The Role of Minocycline in Neuro-Cognitive Symptoms in the Episodes of Primary Psychosis: A Clinical Trial

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Abstract- This study was conducted to compare the neurocognitive changes in an episode of primary psychosis in a group treated with minocycline and control. In this randomized controlled clinical trial, 40 patients with schizophrenia were randomized into two groups and underwent eight weeks of treatment with either minocycline (100 mg twice per day) or placebo in addition to routine treatment. Patients were evaluated using the Wechsler Adult Intelligence Scale (WAIS), Positive and Negative Syndrome Scale (PANSS), and Wisconsin Card Sorting Test (WCST) at baseline and at weeks 4 and 8. General linear model repeated measures showed a significant effect for time treatment interaction on the scores of WAIS, PANSS, and WCST of patients in the minocycline group (P>0.05). Regardless of the type of intervention, there was a remarkable difference between the mean scores of WAIS, PANSS, and WCST measured on three stages. Minocycline seems to be a safe and effective adjuvant in the management of patients with schizophrenia.

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Introduction

Schizophrenia is a devastating neurobiologic psychiatric disorder that typically strikes the brain function and affects about 1% of the population worldwide (1). The causes of schizophrenia are unknown, but there is evidence of heredity factors and imbalance in brain chemistry, Genetic studies indicate the possibility of inheritance (Ghoreishi, 2015). There is a lack of a certain cure for the disorder, so lifelong antipsychotic therapy is recommended. The only FDA-approved antipsychotic for treatment-resistant schizophrenia is clozapine (2). There are no evidence-based treatments based on some studies for people who have persistent symptoms and are nonresponsive to clozapine (3).

Lamotrigine is one of the recommended medication that has synergistic effect adjunctive to clozapine on psychotic symptoms (4). But it's efficacy has been confirmed (5) and not been replicated, so it remains questionable if it is an effective treatment (6).

Minocycline is a synthetic derivative of tetracycline with a tolerable side effect that affects the GluR1 AMPA receptor subtype (7). Increased membrane localization of a GluR1 AMPA receptor subtype leads to glutamatergic activity and modulators of neuroplasticity (8). It seems that these receptors have a role in the pathobiology of schizophrenia (9,10). Minocycline also has anti-inflammatory effects (11). Recently it is suggested that there is a strong relationship between immunological effects and the pathophysiology of schizophrenia (12).

In some previous studies, potential benefits from minocycline in schizophrenia are reported. The role of minocycline in the improvement of persistent psychotic symptoms, which linked minocycline to reductions in the Positive and Negative Syndrome Scale (PANSS) general psychopathology scale scores are reported (13,14). A recent meta-analysis has shown mostly negative symptoms benefits of minocycline in schizophrenia (15-17).

The aim of this study was the assessment of adjunctive minocycline to routine treatment of schizophrenia in Iran.

Materials and Methods

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In this randomized, double-blind placebo controlled comparison of adjunctive minocycline and placebo, after receiving the ethics approval and patient informed consent, 30 Patients with schizophrenia, schizoaffective and schizophrenic form with the diagnosis time of fewer than ten years referred to Shahid Beheshti Hospital, Zanjan, Iran in 2016 were selected by simple random sampling. The schizophrenia, schizoaffective, and schizophrenic form disorders were diagnosed by a psychologist with ten years of experience. Patients were randomized into two groups (cases and controls) by a computer-generated randomization list. The Wisconsin, Wechsler Intelligence Scale, and positive and negative syndrome scale (PANSS) test were done in all patients. Both groups treated with usual antipsychotic treatment. But cases received in addition to the usual antipsychotic treatment, 100 mg minocycline two times a day for eight weeks. The Wisconsin, Wechsler Intelligence Scale for Adults and PANSS results were compared four weeks and eight weeks after intervention.

Patients with schizophrenia, schizoaffective and schizophrenic form with the diagnosis time of fewer than ten years that their symptoms are under control (without highlighting positive and negative symptoms), and there was no change in the antipsychotic drugs in past three months enrolled to the study. Patients with the unwillingness to continue the treatment and lack of acceptance and compliance medication orders were excluded from the study.

Individuals were asked to sign an informed consent form. All the personal information remained anonymous.

Ethical consideration

This research study followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all patients. The study was approved by the Ethics Committee of Zanjan University of Medical Sciences.

Statistical analysis

Data were analyzed using statistical package for social sciences (SPSS) version 22 (SPSS Inc. Chicago, IL) for windows. The sample size calculated by using sample size formula. We considered α=0.05 and power=90%. Normal distribution variables (approved by one-sample Kolmogorov–Smirnov test) were compared using an independent sample t-test between the groups and paired sample t-test within the groups. The *Chi*-square test also was used to compare categorical variables in the two groups. P<0.05 considered statistically significant.

Results

Eventually, 30 cases (53.3% males and 47.7% females) with the mean age of 35±7.7 years underwent analysis. Fourteen Patients received Minocycline supplementation, and 16 were treated only by routine treatment. Age and gender distribution were similar between the two groups. (P=0.92) (Table 1) There were no significant differences between cases and controls in terms of gender distribution and educational status. But marital status showed significant differences. So that 84.7% of the total were single or divorced. (Table1)

Table 1. Demographic Data

Variables		Cases	Controls	Total
Gender	**Male**	7(50%)	9(56.3%)	14(46.7%)
	Female	7(50%)	7(43.8%)	16(53.3%)
P	0.73			
Marital status	**Single**	7(50%)	9(56.3%)	16(53.3%)
	Married	3(21.4%0	7(43.8%)	10(33.8%)
	Divorced	4(28.6%)	0	4(13.3%)
P	0.05			
Educational status	**< Diploma**	12(85.7%)	13(81.25%)	25(83.4%)
	Diploma	1(7.1%)	3(18.8%)	4(3.3%)
	Academic	1(7.1%)	0	1(3.3%)
P	0.47			

Wechsler Adult Intelligence Scale (WAIS) scores increased much stronger in patients who received minocycline in all four verbal and performance WAIS scales including Picture Completion, Digit Span, Block Design and Arithmetic, before, four weeks and eight weeks after intervention although this difference was not significant between groups, except in picture completion at eight weeks after the intervention that was higher in cases significantly (P=0.00). This shows the efficacy of minocycline in increasing the Wechsler test score in

Picture Completion (Table 2). PANSS test results before the intervention conducted that the mean score of the controls was significantly lower than the cases (P=0.005). At the end of four weeks and eight weeks after the intervention, PANSS test scores decreased much stronger in patients who received minocycline. (P=0.48, P=0.56 respectively) (Table 2). In the Wisconsin Card Sorting Test, no significant differences were seen between two groups before the intervention, four weeks and eight weeks after intervention (P>0.005) According to the test results, the mean score of patients in both groups was improved and the rate of errors decreased, but these changes were much bigger in patients who received minocycline (Table 2).

Table 2. Wechsler Adult Intelligence Scale (WAIS), PANSS and Wisconsin Card Sorting Test

WAIS Scales	Cases	Controls	*P*
Picture Completion	Week0: 3.29 ± 2.4	Week0: 5.13 ± 3.79	Week0: 0.14
	Week4: 6.36 ± 2.71	Week4: 4.50 ± 2.83	Week4: 0.07
	Week8: 10.64±3.08	Week8: 6.55±2.30	Week8: 0.00
Digit Span	Week0: 3.71 ± 2.79	Week0: 69 ± 2.65	Week0: 0.33
	Week4: 5.64 ± 2.41	Week4: 4.75 ± 2.86	Week4: 0.36
	Week8: 6.55±2.51	Week8: 5.18 ± 1.94	Week8: 0.16
Block Design	Week0: 11.07 ± 9.80	Week0: 13.88 ± 10.4	Week0: 0.45
	Week4: 15.93 ± 6.43	Week4: 16.56 ± 8.57	Week4: 0.82
	Week8: 22.09±6.33	Week8: 18.55±7.17	Week8: 0.23
Arithmetic	Week0: 3.93 ± 2.17	Week0: 6.06 ± 3.70	Week0: 0.06
	Week4: 6.14 ± 3.16	Week4: 6±2.99	Week4: 0.9
	Week8: 8.64±3.50	Week8: 7±2.57	Week8: 0.22
Wisconsin Card Sorting Test			
Number of trials	Week0: 3.65±0.93	Week0: 3.53±0.91	Week0: 0.67
	Week4: 4.36±0.84	Week4: 4.31±0.95	Week4: 0.89
	Week8: 5.09±0.54	Week8: 4.64±0.81	Week8: 0.13
Number correct	Week0: 38.1±12.4	Week0: 38.3±9.5	Week0: 0.95
	Week4: 48.4±7.5	Week4: 46.6±9.2	Week4: 0.56
	Week8: 55.4±4.1	Week8: 52.2±7.5	Week8: 0.22
Perseverative responses	Week0: 6.95±4.07	Week0: 6.95±3.94	Week0: 0.90
	Week4: 3.64±2.85	Week4: 4.25±3.73	Week4: 0.62
	Week8: 1±1.33	Week8: 2.7±3.20	Week8: 0.13
Total errors	Week0: 12.4±5.7	Week0: 13.7±5.6	Week0: 0.45
	Week4: 7.9±5	Week4: 8.5±4.7	Week4: 0.71
	Week8: 4.1±2.7	Week8: 5.9±4.6	Week8: 0.30
Positive and Negative Syndrome Scale (PANSS)			
	Week0: 102.9±21.6	Week0: 82.65±21.9	Week0: 0.005
	Week4: 83.6±11.4	Week4: 79.3±20.6	Week4: 0.48
	Week8: 75.8±11.2	Week8: 72.6±14.1	Week8: 0.56

Discussion

Results of a recent study indicated the important and effective role of minocycline on neuro-cognitive symptoms and positive and negative symptoms in patients with the primary psychotic episode (schizophrenia, schizoaffective, and schizophreniform) who were under treatment with usual treatment.

Du *et al*., (18) showed the neuroprotective effects of minocycline in animal models of ischemic injury and Huntington's disease and reported that minocycline could stop the neuronal degeneration of dopamine in Parkinson's disease animal model. They concluded that minocycline has a significant role in the treatment of disorders associated with neuronal injury (18).

According to the Miyaoka study, minocycline as an adjunct treatment raised significant improvement in people with severe catatonic schizophrenia (13).

This study was supported by a report of a patient with schizophrenia that received a fixed-dose olanzapine 20 mg/day in addition to receiving minocycline 200 mg/day for eight weeks (19). The combination of minocycline and sedative therapy significantly reduced positive symptoms, and no negative symptoms were observed.

Miyaoka *et al.*, (14) concluded that the use of minocycline for four weeks as an additional treatment to antipsychotic drugs created a significant clinical improvement in both positive and negative syndrome in patients with Schizophrenia. The study lacked a control group, and therefore the impact of the additional treatment (administration of minocycline) cannot be an explanation for improvement minocycline.

Based on some previous studies, minocycline has a certain impact on the negative symptoms and cognitive

function in schizophrenia patients (20,21). The recent study suggests the effective role of added minocycline in the treatment of negative symptoms of schizophrenia.

According to Levkovitz *et al.*, study (15), treatment with added minocycline 200 mg/day for six months had a beneficial effect on negative symptoms of early-phase schizophrenia. This finding confirmed in our study.

The results of a randomized, double-blind placebo-controlled clinical trial also suggested that the increase minocycline (200 mg/day for one year), can reduce negative symptoms of early psychosis patients without affecting recognition (17).

In conclusion, minocycline as a microglial activation inhibitor, an anti-inflammatory, antioxidant, and anti-apoptotic and can modify glutamate-induced excitotoxicity. The ability of minocycline in the treatment of schizophrenia is demonstrated in studies using animal models. Our recent study also proved that minocycline could be used as an added treatment in schizophrenia, especially to correct positive and negative symptoms. The results of our study showed that minocycline could be a safe and effective adjunctive therapy besides the antipsychotic treatment in the treatment of schizophrenia. Finally, further studies with a larger sample size are suggested to confirm the results of this study. Also, considering the complex etiology of schizophrenia classification of disease phenotype in subsequent studies, including the patient's condition and severity of negative symptoms, are recommended.

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