ORIGINAL ARTICLE

A triple-blinded, randomized, placebo-controlled trial to examine the efficacy of buspirone added to typical antipsychotic drugs in patients with chronic schizophrenia

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Background: The purpose of this study was to test the hypothesis that the addition of buspirone, a partial agonist of 5HT1A receptor, to ongoing treatment with typical antipsychotics would improve the positive and negative symptoms in patients with chronic schizophrenia. **Materials and Methods:** In this study, 50 patients including 40 male and 10 female were recruited with chronic schizophrenia who were inpatients at psychiatric teaching hospital or asylums, aged between 18 and 65 years (mean age = 47 ± 10.02). All patients were on the stable dose of typical antipsychotics for at least 1-month, and their acute symptoms were controlled. Patients were allocated in a random fashion: 25 patients to buspirone at 30 mg/day plus typical antipsychotic and 25 patients to placebo plus typical antipsychotic. The positive and negative syndrome scale (PANSS), Simpson–Angus extrapyramidal rating scale (SAS) and mini mental state examination (MMSE), were administered at baseline, and 2, 4, and 6 weeks after the addition of buspirone. **Results:** The 30 mg/day buspirone was well-tolerated, and no clinically important adverse effects were seen. There was no statistically significant difference between the two groups in MMSE and SAS scales. There was a significant reduction in subscales of negative, general, positive, and total of PANSS over the 6-week trial in buspirone group. There was a statistically significant difference between the two groups negative subscale (mean ± standard deviation [SD] = 14.08 ± 1.4 in buspirone group) $P = 0.0219$, general subscale (mean ± SD = 27.42 ± 2.1 in buspirone group) $P = 0.0004$, and total subscale (mean ± SD = 55.63 ± 3.9 in buspirone group) $P = 0.0298$, of PANSS in the 6-week of trial. **Conclusion:** The results suggest that adjunctive treatment with 5HT1A agonist such as buspirone may improve the negative symptoms of schizophrenia. Further studies are indicated to determine the efficacy of 5HT1A agonist treatment in chronic schizophrenia.

Key words: 5HT1A, buspirone, chronic schizophrenia

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INTRODUCTION

Schizophrenia is a severe, debilitating, and chronic mental disorder characterized by positive (hallucinations, delusions) and negative (withdrawal, apathy, anhedonia) symptoms.[1,2] It is a lifelong illness with a peak age of onset in the mid-20s.[1,2] Although the severity of schizophrenia has recognized its etiology but pathophysiological characteristics are not fully understood.[1-3] The second-generation antipsychotic drugs (such as risperidone and olanzapine), have shown promise in reducing the negative symptoms of schizophrenia.[4] Negative symptoms have been associated with detrimental effects on patients functional status and they are the most stable symptoms over the course of illness.[1-3] The ability of drugs such as clopzapine, olanzapine, ziprasidone, and risperidone to increase dopamine release in the prefrontal cortex is mediated by a variety of mechanisms including 5HT1A agonism.[4,5]

A role for 5HT1A receptor in cognitive enhancement is supported by postmortem studies which report that 5HT1A receptor density in increased in frontal and temporal cortices in schizophrenia.[6] Therefore, there is a need for the development of more effective treatments for schizophrenia to use as adjuncts to antipsychotic drugs.[7]

In previous investigations, an adjunctive treatment with 5HT1A agonists to atypical antipsychotic medication produced inconsistent results with regards to clinical improvements in schizophrenia.[3,8] Buspirone, an azapirone derivative, is a partial agonist at 5HT1A receptors with weak D2 receptor blocking

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properties compared to typical antipsychotic drugs.[6] A few trials studied the effect of the addition of buspirone on psychopathology in patients with chronic schizophrenia.[6,9,10] However, to our knowledge, none of those studies had the control group.

The goal of this randomized, placebo-controlled, triple-blind study was to t est the hypothesis that the addition of buspirone to typical antipsychotic medications in patients with chronic schizophrenia would improve the psychopathology in these patients.

MATERIALS AND METHODS

The trial was a triple-blind, prospective 6-week study of two groups of patients with chronic schizophrenia and it was performed in psychiatric teaching hospital and 2 asylums in Sari, the capital of Mazandaran province, Iran from July 2012 to February 2013. Participants were 40 men and 10 women, 18-65 years at the time of screening, with the diagnosis of schizophrenia (paranoid or nonparanoid subtype), based on the structured clinical interview for DSM-IV-TR,[11] for at least 2 years. These patients were selected among 200 patients of Schizophrenia after checking the inclusion and exclusion criteria. The acute symptoms of illness were controlled by typical antipsychotics at least for 1-month. All the participants were required to have a positive and negative syndrome scale (PANSS) total score of more than 60 and a negative subscale score of more than 15.[3,12]

Patients were treated with typical antipsychotics before randomization and remained on a stable dose for at least 4 weeks before randomization and throughout the trial. Women of childbearing potential were required to have a negative pregnancy test at the time of screening. Criteria for exclusion were, any chronic untreated medical condition; substance dependency; any other psychiatric disorder in Axis I or II; use of any medications identified as contraindicated to buspirone; any abnormalities in vital sign or electrocardiogram. Pregnant or lactating women and those of reproductive age without adequate contraception were excluded. After complete description of the study to the subjects, written informed consent was provided by patients, guardians or legally authorized representative. The trial was approved by the Ethics Committee at the Mazandaran University of Medical Sciences. This trial was registered with the Iranian Clinical Trial Registry (IRCT201106026691N1).

Eligible patients were assigned to receive either placebo or buspirone. We randomized the patients using permuted blocks. We wrote the type of intervention on a paper and put it in a black sealed box and along with every patient who entered the study we picked a box. Twenty-five patients were randomly allocated to typical antipsychotic medication and buspirone 30 mg/day (3 times a day) and 25 patients were chosen to receive typical antipsychotics plus placebo. Patients received buspirone with dosing titration as follows: 1st week 5 mg twice daily, and the dosage was then increased to 30 mg/day after 1-week the patients in the placebo group received identical tablets. One patient (in buspirone group) dropped out of the study due to headache and vertigo which relieved after the medication stopped. All patients were assessed at the baseline and after 2, 4, and 6 weeks after the start of medication by a psychiatry resident.

The PANSS is a 30-item scale, developed to assess both the positive and negative syndromes of patients with schizophrenia. The PANSS total score is rated based on a structured clinical interview with the patient (conducted by a resident of psychiatry). Each item is scored on a continuous 7-point scale and provides evaluation of positive and negative symptoms, as well as general psychopathology. The PANSS rating scale has been used in several studies in Iran, and it has high reliability and validity.[3,13,14]

The extrapyramidal symptoms were assessed using the Simpson-Angus scale (SAS), assessment of mental state and global functioning were performed using the mini mental state examination (MMSE) scale. The SAS and MMSE scale were used in several studies in Iran, and they have a high reliability and validity scores.[13,14]

Adverse effects were recorded throughout the study and were assessed using a checklist by a resident of psychiatry after 1, 2, 4, and 6 weeks after the start of medication. The checklist had 14 items such as, headache, nausea, vomiting, palpitation, dyspepsia, excitement, seizure, suicidal idea, slurred speech, congestive heart failure, extrapyramidal symptoms, bradycardia, phobia, and vertigo. During the study, the person who administered the medication, the rater, the patient, and the statistical analyzer were blind to their assessment.

Statistical analysis

We collected all data throughout the 6-week trial. The data were reported as mean ± standard deviation [SD] and frequency (percent) and analyzed using the repeated measure ANOVA. For comparing the data between the two groups for each week, independent *t*-test was used. Chi-square test was used for comparing proportion. For all analyses, SPPSS package, (SPSS Inc. released 2009. PASW Statistics for Windows, version 18.0. SPSS Inc., Chicago, USA) was used. Significance level of 0.05 considered in all analysis [Figure 1].

RESULTS

Fifty patients were randomly assigned into two groups for trial medication (25 patients in each group) by using permuted random blocks. The mean ± SD of age were

46.68 ± 9.46 and 47.32 ± 10.58 in buspirone and placebo group, respectively.

There were no significant differences between the two groups in basic demographic data such as age, sex, marital status, and subtype of schizophrenia [Table 1]. Only one patient dropped out from buspirone group because of experiencing severe vertigo and headache right after starting the administration of buspirone. There was no death in this study. Review of the checklist of adverse effects revealed clinically and statistically unremarkable differences between the two groups, from baseline to endpoint. There were 20 men and 5 women in each group and the mean ± SD of age in buspirone group was 46.68 ± 9.46, and it was 47.32 ± 10.58 in the placebo group (P = 0.82). Furthermore, the two groups had no significant differences in the type of typical antipsychotic medication that they were receiving [Table 1].

Negative symptoms

The mean ± SD scores of the two groups of patients are shown in Table 2 [Figure 2]. There was no significant differences between the two groups at week 0 on the negative subscale of PANSS (P = 0.65). But there was a significant difference between the two group at the endpoint (week 6, P = 0.021). The changes at the endpoint compared with baseline were: (mean ± SD buspirone group = 14.08 ± 1.4 and placebo group = 18.44 ± 1.09).

Positive symptoms

The mean ± SD score of the two groups of patients is shown in Table 2. There were no significant differences between the two groups at week 0, 2, 4, 6 on the positive subscale of PANSS. The mean scores at the baseline were: 19.4 ± 1.74 and 18.36 ± 1.81 for buspirone and placebo, respectively (P = 0.68). The mean scores for the two groups at the endpoint (week 6) were: 13.75 ± 1.48 in buspirone group and 16.16 ± 1.72 in the placebo group (P = 0.29).

Positive and negative syndrome scale general scores

The mean ± SD scores of two groups of patients are shown in Table 2. We found no significant differences between the two groups at weeks 0, 2, and 4 on the general subscale of PANSS (P = 0.24 at the baseline). But there was a significant difference at the endpoint between the two groups (P = 0.0004). The changes

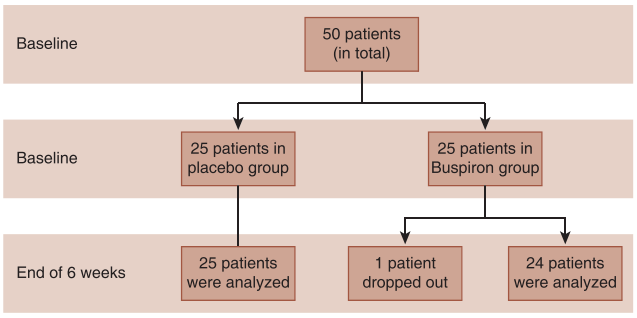

Figure 1: Patient's diagram

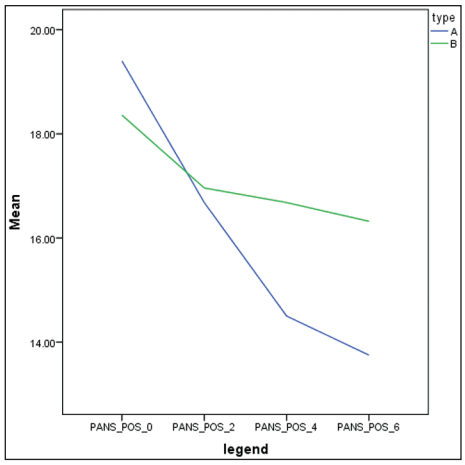

Figure 2: The changes of positive and negative syndrome positive score

Table 1: Baseline demographic characteristics between buspirone and placebo group

Characteristics	Buspirone + antipsychotic *n* (%)	Placebo + antipsychotic *n* (%)	*P*
n	25	25	
Men	20 (80)	20 (80)	0.500
Marital status			
Married	3 (12)	4 (16)	0.913
Single	17 (68)	15 (60)	
Divorced	5 (20)	6 (24)	
Type of schizophrenia			
Paranoid	12 (48)	14 (56)	0.57
Nonparanoid	13 (52)	11 (44)	
Type of antipsychotic drugs			
Haloperidol	9 (36)	10 (40)	0.58
Perphenazine	6 (24)	3 (12)	0.46
Modecate	12 (48)	11 (44)	1.00
Largactil	5 (20)	3 (12)	0.70
Thiothixene	2 (8)	2 (8)	1.00
Eskazina	6 (24)	1 (4)	0.09

Table 2: Clinical psychopathology symptom measures

Variable (week)	Buspirone + antipsychotic (mean ± SD)	Placebo + antipsychotic (mean ± SD)	*P* (*t*-test)
PANSS			
Positive (week 0)	19.4±1.74	18.36±1.81	0.68
Positive (week 2)	17.28±1.66	16.8±1.47	0.84
Positive (week 4)	14.25±1.49	16.52±1.84	0.34
Positive (week 6)	13.75±1.48	16.16±1.72	0.29
Negative (week 0)	23.12±1.3	22.32±1.77	0.65
Negative (week 2)	20.44±1.55	19.6±1.12	0.66
Negative (week 4)	17.83±1.71	18.6±1.05	0.7
Negative (week 6)	14.08±1.49	18.44±1.09	0.021*
General (week 0)	40.48±2.01	37.36±1.69	0.24
General (week 2)	37.56±2.22	34.64±1.83	0.31
General (week 4)	31.92±2.14	32.24±1.6	0.90
General (week 6)	27.42±2.14	18.44±1.09	0.0004*
Total (week 0)	82.92±3.07	78.04±3.21	0.27
Total (week 2)	74.96±3.12	71±3.32	0.38
Total (week 4)	63.79±3.86	67.36±3.3	0.48
Total (week 6)	55.63±3.9	66.88±3.18	0.029*
SAS			
Week 0	1.96±0.34	2.92±0.56	0.15
Week 2	1.72±0.31	2.92±0.56	0.07
Week 4	1.6±0.34	2.75±0.57	0.09
Week 6	1.6±0.34	2.75±0.57	0.09
MMSE			
Week 0	23.25±0.98	24.2±0.88	0.47
Week 2	23.25±0.98	24.32±0.9	0.42
Week 4	24.13±0.92	23.25±0.98	0.52
Week 6	23.25±0.98	24.13±0.92	0.52

Clinical psychopathology symptom measures (by independent *t*-Test, repeated measure). Note: week 0, baseline; PANSS (Positive and Negative Syndrome Scale); SAS (Simpson-Angus Rating Scale); MMSE (Mini Mental State Examination. *P*-value<0.05 is considered significant

at the endpoint compared with baseline were: In buspirone group = 27.42 ± 2.1 and placebo group = 18.44 ± 1.09).

Positive and negative syndrome scale total scores

The mean ± SD scores of two groups of patients are shown in Table 2. There were no significant differences between the two groups at weeks 0, 2, and 4 on the total subscale of PANSS ($P > 0.05$). But there was a significant difference between the two group at the endpoint ($P = 0.029$). The changes at the end point compared with baseline were: In buspirone group, 55.63 ± 3.9 and placebo group, 66.88 ± 3.18).

Extrapyramidal symptoms rating scale and minimental state examination

The mean ± SD scores of extrapyramidal symptom rating scale and MMSE of the participants are shown in Table 2. There was not any significant differences in SAS between the two group during the study (week 0 $P = 0.15$). The mean ± SD scores at the endpoint (week 6) were: 1.6 ± 0.34 in buspirone group and 2.75 ± 0.57 in the placebo group (week 6 $P = 0.09$).

There were no any significant differences in MMSE between the two group throughout the study (week 0 $P = 0.47$). The mean ± SD scores at the endpoint were: 23.25 ± 0.98 and 21.13 ± 0.92 for buspirone and placebo, respectively ($P = 0.52$), [Table 2].

Adverse effects

Seven types of adverse effects were seen throughout the trial. The difference between the buspirone and the placebo group in the frequency of adverse effects was not significant [Table 3].

DISCUSSION

In this study, both groups of patients showed improvement on the PANSS total, negative, positive, and general subscales throughout the 6-week trial and according to our hypothesis, the buspirone group had significantly greater improvement on negative and total subscales. There were no differences between two groups in sex, age, marital status, and subtype of schizophrenia. Therapy with 30 mg of buspirone/day was very well-tolerated, and no clinically important adverse effect was seen. It is possible that the participants in this study (patients with chronic schizophrenia with moderate residual positive and negative symptoms) may not have been the optimal population for studying the effect of

Table 3: Summary of AEs over the 6-week trial

Adverse effects	Buspirone *n* (%)	Placebo *n* (%)	*P*
Numbers of patients with AEs	13 (52)	5 (20)	
Number of patients who discontinued the trial because of AEs	1 (4)	0	
Treatment-emergent AE			
Vertigo	3 (12)	0	NS
Nausea	1 (4)	0	NS
Insomnia	1 (4)	0	NS
Headache	3 (12)	2 (8)	NS
Tremor	3 (12)	3 (12)	NS
Sedation	1 (4)	0	NS
Dizziness	1 (4)	0	NS
Palpitation	0	0	NS

AEs = Adverse events

buspirone, and this could be considered as one of the limitations of this study.

In the agreement with our results, Ghaleiha *et al*.[3] found improvement in the negative, positive, general, and total scores of PANSS during an 8-week trial. They treated 46 patients with chronic schizophrenia by 6 mg/day risperidone and up to 60 mg/day buspirone. Brody *et al*.[15] administered 10-60 mg of buspirone to seven patients with schizophrenia and reported no improvement in positive and negative symptoms throughout 4-week study.

In the study of Ghaleiha *et al*.,[3] it has been suggested that, low doses of buspirone (<30 mg/day) induce serotoninergic effects, whereas high doses (>30 mg/day) may induce postsynaptic dopaminergic antagonism as well. Maybe the low dose of buspirone in our study (30 mg/day) was the reason that there was no improvement in positive symptoms of patients in our study.

Piskulic *et al*.[8] added 15-30 mg/day buspirone to the ongoing treatment with atypical antipsychotics in a 6-week double-blind, placebo-controlled trial. They found no statistically significant differences between placebo and buspirone group on cognitive function measures. As noted above, most of the studies on the effect of buspirone had been on atypical antipsychotics which have an overlapping effect with buspirone in 5HT1A agonism. To our knowledge, there have been only two studies on buspirone added to typical antipsychotics. One has been done by Goff *et al*.[10] It was an open 6-week trial with an adjunct of 30 mg/day buspirone to a stable dose of typical antipsychotics and reported a modest decrease of clinical ratings of positive symptoms in 20 schizophrenic patients. Another study was carried out by Sirota *et al*.[9] 13 patients with schizophrenia who were receiving haloperidol, received up to 100 mg/day buspirone and there was a decrease in the mean PANSS score and all 3 subscales during a 6-week trial this study had no control group.

In the present study, we used a triple-blind method to collect and evaluate the subjects. We also had a control group which was a match to our intervention group regarding sex, age, marital status, and type of schizophrenia. Four scales including MMSE, PANSS, SAS, Global Assessment of Functioning were assessed in this study.

The limitations of this study are short duration of the study, studying the chronic patients with moderate residual symptoms which indicate the need for further research.

CONCLUSION

Buspirone has been shown to be effective in the improvement of negative symptoms of schizophrenia. Nevertheless, results of larger controlled trials are needed before any recommendation for abroad clinical application.

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AUTHOR'S CONTRIBUTION

The authors conceived and designed the evaluation and drafted the manuscript. The corresponding author collected the clinical data, the forth author interpreted the clinical data and performed the statistical analysis. The fifth author provided the drugs and the placebos. All authors revised the manuscript and read and approved the final manuscript.

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