ORIGINAL ARTICLE

The Effect of Aspirin on Schizophrenia; A Double Blind Placebo Controlled Study

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ABSTRACT

Objective: To determine the beneficial antipsychotic effects of aspirin plus atypical antipsychotic agents in the treatment of schizophrenia.

Study Design: A double blind placebo controlled study.

Place and Duration of Study: The study was conducted in Psychiatry ward of Imam Reza and Shahid Hashemi Mental Hospital in Arak, from April to December 2011.

Materials and Methods: This double blind placebo controlled study was conducted on 60 patients with schizophrenia. Patients were assigned to case group who received an atypical antipsychotic agent (olanzapine, risperidone, clozapine) as the standard treatment of the schizophrenia plus aspirin 1000 mg /daily (aspirin or case group n=30), and 30 patients received standard treatment and placebo (control group, n=30). The PANSS questionnaire was used to evaluate patients at 0, 2,4,6 and 8 weeks after treatment. SPSS software was used for data analysis. Student's t-test was applied and repeated measurement test to compare two groups

Results: The difference between two groups regarding positive and negative symptoms was not significant (Repeated Measure/P=0.20 and P =0.20 respectively). However, there was a significant difference between two groups regarding general and total symptoms (Repeated Measure/P=0.003 and P=0.032 respectively). The results did not show any remarkable related side effects to aspirin in two groups.

Conclusion: The trial revealed that aspirin 1000 mg /day in combination with antipsychotic drugs for 8 weeks is an effective agent for the reduction of general and total symptoms of schizophrenia. Nonetheless, it did not modify the positive and negative symptoms.

Key Words: *Aspirin, Atypical Antipsychotic, Adjunctive Therapy, Schizophrenia.*

Introduction

Schizophrenia is a chronic disorder and 21 million of people are involved globally.[1] The symptoms of schizophrenia are usually categorized into positive, negative and cognitive symptoms. Positive symptoms include hallucinations and delusional thoughts are diagnostic for schizophrenia. Negative symptoms are lessened motivation, difficulty with social interaction and withdrawal. Moreover, poor attention, limited working memory, and restricted executive functioning show the cognitive disorder in these patients.[1-4] It usually initiates in the third decade of life and it is rare in children and people who are more than 45 years old.[3] Positive symptoms, reflect an excess or distortion of normal functions, negative symptoms, refer to a diminishment or absence of characteristics of normal function and may appear with or without positive symptoms and cognitive deficits lead to the executive dysfunction.[5,6] Several hypotheses were presented regarding the cause of schizophrenia, however, the exact reason of schizophrenia is not well known, although the most scientists have been focused on dopamine system.[7] Recently scientists[8,9] have discussed the role of immune dysfunction and inflammation in patients with schizophrenia. A study in patients with schizophrenia demonstrated that higher blood levels of C-reactive protein (CRP) or white blood cell count (WBC) were related with worse symptoms.[10] Therefore, these scientists recommended that inflammation might play an important role in the development of cognitive deficits in patients with schizophrenia[11], Sommer et al. in a review of 26 double-blind studies showed Acetylsalicylic acid (aspirin) is effective as an adjuvant agent in the treatment of schizophrenia.[12] Some studies supposed that inflammation has a key role in schizophrenia, therefore, this study was steered based on the psycho-neuro-immunological hypothesis that a lipophilic anti-inflammatory

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substance may lead to therapeutic benefits in schizophrenia. So this study was planned to determine the beneficial antipsychotic effects of aspirin plus atypical antipsychotic agents in the treatment of schizophrenia.

Materials and Methods

This double blind placebo controlled study was conducted on 60 patients in Imam Reza and Shahid Hashemi mental hospital in Arak from April to December 2011. In this controlled trial 60 schizophrenic patients based on DSM-V criteria[13] were randomized in two groups. The enrolled participants were counseled, and informed consent was obtained before randomization, as per the institution's protocol. Moreover, the study protocol was approved by the ethics committee of Arak University of Medical Sciences (IRCT registration number: 201108197373N1). The Helsinki Declaration was respected and the patients were presented by a code and remained anonymous during the study. The criteria for enrollment were, schizophrenia based on DSM-IV criteria, age 15-55, at least, PANSS 60. On the other hand breastfeeding and pregnancy, peptic ulcer, aspirin or proton pump inhibitors contraindication and drug abuse were exclusion criteria.

To randomization we used sequential numbers, in this case, the first number was given to the first patient and received an atypical antipsychotic agents (17 patients received Olanzapine, 9 patients Risperidone, and 4 patients Clozapine) as standard treatment of the schizophrenia, also, aspirin 1000 mg /day (aspirin or case group, n=30) . Sequentially the next number was given to next patient and received standard treatment, 14 patients received Olanzapine, 11 patients Risperidone, and 5 patients Clozapine) and placebo (control group, n=30). Each placebo tablet contained dextrin and was identical in appearance to the 500 mg aspirin tablet. Pantoprazole 20 mg/daily was administered for all patients. Aspirin and placebo were the same in shape, color, and taste. Both participants and study staff (researcher, examiner, and analyzer) were masked to treatment allocation. The PANSS was used to evaluate patients at 0,2,4,6,8 weeks after treatment. The PANSS is a common and validated questionnaire in clinical studies and assessed the symptoms of schizophrenia based on positive and negative syndrome scale. The 30 items are arranged as 7 positive symptoms (P1-P7), 7negative symptoms (N1-N7) and 16 general psychopathology symptoms items(G1-G7).The patients in the psychiatric ward in Imam Reza and Shahid Hashemi mental Hospitals were rated within the first week of admission and at weekly intervals for 8 weeks. Baseline PANSS scores on the conceptual disorganization item and the total negative scale score predicted which patients would respond to antipsychotic treatment within 8 weeks.

Statistical analysis

The data were analyzed using Statistical Package for Social Studies version 20.0 (SPSS Inc, Chicago, Ill). Categorical data are presented as numbers (%), and continuous data as mean ± SD. We used the Student's t-test and repeated measurement test to compare two groups.$\alpha < 0.05$ was considered significant.

Results

Sixty patients mean age 30.11±7.80 were enrolled in the trial. Regarding sex and age distribution the difference between two groups was not significant (P=0.5)(table I). The Mean±SD of positive and negative syndrome scale (PANSS) rating criteria in patients at admission, week 2,4,6 and 8 were assessed. The difference between two groups regarding positive symptoms was not significant at admission and week 2 (Independent t-test /p=0.14 and 0.33 respectively) and was significant at week 4,6 and 8(Independent t-test /p=0.001).

Table I: The Demographic Data of Patients

Characteristic		Control	Case	P
Sex	Male	15(50%)	16(53%)	0.5
	Female	15(50%)	14(47%)	
Age		30.01±8.8	29.3±6.8	0.6
Duration of Disease		10.1±5.2	9.3±5.0	0.5
Admission No		4.40±1.90	3.90±1.60	0.20

Regarding negative symptoms, The difference between two groups was not significant at admission, week 2,4,6,8 (Independent t-test; p=0.14, p= 0.49, p=0.09,0.19 and p=0.29 respectively). There was no significant difference between two groups regarding general symptoms at admission and week 2 (Independent t-test /p=0.08 and 0.1 respectively) and was significant at week 4,6 and 8(Independent t-test /p=0.001). Moreover, we did not detect significant difference between case

and control groups regarding total symptoms at admission week 2 and 4 (Independent t-test /p=0.2, p=0.1, p=0.06 respectively) but we showed significant difference at weeks 6 and 8(Independent t-test /p=0.002, p= 0.006 respectively)(table II)(fig 1). Generally, the difference between two groups regarding positive and negative symptoms was not significant (Repeated Measure/p=0.20 and 0.20 respectively). However, there was a significant difference between two groups regarding general and total symptoms (Repeated Measure/p=0.003 and 0.032 respectively) (table 2, fig1). We did not detect any remarkably related side effects to aspirin in two groups.

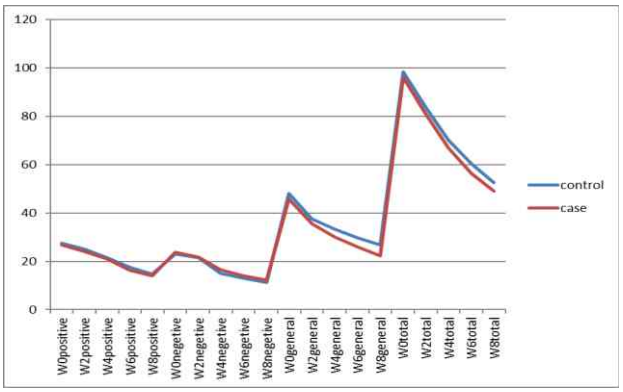

Fig 1: The Changes of the Negative, Positive, General before and after 8 Weeks Treatment and Total Symptoms in Two Groups

Table II: The Mean±SD Positive and Negative Syndrome Scale (PANSS) Rating Criteria in Patients

Symptoms		Control Mean±SD	Case Mean±SD	P
Positive	Admission	27.60±3.90	29.10±3.60	0.14
	Week 2	25.30±3.30	24.10±3.50	0.33
	Week4	21.60±3.10	17.70±3.30	0.001
	Week 6	17.50±3.50	13.90±2.70	0.001
	Week 8	14.70±2.50	10.10±2.20	0.001
Negative	Admission	23.10±3.60	21.80±3.00	0.14
	Week 2	21.60±2.80	21.00±2.80	0.49
	Week4	15.00±2.40	16.20±2.90	0.09
	Week 6	13.00±2.90	13.90±2.70	0.19
	Week 8	11.30±2.80	12.00±2.70	0.29
General	Admission	48.20±3.90	46.20±4.40	0.08
	Week 2	37.30±4.30	35.40±4.30	0.1
	Week4	33.20±4.60	29.10±3.60	0.001
	Week 6	29.70±2.90	24.80±3.20	0.001
	Week 8	26.90±3.40	21.60±2.60	0.001
Total	Admission	98.27±4.52	96.13±9.61	0.2
	Week 2	83.97±3.40	81.2±7.80	0.1
	Week4	70.07±5.50	66.70±7.90	0.06
	Week 6	60.20±3.4	56.23±7.50	0.002
	Week 8	52.40±3.30	56.23±5.30	0.006

Discussion

Recent experiences have indicated the role of infection and inflammation in schizophrenia, these findings designated that prenatal bacterial or viral infections during pregnancy increased the risk of schizophrenia in children.[14,15] Moreover, comprehensive studies revealed that the levels of interleukin-1 (IL-1) and IL-2, in the CSF were higher among patients with schizophrenia than the general population[16,17] and complementary studies detected that high level of IL-2 in the CSF was a predictor of relapse of schizophrenia among these patients.[18] Following these findings, some scientists practiced anti-inflammatory agents such as celecoxib and aspirin in schizophrenia as an adjunctive therapy and reported that with these anti-inflammatory agents are disease modifier.[19-22] In a controlled trial Laan et al. examined the effect of aspirin in schizophrenia and revealed more improvement among patients treated with aspirin than the placebo group, regarding the PANSS positive and total scores, particularly in patients with cytokines elevation. Furthermore, the authors did not reveal side effects owing to the high dosage of aspirin.[20] In the current controlled trial, we used aspirin 1000 mg /daily as adjunctive treatment with atypical antipsychotic agents on sixty patients mean age 30. 11±7.80 for 8 weeks. The difference between two groups regarding the improvement of positive and negative symptoms was not significant. However, there was a significant difference between two groups regarding the improvement of general and total symptoms. In accord with our findings, Müller et al in 2002 revealed that celecoxib add-on treatment presented beneficial effect on treatment of schizophrenia, similar to our results positive and negative syndrome scale (PANSS) after five weeks treatment with celecoxib improved in two groups and difference between two groups was not significant while like our practice the celecoxib significantly improved the total score.[21] Consistently 2 years later in another experience, Muller et al. reported that celecoxib significantly improved PANSS total scale.[22] Additionally, Muller et al in 2010 evaluated the effect of Celebrex on forty-nine patients with the first episode of schizophrenia and as oppose to our findings showed significant improvement in Celebrex group regarding positive and negative

symptoms scale (PANSS). Also, they revealed significant improvement in the CGI (clinical global impression) scale in celecoxib group.[23] Another trial in agreement to our work in Iran by Akhondzadeh et al. on 60 patients with schizophrenia showed risperidone plus celecoxib significantly improved general psychopathology symptoms, total PANSS score and as oppose to us positive symptoms scales.[24] The patients in our experience were well matched and the demographic characteristics, such as sex, age, and duration of the disorder, did not differ significantly between two groups and did not correlate with the therapeutic outcomes, so, we concluded that the therapeutic effect could be attributed to the aspirin. In line with our findings, Müller et al in 2002 indicated that sex, duration, and severity of the disorder were not correlated with therapeutic outcomes.[21]

Previous studies have not explained any notable side effects in association with anti-inflammatory agents,[19-21] consistently we did not reveal any related side effects with the aspirin in this practice.

Some limitations such as relatively small sample size and short duration of the treatment adhered to this practice and it would be interesting to evaluate the aspirin efficacy in larger series of patients with schizophrenia over a longer period exclusively to examine effects of aspirin on negative symptoms. In theory, the effect of aspirin and other anti-inflammatory agents without an antipsychotic medication would be more exciting; however, from ethics viewpoint is not acceptable.

Conclusion

We detected that aspirin 1000 mg /day in combination with antipsychotic agents significantly decreases the general and total symptoms of schizophrenia after 8 weeks treatment. However, aspirin was not effective on positive and negative symptoms and more clinical trials are needed to confirm the results of this practice.

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