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Effect of Magnesium Supplementation in Selective Serotonin Reuptake Inhibitors Treated Major Depressive Disorder Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Aim: Current treatment options for depression have remained unsatisfactory because some patients experience symptoms even after completing multiple antidepressants and more aggressive treatments, besides experiencing side effects and uncertain adherence. Several studies have shown an association between magnesium and depression but have not consistently shown significant results.

Methods: Ninety subjects with moderate or severe major depressive disorder were randomized into a double-blind placebo-controlled trial to receive a treatment of 200 mg of magnesium glycinate or placebo tablets twice daily orally with selective serotonin reuptake inhibitors for the 8 weeks intervention period. Subjects were assessed with the Depression Anxiety Stress Scale 21 items Bangla Version for depression symptoms at baseline, at the end of the 4 weeks, and at the end of the 8 weeks intervention, and to evaluate the appearance of adverse effects.

Results: Supplementation of oral magnesium glycinate for 8 weeks resulted in a significant reduction in Depression Anxiety Stress Scale 21 items score from baseline ($P < 0.05$) and this reduction was observed from the end of 4 weeks treatment. Also, at the end of 8 weeks, the Depression Anxiety Stress Scale 21 items score was significantly lower than that of the control arm ($P = 0.02$). No changes were noted in the reporting of adverse effects while on the treatment.

Conclusion: Magnesium glycinate significantly reduces symptoms in moderate to severe depression, works quickly, and is well tolerated; this result is consistent with the literature. The link between changes in the Depression Anxiety Stress Scale 21 items and the severity of depression symptoms supports the idea that magnesium glycinate could be utilized to treat major depressive disorder, a persistent medical problem.

Trial was registered in the ClinicalTrials.gov with the trial ID number NCT04880460.

Keywords: *Control; DASS-21; Depression; Intervention; Magnesium; SSRIs*

Abbreviations

BSMMU: Bangabandhu Sheikh Mujib Medical University; BMI: Body Mass Index; DASS-21: Depression Anxiety Stress Scale 21 Items; DASS-21 BV: Depression Anxiety Stress Scale-21 Items Bangla Version; DALY: Disability Adjusted Life Years; DSM-5: Diagnostic and Sta-

tistical Manual of Mental Disorders, Fifth Edition; IRB: Institutional Review Board; Mg: Magnesium; MDD: Major Depressive Disorder; NMDA: N-Methyl-D-Aspartate; SSRI: Selective Serotonin Reuptake Inhibitors; YLD: Years of Healthy Life Lost Due to Disability.

Introduction

Major Depressive Disorder (MDD) is a common and recurrent mental illness that affects 322 million people worldwide, which is the largest number (85 million) in the South-East Asia region. In 2015, the estimated prevalence was 4.1% in Bangladesh [1]. But it increased by about 6.7% (5.8 to 7.6%) in 2018 - 1019 [2]. The increasing prevalence may be due to the long time required to get relief from symptoms, a lack of awareness, and social stigma about mental health diseases [3]. By 2030, it is anticipated to be the main contributor of disability globally [4].

It is evident that MDD has multifactorial reasons, including genetic, environmental, and psychosocial factors and its pathogenesis is complex [5]. However, reliable biomarkers for diagnosis is still insufficiently specific and sensitive for clinical use [6]. Therefore, till now, the severity of clinical symptoms has been assessed by questionnaires [7]. Many treatment modalities remain, including pharmacologic, non-pharmacologic treatments, and dietary supplements. Based on the most commonly accepted theory "monoamine hypothesis", different classes of antidepressants have been developed [8]. But still have some limitations, include delayed efficacy (2 weeks or more) and side-effects that are a major reason for treatment discontinuation [9,10]. 30% to 50% patients do not respond to an initial antidepressant of an adequate dose and duration, even 60% to 70% of responded patients do not achieve complete remission [11]. Most patients respond well to an additional antidepressant, despite 15% to 20% continued to suffer for up to 2 years after the initial onset of MDD [12-14]. Several therapeutic options are being explored; those target the neurotransmitter system outside of the standard monoamine hypothesis [15]. Magnesium supplementation is one of the therapeutic strategies, as it is the fourth most abundant mineral in the human body and plays a fundamental role in the proper functioning of the central nervous system, specifically, for psychiatric illnesses [16,17]. As magnesium (Mg) is a natural calcium channel blocker in the N-methyl-D-aspartate (NMDA) receptor, a low level of Mg leads to high calcium and glutamate levels, resulting in deregulated synaptic function; so, Mg is believed to have a role in the pathophysiology of depression [18]. Among different forms of Mg salts, magnesium glycinate (also called magnesium bisglycinate) is well-tolerated and absorbed in the body [19].

The association between depression and magnesium is well documented although the antidepressant action of magnesium is still unknown [21-24]. Although few clinical trials exist, improvement in depression has been reported inconsistently [25]. Accordingly, this research was designed and conducted considering the potential therapeutic role of magnesium in reducing depression symptoms to evaluate the additional reduction of symptoms in selective serotonin reuptake inhibitors (SSRIs) treated MDD patients.

Materials and Methods

Trial design

This was a randomized, double-blind, placebo-controlled trial.

Trial participants

The trial was conducted with approval from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU) for human subjects' research. Potential participants (n = 90) were identified from the outpatient department of psychiatry, BSMMU. One hundred forty patients were recruited for the baseline screening, and ninety patients with moderate to severe depression were enrolled after the baseline screening and assigned to one of the two study arms.

Inclusion and exclusion criteria

Inclusion criteria were: (i) newly diagnosed 18 years or older MDD patients of both genders according to the DSM-5, at the outpatient department of psychiatry, BSMMU, (ii) moderate to severe MDD according to the DASS- 21 (scores of 14 - 27), and (iii) patients prescribed only SSRIs. Exclusion criteria were: (i) patients having any other psychiatric disease, kidney disease, or gastrointestinal disease, (ii) taking dietary supplements in the last two months, (iii) taking fluoroquinolones, aminoglycosides, tetracyclines, calcium channel blockers, bisphosphonates, and skeletal muscle relaxants, and (iv) pregnancy and lactation.

Screening

A preliminary screening was conducted using DASS-21 items on every diagnosed MDD patient by the psychiatrist according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) [26] to determine if the potential participant met criteria to take part in the study. If preliminary screening was acceptable, the participant was scheduled for informed consent and study protocol procedures. The patients were encouraged to voluntarily participate.

Randomization

After completing screening and baseline measurements, participants were randomly assigned to one of two arms: (i) 200 mg magnesium glycinate tablet or (ii) 200 mg placebo tablet for 8 weeks. Treatment assignment was done by online graph pad software using a computer from the website (http://www.graphpad.com/quickcales/ranMenu) which automatically generated two distinct sets of random numbers after giving necessary inputs, by one senior faculty member from department of Biochemistry and Molecular Biology, BSMMU. All subjects and investigators were blind to the treatment condition and remained blinded until unblinding the codes during data analysis.

Intervention schedule

Patients were instructed to take 200 mg magnesium glycinate or 200 mg placebo tablet: 1 tablet twice daily after meals for 8 weeks along with SSRI treatment (any of the SSRIs, namely sertraline, escitalopram, fluoxetine, and paroxetine) given by the psychiatrist. Patients were scheduled for assessments at the end of 4 weeks and 8 weeks of the treatment. Magnesium or placebo tablets were provided free of charge.

Intervention protocol

Throughout the treatment, patients were not instructed to change their food, physical activity habits, or prescription medicine usage habits. They were also told not to use any magnesium-containing dietary supplements while participating in the experiment. Regular intake of medicine was confirmed over the telephone by an audio call or text message, pill count, and compliance sheet. Adverse effects were evaluated by a pre-formed checklist, and patients were asked over the phone to report any unwanted effects after medicine administration during the trial period while on the treatment.

Outcome and assessments

The DASS-21 item is a set of three self-report questionnaires to assess the severity of depressive symptoms related to dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. Here, each of the three DASS-21 scales contains seven items, and each item is rated from 0 to 3, and the depression subscale scores range from 0 to 21, with the following severity: 0 - 9 normal; 10 - 13 mild; 14 - 20 moderate; 21 - 27 severe; 28+ extremely severe [27,28]. To get the final score, the sum of the

scores of the 7 items from DASS-21 was multiplied by 2. The original 42-item DASS developed by Lovibond and Lovibond was modified into a shorter version consisting of 21-items [29]. It is validated in Bangla and is considered to be a reliable tool for depression [30]. The administration of the evaluation battery took 30 to 40 minutes, depending on the day.

Baseline

At baseline, a preformed questionnaire was completed, which elicited the required demographic data, BMI, concomitant or recently taken medications, nutritional supplements, address, and phone number. After that, the completion of DASS-21 items was done for the assessment of the severity score of depression symptoms.

End of 4 weeks treatment

The DASS-21 items were completed.

End of 8 weeks treatment

The DASS-21 items were completed, and after finishing the procedures, the participants were discharged from the study.

Data analysis

Data were analyzed following per-protocol principle using Microsoft Office Excel. Unpaired t-test, paired t-test, chi-square test and two proportion z-test were done to compare the differences between the arms. The level of significance was considered to be a p-value lower than 0.05.

Results

The trial was conducted between March, 2020 and January, 2022. Out of 140 identified patients from OPD psychiatry, 90 were enrolled and randomized. 45 patients were randomized to magnesium treatment and 45 to placebo treatment, and all patients commenced treatment based on their allocation. 7 patients from the control arm and 5 patients from the intervention arm have dropped out before analysis; a change in another antidepressant's treatment was the most common reason of dropped out. 78 patients completed all 8 weeks of the trial and were finally analyzed (Figure 1).

Demographics

The two arms were similar considering all baseline characteristics. The mean age of the patients in the control arm was 32.56 years compared to a mean age of 30.68 years in the intervention arm (SD, 11.79; range, 19 - 60 vs. SD, 10.22; range, 18 - 50; P = 0.42). The intervention arm had fewer males than the control arm (31.11% vs. 35.56%; P = 0.65) but had more females than the control arm (68.89% vs. 64.44%; P = 0.65). The sample had a mean body mass index (BMI) of 22.76 in the control arm compared to 23.16 (SD, 2.64; range, 17.60-29.70 vs. SD, 2.73; range, 16.40-31.10; P = 0.47) in the intervention arm (Table 1).

DASS-21

A noticeable but not statistically significant difference was found at the end of 4 weeks (20.74 ± 3.90; range, 14 - 26 vs. 19.95 ± 2.95; range, 10 - 26; P = 0.32), but significant difference was noted at the end of 8 weeks (19.37 ± 3.57; range, 12 - 26 vs. 17.00 ± 5.08; range, 8 - 26; P = 0.02) in response to treatment between the control and intervention arms respectively, which was significantly lower (P = 0.02) in the intervention arm than that of the control arm (Table 2).

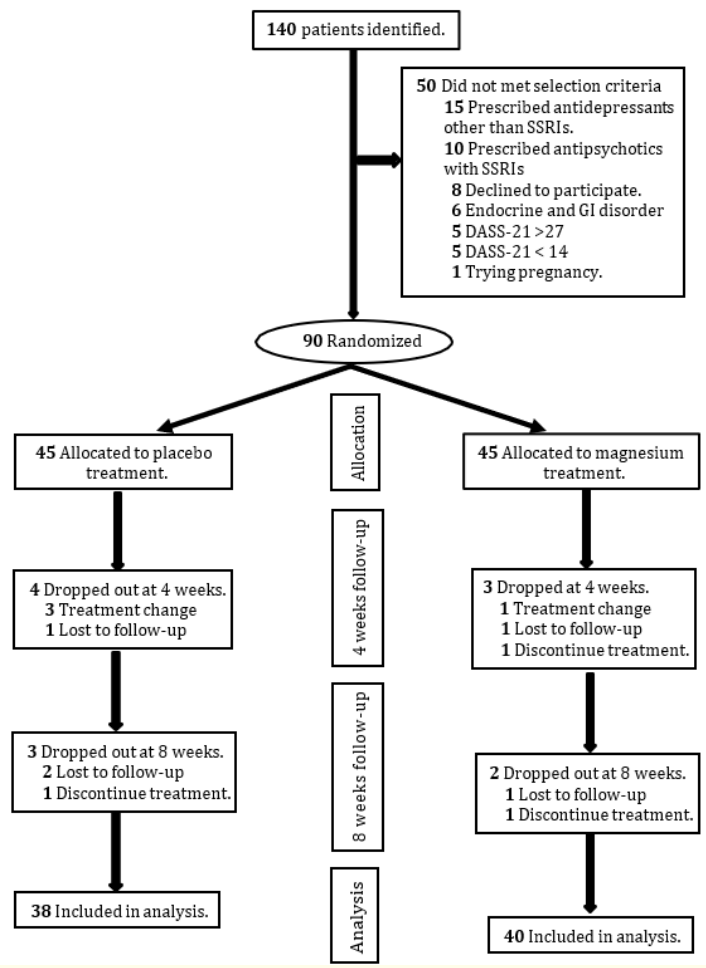

Figure 1: *Flowchart of consolidated standards of reporting trials (CONSORT).*

Characteristics		Control (n = 45)	Intervention (n = 45)	p-value
Age (years)	Mean ± SD	32.56 ± 11.79	30.68 ± 10.22	0.42[x]
		19 - 60	18 - 50	
Gender	Male	16/45 (35.56%)	14/45 (31.11%)	0.65[y]
	Female	29/45 (64.44%)	31/45 (68.89%)	
BMI	Mean ± SD	22.76 ± 2.64	23.16 ± 2.73	0.47[x]
	Range	17.60 - 29.70	16.40 - 31.10	

Table 1: *Demographic characteristics of patients (n = 90) at the period of enrollment.*

n = Number of patients, SD = Standard deviation, [x]student t-tests and [y]chi-square (x^2) test were done.

A significant reduction was noticed in the intervention arm (from 21.10 ± 3.04 to 19.95 ± 2.95; P = 0.00) at the end of 4 weeks of treatment, but there was no significant reduction in the control arm (from 21.10 ± 3.83 to 20.74 ± 3.90; P = 0.05). This reduction had become more significant (P = 0.00) in both arms at the end of 8 weeks of treatment (Table 2).

Depression anxiety stress scale-21 items bangla version (DASS-21 BV) score				p-value[x]
		Control (n = 38)	Intervention (n = 40)	
Baseline	Mean ± SD	21.10 ± 3.83	21.10 ± 3.04	0.99
	Range	14 - 26	14 - 26	
End of 4 weeks	Mean ± SD	20.74 ± 3.90	19.95 ± 2.95	0.32
	Range	14 - 26	10 - 26	
End of 8 weeks	Mean ± SD	19.37 ± 3.57	17.00 ± 5.08	0.02
	Range	12 - 26	8 - 26	
p-value[z]		a = 0.05 b = 0.001 c = 0.00	a = 0.00 b = 0.00 c = 0.00	

Table 2: *DASS-21 BV Score within the control and intervention arms (At baseline, end of the 4 weeks and end of the 8 weeks treatment).*

n = Number of patients, SD = Standard deviation, [x]unpaired and [z]paired t-tests were done, a = Compare between baseline and the end of the 4 weeks, b = Compare between the end of the 4 weeks and the end of the 8 weeks, c = Compare between baseline and the end of the 8 weeks.

Safety evaluation

No significant difference was observed in the reporting of adverse effects while taking magnesium with SSRIs compared to SSRIs treatment. Adverse effects were not so severe that they led to the withdrawal of medicines (Table 3).

Adverse effects	Control (n = 38)	Intervention (n = 40)	p-value
Headache	5/38 (0.13)	4/40 (0.10)	0.67
Dizziness	7/38 (0.18)	3/40 (0.08)	0.19
Agitation	5/38 (0.13)	1/40 (0.03)	0.10
Anorexia	1/38 (0.03)	2/40 (0.05)	0.65
Nausea	2/38 (0.05)	2/40 (0.05)	1.00
Constipation	1/38 (0.03)	2/40 (0.05)	0.65
Sexual dysfunction	1/38 (0.03)	1/40 (0.03)	1.00

Table 3: *Adverse effect within the control and intervention arms during treatment.*

n = Number of patients, SD = Standard deviation, two proportion z-test was done.

Discussion

The incidence of depression is now far more common and is affecting people much earlier in their lives. MDD and dysthymia, playing a substantial role in suicide and ischemic heart disease, contribute to the overall global burden of depressive disorders to 3.8% of global disability-adjusted life years (DALY) [4]. It is ranked as the single largest contributor to non-fatal health loss (7.5% of all YLD, years of

healthy life lost due to disability); the majority of this non-fatal health loss (80%) occurred in low and middle-income countries, and thus, it creates a high economic burden [1]. The prevalence in Bangladesh is also increasing, which may be due to a lack of awareness, social stigma about mental health diseases, and the length of time required to get relief from symptoms [3].

Several therapeutic options are being explored; those that target the neurotransmitter system outside of the standard monoamine hypothesis [5,15], Mg is one of these therapeutic options. Mg is likely safe when taken orally in an appropriate dosage regimen, but sometimes it may cause headaches, stomach upset, nausea, vomiting, diarrhea, and constipation. These adverse effects can be overcome by taking it after a meal. It interacts with some antibiotics such as aminoglycosides, tetracyclines, and quinolones, and with some other drugs like calcium channel blockers, bisphosphonates, and skeletal muscle relaxants [31]. The recommended dietary allowance (RDA) for adults is 310 mg to 320 mg per day for women and 400 mg to 420 mg per day for men [31,32].

But unfortunately, research applying Mg as a treatment option did not show significant results consistently. Given the lack of efficacy of currently available depression medications, the link between depression and hypomagnesemia [24,33], and the relationship between oral Mg intake and anti-depressant effects [34-38], the primary purpose of the study was to determine the effect of magnesium glycinate in patients with moderate or severe MDD in a double-blind, randomized trial.

At the time of recruitment, there were no significant differences in age, gender, or body mass index (BMI). This reveals that control and intervention arms were comparable.

We noted a significant reduction of the DASS-21 score in the intervention arm at the end of 4 weeks, but there was no reduction in the control arm. From this finding, it is understood that the improvement that occurs as a result of adding magnesium was significant at the end of 4 weeks and this reduction had become more at the end of 8 weeks with an average reduction of 4.1 scores from baseline. Also, a significant difference was observed between the control and intervention arms at the end of 4 weeks, and this difference become more significant at the end of 8 weeks. This effect was observed in patients of varying ages and levels of severity of baseline symptoms. The effect may be explained by its interaction with the glutamatergic system through blocking, and consequently, glutamatergic excitotoxicity could not occur [18].

Similar finding was demonstrated after 6 weeks of supplementation with magnesium chloride [34]. A case report showed a very interesting result in response to magnesium treatment in the form of glycinate and taurinate: a rapid recovery (within 7 days) from symptoms [21]. The trial findings were also consistent with another study within 8 weeks of magnesium citrate supplementation [35]. A trial comparing magnesium chloride with imipramine showed treatment with magnesium chloride to be equally effective as that with imipramine, but the difference with the present trial is that patients with hypomagnesemia were recruited [36]. Also, another trial conducted on hypomagnesemia patients showed a significant score reduction after 8 weeks of supplementation with magnesium oxide [37].

The findings of this trial are unlike those reported in some other studies. One trial found no changes in depression scores in treatment-resistant depression patients after 24 hours of intravenous magnesium sulfate supplementation, but scores decreased from baseline to day 7; this dissimilarity was probably due to the short duration of supplementation and a smaller sample size [38]. Similarly, no difference was seen with 8 weeks of magnesium aspartate supplementation compared to placebo in one trial, likely due to the smaller sample size, which was in total 37 [25]. These conflicting findings generate uncertainty about the status of magnesium as an antidepressant.

The adverse effects that were seen in the present trial were not severe enough to cause someone to discontinue the treatment. No statistically significant difference was observed in the reporting of adverse effects while taking magnesium with SSRIs compared to SSRIs alone. Other trials also reported similar adverse effects as in the present trial [34,35].

There are many obstacles to the treatment of depression, including social stigma related to the diagnosis, cost, side effects, and non-adherence. But magnesium supplementation does not come with these stigmata, and the risk of side effects is not as great as that of antidepressants [39].

The trial findings revealed the fact that, with the addition of magnesium to SSRIs in MDD patients for a long duration, the continuous improvement will continue. Although this trial showed positive short-term responses, including an earlier and greater reduction of symptoms in 78 depressed patients, the data regarding its long- term effects was not studied. Thus, various forms of magnesium may offer a rapid and inexpensive treatment approach for improving depression with a lower risk of adverse effects. This preliminary finding is important for its clinical implication in the management of MDD, but to determine how long it can be safely continued and how long does it is required to be given for MDD patients, additional research is required to affirm the long- term efficacy of magnesium as a treatment for depression.

Conclusion

We found magnesium glycinate significantly reduced the severity of depressive symptoms as measured by the DASS-21, and there were no notable side effects. These findings were in line with previous research. Research into the relationship between serum magnesium levels and treatment outcomes after magnesium supplementation should be conducted in conjunction with the studies on the effectiveness of magnesium supplementation. The long-term effectiveness of magnesium as a treatment option for MDD patients who are having trouble with existing standard treatments needs to be confirmed by additional study. Therefore, the overall picture suggests the possibility that administering magnesium to patients with MDD may be advantageous when taking into account both the existing research and our own findings.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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