



# Differentiation in Neurological Soft Sign Scores on Schizophrenic Patients with Antipsychotic Treatment

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## Abstract

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**Funding:** Our findings showed that there were solid differences in the NSS scores between patients and controls.

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**BACKGROUND:** Schizophrenia is a chronic mental illness that affects cognitive aspect of a patient which needs long-term care with antipsychotics. Long-term use of antipsychotic itself causes neurobiological change in the brain which results in alteration of cognitive function. The latest research had demonstrated that Neurological Soft Sign (NSS) reflect a rather wide range of cognitive impairments in schizophrenia which was not accounted for by age, education, or severity of global cognitive deficits.

**AIM:** WE aimed to examine the effects and impact of antipsychotic haloperidol and risperidone treatment in schizophrenic patient.

**METHODS:** Therefore, we examined the effects and impact of antipsychotic haloperidol and risperidone treatment in schizophrenic patient using NSS scores.

**RESULTS:** The study showed that chronic schizophrenic patients had higher NSS scores than acute patients. NSS also significantly associated with all neuropsychological domains of Mini-mental State Examination in both groups and was confirmed when age, education, and severity of global cognitive deficits were not accounted for. This study also obtained a lower NSS score in patients who received risperidone therapy compared to haloperidol with  $p = 0.003$ . Out of 5 NSS domains in the Heidelberg scale, there was a significant improvement in motor coordination and motor sequencing ( $p = 0.004$ ) and ( $p = 0.048$ ) in patients who received risperidone therapy compared to haloperidol. There was an association between the chronicity of the disease and NSS, NSS also shows that it is not influenced by age, education, and severity of global cognitive deficits as a screening instrument.

**CONCLUSION:** The improvement of NSS scores in the risperidone group was far superior compared to the haloperidol group, particularly in motor coordination and motor sequencing.

## Introduction

Schizophrenia is a chronic psychotic disorder, often subsides, with wide variety of clinical manifestations which is caused by a disruption in certain brain structures. The symptom of schizophrenia in the form of hallucinations, delusions, emotional disturbances, and withdrawal from social environment involves a biological mechanism, which can be seen from neuroimaging and neurological examination [1], [2].

The studies using neuroimaging examinations showed that the change of brain volume in the cortex and subcortex regions of individuals with schizophrenia was also related to changes in neurological soft sign (NSS) which is linked with deficits in the functions of sensory integration, motor coordination, and complex motor movements. NSS can be found in various levels of schizophrenia and is very prominent when compared to healthy populations. Within the neurophysiological scope, there is a significant association of chronicity of the disease with a high NSS score [3], [4]. In our previous NSS study at Makassar, we found that NSS scores were higher in patients with chronic

schizophrenia compared to acute patients. Moreover, in 2018 we assessed the relation of NSS scores and the Positive and Negative Syndrome Scale (PANSS) between schizophrenic patients compared to normal controls [5], [6]. Our findings showed that there were solid differences in the NSS scores between patients and controls. Other findings in this research also illustrated the relation between high PANSS score with high NSS scores, especially when looking into cognitive and negative aspects. The research by Herold *et al.* demonstrated that NSS reflects a rather wide range of cognitive impairments in schizophrenia which is not accounted for by age, education, or severity of global cognitive deficits [7].

Risperidone and haloperidol are antipsychotics commonly used to treat schizophrenic patients in Indonesia. The long-term administration of these two antipsychotics can affect the neurobiology of patients. Previous research by Liebermann *et al.* comparing risperidone and haloperidol showed that atypical antipsychotic drugs may have neuroprotective effects resulting in an increase in an individual's cognition functions [8]. This is also supported by the study of He *et al.* which found signs of neurogenesis

from progenitor cells and an increase of Brain-derived Neurotrophic Factor levels in experimental animals who were receiving atypical antipsychotic drugs [9]. In a study conducted by Van Haren *et al.*, using magnetic resonance imaging, they examined vertex in each individual and found that first-generation antipsychotics like haloperidol resulted in a decrease in cortical mass of schizophrenic patients while the second-generation antipsychotic drug such as risperidone showed a reduction in the decrease of cortical mass in human. The study shows that long-term use of antipsychotic can affect the morphology of human brain which hypothesized may be able to affect brain function [10], [11].

The relations between antipsychotics and NSS itself previously investigated in studies of risperidone and NSS scores showed that patients with high NSS scores indicated slower improvement compared to individuals with low NSS scores [12].

Therefore, we decided to investigate the change observed for NSS scores in schizophrenic patients who were receiving risperidone and haloperidol as antipsychotic therapy.

## Methods

### Sampling and recruitment

A total of 30 individuals were collected consecutively for each group. The inclusion criteria of this study were patients diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorder 5<sup>th</sup> edition (DSM V), the patients received haloperidol or risperidone at therapeutic doses, PANSS scores below 95, exclusions criteria are no history of substance abuse and no apparent neurological defect

### Design

This Prospective Cohort design study was conducted at Wahidin Sudirohusodo Hospital, Makassar, Indonesia and its networks from January to March 2019. The population of this study was patients diagnosed with schizophrenia (295.90) using DSM V who fulfilled the inclusion criteria of the study.

### Data collection

The researcher recorded the identity of each sample, including name, gender, age, education, and history of past illness. Each sample tested in Heidelberg Scales and Mini-mental State Examination at initial week, 4<sup>th</sup> week, and 8<sup>th</sup> week of the study.

### Statistical analysis

Statistical analysis was performed using SPSS 20; the result will be presented in the form of data tabulation.

## Results

In this research, we calculated of total 60 patients (30 in each group) which comprised more male (63.3%) subject compared to female (36.7%). The age group showed that majority of the patient was in 30–40 years (55%) followed by 40–50 years (30%) and 20–30 years (15%), respectively. We found that in our study, there are more married subjects (56.67%) than unmarried one (43.33%). The employment group shows us there was more unemployed (68.3%) schizophrenic patient compared to the working one (31.7%). Education shown that majority was consisted from elementary (28.3%) and junior high (45%) groups followed by senior high (21.6) and bachelor group (5%). In our study group, we found that chronic patients (45% and 40%) are more dominant compared with acute one (15%). The study also shows that majority of the patient are treated more than 4 weeks (81.6%) (Table 1).

**Table 1: Clinical characteristic of patient in relation with NSS using Kruskal Wallis test for significance**

Variable	Haloperidol n= 30	Risperidone n= 30	Significance (p)
Gender			
Male	20	18	0.479
Female	10	12	
Age			0.892
20–30 year	5	4	
30–40 year	17	16	
40–50 year	8	10	
Marriage			0.123
Married	18	16	
Not married	12	14	
Employment			0.111
Employed	10	9	
Unemployed	20	21	
Education			0.06
Elementary	12	5	
Junior high	12	15	
Senior high	5	8	
Bachelor	1	2	
Onset			0.031
<1 year	4	5	
1–5 year	13	14	
>5 year	13	11	
Inward treatment			0.045
<4 weeks	7	4	
4>weeks	23	26	

p < 0.05 = significant.

The Wilcoxon Signed rank is used to assess the relationships of 2 groups of data that are not normally distributed and are paired. This study was used to analyze differences in the total NSS scores according to the Heidelberg scale at week 0, week 4, and week 8 of the study. Researchers also used this test to analyze each Heidelberg scale variable at week 0, week 4, and week 8 of the study. The following results were found In the Haloperidol group, there were no significant changes in NSS scores, both at week 4 and at week 8 (all with p > 0.05). In the risperidone group, there was a significant

**Table 2: Comparison of NSS scores within the groups**

Variable	Groups	n	Mean	SD	p
Initial NSS score	Haloperidol	30	20.9	3.9	0.766
	Risperidone	30	20.6	3.4	
NSS score 4 <sup>th</sup> week	Haloperidol	30	21.6	3.8	0.071
	Risperidone	30	19.8	3.3	
NSS score 8 <sup>th</sup> week	Haloperidol	30	20.4	3.2	0.003
	Risperidone	30	16.8	4.6	

p &lt; 0.05 = significant.

decrease in NSS scores, both at week 4 ( $p < 0.05$ ) and at 8 weeks ( $p < 0.001$ ). Likewise, between the 4<sup>th</sup> week and 8<sup>th</sup> week, there was a significant decrease from 19.8 to 16.8 ( $p < 0.001$ ). The above results show that risperidone is better than haloperidol in reducing NSS scores (Table 2).

Mann–Whitney is used to compare variables from two data groups that are not normally distributed and are not paired. In this study it is used to analyze the difference in the total NSS score according to the Heidelberg scale between the haloperidol and risperidone groups and to analyze each Heidelberg scale variable in the haloperidol and risperidone groups. Initial measurement showed no significant differences in NSS scores between the two groups, which were around 20.6–20.9 ( $p > 0.05$ ). Measurement at 4<sup>th</sup> week still showed no significant difference in NSS scores between the two groups, which was around 19.8–21.6 ( $p > 0.05$ ). Measurement at 8<sup>th</sup> week showed NSS scores in the risperidone group (16.8) significantly lower than in the haloperidol group (20.4) ( $p < 0.01$ ) (Table 3).

**Table 3: NSS score changes in each group**

Groups	Variable	n	Mean	SD	P
Haloperidol	Initial NSS score	30	20.9	3.9	0.279
	NSS score 4 <sup>th</sup> week	30	21.6	3.8	
	Initial NSS score	30	20.9	3.9	0.423
	NSS score 8 <sup>th</sup> week	30	20.4	3.2	
	NSS score 4 <sup>th</sup> week	30	21.6	3.8	
	NSS score 8 <sup>th</sup> week	30	20.4	3.2	
Risperidone	Initial NSS score	30	20.6	3.4	0.038
	NSS score 4 <sup>th</sup> week	30	19.8	3.3	
	Initial NSS score	30	20.6	3.4	0.000
	NSS score 8 <sup>th</sup> week	30	16.8	4.6	
	NSS score 4 <sup>th</sup> week	30	19.8	3.3	
	NSS score 8 <sup>th</sup> week	30	16.8	4.6	

p &lt; 0.05 = significant.

Initial measurement using Wilcoxon Signed Rank shows that motor sequencing scores were significantly higher in the risperidone group (5.10) than in the haloperidol group (3.83) ( $p < 0.05$ ). Initial and following measurement shows that spatial ability scores did not differ significantly between the two groups (each with  $p > 0.05$ ). Initial measurement shows that Motor Coordination did not differ significantly between the two groups (each with  $p > 0.05$ ). Initial and following measurement shows Sensory Integration did not differ significantly between the two groups (each with  $p > 0.05$ ). Initial measurement

**Table 4: Comparison of initial NSS component scores by group**

Variable	Groups	n	Mean	SD	p
Initial motor sequencing	Haloperidol	30	3.83	1.98	0.029
	Risperidone	30	5.10	1.92	
Initial visual spatial	Haloperidol	30	6.77	1.45	0.320
	Risperidone	30	7.00	1.89	
Initial motor coordination	Haloperidol	30	6.30	2.00	1.000
	Risperidone	30	6.17	2.36	
Initial sensory integration	Haloperidol	30	1.30	0.95	0.815
	Risperidone	30	1.23	1.04	
Initial hard sign	Haloperidol	30	2.67	1.30	0.000
	Risperidone	30	1.07	1.44	

p &lt; 0.05 = significant.

**Table 5: Comparison of NSS component scores week 4 by group**

Variable	Groups	n	Mean	SD	p
Motor sequencing 4 <sup>th</sup> week	Haloperidol	30	4.07	2.00	0.195
	Risperidone	30	4.77	2.08	
Visual-spatial 4 <sup>th</sup> week	Haloperidol	30	6.87	1.81	0.252
	Risperidone	30	6.57	1.41	
Motor coordination 4 <sup>th</sup> week	Haloperidol	30	7.10	1.03	0.006
	Risperidone	30	5.57	2.18	
Sensory integration 4 <sup>th</sup> week	Haloperidol	30	1.27	0.98	0.903
	Risperidone	30	1.23	1.04	
Hard sign 4 <sup>th</sup> week	Haloperidol	30	2.30	1.15	0.033
	Risperidone	30	1.70	1.09	

p &lt; 0.05 = significant.

shows Hard Sign Score was significantly lower in the risperidone group (1.07) than in the haloperidol group (2.67) ( $p < 0.001$ ) (Tables 4-6).

At the 4<sup>th</sup>-week Motor Sequencing Score, spatial ability and sensory integration did not differ significantly between the two groups (each with  $p > 0.05$ ). Fourth-week measurement, the motor coordination score was significantly lower in the risperidone group (5.57) than the haloperidol group (7.10) ( $p < 0.01$ ). Fourth week the Hard Sign Score was significantly lower in the risperidone group (1.70) than the haloperidol group (2.30) ( $p < 0.05$ ) (Tables 4-6).

**Table 6: Comparison of NSS component scores week 8 by group**

Variable	Groups	n	Mean	SD	p
Motor sequencing 8 <sup>th</sup> week	Haloperidol	30	4.97	2.03	0.004
	Risperidone	30	3.40	1.81	
Visual-spatial 8 <sup>th</sup> week	Haloperidol	30	6.23	1.70	0.169
	Risperidone	30	5.57	2.10	
Motor coordination 8 <sup>th</sup> week	Haloperidol	30	6.03	1.52	0.048
	Risperidone	30	5.40	1.75	
Sensory integration 8 <sup>th</sup> week	Haloperidol	30	1.20	1.06	0.961
	Risperidone	30	1.20	0.89	
Hard sign 8 <sup>th</sup> week	Haloperidol	30	1.93	0.94	0.000
	Risperidone	30	0.87	1.20	

p &lt; 0.05 = significant.

At 8<sup>th</sup>-week measurement, Motor Sequencing scores were significantly lower in the risperidone group (3.40) than in the haloperidol group (4.97) ( $p = 0.004$ ). By the 8<sup>th</sup>-week measurement, we found that. The Motor Coordination score was significantly lower in the risperidone group (5.40) than the haloperidol group (6.03) ( $p = 0.048$ ). Eighth-week measurement shows that the Rough Sign Score was significantly lower in the risperidone group (0.87) than the haloperidol group (1.93) ( $p < 0.001$ ) (Tables 4-6).

## Discussions

This was the first study in Indonesia which revealed that risperidone is superior in improving the magnitude of NSS in schizophrenia patient compared to haloperidol which assumed that risperidone as atypical antipsychotic is far better in improving the cognitive aspect of schizophrenic patient and is highly recommended as a viable choice in long term treatment in Indonesian schizophrenic patient.

In our clinical characteristic, we found that our patients mainly comprised patients with from elementary and junior high school level education (28% and 45% of the total sample, respectively). Our results were in line with data obtained by Yang *et al.*, also showing that some individuals with higher education had better initial NSS scores than lower education individuals even though statically not significant [13]. This suggested that NSS ability in measuring one's cognitive function is not related with the educational background of individuals which is also in line with the study from Herold *et al.* which explains the functions of cognition and education in schizophrenic patients and their relationship with NSS [5].

We found that chronic schizophrenia patients have significantly higher NSS scores than acute patients which proved that chronic schizophrenia patient suffers from more severe neurobiological changes compared to acute schizophrenia patient. This result was the same as shown in a previous study which is conducted by Santosa *et al.* [5]. In addition, in some acute subjects with dominant-negative symptoms, higher NSS scores were obtained compared to acute individuals with pre-dominant positive symptom. This result showed that patients with negative symptoms had worse cognitive function compared to patients with positive symptoms. These findings revealed a link to possible neurobiological impairment, especially in the prefrontal cortex area and showed a relationship between the cognitive function, negative symptoms, chronicity of disease, and NSS in schizophrenia patient [14].

The length of stay in our subjects illustrates that patients who have been exposed and reintegrated in social life provide better improvement in NSS score compared to hospitalized subjects [15], [16]. This is in line with Kaplan's theory which emphasizes the importance of social function as one of the pillars in the treatment of patients with schizophrenia [2], [16].

We had been able to show that risperidone as atypical antipsychotic to improving NSS scores is superior to haloperidol. Moreover, a significant change in NSS function, as a reflection of a soft neurological sign that gives a general picture of brain integration function can be seen in 2 months after atypical antipsychotic drug administration. This explained why the majority of the patient showed detachment from symptom at 6 weeks treatment and more. This finding is consistent with some of the very earliest ideas that antipsychotics produced a state of "indifference" and is also consistent with the more recent, neurobiologically informed notions that antipsychotics work by dampening the salience of psychotic symptoms [17].

We found that at the 4 weeks observation, there was an increase in NSS scores of patients who received haloperidol because of the development of extrapyramidal syndrome (EPS). This explained that EPS symptoms can appear at the beginning of therapy in schizophrenic patients and will affect NSS

signs [18]. On the other hand, this phenomenon can also be a marker for assessing other EPS risks such as akathisia in individuals with acute schizophrenia and can be a consideration in the long-term management of schizophrenic patients.

Based on the comparison of NSS components in 4<sup>th</sup> and 8<sup>th</sup> week, we found that risperidone had a superior benefit compared to haloperidol in motor coordination and motor sequencing with risperidone after 8 weeks of administration. This is in accordance with the theory of neurogenesis as suggested in a study which showed neurogenesis in the cortico frontal structures of experimental animals who received risperidone. Improvements in this structure are thought to have a relationship with improvement in motor integration functions of individuals with schizophrenia [19].

Based on the observed changes in NSS scores in the two treatment groups, we could confirm the superiority of atypical drugs (risperidone) compared to typical drugs (haloperidol). This is supported by the theory of Bachman, who suggested the neuroprotective effects of antipsychotics on NSS [20].

The study is limited by the short timeframe and the sample which is not randomized.

## Conclusions

In summary, atypical antipsychotics are superior in improving NSS scores and cognitive function of schizophrenia patient compared to typical antipsychotic, we also found that NSS may be used to evaluate the improvement of cognitive function in antipsychotic treatment and also as a tool to differentiate chronic or acute schizophrenia. All of these findings give us insight in the course of schizophrenic patient and long-term treatment for the illness.

## Declarations

### Authors' contributions

All the authors were involved in the conception of this study. WT, EL, SS, and STL, to interpretation of the research findings and contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

### Acknowledgments

We would like to acknowledge and thank the participants who took part in this study.

### Ethics approval and consent to participate

Because we only considered professionals' views and not those of patients, this project is not subjected to Indonesian's Health Research Law, and thus approval from The Regional Committee for Medical and Health Research Ethics was not applicable. Therefore, the Hasanuddin University Medical Committee was contacted. The research has been permitted and acknowledged by Hasanuddin University Medical Committee. Before each interview, each participant was given written information on the study. Each participant was also informed that his or her participation was voluntary. Before each interview, we emphasized the importance of maintaining confidentiality in relation to patient cases. All participants provided written consent to participate in the study.

### Consent for publication

All participants provided written informed consent for publication.

### Availability of data and materials

The datasets used and analyzed for this study are available from the corresponding author on reasonable request.

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