent or reduce the severity of future episodes of depression. From the discussion above, it is clear that supplementing Escitalopram with MgO in the treatment of individuals with MDD improves their feelings of inadequacy, despondency, decreased activity, pessimism, anhedonia, and melancholy, offers them a quality of life, and eventually minimizes suicidal attempts.

There were some limitations of the study such as relatively small sample size, conducted at a single centre, blinding technique was not followed and vitamin D and calcium levels were not measured.

Conclusion

Due to recurrence of MDD readily, it is crucial to choose those antidepressant drugs that allows high therapy continuity for pharmacological treatment. The study concluded that Escitalopram with MgO combination therapy could be the right approach for patients with MDD.

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