VITAMIN B_6 AND MAGNESIUM ON NEUROBEHAVIORAL STATUS OF AUTISM SPECTRUM DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY

FARHANA KHAN[1], MD SAYEDUR RAHMAN[2], SHAHEEN AKHTER[3], ABDUL BASIT IBNE MOMEN[4], SHEIKH GOLAM RAIHAN[5]

Abstract

Background: *Autism Spectrum Disorder (ASD) is a neurobehavioral disorder for which till date, no pharmacological treatment has been proven effective. Some studies on complementary alternative medicines have shown neurobehavioral improvements among children diagnosed with ASD, notably with the administration of a combination of Vitamin B_6 and Magnesium.*

Methods: *This trial was designed to observe the effectiveness of a combination of Vitamin B_6 and Magnesium in children with ASD with hyperactivity. One of the primary aim was to investigate any improvement among the six domains of ASD: general observation, cognition, emotion, social behavior, communication, and sensory deficits. Patients attending the outpatient department of the Institute of Pediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University, diagnosed as ASD, were selected for this trial on meeting the selection criteria diagnosed by DSM 5 (Diagnostic and Statistical manual of Mental disorders) and ADCL (Autism Diagnostic CheckList). Then the patients were randomly assigned into intervention group (Vitamin B_6 and Magnesium) or placebo group. The intervention group received tablets of Vitamin B_6 and Magnesium daily, for 3 months, where the dosage was pre-determined by age of the subjects. Patients aged 2-3 years received 50mg Magnesium and 25mg Vitamin B_6 daily, aged 4-8 years received 100mg Magnesium and 50mg Vitamin B_6 daily, and patients aged 9-12 years were given 200mg Magnesium and 100mg Vitamin B_6 daily. The placebo group received similar looking oral placebo tablets for the duration as the intervention group. After 3 months, each patient was assessed once again using ADCL tool by a psychologist.*

Results: *Seventy (70) patients were enrolled for this study over a period of seven months. Among them fifty (50) met all criteria to be eligible for analysis. Therefore, intention to treat (ITT) was seventy (70) and per protocol treatment was fifty (50). Of these patients, twenty-seven (27) received Vitamin B_6 and Magnesium and twenty-three (23) received placebo. The improvement observed in the proportion of patients in the intervention group (81%) was significantly (pd"0.05) higher compared to placebo (47%) group. This study revealed an overall improvement in the symptoms of autism along with improvements in specific domains e.g., Emotion (pd"0.01) and Cognition (pd" 0.05).*

Conclusion: *Despite the small population size, this study demonstrated neurobehavioural improvement among children with ASD with hyperactivity and irritability. Consequently, this can be expected that future studies conducted on a larger scale might help to establish the beneficial role of Vitamin B_6 and Magnesium as a complementary treatment for autism with hyperactivity and irritability.*

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1. Senior Lecturer, Department of Pharmacology, Ad-Din Women's Medical College
2. Professor and Chairman, Department of Pharmacology, BSMMU
3. Director, Institute of Pediatric Neurodisorder and Autism, BSMMU
4. Registrar, Department of Medicine, Bangladesh Medical College
5. Medical Officer, Department of Blood Transfusion, Bangladesh Medical College

Address of Correspondence: Dr. Farhana Khan, 9/B Eastern Housing Apartment Shiddheshwari, 104, Baramagbazar, Dhaka-1217, Email: farhanakhan488 @gmail.com

Introduction

Autism Spectrum Disorder (ASD) is a lifelong neurobehavioral disorder which is not curable. There is no specific treatment for autism. There are some guidelines for treating ASD, such as NICE guidelines[1], recommendations by American Academy of Child & Adolescent psychiatry[2]and Indian Clinical Practice guideline for autism[3]. All of these guidelines do not advocate a specific protocol for treating autism.

The Food and Drug Administration (FDA) has approved Risperidone and Aripiprazole for the treatment hyperactivity and irritability present in ASD patients[4][5]. Combinations of medicines, parent teacher training as well as other interventions are more fruitful for behavioral issues and for proper functioning.

For many years the target has been switched to notice the relations between metabolic and nutritional disturbances and developmental disorders, for example attention deficit hyperactive disorder or intellectual disorder or learning disorder[6].

There are some studies on vitamins and minerals showing mixed results, such as those with-Vitamin A [7], Vitamin B[8], Vitamin C[9], Vitamin D[10], Folinic Acid[11], Zinc[12], Among these studies vitamin B_6 and magnesium given by parents to ASD children have been observed to produce improvement for about 30 years[13][14][15].

Although a lot of researches have been conducted for treatment of ASD; the treatment options are still lacking. There exists behavioral therapies but unfortunately pharmacological interventions are inadequate. Studies have observed that the children with ASD do show some improvement with supplementation of Vitamin B_6 and Magnesium in many areas like language, eye contact and behavior. So this study is being conducted to investigate the benefits of using Magnesium and Vitamin B_6 in patients of ASD with hyperactivity and irritability.

Methods

Trial design

The trial was a single site, randomized, double-blind, placebo controlled trial to evaluate the effect of vitamin B6 and Magnesium on the neurobehavioral status of ASD conducted on the out patients in a tertiary level hospital in Bangladesh. According to the eligibility criteria patients were enrolled in the study with informed written consent given by their parents. After that each patient was then randomly provided with a medicine or placebo with prescription. Patients in the intervention arm received Magnesium and Vitamin B_6 tablets and control arm received placebo for three months starting after the day of initial assessment.

Patients

The patients were eligible to be included in the study if they were a newly diagnosed patient of ASD, Children between 2 to 12 years diagnosed & confirmed by DSM 5, Children between 2 to 12 years grading done by ADCL, have Co-morbid neurological disorder like hyperactivity and irritability. Excluding criteria included patient having history of epilepsy and parents unwilling to give informed consent.

Randomization was done by online graph pad software by using computer. The software automatically generated two distinct sets of random numbers after giving necessary inputs (sample size, sets of number). The online graph pad calculator equally distributed the patients into two comparable groups. The randomization was conducted by a competent third person, a researcher who has no relationship with this research. Immediately after randomization, random numbers of the two sets were assigned as patient code number. One set was designated as intervention group and another set was placebo group. Then the set of code numbers that belongs to the intervention group were written as patient ID numbers on the packages contained Magnesium and Vitamin B_6 tablets. On the other hand, the set belonged to the placebo group were designated as patient ID numbers on the packages contained placebo. The participants, caregiver and the outcome assessor who require being blind for such study, were effectively blinded.

Treatment

In the intervention arm Magnesium tablets were given to the patients in following dose: 50 mg for ages 2-3 years, 100 mg for ages 4-8 years and 200 mg for ages 9-12 years for three months. Vitamin B_6 tablets were given to the patients in following dose: 25 mg for ages 2-3 years, 50 mg for ages 4-8 years and 100 mg for ages 9-12 years for three months.In the other arm patient received oral placebo in the same manner, schedule and time frame. Patients in both arm received Risperidone for hyperactivity and irritability.

Outcome

The outcome was any improvement in the six domains of general observation, cognition, emotion, social, communication and sensory deficiency evaluated at 90 days of initial therapy by a psychologist using ADCL tool who was completely unaware about the study.

Statistical analysis

Appropriate statistical test (Unpaired t-test) and Chi – squared test were done in this study for drawing an appropriate conclusion.

Unpaired t-test was done to compare the age distribution between the placebo and intervention

groups, and comparison of score of DSM-5 between placebo and intervention group both before and after the intervention and comparison of neurobehavioral improvement between patients receiving placebo and intervention assessed by ADCL

Chi – square (x^2) test was done to compare the sex distribution between the placebo and intervention group, to see the distribution of mild, moderate and severe cases in the placebo and intervention group.

Result

Characteristics of the patients

From January 2019 to July 2019, 70 patients were recruited based upon eligibility criteria as has been designated for the study. Of which thirty five (35) patients received intervention and thirty five (35) received placebo. Twenty (20) patients were dropped out during the research due to denial to take medication (n=5), unable to travel (n=10), non-compliance (n=5). For these patients, determination of end point was not possible and therefore they were excluded per-protocol analysis. At the end of the research a total of 50 patients were assessed and evaluated.

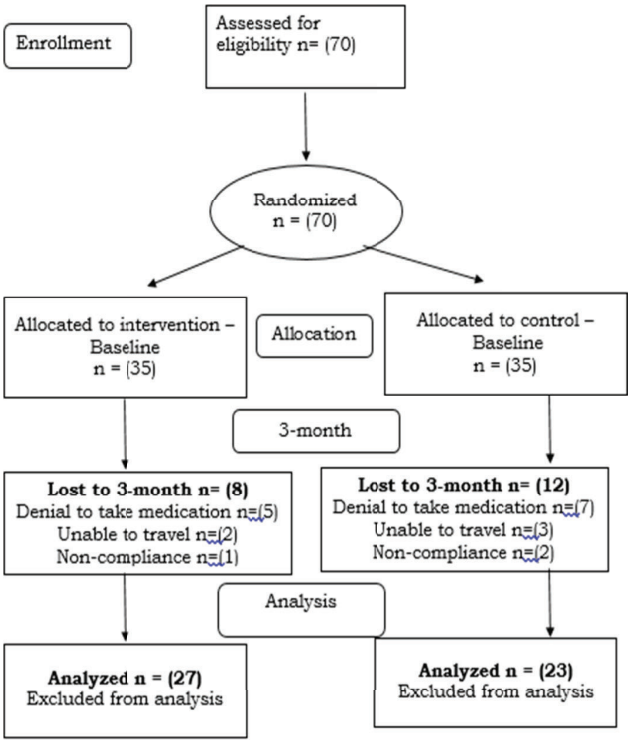

Table 1: There was no significant difference in age (p = 0.58), gender (p = 0.88), age of mother and father (p = 0.96, 0.85). In the placebo group the mean age and SD of the patients were 3.85 ± 0.99 years. Whereas, the mean age and SD of the patients in the intervention were 3.68 ± 1.24 years. In the placebo group, out of twenty three (23) patients, fourteen (14) were males and nine (9) were females. While in the intervention group seventeen (17) were males and ten (10) were females.In the placebo group out of twenty three (23) patients, three (3) patients (13.04%) had mild, eight (8) patients (34.78%) had low moderate, eleven patients (47.83%) had high moderate and one (1) patient (4.35%) had severe ASD when assessed with ADCL tool during initial assessment. While in the intervention group out of twenty seven (27) patients, three (6) patients (22.22%) had mild, seven (7) patients (25.93%) had low moderate, twelve patients (44.44%) had high moderate and two (2) patients (7.41%) had severe ASD when assessed with ADCL tool during initial assessment. The distribution of severity between the placebo and intervention group was statistically insignificant (p = 0.20).

Table 1

Variables	Placebo[a]	Intervention[b]	P value
n=50	23	27	
Age in years (Mean ± SD)	3.85 ± 0.99	3.68 ± 1.24	0.58 [x]
Male	14	17	0.88 [y]
Female	9	10	
Distribution according to severity			
Mild	3 (13.04%)	6 (22.22%)	0.20 [z]
Low Moderate	8 (34.78%)	7 (25.93%)	
High Moderate	11 (47.83%)	12 (44.44%)	
Severe	1 (4.35%)	2 (7.41%)	

[a] Placebo patients received placebo tablets
[b] Intervention patients received Magnesium and Vitamin B6 tablets
[x] Unpaired t-test was done. P e" 0.05 = statistically insignificant
[y] Chi – square (x^2) test was done. P ≥0.05 = statistically insignificant
[z]Chi – square (x^2) test was done. P ≥0.05 = statistically insignificant

Outcome

Assessment after 90 days showed (Table II) that in the placebo group out of twenty three (23) patients, two (2) patients (8.69%) had mild, eleven (11) patients (47.83%) had low moderate, nine patients (39.13%) had high moderate and one (1) patient (4.35%) had severe ASD when assessed with ADCL tool during final

assessment. While the in the intervention group out of twenty seven (27) patients, thirteen (13) patients (48.15%) had mild, twelve (12) patients (44.44%) had low moderate, two patients (7.41%) had high moderate and zero (0) patients (0%) had severe ASD when assessed with ADCL tool during the final assessment. The distribution of severity between the placebo and intervention group was statistically significant (p d" 0.01).

Table-II

Comparison of Distribution of Patients According to Severity Assessed by ADCL in the Placebo and Intervention Group at Final Assessment

	Placebo[a]	Intervention[b]	P value
Mild	2 (8.69%)	13 (48.15%)	≤0.01 [z]
Low Moderate	11 (47.83%)	12 (44.44%)	
High Moderate	9 (39.13%)	2 (7.41%)	
Severe	1 (4.35%)	0 (0%)	

[a] Placebo patients received placebo tablets

[b] Intervention patients received Magnesium and Vitamin B_6 tablets

[z]Chi – square (x^2) test was done. P d" 0.05 = statistically significant

* ADCL (Autism Diagnostic Check List)

Forty three (43%) percent of the patients in the placebo group (Table 3) improved with ADCL assessment when the initial and final assessment were compared. While in the intervention group eighty one (81%) percent of the patients improved with ADCL assessment when the initial and final assessment were compared.

Table 3

	Placebo[a]	Intervention[b]
Overall	43.48%(10/23)	81.48%(22/27)

[a] Placebo patients received placebo tablets

[b] Intervention patients received Magnesium and Vitamin B6 tablets

The mean score and SD (Table 4) in the placebo and intervention group in overall score was 2.61 ± 19.1 and 17.44 ± 19.70 respectively. In general observation score was 2.87 ± 5.55 and 4.41 ± 6.30 respectively. In cognition score was -1 ± 3.12 and 1.56 ± 3.92 respectively. In emotion score was 1.48 ± 3.91 and 5.07 ± 4.73 respectively. In social score was 0.48 ± 4.12 and 0.78 ± 3.39 respectively. In communication score was -0.17 ± 5.97 and 2.37 ± 5.68 respectively. In sensory deficiency score was -0.78 ± 7.38 and 3.04 ± 6.12 respectively. The improvement when comparing the placebo group and intervention group in overall score was statistically significant (p d" 0.01). The improvement when comparing the placebo group and intervention group in general observation score was statistically insignificant (p = 0.36). The improvement when comparing the placebo group and intervention group in cognition score was statistically significant (p = 0.01). The improvement when comparing the placebo group and intervention group in emotion score was statistically significant (p d" 0.01). The improvement when comparing the placebo group and intervention group in social score was statistically insignificant (p = 0.78). The improvement when comparing the placebo group and intervention group in communication score was statistically insignificant (p = 0.13). The improvement when comparing the placebo group and intervention group in sensory deficiency score was statistically insignificant (p = 0.06).

Table-IV

Comparison of Neurobehavioral Improvement Between Patients Receiving Placebo and Intervention Assessed by ADCL

	Improvement (Mean ± SD)		
	Placebo [a]	**Intervention [b]**	**P - value**
Overall	2.61 ± 19.1	17.44 ± 19.70	d" 0.01
General observation	2.87 ± 5.55	4.41 ± 6.30	0.36
Cognition	-1 ± 3.12	1.56 ± 3.92	d" 0.05
Emotion	1.48 ± 3.91	5.07 ± 4.73	d" 0.01
Social	0.48 ± 4.12	0.78 ± 3.39	0.78
Communication	-0.17 ± 5.97	2.37 ± 5.68	0.13
Sensory Deficiency	-0.78 ± 7.38	3.04 ± 6.12	0.06

[a] Placebo patients received placebo tablets

[b] Intervention patients received Magnesium and Vitamin B_6 tablets

Unpaired t-test was done. P d" 0.05 = statistically significant, P e" 0.05 = statistically insignificant.

Discussion:

Autism spectrum disorder has been in existence for a long time and even though several guidelines do exist for its treatment, there are however no recommendable drugs to treat it due to their tendencies to show inconsistent results. One combination is the use of Vitamin B_6 and Magnesium to observe the effectiveness in the neurobehavioral improvement in autism.

Rimland[16] found significant improvement with the use of high doses of pyridoxine, however high doses of pyridoxine showed side effects which could be negated by co-administering Magnesium. In another study, patients were divided into three groups, and were given only Magnesium, Vitamin B_6 and Vitamin B_6-Magnesium combination respectively[15], the patients in the group who got the combination of both showed the most improvement.

This study was done to find if there were any improvements though the use of Vitamin B_6 and Magnesium combination. The study showed that patients in the intervention group (81%) showed improvement compared to the placebo study (43%), where another study reflects that twenty out of thirty three patients showed improvements (60%)[17]. A 2007 survey found improvements in 47% of patients[(18)]. According to LeLord[(19)] 34% patients showed improvements out of 44 patients.

Our current study found an overall improvement in the symptoms of autism along with improvements in specific domains.[20] found a global improvement in children when magnesium was used along with decreased autistic and behaviors and other signs. This study found improvement mainly in two domains in autistic children, emotion and cognition. Emotion domain has many attributes such as hyperactivity, aggressiveness, emotional lability, stress. The possible explanation may be Magnesium inhibits the excitatory channel glutamate N—methyl—D—aspartate (NMDA)[21] and reduces hyperactivity- a part of emotional domain.Integral to cognition are memory and learning, which are affected by environment and diet. In ratsit had been seen that memory- both short and long term, ability to learn and working memory are somehow enhanced by using magnesium or magnesium related compound.Mg increases pre-synaptic releases that suggest that Mg in brain enhances both short term and long term synaptic facilitation and long-term potentiation and improves learning and other memory functions.[22]

According to Cochrane database of systemic reviews done in 2005 of Combined Vitamin B_6-Magnesium treatment in autism spectrum disorder, only three studies could be regarded as valid as the others were plagued with many methodological flaws. Tolbert[23] found that there was no significant difference between placebo and intervention, also Findling[24] found no improvement. The possible explanation could be that one of these studies were conducted with Magnesium oxide, which is poorly absorbed from the intestine which fails to dissolve in water. Compared to the oxide form, magnesium citrate, glycinate, malate and threonate dissolve into water far better in absorption, tolerability, and other health benefits. In our study we have used Magnesium glycenate, which is absorbed quite easily from the intestine and may show some promising effects. Kuriyama[25] also did not find any significant difference, but he concluded that his study should not be used as a recommendation due to the short duration of study period and the limited number of patients it was conducted on.

Mousain-Bosc[17] found that when Vitamin B_6 and Magnesium were stopped, the previous symptoms reappeared in the patients. So further studies should be designed to look into the effects of discontinuation of the medication on the patients suffering from ASD. This study almost half of the autistic children showed an intra-erythrocyte Mg depletion. Erythrocyte-Magnesium (Erc-Mg) level can be considered as a representative of some intracellular Mg2+, any decrease in Erc-Mg without a change in serum Mg concentration could be the result of an alteration of Mg2+ transport through the plasma membrane. Genes involved in primary inherited hypomagnesaemia has been identified on the basis that TRPM receptors are involved in Mg homeostasis [26,27]. The Mg channels on the cell membranes belongs to the family of TRPM proteins[28,29]. So further studies should be done to look into the genetic background of autism.

Moreover, this study has not utilized the maximum tolerable dose of vitamin B_6. Thereupon dose escalation should be considered in further studies as Vitamin B_6 is water soluble and non-toxic.

Many studies were done to look into the effects of the combination in patients of ASD. We found a positive relationship between the combination and ASD with hyperactivity in improving the overall status of autism plus cognition and emotion aspects of ASD. But we cannot recommend it due to the small number of patients and study period. So we hope that in the future a larger well designed study will be conducted to further establish the role of Vitamin B_6–Magnesium in the management of patients with autism spectrum disorder with hyperactivity and irritability.

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