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Original Research Article

EFFECT OF RISPERIDONE ON HEART RATE DYNAMICS OF PATIENTS HAVING SCHIZOPHRENIA

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Abstract: *Risperidone is a first-line antipsychotic drug for treating schizophrenia. It has antiadrenergic action but has a negligible impact on neurocardiac regulation. However, due to the relationship between cardiac autonomic regulation and a psychotic state, risperidone induces treatment-associated changes in heart rate variability (HRV). This Prospective study was designed to assess the effect of risperidone therapy on the heart rate dynamics of schizophrenic patients. Psychiatry & Medicine Department, Nishtar Medical Hospital, conducted this study from January 2021 to January 2022. After screening, patients with psychosis causing psychosocial impairment (PANSS score 70) were included in the study. Fifteen patients were selected after the screening. All were administered risperidone. A Control group having age and gender-matched subjects was selected, and ECG was done. Data from 15 controls and 15 patients were analyzed. Clinical Global Impressions-Severity of illness scale (CGI-S) and Positive and Negative Syndrome Scale (PANSS) were used for quantifying psychiatric symptoms. Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) was used to measure drug-associated movement disorders. The mean risperidone dose was 3.2± 0.8 mg/ day. Data collected after 6 weeks of treatment showed that the mean PANSS score, positive symptoms subscale score, negative symptoms subscale score, CGI-S score and general psychopathology score decreased significantly (p< 0.001). Comparison of HRV parameters between the control group (healthy subjects) and unmedicated patients showed a significant group effect (p<0.001). Evaluation of the association between the severity of psychotic symptoms and HRV measures shows the negative correlation between PANSS positive symptoms score changes and SDNN changes (p= .012).Risperidone treatment in acutely ill schizophrenic patients leads to an increase in cardio-vagal activity, thus causing improvement in sympathovagal imbalance.*

Keywords: Risperidone, Heart rate variability, Schizophrenia, Psychosis

Introduction

Heart rate variability (HRV) is used for assessing neuro-cardiac functions. Association between HRV and psychotherapy and treatment-associated adverse impacts in schizophrenic patients have been studied (Fernandez, 2018; Lee et al., 2020; Refisch et al., 2021). It was found that acutely ill schizophrenic patients have lowered vagal activity (Kheder et al., 2018). HRV measures have three domains-complexity, frequency and time. The significance of frequency and time is well-established in various medical fields (Baik et al., 2019). Assessing HRV pattern in schizophrenic patients using these measures show that these patients have decreased vagal tone compared to normal subjects (Newton et al., 2018). Antipsychotic medicines have an unpredictable and complex effect on heart rate variability, regardless of neurochemical profiles (Moon et al., 2021). For instance, clozapine is a potent anticholinergic drug leading to HRV and decreased vagal tone. At the same time, olanzapine does not have a prominent effect on heart rate dynamics because of balanced antiadrenergic and anticholinergic actions (BHARGAVA and ACHARYA, 2019). Risperidone is the first-line antipsychotic drug for treating schizophrenia. It has antiadrenergic action but has a negligible impact on neurocardiac regulation. However, due to the relationship between cardiac autonomic regulation and a psychotic state, risperidone induces treatment-associated changes in HRV. This study aims to

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assess the effect of risperidone therapy on heart rate dynamics of schizophrenic patients.

Methodology

The prospective study was conducted in Psychiatry and Medicine Department, Nishtar Medical Hospital, from January 2021 to January 2022. DSM-IV criteria were used for the diagnosis of schizophrenia. Experienced psychiatrists screened medication-free patients with psychotic symptoms. After screening, patients with psychosis causing psychosocial impairment (PANSS score 70) were included in the study. Patients with any chronic illness were excluded. Fifteen patients were selected after the screening. All were administered risperidone. All subjects were initially medication free, meaning they did not take antipsychotic drugs for at least a month. A Control group having age and gender-matched subjects was selected, and ECG was done. Independent researchers evaluated clinical variables. During the initial 2 weeks, the patient could take concomitant drugs to control psychiatric symptoms. Data from 15 controls and 15 patients were analyzed. Informed consent of the patients was taken. The ethical board of the hospital approved the study. Clinical Global Impressions-Severity of illness scale (CGI-S) and Positive and Negative Syndrome Scale (PANSS) were used for quantifying psychiatric symptoms.

Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) was used to measure drug-associated movement disorders. All subjects were advised not to exercise vigorously, smoke, or consume caffeinated drinks before ECG. After signal stabilization, a resting ECG was recorded. HEV signals were generated using time series data without premature ventricular beats and noises. SPSS 22.0 was used for data analysis. Risperidone-associated changes in DIEPSS and PANSS were assessed using paired sample t-test. The magnitude of the drug effect was measured using Cohen's d statistics. HRV measures of the control group and patients were compared using multivariate analysis, followed by univariate analysis. Spearman's correlation coefficients were used for correlating variable changes. P value < 0.05 was considered statistically significant.

Results

The baseline data of participants are summarized in Table I. The mean risperidone dose was 3.2± 0.8 mg/ day. No clinical abnormalities were reported in baseline ECG. Data collected after 6 weeks of treatment showed that the mean PANSS score, positive symptoms subscale score, negative symptoms subscale score, CGI-S score and general psychopathology score decreased significantly ($p< 0.001$). The severity of psychopathology is affected mainly by risperidone. The mean total DIEPSS score significantly increased in subjects receiving risperidone ($p<0.001$).

Comparison of HRV parameters between the control group (healthy subjects) and unmedicated patients showed a significant group effect ($p<0.001$). Univariate analysis revealed a significant difference in SDNN ($p=0.001$), HF ($p<0.001$) and pNN20 ($p= 0.003$) between both groups. HRV parameters are displayed in Table II.

Evaluation of HRV measures within the subject showed that the time effect was significant ($p= .029$). Univariate analysis showed that after risperidone treatment mean RR interval increased significantly ($p<.001$). Evaluation of an association between the severity of psychotic symptoms and HRV measures shows the negative correlation between PANSS positive symptoms score changes and SDNN changes ($p= .012$). A shift in psychotic symptom score and complexity measures were not significantly correlated.

Table I Baseline data of the subjects

Variables	Control group n=15	Patients n=15
Male: female	9:6	9:6
Age (years)	36.9±6.3	36.1± 7.0
Duration of disease (years)	-	4.2± 5.3
Drug naïve: drug-free	-	9/6
PANSS score		
Total	-	98.7± 14.7
+symptoms		26.7± 4.3
- symptoms		24.8± 4.3
General psychopathology	-	47.5± 8.6
CGI-S score	-	4.2± .7

Table II HRV indices

Variable	Control group	Risperidone Group	
		Baseline	**6 Weeks**
Mean RR	846.21± 85.21	762.01± 73.05	872.67± 99.78
SDNN	40.89± 8.65	32.61± 7.38	29.77± 9.46
RMSSD	36.68± 13.01	23.75± 16.42	27.81± 15.08
InLF	5.52± .61	5.23± .49	4.63± .76
InHF	6.22± .41	4.87± .96	5.38± .75
SampEn	2.61± .66	1.78± .62	1.89± .63
InCSE20	0.72± .26	0.67± .56	.72± .76

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Note: SDNN =standard deviation of RR intervals
RMSSD = square root of the mean squared differences of successive RR intervals
HF= high-frequency power
LF= low-frequency power
SampEn =sample entropy
CSE20= corrected Shannon entropy

Discussion

This study found that acutely ill schizophrenic patients have prolonged RR intervals, and the cardiac sympathy-o-vagal mechanism was predominantly parasympathetic after 6 weeks of risperidone treatment. Cardio-vagal modulation is diminished in schizophrenic patients (Schulz et al., 2020). Additionally, electrogastrography of schizophrenic patient show decreased parasympathetic activity long with sympathovagal imbalance (Schulz et al., 2019). In this study, RMSSD and SDNN were lower in unmedicated schizophrenic patients than in healthy subjects. It was in line with previous study findings (Tajiri et al., 2018). Schizophrenic patients have lower ApEn, SampEn and CSE of HRV than healthy controls, which indicates that heart rate data has less complexity (Heiss et al., 2021). In this study, the acute treatment phase had no significant impact on change in complexity measures.
Previous studies show that the risperidone effect may influence neuronal activity in the prefrontal cortex, which explains its antipsychotic effect (Robinson et al., 2019). As schizophrenia associated autonomic imbalance is due to diminished activation of the amygdala–the prefrontal circuit. Risperidone significantly affects sympathovagal imbalance by inducing changes in the neuronal activity of the prefrontal cortex. Cardiac autonomic activity is also affected by the antipsychotic's receptor profile (Edinoff et al., 2022). However, the clozapine association between autonomic modulation and receptor profile is unclear (Dijkhuis et al., 2019). Overall, the sympathovagal imbalance in schizophrenic patients may be not only influenced by the biochemistry of antipsychotic drugs but also by the interaction between antipsychotic treatment and psychopathology. Schizophrenia increases the risk of cardiac mortality. The mechanism of schizophrenia-associated cardiac morbidity is changing in autonomic regulation (Vickers et al., 2022). Therefore, it is crucial to assess changes in the autonomic modulation of schizophrenic patients treated with antipsychotic drugs. This study has a few limitations. Firstly, the sample size was small. Although the statistical analysis was done, the sample size was insufficient to examine the HRV parameter. There is a need fora more extensive study to confirm the findings of our study. Secondly, dose–response relationship was not fully evaluated due to varied risperidone dose among patients. The confounding impact of disease independent factors on association between heart rate dynamics and psychotic symptoms is another limitation of this study.

Conclusion

Risperidone treatment in symptomatically ill schizophrenic patients leads to an increase in cardio-vagal activity, thus causing improvement in sympathovagal imbalance.

Conflict of interest

The authors declared absence of conflict of interest.

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