Effect of Non-Computerized Cognitive Remediation and Risperidone to Improve Disability Function in Schizophrenia

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Abstract

The aim of the study was to find out the effect of non-computerized cognitive remediation and risperidone therapy to improve cognitive function and disability condition in schizophrenia patients. This study was an experimental research design, with fourteen participants divided into two group as the experimental group and the control group. The experimental and control groups both received Risperidone. In addition, the experimental group was given the non-computerized cognitive remediation (CR). The non-computerized cognitive remediation will be carried out in 12 sessions (3 sessions per week) using mainly paper and pencil tasks and is based on cognitive strategy instruction. Moreover, all samples will be measured for PANSS (Positive and Negative Symptom Scale), WHODAS 2.0 (World Health Organization Disability Assessment Schedule), and SCoRS Vi (Schizophrenia Cognition Rating Scales Indonesian Version) scores. As the results, both experimental and control group showed a significant decrease in the SCoRS Vi and WHODAS 2.0 score (p=0.001). However, the experimental group showed greater improvement compared to the control group. Synergistic effect of Non-computerized Cognitive Remediation and Risperidone can improve disability condition in schizophrenia patients.

Keywords: *Schizophrenia, Non-computerized Cognitive Remediation, Risperidone, Disability*

Introduction

Schizophrenia is a chronic mental illness characterized by hallucination, delusion and thought disorder as well as cognitive and psychosocial impairments.[1] Cognitive deficits are core features of schizophrenia, contribute substantially to poor functional outcome of the patients and are likely as important as positive and negative symptoms for clinical treatment of the illness.[2] Schizophrenia is a psychotic disorder that affects about 26 million people around the world. It is typically diagnosed in early childhood and mostly persist through-out people's live. Several long-term follow up studies have challenged the view about schizophrenia poor outcome and proved that varying degrees of improvement is still one of the main causes of disability worldwide.[3] Patients with schizophrenia have difficulty succeeding at school, obtaining or maintaining a job, having social relationship, living independently and even for some taking care of their basic daily needs.[4]

The decline occurring in schizophrenia had been broadly classified as something related to neurocognition and social cognition.[5] While all domains of cognition are affected in schizophrenia, there are selective areas of increased impairment – particularly verbal and visuo-spatial memory, attention, executive function and speed of processing.[6] Antipsychotic drugs can relieve the main symptoms of schizophrenia but have no therapeutic effect on this cognitive impairment and the overall outcome is generally unsatisfying which explains the increasingly widespread use of cognitive remediation for schizophrenia.[7,8] Alternate theories of schizophrenia point to neurodevelopmental abnormalities as a potential cause. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor essential for development of the

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central nervous system and modulation of neuronal connections that may be involved in the pathophysiology of schizophrenia and its associated cognitive impairment, especially immediate memory.[9,10]

In 20 clinical trials for cognitive enhancement, atypical antipsychotic medication moderately improved some aspects of cognitive functioning in patients with schizophrenia. Next, the influence of neurocognitive rehabilitation on neurocognitive functioning come to attract attention. Cognitive remediation was associated with a medium effect size for cognitive performance.[11] Then, are there any synergistic effect of cognitive remediation and antipsychotic that can improve disability in schizophrenia patients? It was generally thought that atypical antipsychotic would improve neurocognitive functioning but some published reports suggest that the magnitude of neurocognitive functioning for antipsychotic is lower than previously expected.[11] Thus, developing medications and cognitive therapies to treat the cognitive deficits associated with schizophrenia is a high priority.[12,13]

According to the WHO-ICF, disability encompasses impairments of body functioning, activity limitations, or participation restriction, arising as interconection result between health condition and contextual factors. A person with schizophrenia, might experience disability due to impairment of thought or perceptual functions.[3] In previous research, showed the significant improvement (p=0,002) in cognitive function after given 12 session of non-computerize cognitive remediation in schizophrenia treated with atypical antipsychotic.[14] However, the study did not link the benefits or impact of cognitive function improvement with disability condition. Therefore, we were interested to conduct further research to determine the effect of non-computerized cognitive remediation and risperidone on disability improvement in schizophrenia patients.

Materials and Methods

Location and Time: The study was conducted at the Rumah Sakit Khusus Daerah (RSKD) Hospital in Makassar, South Sulawesi, Indonesia, from April to July 2018.

Ethical Clearance: Ethical approval for the study was given by the Ethics Commission on Biomedical Research in Humans, Medical Faculty of Hasanuddin University, Makassar, Indonesia.

Participants

The participants were diagnosed schizophrenia by psychiatric, in a stable state (PANSS score 50-70), irrespective gender or race, age 18 to 45 years, minimal level of education is elementary school, no evidence of head injury or organic disorder, who were hospitalized in Rumah Sakit Khusus Daerah (RSKD) Hospital. The participants were taken from April 2018 until July 2018 by Consecutive sampling method.

Procedure

All participants gave informed written consent (N=14). All assessments were carried out by medical graduation. Sociodemographic data were collected from case note, nurses and participants. All participants were assessed on the measures of PANSS, WHO DAS 2.0 and SCoRS Vi before and 4 weeks postbaseline. Every participant received (TAU) treatment as usual (Risperidone) and randomly assigned to receive non-computerized cognitive remediation. The participants were divided into 2 groups, experimental group (TAU plus CR, n=7) and control group (TAU, n=7).

Interventions

Participants in experimental group have received CR for 12 sessions (3 sessions per week). The intervention should have been performed in a clinical setting by a medical graduation with qualification in CR. The CR was either a paper and pencil format and the length of therapy should be from 45 minutes to 1 hour.

Data Analysis

All data were presented in mean value and statistically analyzed with SPSS computer software. The data were analyzed using Mann-Whitney test and Wilcoxon test, with the significant value was determined if the $p< 0.05$.

Results

The study was conducted at the Rumah Sakit Khusus Daerah (RSKD) Hospital in Makassar, Indonesia, from April to July 2018. In Table 1, most subjects in experimental group were male (57,1%), in contrast with

mostly female in control group (57,1%). Most subjects were between 30 – 39 years old (57,1%) in both groups. In the experimental group, the education level was equally for Elementary School and Senior High School (42,9%) and in control group was mostly Elementary School (57,1%). For occupation, unemployed subjects were 57,1 % in the experimental group and 85,7% in the control group. For marital status, unmarried were 42,9% in the experimental group and 85,7% in the control group. Moreover, for the diagnosis, schizophrenia unspecified (F20.9) was dominated (57,1%) in both groups.

Table 1. Subjects Profile

Variable	Experimental Group		Control Group	
	N	(%)	n	(%)
Gender				
Male	4	(57,1)	3	(42,9)
Female	3	(42,9)	4	(57,1)
Age				
≤ 20	0	(0)	0	(0)
21-29	2	(28,6)	1	(14,3)
30-39	3	(42,9)	4	(57,1)
≥ 40	2	(28,6)	2	(28,6)
Education				
Elementary School	3	(42,9)	4	(57,1)
Junior High School	1	(14,3)	1	(14,3)
Senior High School	3	(42,9)	2	(28,6)
Occupation				
Employee	3	(42,9)	1	(14,3)
Unemployment	4	(57,1)	6	(85,7)
Marital Status				
Married	4	(57,1)	1	(14,3)
Unmarried	3	(42,9)	6	(85,7)
Schizophrenia Subtype				
Paranoid Schizophrenia	3	(42,9)	3	(42,9)
Schizophrenia Unspecified	4	(57,1)	4	(57,1)

In Table 2, we conclude the comparison of SCoRS Vi and WHODAS 2.0 scores in the experimental group and control group. In the experimental group, the baseline SCoRS Vi scores was higher than the scores on the fourth week. Meanwhile, WHODAS 2.0 scores decreased on the fourth week of treatment and this was also the same in the control group. Using the Independent sample t-test analysis, the baseline SCoRS Vi scores in both groups, did not show any significant difference (p=0,056), as well as the result on the fourth week of treatment (p=0,831). There was also no significant difference in the baseline of the WHODAS 2.0 scores between the two groups (p=0,094), but there was a significant difference in WHODAS 2.0 scores on the fourth week in both groups (p=0,000).

Table 2. The Comparison of SCoRS Vi and WHODAS 2.0 Scores in Experimental And Control Group

Scale	N	Treatment Group		Control Group		P
		Median (Minimum-Maksimum)	Mean ± SD	Median (Minimum-Maksimum)	Mean ± SD	
SCoRS Vi Baseline	7	72 (68-76)	71.7143 2.49762	65 (60-75)	66.1429 6.51738	0.056
SCoRS Vi On the 4th wk	7	63 (55-70)	61.8571 5.36745	62 (55-70)	62.5714 6.77882	0.831
WHODAS 2.0 Baseline	7	37 (30-40)	36.571 3.4572	39 (36-45)	39.714 2.9841	0.094
WHODAS 2.0 On the 4th wk	7	28 (20-35)	27.8571 4.52506	37 (34-40)	37.1429 2.34013	0.000

In Table 3, in the experimental group, there was a significant difference in SCoRS Vi and WHODAS 2.0 scores at the baseline and after fourth week of treatment (p=0,001).

Table 3. The Differences of SCoRS Vi and WHODAS 2.0 Scores in Experimental Group

Scale	n	Experimental Group		P
		Median (Minimum-Maksimum)	Mean±SD	
SCoRS Vi Baseline	7	72 (68-76)	71.71±2.49	0.001
SCoRS Vi On the 4th wk	7	63 (55-70)	61.85±5.36	
WHODAS 2.0 Baseline	7	37 (30-40)	36.57±3.45	0.001
WHODAS 2.0 On the 4th wk	7	28 (20-35)	27.85±4.52	

In Table 4, in the control group, there was also a significant difference in SCoRS Vi and WHODAS 2.0 scores at the baseline and on the fourth week of treatment (p=0.001).

Table 4. The Differences of SCoRS Vi and WHODAS 2.0 Scores in Control Group

Scale	n	Control Group		P
		Median (Min-Max)	Mean±SD	
SCoRS Vi Baseline	7	65 (60-75)	66.14±6.5	0.001
SCoRS Vi On the 4th wk	7	62 (55-70)	62.57±6.77	
WHODAS 2.0Baseline	7	39 (36-45)	39.71±2.98	0.001
WHODAS 2.0 On the 4th wk	7	37 (34-40)	37.14±2.34	

In Table 5, there were an improvement of SCoRS Vi and WHODAS 2.0 scores and were equally significant (p=0,003) in both groups. However, the improvement of SCoRS Vi and WHODAS 2.0 scores in the experimental group was higher than in the control group. It means that the administration of Risperidone in combination with non-computerized cognitive remediation showed a better outcome compared to Risperidone only.

Table 5. The Deviation of SCoRS Vi and WHODAS 2.O Scores in Experimental and Control Group

Scale	n	Control Group		Experimental Group		P
		Median (Min-Max)	Mean ± SD	Median (Min-Max)	Mean ± SD	
Deviation SCoRS Vi	14	3 (2-5)	3,5 (1,39)	8 (5-16)	9,8 (4,37)	0.003
Deviation WHODAS 2.0	14	2 (2-5)	2,5 1,13	9 (3-16)	8,7 (4.11)	0.003

Discussion

Cognitive impairment has emerged as an important new target in schizophrenia therapeutics in light of evidence that cognitive deficits are critically related to the functional of disability that is characteristic of the illness.[15] Schizophrenia has a range of cognitive deficits that may evolve from decreased BDNF.[10] This study showed that there was a significant decrease in the SCoRS Vi score, both in the treatment and control groups, as well the WHODAS 2.0 score. However, the improvement in the experimental group was greater than in the control group.

One of the targets, the treatment of schizophrenia is improvement of cognitive function. Cognitive remediation is a therapeutic process to increase or improve the capacity of individuals to process and use information, and enable improvement of daily life functioning.[16,17] Cognitive remediation is a training activity on the cognitive function of schizophrenia patients. By giving cognitive remediation, it will indirectly improve the cognitive function of schizophrenia patients. Thus, it will improve the disability of the schizophrenia patient, especially in the daily life functioning (such as bathing, dressing and participating in other group activities). Cognitive remediation is the gold-standard practice to address cognitive deficits in schizophrenia.[18]

In this study, it appeared that both the experimental and control group had the improvement of the SCoRS Vi and WHODAS 2.0 scores and were equally significant (p=0.005). However, the degree of improvement in the experimental group was greater than in the control group. It meant that the improvement of SCoRS Vi and WHODAS 2.0 scores was better with the addition of remediation compared to risperidone treatment only. The scores of SCoRS Vi and WHODAS 2.0 were improved after 12 sessions of non-computerized cognitive remediation which was given 3 times per week for 4 consecutive weeks. Previous study showed that addition of non-computerized cognitive remediation could influence neurobiological changes.[19] It was reported that patients receiving the non-computerized cognitive remediation showed an increase in BDNF serum levels and activation of the inferior frontal gyrus which was assessed through fMRI examination compared to the control group.[17,18] This result was consistent with the results of other studies, showed that BDNF levels began to increase in the second week,[20] and reached high levels at the end of the third week.[21] Brain derived neurotropic factor (BDNF) is considered to a putative biomarker for cognitive recovery in schizophrenia.[22]

Conclusions

This study concluded that the addition of risperidone, in combination with 12 sessions of non-computerized cognitive remediation was better to improve the disability condition in schizophrenia patient. We suggested that the non-computerized cognitive remediation therapy to be given in addition with risperidone treatment. Limitations in this study are that it is only examined the diagnosed type of schizophrenia which did not represent to all types of schizophrenia and that some participants were not interested in remediation process.

Conflict of Interest: The authors declare that there are no conflicts of interest.

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Ethical Clearance: Ethical approval for the study was given by the Ethics Commission on Biomedical Research in Humans, Medical Faculty of Hasanuddin University, Makassar, Indonesia.

References

1. Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. Socioaffective neuroscience & psychology. 2016 Jan 1;6(1):30054.
2. Fan F, Zou Y, Tan Y, Hong LE, Tan S. Computerized cognitive remediation therapy effects on resting state brain activity and cognition in schizophrenia. Scientific reports. 2017 Jul 6;7(1):4758.
3. Nowak I, Sabariego C, Świtaj P, Anczewska M. Disability and recovery in schizophrenia: a systematic review of cognitive behavioral therapy interventions. BMC psychiatry. 2016 Dec;16(1):228.
4. Rajji TK, Miranda D, Mulsant BH. Cognition, function, and disability in patients with schizophrenia: a review of longitudinal studies. The Canadian Journal of Psychiatry. 2014 Jan;59(1):13-7.
5. Eack SM. Promoting long-term functional improvement after cognitive remediation in schizophrenia. Schizophrenia research. 2018 Mar 1;193:37-8.
6. Hurford IM, Kalkstein S, Hurford MO. Cognitive rehabilitation in schizophrenia: Strategies to improve cognition. Psychiatric Times. 2011 Mar 1;28(3):43-.
7. Bon L, Franck N. The impact of cognitive remediation on cerebral activity in schizophrenia: Systematic review of the literature. Brain and behavior. 2018 Mar;8(3):e00908.
8. Zhou Z, Zhu Y, Wang J, Zhu H. Risperidone improves

interpersonal perception and executive function in patients with schizophrenia. Neuropsychiatric disease and treatment. 2017;13:101.

9. Gören JL. Brain-derived neurotrophic factor and schizophrenia. Mental Health Clinician. 2016 Nov;6(6):285-8.
10. Zhang XY, Liang J, Xiu MH, De Yang F, Kosten TA, Kosten TR. Low BDNF is associated with cognitive impairment in chronic patients with schizophrenia. Psychopharmacology. 2012 Jul 1;222(2):277-84.
11. Matsuda Y, Sato S, Iwata K, Furukawa S, Hatsuse N, Watanabe Y, Anzai N, Kishimoto T, Ikebuchi E. Effects of risperidone and aripiprazole on neurocognitive rehabilitation for schizophrenia. Psychiatry and clinical neurosciences. 2014 Jun;68(6):425-31.
12. Penadés R, Catalán R. Cognitive remediation therapy (CRT): improving neurocognition and functioning in schizophrenia. InSchizophrenia in the 21st Century 2012. InTech.
13. Buonocore M, Spangaro M, Bechi M, Baraldi MA, Cocchi F, Guglielmino C, Bianchi L, Mastromatteo A, Bosia M, Cavallaro R. Integrated cognitive remediation and standard rehabilitation therapy in patients of schizophrenia: persistence after 5 years. Schizophrenia research. 2018 Feb 1;192:335-9.
14. Lisal ST, Syamsuddin S, Arung KR, Ganda IJ, Singara T, Renaldi R. Effect of Non-Computerized Cognitive Remediation on the Cognitive Function of the Schizophrenic Patients Treated with Typical Antipsychotic. International Journal of Clinical Psychiatry. 2018 Jun;6(2):27-33.
15. Nieto R, Kukuljan M, Silva H. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Frontiers in psychiatry. 2013 Jun 17;4:45.
16. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. American Journal of Psychiatry. 2011 May;168(5):472-85.
17. Barlati S, Deste G, De Peri L, Ariu C, Vita A. Cognitive remediation in schizophrenia: current status and future perspectives. Schizophrenia Research and Treatment. 2013;2013.
18. Campos C, BF Rocha N, Lattari E, E Nardi A, Machado S. Exercise induced neuroplasticity to enhance therapeutic outcomes of cognitive remediation in schizophrenia: analyzing the Role of Brai Nderived Neurotrophic Factor. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2017 Aug 1;16(6):638-51.
19. Wykes T, Reeder C, Huddy V, Taylor R, Wood H, Ghirasim N, Kontis D, Landau S. Developing models of how cognitive improvements change functioning: mediation, moderation and moderated mediation. Schizophrenia research. 2012 Jun 1;138(1):88-93.
20. Vinogradov S, Fisher M, Warm H, Holland C, Kirshner MA, Pollock BG. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. American Journal of Psychiatry. 2009 Sep;166(9):1055-62.
21. Angelucci F, Peppe A, Carlesimo GA, Serafini F, Zabberoni S, Barban F, Shofany J, Caltagirone C, Costa A. A pilot study on the effect of cognitive training on BDNF serum levels in individuals with Parkinson's disease. Frontiers in human neuroscience. 2015 Mar 16;9:130.
22. Penadés R, López-Vílchez I, Catalán R, Arias B, González-Rodríguez A, García-Rizo C, Masana G, Ruíz V, Mezquida G, Bernardo M. BDNF as a marker of response to cognitive remediation in patients with schizophrenia: A randomized and controlled trial. Schizophrenia research. 2018 Jul 1;197:458-64.