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Immunological Interplay in Schizophrenia: Impact of Clozapine and Risperidone Treatment- A Randomized Study

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Abstract

Background: Recent research highlights the neuroimmunological basis of schizophrenia with an intrigue into biomarkers for schizophrenia.

Methods: It was a prospective, randomized, interventional study. Patients with ICD-11 diagnosis of schizophrenia were randomized to receive either clozapine or risperidone after baseline assessment (socio-demographic and clinical parameters, blood investigations, immunoglobulins (IgM, IgA, IgG and IgE)). Levels of immunoglobulin were reassessed at 6 and 12 weeks, along with the application of PANSS and Glasgow antipsychotic side effect checklist.

Results: 30 patients in the clozapine group and 24 in the risperidone group completed the study. As compared to the risperidone group, in the Clozapine group, IgG and IgM were higher at baseline and had a rise over 6 and 12 weeks, IgA was lower at baseline and had a significant rise from week 6 to week 12 and Ig E showed a steady decline. For the clozapine group, at baseline, the correlation analysis showed Ig A to be significant for positive, general and total scores of PANSS, while Ig G was significantly correlated with total scores of PANSS and Ig M and Ig E with General scores on PANSS.

Conclusion: The change in immunoglobulin levels from baseline in both clozapine and Risperidone groups validates the immunological basis of schizophrenia. There was no known immunodeficiency found in either of the groups during the study period ratifying that the immunodeficiency with clozapine, if any, takes more than 12 weeks.

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Introduction

Schizophrenia has been linked with chronic inflammation in the central nervous system.[1] The aberrant immune mechanisms in the peripheral and central nervous system have been shown to influence the etiology of schizophrenia and the pathophysiology of psychotic symptoms that define the illness by its effect on the monoamine metabolism, neuroendocrine function, and synaptic plasticity. Many investigators have reported the involvement of immunological dysfunction in patients with schizophrenia.[2-4] The studies on serum immunoglobulins also report inconsistent and nonspecific changes with a lack of concordance among various reports.[2,3]

Antipsychotics also affect the immunological parameters like interleukin and immunoglobulin levels. Clozapine, the most effective antipsychotic for schizophrenia,[4] acts as an immunomodulator and has been reported to mediate several effects on humoral immunity by altering the levels of immunoglobulin.[5] Ponsford *et al*.[6] discovered a substantial reduction in immunoglobulin levels and a significant inverse link between IgG levels and duration of clozapine therapy.

Risperidone, another widely used antipsychotic, may have a direct effect on inflammatory status and can significantly affect immunoglobulin levels in patients with schizophrenia.[7-9]

Indian literature has meager research on the immune profile in patients with schizophrenia. Thus, the present study was carried out to evaluate the immunological parameters in patients with schizophrenia who were drug naïve or off treatment for 2 weeks and to compare the effect of clozapine and Risperidone on the levels of immunoglobulins (IgM, IgG, IgA, IgE) in patients with schizophrenia and study their correlation with the clinical response.

Methods

This was a randomized study carried out at the outpatient and inpatient facility of the Department of Psychiatry of a tertiary care teaching hospital of North India. Based on previous literature with regard to the percentage change in immune parameters, the sample size was calculated with 90% confidence level and 15% absolute precision. The optimum sample size with adjustment for loss to follow-up was proposed to include 60 patients in this study. Patients with the diagnosis of schizophrenia according to ICD-11(WHO),[10] in the age group of 18 to 45 years, not on any antipsychotic drug for the last 2 weeks and having the capacity and willingness to give written informed consent were inducted in the study. For patients who lacked capacity, written informed consent was obtained from a nominated representative. Patients on immunosuppressants, with overt infection in the past 2 weeks, hematological disorders, chronic liver or kidney disease, autoimmune disorders, chronic inflammatory disease, on antibiotics (chloramphenicol, tetracycline, rifampicin, polymyxin b, nitrofurantoin), with known immunodeficiency disorder, with epilepsy, agranulocytosis or granulocytopenia, paralytic ileus, CNS depression, myeloproliferative disorder, substance use disorder except tobacco and caffeine, pregnant and lactating women and those who received depot antipsychotics in the past 3 months were excluded to avoid confounding.

Procedure

Patients with a diagnosis of schizophrenia according to ICD-11 fulfilling inclusion and exclusion criteria were inducted into the study (between 14 February 2020 and November 2021). After written informed consent, the patients were enrolled in the study. The baseline socio-demographic and clinical profile was recorded on a performa designed for the study. The baseline severity of symptoms was assessed by administrating the positive and negative syndrome scale (PANSS).[11]

A baseline blood sample of 4 mL was drawn for a complete hemogram biochemical testing (FBS, LFT, RFT and Lipid profile). Another blood sample of 5 mL was taken for immunoglobulin estimation in plain vial; IgM, IgA and IgG measurements were done by immunoturbidimetric method (IMOLA). Normal range was defined for immunoglobulins as the following- IgM: 0.4–2.3 g/L; IgG: 7–16 g/L, IgA: 0.9–4.5g/L; IgE :1.5–144 IU/L according to the kits used.

After assessment of baseline psychopathology, hemogram, interleukins and immunoglobulin levels, patients were randomized to receive either clozapine or risperidone on the basis of a computer-generated random number table with parallel design in 1:1 allocation. The dosage was kept in the therapeutic dose range of Maudsley's prescription guidelines (Clozapine: up to 900 mg/day and risperidone: 2–8 mg/day). Clozapine was started with an initial dose of 12.5 mg once a day, which was gradually escalated to achieve the maximum tolerable therapeutic doses by the end of 4-6 weeks. An initial dose of 2 mg/day for risperidone was started, which was gradually titrated to the maximum tolerable therapeutic dose by the end of 4 to 6 weeks. The response was assessed as a ≥50% improvement in the PANSS from baseline.[12] Thereafter, participants were continued on the same dose till the completion of the study period, i.e., 12 weeks and further

continued clinical care. In the case of violent and aggressive patients, Benzodiazepines-sublingual or intramuscular (Clonazepam, Diazepam and Lorazepam) were used and for control of extra-pyramidal symptoms, oral trihexyphenidyl was allowed and a dose of these medicines were documented for both the groups.

Patients were followed up on a weekly basis and a complete blood count (CBC) analysis was carried out weekly before up-titrating the dose of clozapine. Repeat levels of immunoglobulin were assessed at 6 weeks and 12 weeks (end of study) along with PANSS and Glasgow antipsychotic side effect checklist was applied. In case of TLC <4000/mm^3 or neutrophil count <1000/ mm^3 in clozapine group, patients were planned to be immediately dropped from the study and managed accordingly. If patients developed immunoglobulin deficiency, i.e., IgA<0.5 g/l, IgG<5 g/l, IgM <0.4 g/l till the second assessment at week 6, the patients were planned to be dropped from the study and managed with standard protocol. 1 patient developed IgM deficiency at week 12 and was dropped out from the study and managed as per protocol. The study was approved by the institutional ethics committee and registered with the Clinical Trial Registry-India vide CTRI number: CTRI/202/02/023214.

Statistical Analysis

Statistical analysis was performed using SPSS version 16. Summary statistics were used to describe demographic and clinical characteristics of the sample. The *p-value* of <0.05 was considered significant.

Primary outcomes were assessed in each group using repeated measures analysis of variance (ANOVA). We used Greenhouse-Geisser correction in case sphericity was violated. The sphericity was evaluated using Mauchlay's test of sphericity. Post-hoc Bonferroni test was used to distinguish the difference in case of any statistically significant findings. Four separate models were applied, with level of IgG , IgM, IgA and IgE as the primary outcomes of interest. In each model, time was modeled as a fixed effect and treated as a categorical variable (baseline, week 6 and week 12).

In an exploratory analysis, we used Pearson's correlations to investigate whether changes in Ig were associated with the percentage change in PANSS total scores after 12 weeks of clozapine and risperidone treatment. Percentage change in PANSS total score was calculated using the formula: (12-week score – baseline score) / baseline score x 100). (Supplementary Table 3)

Results

A total of 65 patients were enrolled in the study – 31 in the clozapine group and 34 in the risperidone group. With attrition, at 12 weeks, there were 30 patients in the clozapine group and 24 in the risperidone group as shown in Supplementary Figure 1. Between group comparisons of mean scores of different immunoglobulin levels at baseline, at 6 weeks and at 12 weeks as shown in Figure 1

Hence, 54 patients completed the study and were analyzed for the results.

The mean age of the sample was 33.63 $\pm$ 5.94 years for the clozapine group and 31.96 $\pm$ 6.15 years for risperidone group. Both groups had a higher preponderance of males. Both the groups were comparable on rest of the socio-demographic parameters as shown in supplementary Table 1.

There was statistically significant difference in the baseline IgG levels which were higher in the clozapine group. The total PANSS score (*p-value* <0.001), positive symptom score (*p-value* = 0.003) and general symptom scores (*p-value* <0.001) were significantly higher in the clozapine group than the Risperidone group at baseline (Supplementary Table 1).

While there was no significant difference between the two groups in terms of total leucocyte count, the neutrophil, monocyte and eosinophil counts were significantly higher in the Clozapine group, but the mean values were within a normal range (normal values: neutrophil: 40–80%, monocyte: 2–10%, eosinophil: 1–6%) (Supplementary Table 2).

The difference between Ig G and Ig M at 6 weeks and Ig A at 12 weeks is significant between the two antipsychotics as shown in Table 1.

Ig G and Ig M were found to be statistically significant at both time points in pairwise comparison as shown in Table 2.

Table 1: Comparison of immunoglobulin levels with clozapine and risperidone: Repeated measures ANOVA

Immunoglobulins	Drugs	Baseline	6 weeks	12 weeks	Main effect of time		Main effect of time	
					Wilks' Lamda	*p-value*	Wilks' Lamda	*p-value*
IgG	Clozapine	12.34 ± 2.78	13.71± 2.54	14.08 ±2.87	0.710	<0.001*	0.963	0.378
	Risperidone	10.45 ±2.67	11.65 ± 1.81	13.2± 2.07				
IgM	Clozapine	1.54 ±1.47	1.73 ±1.45	1.81 ±1.3	0.633	<0.001*	0.948	0.254
	Risperidone	0.89 ±0.33	1.33 ±1.01	1.36 ± 0.69				
IgA	Clozapine	2.23 ± 0.94	2.26 ±0.92	2.8 ±0.86	0.987	0.717	0.739	<0.001*
	Risperidone	2.39 ± 0.96	2.14 ± 0.78	1.83 ±0.62				
IgE	Clozapine	399.0 ± 502.25	363.79 ±329.44	330.19 ±328.83	0.977	0.555	0.977	0.550
	Risperidone	258.19±508.84	450.28±721.46	308.15±259.58				

*Significant as $P < 0.05$

Table 2: Pairwise comparison of immunoglobulins between different time points

Category	Time Point	Reference time point	Mean difference	Standard error	*p-value*	95% CI for difference
IgG	1[@]	2[#]	-1.284	0.426	0.012*	(-0.23, -2.34)
		3[$]	-2.244	0.489	0.000*	(-1.03, -3.45)
	2[#]	3[$]	-0.960	0.426	0.085*	(-2.01, 0.09)
IgM	1[@]	2[#]	-0.316	0.108	0.015*	(-0.58, -0.05)
		3[$]	-0.371	0.086	<0.001*	(-0.58,-0.16)
	2[#]	3[$]	-0.054	0.146	1.000	(-0.41, 0.31)
IgA	1[@]	2[#]	0.108	0.167	1.000	(-0.31,0.52)
		3[$]	-0.012	0.141	1.000	(-0.36, 0.33)
	2[#]	3[$]	-0.120	0.150	1.000	(-0.49, 0.25)
IgE	1[@]	2[#]	-78.44	102.36	1.000	(-331.68,174.8)
		3[$]	9.42	85.50	1.000	(-202.1,220.95)
	2[#]	3[$]	87.86	80.52	0.841	(-111.33, 287.06)

1[@]- Baseline, 2[#] - First follow up (6 weeks) , 3[$] - Second follow up (12 weeks).
*Significant as $p < 0.05$

Discussion

To our knowledge, this is the first longitudinal study to measure immunoglobulin levels in patients with schizophrenia following the initiation of clozapine and its comparison with Risperidone in India. Through this study, we highlight the interplay of immunoglobulins with two commonly used atypical antipsychotics in patients with schizophrenia. The mean age of the sample (33.63 ± 5.94 years -Clozapine group; 31.96 ± 6.15 years - Risperidone group) is comparable to previous studies[13,14] with a higher preponderance of males (60 and 62.5%).[15,16] Though the mean total duration of illness was higher in the clozapine group, the difference wasn't statistically significant (12.03 ± 6.64 *versus* 8.77 ± 6.28), which supports the usual clinical dictum of clozapine use after failure of clinical response with at least two antipsychotics. At baseline, the clozapine group had higher levels of Ig M, G and E. Clozapine group had a significantly higher level of IgG (long-standing immune response) which further potentiated the

inflammatory process in schizophrenia due to the longer duration of illness and exclusion of other confounding factors such as infections and past exposure to antipsychotics.

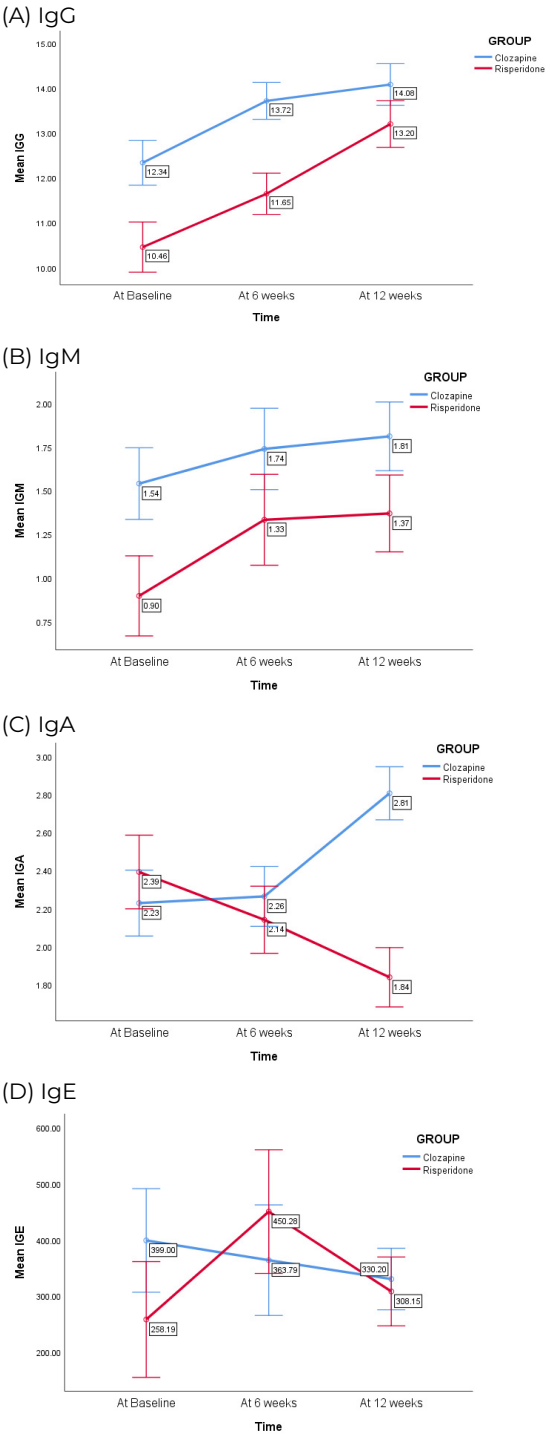

Figure 1: Between group comparisons of mean scores of different immunoglobulin levels at baseline, at 6 weeks and at 12 weeks

Trends in Immunoglobulins

In the current study, both the groups (Clozapine and Risperidone) had a significant rise in IgG and IgM at week 6 which persisted up to week 12. Though most of the literature reports a decrease in IgG and IgM with clozapine,[5,6] these studies do not define the trend of IgG and IgM, i.e., when their levels actually begin to fluctuate. Only a study by Griffith *et al.*[17] show the trends in immunoglobulins with clozapine. The current study might have shown a rise due to short-term exposure of clozapine, thus substantiating that the mechanisms to decrease IgG did not set in till at least 12 weeks (study period) of Clozapine therapy and hence clozapine doesn't suppress the immune system as a short-term effect also supported by Griffith *et al.*[17] which shows decrease in Ig G at 24 weeks. In contrast, Hinze *et al.*[8] in their longitudinal study, reported that clozapine led to an increase in IgG levels at the end of week 6 but IgM and IgA showed no significant alterations which contrasts with our study. This disparity may be due to Hinze *et al.* reporting *in-vitro* parameters.

The level of IgG, as seen in our study, progressively increased over 12 weeks. This can be explained as clozapine has been seen to induce antibodies in certain patient populations, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) through a possible IgG associated mechanism.[18]

This study also contrasts with Griffith *et al.* as there was increase in Ig M in all patients except one but Griffith *et al.* reported a decrease in Ig M at 12 weeks.[17] Lozano *et al.*[19] reported a high prevalence of IgM deficiency secondary to clozapine as compared to our study wherein only 1 patient developed IgM deficiency in clozapine group.

The IgA levels showed a gradual increase with clozapine and a decline with risperidone, whereas IgE showed a consistent decline with clozapine while in the Risperidone group, there was a rise at 6 weeks but fall by 12 weeks (but still higher than at baseline). In contrast to our study, Ponsford *et al.*[20]had reported an association between clozapine and antibody deficiency with an immediate decrease in IgA and IgM and a significant association between a decline in IgG and duration of treatment with clozapine. Our

study findings are in concurrence with this study in terms of fall in levels of immunoglobulin E only, but it was not statistically significant. Other findings of immunoglobulin deficiency, i.e., decrease in IgM, IgA and IgG levels, were not corroborated in our study, which might be due to different patient populations, further supporting the fact that the antibody deficiency with clozapine is not very common in the Indian population. Our study reported an increase in levels of immunoglobulins(G, M, A with Clozapine and G, M with Risperidone) and this variation in response to antipsychotics was also seen by Tiwari *et al*.[21] who had reported immunopotentiation in the form of increased IgG and IgA in the Indian population by psychotropics (e.g., with Haloperidol) which are known to cause a decrease in the immune parameters in the western population. This is the only study from India to study the evolving pattern of IgE in schizophrenia with Clozapine and Risperidone. Though the authors couldn't find any significant correlation, this study refutes raised Ig E as a subgroup of non-response in schizophrenia as proposed by Ramchand *et al*.[13,22,23] There was no incidence of myocarditis which was hypothesized to be Ig E induced.

Response to treatment

In the clozapine group, change in Ig M correlated with the percentage change in positive symptoms and change in Ig A correlated with the percentage change in negative symptoms of schizophrenia, while in the risperidone group, change in Ig M correlated negatively with the percentage change in negative symptoms. This is in contrast to Griffith *et al*.[17] wherein the correlations were significant for IgA and IgG and percentage change in PANSS total scores over 12 weeks. Besides the major ethnocultural differences emulating the genetics and geographical realms between the two studies (India *versus* England), the mechanisms underlying these need further exploration.

The index study has strengths of randomization eliminating selection bias, prospective in nature, laboratory investigations relevant to different medical conditions were done at baseline and confounding factors like immunomodulating drugs and conditions were excluded, use of standardized and validated tools like PANSS ensure robust methodology. Of the immunoglobulins, Ig E is not commonly studied in the available literature for schizophrenia. The three-point assessment makes the results of the study very reliable, indicating a clear trend. This study adds to the minuscule literature from India about the effect of antipsychotics and the correlation of response with immune parameters in schizophrenia. However, a few limitations in the form of a small sample size, which hamper the generalization of results, short duration of follow-up, inability to type antibodies towards an antigen and unavailability of serum Clozapine and Risperidone levels to see dose-dependent effect impair detailed understanding of the interplay of immune parameters with antipsychotics in schizophrenia.

Conclusion

It can be concluded from the findings of the study that the elevated immunoglobulin levels (Ig) at baseline in both clozapine and risperidone groups support the immunological basis of schizophrenia. Secondary immunoglobulin deficiency is not a common event with clozapine hence its use should be optimized. This study not only strengthens the biological basis of the disorder but also paves the way for establishing these elevated immunoglobulins as biomarkers in schizophrenia.

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Declaration of competing interest

The authors declare that there are no competing interests.

Author Contribution

Sumeesha Jaswal -conception and design of the study, collection of data, review of literature, a draft of paper and analysis of data.
Ajeet Sidana- conception and design of the study, revising the draft critically for important intellectual content, drawing relevant interpretations following data analysis.

Shivangi Mehta - conception and design of the study, revising the draft critically for important intellectual content, drawing relevant interpretations following data analysis.

Seema Gupta -conception and design of study, drawing relevant interpretations following data analysis.

Gurjit Kaur - conception and design of study.

IEC No. GMCH/IEC/2019/206

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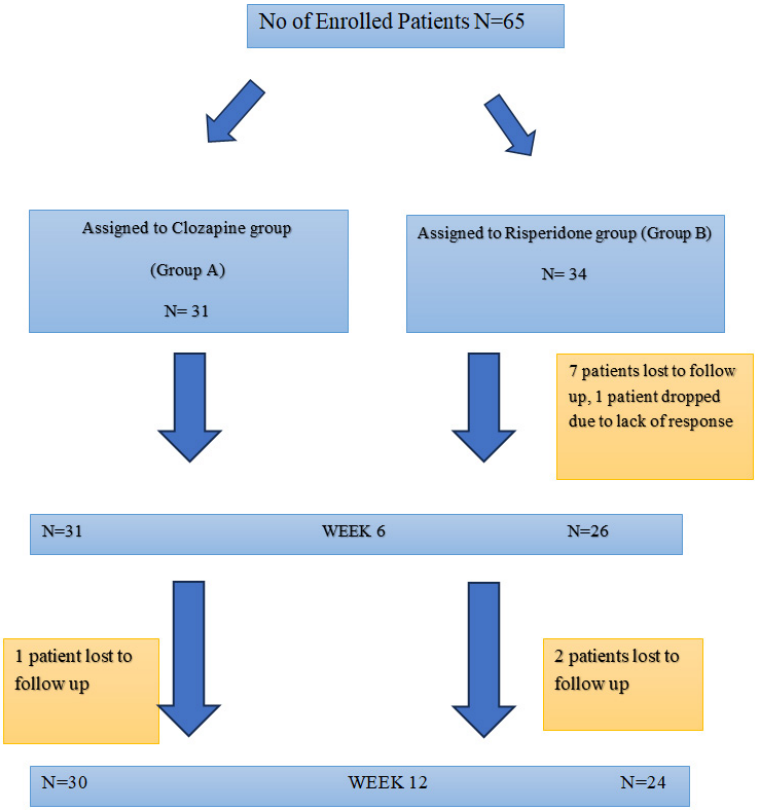
Supplementary Data



Supplementary Figure 1: Flow diagram showing induction process

Supplementary Table 1: Comparison between Clozapine and Risperidone groups in Sociodemographic and Clinical parameters at Baseline

Parameter	*Group*		*p-value*
	Clozapine (N=30) Group(A)	*Risperidone (N=24) Group (B)*	
Age (Mean ± SD)	33.63±5.94	31.96 ±6.15	0.316
M:F	18:12(60%: 40%)	15:9(62.5%:37.5%)	0.538
Rural/Urban	11:19	12:12	0.240
TDI (years) (Mean ± SD)	12.03±6.64(2,25)	8.77±6.28(0.5,20)	0.072
Current exacerbation duration (months) (Mean ± SD)	4.13±1.61(2,8)	3.42±1.44(1,6)	0.095
Additional drugs 0 1 2 3	 21 7 1 1	 24 0 0 0	0.034
BASELINE			
Positive	26.23±9.28	19.67±4.62	0.003*
Negative	9.03±2.34	9.00±2.40	0.781
General	25.13±6.39	21.17±3.53	0.009*

Total PANSS	60.27±10.94	49.83±6.11	<0.001*
IgG	12.34±2.79	10.46±2.67	0.005*
IgM	1.54±1.47	0.90±0.34	0.100
IgA	2.23±0.94	2.39±0.97	0.537
IgE	399.00±502.25	258.19±508.84	0.055

*Significant (Normal IgM: 0.4-2.3 g/L; IgG: 7-16 g/L; IgA: 0.9-4.5 g/L; IgE :1.5- 144 IU/L)

Supplementary Table 2 : Clinical and biochemical profile- in between group comparison

Parameter	*Group*		*t-value/ Mann-Whitney U (Z)#*	*p-value*
	Clozapine (N=30)	*Risperidone (N=24)*		
	Mean±SD	*Mean±SD*		
HB (g/L)	13.11±2.11	12.96±2.03	.267	.791
RBC (X 10^8/L)	4.57±.77	4.4±0.56	1.440#	.150
TLC (X 10^9/L)	6.14±.96	6.52±1.27	.906#	.365
Neutrophil (%)	62.93±8.66	55.4±12.14	2.655	.010*
Lymphocyte (%)	36.06±5.54	33.01±8.06	1.648	.105
Basophil (%)	.73±1.23	1.86±2.38	1.705#	.088
Monocyte (%)	5.49±2.22	1.22±1.66	5.462#	<0.001*
Eosinophil (%)	2.73±2.32	0.48±1.06	4.342#	<0.001*
Platelet (X 10^9/L)	145.40±21.65	231.96±54.05	5.824#	<0.001*
Na (mEq/L)	134.97±1.40	138.01±3.01	4.923	<0.001*
K (mEq/L)	4.39±.21	4.31±0.17	1.629#	.103
Urea (mg/dl)	28.97+2.88	16.8±5.31	10.747	<0.001*
Creatinine (mg/dl)	.67±.22	0.67±0.14	.151	.881
Bilirubin (mg/dl)	.74±.28	0.88±0.23	1.892	.064
ALP (IU/L)	52.20±14.95	74.21±23.34	4.204	<0.001*
SGOT (IU/L)	36.20+18.00	25.54±8.32	2.232#	.026*
SGPT (IU/L)	38.43+13.93	27.7±9.04	3.262	.002*
Albumin (g/dl)	3.94+.91	7.14±0.83	13.305	<0.001*
Protein (g/dl)	7.00+1.66	4.18±0.59	7.902	<0.001*
Cholesterol (mg/dl)	168.20+28.48	160.13±25.98	1.076	.287
Triglycerides (mg/dl)	81.23+18.69	116.71±21.15	6.537	<0.001*
HDL (mg/dl)	50.30+7.61	41.91±10.16	2.815#	.005*
LDL (mg/dl)	89.60+5.76	63.43±22.63	6.105	. <0.001*
FBS (mg/dl)	88.60+9.51	89.13±8.48	.211	.833
QTC (msec)	444.70+3.72	444.71±3.24	.009	.993

*Significant

While there was no significant difference between the two groups in terms of total leucocyte count, the neutrophil, monocyte and eosinophil counts were significantly higher in the Clozapine group, but the mean values were within normal range (normal values: neutrophil: 40-80%, monocyte:2-10%, eosino-

phil:1-6%). The platelet count was higher in the Risperidone group. The groups also differed with regards to the total albumin and total proteins level. Total proteins were significantly higher in the Clozapine group. The Triglyceride levels were higher in the Clozapine group while HDL and LDL levels were higher in the Risperidone group and were statistically significant.

Supplementary Table 3 : Correlation of treatment response (percent change in PANSS domains) with change in immunoglobulins

Ig/PANSS domain	*Ig G*	*Ig M*	*Ig A*	*Ig E*
Clozapine -study period (0 - 12 weeks)				
Positive	-0.2104105	0.45899285*	-0.0640683	-0.2829184
Negative	0.38824461	-0.0915659	0.49899874*	0.21099127
General	-0.1495461	0.03949908	0.25787766	-0.0205541
Total	-0.0580562	0.27247189	0.3007363	-0.1335379
Risperidone – study period (0-12 weeks)				
Positive	0.13488539	-0.0701015	0.19754701	-0.0020382
Negative	0.11588616	-0.4095044*	-0.0544257	-0.2023115
General	0.26423369	0.18824563	-0.1326178	-0.3024859
Total	0.26423369	0.26423369	0.26423369	0.26423369

*- moderate corelation.