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Adjunctive Statin Therapy on Cholesterol and Clinical Symptoms in Schizophrenia Treated with Risperidone

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ABSTRACT

Background: *Schizophrenia is associated with the metabolic side effects of atypical antipsychotics, such as hypercholesterolemia.*
Objective: *To evaluate the effect of adjuvant statin therapy on total cholesterol levels and clinical symptoms in patients with schizophrenia treated with risperidone.*
Methods: *This randomized clinical trial was conducted on 36 patients with schizophrenia at RSKD Dadi, South Sulawesi. The subjects were randomized into risperidone-only and risperidone plus statin groups.*
Results: *Statin adjuvant therapy reduced total cholesterol levels and improved clinical symptoms (PANSS scores) compared to the control group.*
Conclusion: *Adjuvant statin therapy is potentially beneficial in reducing cholesterol levels and improving clinical outcomes in patients with schizophrenia receiving risperidone.*

Keywords: *Schizophrenia; Risperidone; Statin; Cholesterol; PANSS*

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INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by disturbances in thoughts, perceptions, and behaviors. According to the World Health Organization (WHO), approximately 23 million people worldwide suffer from schizophrenia, making it a significant global health concern.[1] In Indonesia, the prevalence of schizophrenia has steadily increased, from 1.3 per 1000 households in 2013 to 6.7 per 1000 households in recent years. In South Sulawesi, the prevalence reached 8.85% in 2018.[2]

Pharmacological interventions are the cornerstone of schizophrenia management. First-generation antipsychotics, while effective in reducing psychotic symptoms, are associated with the emergence of negative symptoms.[3] Therefore, second-generation antipsychotics such as risperidone, are preferred because of their broader spectrum of efficacy and improved tolerability. Risperidone has a high affinity for dopamine D2 and serotonin 5-HT2A receptors, and is effective in improving positive, negative, and cognitive symptoms.[4,5]

Despite their benefits, atypical antipsychotics are associated with metabolic side effects. Several studies have reported weight gain, hypercholesterolemia, and other metabolic disturbances in patients receiving these medications.[6,7] Long-term use has also been linked to glucose intolerance, unhealthy lipid profiles, and increased risk of cardiovascular disease and diabetes.[8]

Importantly, dyslipidemia is not only a consequence of antipsychotic use but has also been observed in patients with schizophrenia who are not treated. This suggests that abnormal lipid metabolism may play a role in the pathophysiology of the disorder itself.[9] The link between lipid disturbances and schizophrenia underscores the need for therapeutic approaches that address the psychiatric and metabolic aspects of the illness.

Statins, which act as competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are widely prescribed to lower cholesterol levels in patients with hyperlipidemia. Beyond lipid-lowering, statins have additional anti-inflammatory and immunomodulatory effects by inhibiting the synthesis of isoprenoid intermediates in the mevalonate pathway.[10,11] These pleiotropic effects position statins as promising agents for the management of schizophrenia.

Several studies have investigated the potential role of statins in the treatment of schizophrenia. For example, simvastatin has been shown to improve negative and positive symptoms when used as an adjunctive therapy.[12] Statins' anti-inflammatory properties, particularly their ability to reduce proinflammatory markers such as interleukin-1 and tumor necrosis factor-alpha, may contribute to these psychiatric benefits.[13,14]

However, the evidence remains inconclusive. While some studies support the beneficial role of statins in improving clinical symptoms, others report no significant effect.[15] This inconsistency highlights the need for further well-designed randomized clinical trials to clarify the role of statins as adjunctive therapy in schizophrenia.

Given the high prevalence of dyslipidemia among patients with schizophrenia and the metabolic risks associated with antipsychotic treatment, exploring the use of statins is clinically relevant.[16,17] Combining risperidone with statin therapy may not only optimize psychiatric outcomes but also mitigate metabolic complications. This dual effect could significantly improve the prognosis and quality of life of patients.

Moreover, the pleiotropic effects of statins may directly impact neuroinflammation, which has been implicated in the pathophysiology of schizophrenia. By reducing neuroinflammatory responses, statins could potentially target one of the underlying mechanisms of the disorder, thus complementing the action of antipsychotics.[18,19]

Based on these considerations, this study was designed to evaluate the effect of adjuvant statin therapy on total cholesterol levels and clinical symptoms in patients with schizophrenia who were treated with risperidone. The findings are expected to provide valuable evidence for optimizing pharmacological management and improving long-term outcomes in patients with schizophrenia.

METHODS

This study was an experimental randomized double-blind clinical trial conducted from September to December 2023 at Rumah Sakit Khusus Daerah (RSKD) Dadi Hospital South Sulawesi, Indonesia. A total of 36 patients with schizophrenia who had passed the acute phase (PANSS-EC < 15) were enrolled and randomly assigned to either a control group receiving risperidone alone or an intervention group receiving risperidone plus simvastatin. Patients were evaluated at baseline and at weeks 4 and 8. Eligible participants were aged 20–45 years, diagnosed with schizophrenia according to PPDGJ-III criteria, had a disease onset of less than three years, received risperidone at a dose of 4–6 mg/day, had a body mass index < 25 kg/m², and provided written informed consent. Patients with organic comorbidities, a history of substance use, or concurrent use of anti-inflammatory or antibiotic medications were excluded. Participants who failed to adhere to treatment, withdrew consent, or died during the study were excluded from the analysis.

The intervention group received simvastatin 40 mg once daily for eight weeks in addition to standard risperidone therapy, while the control group continued risperidone monotherapy. Primary

outcomes included changes in total cholesterol levels and clinical symptoms assessed using the Positive and Negative Syndrome Scale (PANSS). Total cholesterol levels were measured at baseline and week 8, and PANSS assessments were performed at baseline and weeks 4 and 8 by trained psychiatrists blinded to group allocation. Venous blood samples were collected from the median cubital vein using vacuum phlebotomy for cholesterol analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board, and all participants provided written informed consent.

RESULTS

A total of 36 patients with schizophrenia met the inclusion criteria and were randomized into two groups: risperidone only (control group, n = 18) and risperidone plus simvastatin (intervention group, n = 18). All participants completed the 8-week study. The baseline demographic and clinical characteristics were comparable between the two groups, with no significant differences in age, sex distribution, disease duration, or BMI, as shown in Table 1.

At baseline, the mean total cholesterol levels were not significantly different between the two groups. After 8 weeks, the intervention group receiving simvastatin showed a significant reduction in mean total cholesterol compared to the control group. In contrast, the control group demonstrated a mild increase in cholesterol levels over the same period, as shown in Table 2.

Clinical symptoms, as assessed using the Positive and Negative Syndrome Scale (PANSS), showed improvements in both groups. However, the reduction was more pronounced in the intervention group. In Table 3, the intervention group demonstrated a greater decline in PANSS total scores compared to the control group at week 4, and this trend continued through week 8.

Table 4 shows that the intervention group exhibited significant improvements in both positive and negative symptom scores. Positive symptoms, such as delusions and hallucinations, showed faster and more consistent improvement in the treatment group. Similarly, negative symptoms, including anhedonia, avolition, and blunted affect, were markedly reduced in the group receiving adjunctive simvastatin. The cognitive and general psychopathology domains of PANSS also demonstrated improvement in the intervention group, although the magnitude of change was less than that of the positive and negative symptom domains. The control group showed modest improvements across all PANSS domains, consistent with risperidone's known efficacy, but these were not as substantial as those in the intervention group. Between-group comparison at week 8 revealed statistically significant differences in both primary outcomes.

This study suggested that patients in the intervention group had lower mean total cholesterol and PANSS total scores than those in the control group. These findings suggest a dual benefit of statin therapy: amelioration of metabolic complications and augmentation of psychiatric symptom improvement in patients with schizophrenia.

No serious adverse events were observed during the study. Minor complaints, such as mild gastrointestinal discomfort, were reported by two patients in the treatment group but did not necessitate the discontinuation of therapy. Adherence to risperidone and statin therapy was satisfactory in both groups. Overall, these findings demonstrate that adjuvant statin therapy is effective in reducing total cholesterol levels and improving clinical symptoms in patients with schizophrenia treated with risperidone.

Table 1. The characteristics of research subjects

Characteristic	Intervention n (%)	Control n (%)	*p*
Age (years old)	31.44 ± 7,92*	34.22 ± 7.01*	0.273[a]
Educational			
Elementary School	11 (61.1)	10 (55.6)	
Junior High School	6 (33.3)	5 (27.8)	0.566[b]
Senior High School	1 (5.6)	3 (16.7)	
Occupation			
Employed	6 (33.3)	5 (27.8)	0.717[b]
Unemployed	12 (66.7)	13 (72.2)	
Marital Status			
Married	7 (38.9)	3 (16.7)	0.137[b]
Unmarried	11 (61.1)	15 (83.3)	

**Data were shown in mean ± standard deviation, [a]Independent sample t test, [b]chi-square test*

Table 2. The comparison of total cholesterol level of schizophrenic patients in intervention and control groups

Time	Groups		p^a
	Intervention (mg/dL)	Control (mg/dL)	
Total Cholesterol Level			
Before	147.94 ± 33,52	143.94 ± 42.07	0.537
After	100.72 ± 5,35	147.44 ± 37.32	0.001***

**Data were shown in mean ± standard deviation. [a]Mann Whitney test; ***p<0.005*

Table 3. The comparison of clinical symptoms (PANSS Score) of schizophrenic patients in intervention and control groups before and after 4 or 8 weeks of treatments

Time	PANSS Score		p^a
	Intervention	Control	
Before	99,50 ± 4,68	91,78 ± 9,42	0,031*
4 weeks	74,28 ± 5,59	84,38 ± 7,47	0,001***
8 weeks	56,00 ± 5,76	70,11 ± 4,68	0,001***

**Data were shown in mean ± standard deviation. [a]Mann Whitney test; *p<0.05; **p<0.005*

Table 4. The comparison of the clinical symptom (PANSS Score) improvements of schizophrenic patients in intervention and control groups before and after 4 or 8 weeks of treatment

Time	PANSS Score				p^a
	Intervention (Δ)	Improvement degree	Control (Δ)	Improvement degree	
Before	25,22 ± 5,22	Mild	7,39 ± 3,42	None	0,001**
4 weeks	18,28 ± 5,08	Mild	14,28 ± 4,56	None	0,022*
8 weeks	43,50 ± 6,42	Moderate	21,67 ± 6,11	Mild	0,001**

**Data were shown in mean ± standard deviation. [a]Mann Whitney test; *p<0.05; **p<0.005*

DISCUSSION

The present study showed that risperidone alone did not significantly reduce total cholesterol levels, whereas the combination of risperidone and adjuvant statin therapy led to a significant decrease in total cholesterol levels. This finding highlights the specific contribution of statins to improving the

lipid profiles of patients with schizophrenia. Our results are consistent with previous studies reporting that statins significantly lower cholesterol, triglycerides, and LDL, while increasing HDL levels.[10]

The mechanism of action of statins is well-established. Statins competitively inhibit the rate-limiting enzyme in the mevalonate pathway, HMG-CoA reductase, thereby preventing the conversion of HMG-CoA to mevalonate. In the liver, this leads to reduced cholesterol synthesis, upregulation of HMG-CoA reductase expression, and increased LDL receptor expression on the hepatocyte surface. Consequently, there is enhanced clearance of circulating LDL cholesterol, resulting in decreased serum cholesterol levels.[20]

Beyond lipid-lowering, this study also demonstrated that both risperidone monotherapy and risperidone plus statin improved clinical symptoms, as measured by the PANSS, at weeks 4 and 8. Importantly, combination therapy produced greater clinical improvement than risperidone alone. This suggests a potential synergistic effect of statins in augmenting the efficacy of antipsychotics.

The clinical improvement observed with risperidone is consistent with its pharmacological effects. Risperidone reduces positive symptoms by blocking dopamine D2 receptors, particularly in the mesolimbic pathway, while also antagonizing 5-HT2 receptors, which is thought to contribute to improvements in negative symptoms.[9,21,22] The additional benefit of statins in our study extends these effects, suggesting a role beyond standard antipsychotic pharmacology.

Our findings are aligned with those of prior research showing that adjunctive statins can significantly reduce both positive and negative PANSS scores. Previous study demonstrated that simvastatin as add-on therapy reduced schizophrenia symptoms over 14 weeks.[11,23] Similarly, another study reported that statins, including simvastatin, improved both positive and negative symptoms.[24] These consistent findings reinforce the potential of statins as useful adjuncts in the management of schizophrenia.

One possible explanation for this is the anti-inflammatory properties of statins. Statins reduce the levels of interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and IL-6. Inflammation is increasingly recognized as a contributor to schizophrenia pathophysiology. Therefore, the reduction of proinflammatory markers by statins may underlie their beneficial effects on clinical symptoms.[25–27]

Another mechanism involves drug–drug interactions mediated by P-glycoprotein (P-gp) activity. P-gp), a membrane transporter at the blood-brain barrier, regulates the penetration of many drugs, including risperidone and simvastatin, into the central nervous system. When used concurrently, both drugs compete as P-gp substrates, potentially enhancing brain concentrations of one or both agents.[20,28]

This pharmacokinetic interaction may explain the observed greater clinical improvements in the combination therapy group.

Additionally, hyperlipidaemia may be mechanistically linked to schizophrenia. Antipsychotic treatment, including risperidone, often induces lipid abnormalities that may worsen psychiatric symptoms and metabolic outcomes. By targeting hyperlipidaemia, statins may not only improve metabolic health but also indirectly ameliorate psychiatric manifestations in patients with schizophrenia. This dual action positions statins as particularly beneficial in this patient population.[16,23,29]

Taken together, these mechanisms—anti-inflammatory effects, pharmacokinetic interactions, and lipid regulation—support the conclusion that adjunctive statin therapy provides superior benefits compared with risperidone monotherapy. The improvement in both cholesterol profiles and clinical symptoms observed in this study highlights the value of integrated treatment approaches that address the interplay between metabolic and psychiatric factors in schizophrenia.

In summary, this study provides evidence that adjunctive statin therapy enhances the therapeutic effects of risperidone in schizophrenia by improving lipid profiles and alleviating psychiatric symptoms. These findings underscore the need for further research to confirm the long-term benefits and safety of statins as adjunctive agents in schizophrenia and to explore their role across different stages of the illness and in combination with various antipsychotic regimens.

CONCLUSION

This study demonstrated that adjunctive statin therapy in patients with schizophrenia treated with risperidone significantly reduced total cholesterol levels and provided greater improvement in clinical symptoms than risperidone alone. These findings highlight the dual benefits of statins in addressing both metabolic disturbances and psychiatric manifestations of schizophrenia.

Adjunctive statin therapy may be a promising strategy to optimize treatment outcomes and improve the quality of life of patients with schizophrenia. Further large-scale, long-term studies are warranted to confirm these findings and establish statins as a potential adjunctive therapy in routine clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest related to this work. No financial relationships, personal relationships, or affiliations that could influence the results or interpretations of this manuscript are present. All authors have completed the ICMJE Disclosure Form and declare no relevant interests to be disclosed.

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