Original Article

A Randomized Clinical Trial of Group Cognitive- Rehabilitation Therapy for Patients with Schizophrenia Resistant to Medication

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Objectives: Against the background of evidence-based treatments for schizophrenia resistant to medication, the implementation of cognitive- Rehabilitation therapy (CRT) becomes more important, especially about patients who don't response to medication. There is less evidence for group format and face- to face structure of CRT and also for resistant to medication patients. This research investigates the efficacy of GCRT decreasing positive and negative symptoms of schizophrenia and improving cognitive function.

Methods: A Randomized Controlled Trial was used to compare the efficacy of GCRT that of patients who receive treatment as usual (TAU). From Razi hospital in Tehran, 40 inpatient people with schizophrenia resistant to medication and persistent negative and positive symptoms were assigned. Patients were included if they were aged 25 to 55 years; had diagnosis of schizophrenia for at least 2 years and were persistent to medication for 2 years. 20 of them received a 16 session's treatment over 2months and 20other ones were in waiting list. All Patients received TAU throughout the study. In all, 40 completed treatment. The positive and negative symptoms scales, NOSIE & NCSE completed for all patients before, in the middle and after treatment.

Results: Spss 11.5 and multivariate repeated measure was used. There were significant differences between the GCBT and TAU on positive and negative symptoms of schizophrenia. Significant improvement were found in the severity and number of positive (P= 0/05) and negative (P= 0/001) symptoms in patients treated with GCRT. GCRT leaded to improvement in cognitive functions (p=0/001) but there was no change in behavioral functions. In control group there were no significant differences between three measures (pre, middle and post).

Conclusion: GCRT is a useful adjunct therapy in the management of patients with schizophrenia resistant to medication in treating negative &positive symptoms as well as cognitive deficits.

Keywords: Schizophrenia, Group Cognitive – Rehabilitation Therapy (GCRT), Negative symptoms, Positive symptoms, Cognitive functions, Behavioral functions.

Introduction

Schizophrenia is a severe psychiatric illness, afflicting approximately 1% of the population worldwide (1).

As is clear from a review of the characteristic symptoms and impairments of schizophrenia, this disorder is multiply handicapping, impacting on all aspects of life functioning. Schizophrenia remains a debilitating disorder despite the development of drug treatments (2).

Schizophrenia is characterized by two broad classes of symptoms: Positive symptoms and

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negative symptoms. Common examples of positive symptoms include hallucinations , delusions, and bizarre behavior (3).

Negative symptoms, refer to the absence or diminution of cognitions, feelings, or behaviors. Common negative symptoms include blunted or flattened affective expressiveness, poverty of speech, anhedonia, apathy, psychomotor retardation, and physical inertia (3).

Aside from the characteristic symptoms of schizophrenia, many patients have cognitive impairments. Cognitive deficits in areas such as attention, memory, and abstract thinking are frequently present(4).

Cognitive deficits were described by Kraepelin and Bleuler as 'the core deficit' in schizophrenia but recent evidence suggests that such deficits in processing information may not be refractory but are open to novel interventions collectively called Cognitive Rehabilitation Therapy (CRT). CRT is a novel rehabilitation approach designed to improve neurocognitive abilities sus attention, memory and executive function. These impairments require specially tailored clinical procedures designed to remediate or compensate for these basic deficits (5-6).

Alternatively, novel strategies may be adopted to improve overall processing which are reflected in the neural mechanisms involved in completing a task.

The mechanism for cognitive improvement following CRT is not well understood but may be related to changes in specific aspects of brain function or to global changes, at a behavioral level, perhaps attributable to non-specific changes in arousal (7).

The aim of CRT is improving cognition and thereby increasing the likelihood of improved functioning outcomes. Cognitive rehabilitation therapy is an umbrella term for a number of different interventions defined by their procedural characteristics such as use of a therapist, use of a computer and the method of training (8).

Wykes and reeder (2007) evaluate the effectiveness of cognitive remediation therapy on cognitive difficulties experienced by people with schizophrenia. They selected 40 patients with a diagnosis of schizophrenia, a social behavior problem and a cognitive difficulty. They were randomized to 40 sessions of cognitive rehabilitation or treatment as usual in a randomized controlled trial. Their findings showed cognitive remediation therapy is associated with durable improvements in memory, which in turn are associated with social functioning improvements (8).

Lecardeur and et.al (2009) demonstrate that CRT can be useful to reduce clinical symptoms while they suggest an impact of CRT on cognitive complaints in patients with schizophrenia (9).

Doolatshahi and et.al (2004) showed cognitive rehabilitation therapy is effective for attention deficits, memory and executive function. It is also effective on negative symptoms but it's not effective for positive symptoms (10).

There is some evidence of efficacy for face-to-face therapy from small studies; however, no large study has investigated the effects and cost-effectiveness of face-to-face therapy. In addition,. It is, therefore, not yet possible to identify whether this form of cognitive therapy will have an impact on those with a spectrum of cognitive difficulties. The key effectiveness questions for cognitive rehabilitation therapy concern its likely success when the recipients have a variety of cognitive difficulties as well as a diagnosis of schizophrenia.

As we see relapse, hospitalization and recovery, this research is based on an intensive manual for patients with recurrent symptoms.

The present study attempts to determine the efficacy of face to face group cognitive rehabilitation therapy in a population of medication-resistant patients in the Razi hospital in Tehran, meeting diagnostic criteria for schizophrenia, and with negative symptoms of at least 2 year duration to overcome many of the limitations of previously published work. The aim was to compare Group CRT with a control group in reducing psychiatric symptoms among people with schizophrenia. In addition, this is an intensive method for decreasing primary symptoms of schizophrenia and increasing empowerment.

Materials and Methods

Design

A two-group randomized controlled trial was followed. The experimental group received group Cognitive Rehabilitation Therapy (CRT) in addition to standard care, and the control group received treatment as usual (TAU). Standard psychiatric care in the Razi hospital is pharmacotherapy.

Sample

Patients were recruited into the study from Razi psychiatry hospital in Tehran. a sample size of 20 would demonstrate a significant difference between the 2 treatments with 80% power, 0/05 level of confidence and 0/02 error on the basis of Cohen sample size table. As we considered drop-out, we selected 42 sample (21 patients for each group).

Inclusion criteria were:

Had a diagnosis of schizophrenia according to both DSMIV- TR criteria and SCID structured interview.

They were aged 25 to 50 years

Had symptom(s) causing dysfunction that had persisted for at least 1 year despite adequate trials of antipsychotic medication

Exclusion criteria were:

The patient is not in acute phase

No diagnosis of current abuse of drugs or alcohol warranting specific clinical

Intervention.

Had brain injury, dementia, any specific neurological disorder which need special care.

Had evidences for serious side effects of any antipsychotic drugs which leads to specific treatment.

Had receive ECT for at least 6 months before the research or during the therapy.

ASSESSMENTS AND PROCEDURES

The main outcome assessments were the Cognistat (NCSE), NOSIE, the Scale for

Assessment of Negative Symptoms (SANS) and the Scale for Assessment of Positive Symptoms (SAPS).

The Cognistat is a standardized neurobehavioral screening test. It describes performance in central areas of brain-behavior relations: level of consciousness, orientation, attention, language, constructional ability, memory, calculations and reasoning (11).

NOSIE developed by Honigfeld & Klett. It is a 30 item scale to assess behavior pathology of patients. It contains 30 designated behaviors. Inter-rater reliability is 0/73 to 0/74 (12).

SANS and SAPS is designed by Anderson (1983) with24 and 35 items on a likert scale from 0 to 6. Use of this measurement is common due to high validity and reliability. Internal consistency for SANS is 0/94 and SAPS is 0/83 and pre – post reliability of SANS is 0/92 and SAPS is 0/88 (13-14).

Psychologists were asked to introduce patients to the study, and those referred had schizophrenia eligibility confirmed by their last diagnosis by a psychiatrist. The DSM-IV –TR criteria and SCIDS structured interview for diagnosis of schizophrenia were confirmed by a psychiatrist/ clinical psychologist.

Patients were then assigned to one of the treatment arms using simple randomization applied independently for the randomization by a person not involved with either the assessments or the treatments.

First assessment were carried out by nurses, Further assessments were carried out in session 8 and then at the end of therapy (session 16).

Assessments were conducted by independent assessors who were masked to allocation of participants and remained blind to each patient's assigned group throughout the study.

INTERVENTIONS

Patients received group Cognitive rehabilitation therapy from 1 of 8 therapists. Therapists were B.Sc or M.Sc in clinical psychology and they were trained in 16 sessions by one of the researchers. Frequency of sessions was 2 times in a week and duration of the sessions were flexible from 30 minutes to 45 minutes to accommodate the needs of group. The research last up 2 months and at the end of treatment, the post test was assessed.

Each session involved a number of paper and pencil tasks that provide practice in a

Variety of cognitive skills that are set out in a manual.(a copy of manual can be obtained from the first author).

The session plan included setting the day's agenda, introducing the main topic, reviewing homework, applying the topic to individuals' own experiences, problem formulations in small groups, discussion and comparison of group members' experiences, setting homework and eliciting feedback on the session.

2 patients were quit, one of them due to death and the other one due to relapse. Data analysis was performed for 40 patients. Multivariate repeated measure was used for data analysis.

Results:

A total of 42 patients were enrolled in the Cognitive Rehabilitation Therapy (CRT). 20 patients randomized to CRT group and for 20 ones served as treatment-as-usual controls.

20 of the 21 patients in the CRT group completed the study, with each subject receiving 16 CRT sessions. 20 TAU patients completed the study.

Treatment effects were calculated, using multivariate repeated measure Test. It were employed for SANS, SAPS, NCSE and NOISE in session 1, 8 and 16 between CRT group and control group. The results are presented in Table 1:

Table 1: characteristics of the sample in three level: pre test- middle of treatment and post-test

	CONTROL			CRT		
SD	**M**	**N**	**SD**	**M**	**N**	
15/21	66/85	20	13/98	66/15	20	SAPS1
15/61	66/20	20	10/27	55/75	20	SAPS2
17/71	66/35	20	12/32	53/75	20	SAPS3
10/29	63/15	20	13/05	59/35	20	SANS1
10/60	62/55	20	11/35	58/35	20	SANS2
10/83	63/85	20	12/37	54/1	20	SANS3
16/25	64/75	20	20/19	61/5	20	NOISE1
17/58	64/10	20	14/85	54/7	20	NOISE2
14/92	63/75	20	16/43	51/45	20	NOISE3
2/23	4/05	20	1/91	4	20	Orientation1
1/88	5/10	20	2/20	7/35	20	Orientation2

	CONTROL			CRT		
SD	M	N	SD	M	N	
2/02	5/10	20	2/61	7/10	20	Orientation3
1/34	2/30	20	1/03	2/30	20	Attention1
1/04	2/15	20	1/01	4/25	20	Attention2
0/94	2/45	20	0/94	4/50	20	Attention3
3/14	6	20	3/55	7/35	20	Language1
2/56	6/65	20	3/94	9/90	20	Language2
2/89	5/9	20	3/79	10/70	20	Language3
0/81	0/65	20	0/96	1/10	20	Structure1
0/95	1/20	20	0/91	1/90	20	Structure2
0/85	1	20	0/85	1/75	20	Structure3
1/25	2/1	20	1/02	1/90	20	Memory1
0/91	2/1	20	1/08	4/15	20	Memory2
0/92	2/3	20	1/29	5/25	20	Memory3
0/86	0/70	20	0/74	0/65	20	Calculation1
0/76	0/80	20	1/18	2/6	20	Calculation2
0/71	0/75	20	1/04	2/85	20	Calculation3
2/32	4/05	20	2/03	4/40	20	Reasoning1
1/39	3/95	20	2/29	5/30	20	Reasoning2
1/39	3/80	20	2/09	5/75	20	Reasoning3

As shown in Table 1, statistically non significant scores were obtained between the CRT and control group in all scales and subscales.
The Highest score obtained in Pre test and the lowes in Post test. The highest deviation is in Pretest and the lowest in Post-test.
By multivariate test, Philiai's trace and wilks lambda, there was a significant relation between dependent varaiables ($\alpha = 0/05$).
Mauchly's Test of Sphericit showed significances in SANS, SAPS, NOSIE, language and reasoning ($\alpha = 0/05$) and Greenhouse-Geisser was used for normality in a multivariate deviation.
For Orientation, Attention, Constructive ability, Memory and Calculation, Mauchly's Test of Sphericit were not significant and the normality confirmed.
We used Mauchly's Test of Sphericit and Greenhouse-Geisser. The results showed in table 2:

Table 2: Test of with in subject effects

Sig.	df	F		Source
0/00	1/601	6/711	Greenhouse-Geisser	SAPS
0/26	1/366	1/354	Greenhouse-Geisser	SANS
0/03	1/5	4/139	Greenhouse-Geisser	noise
0/00	2	5/085	Sphericity Assumed	Orientation
0/00	2	12/43	Sphericity Assumed	Attention
0/00	1/512	9/729	Greenhouse-Geisser	Language
0/7	2	0/357	Sphericity Assumed	Structure
0/00	1/776	25/595	Greenhouse- Geisser	Memory
0/00	13/558	29/839	Sphericity Assumed	Calculation
0/03	1/377	4/122	Greenhouse- Geisser	Reasoning

As shown in table 2 there were a significant difference between SANS, SAPS, NOSIE, orientation ، attention، language ، memory ، calculation و reasoning in 3 levels. This shows a significant interaction between treatment and time.
The initial analysis detected a significant time by group. According to the initial model there was an estimated reduction in the CRT group of all points except behavioral function at the post-therapy time point (95%) which became enlarged to a statistically significant reduction in post test but the conclusions remained the same in control group.

There was a trend towards an interaction between randomization group and time and towards a main effect of randomization after adjusting for baseline differences. Table 3 show the effectiveness:

Table 3: Test of between subject effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
SAPS	2210/208	1	2210/208	4/089	0/05
SANS	1050/208	1	1050/208	3/951	0/05
NOSIE	2066/700	1	2066/700	2/819	0/10
Orientation	58/800	1	58/800	7/577	0/000
Attention	57/408	1	57/408	53/316	0/000
Language	291/408	1	291/408	10/494	0/000
Structure	12/033	1	12/033	12/667	0/000
Memory	76/800	1	76/800	50/550	0/000
Calculation	49/408	1	49/408	32/085	0/000
Reasoning	44/408	1	44/408	5/284	0/02

Between subject effects showed significant effect (P<0/05) in SAPS ،SANS، orientation ، attention، language ، memory ، calculation و reasoning.
NOSIE is the only scale that dependent variable has no effect on it.

Conclusion:

Cognitive problems are the most obvious sign of a diagnosis of schizophrenia, but for a considerable time following the genesis of the diagnosis little attention was paid to the alleviation of these problems. The prime targets for treatments were the positive symptoms and cognitive difficulties were considered to be reduced by medication. It is only recently that both the pharmacological and psychological research communities have identified improving cognitive skills as an important target. This is, in part, because several studies have now suggested that cognitive problems rather than symptoms are associated with later functional outcome. (8, 14-17).
Cognitive Rehabilitation Therapy for chronic schizophrenia has emerged as an important field in treatment of schizophrenia (18).
The main results revealed that positive and total symptom scores decreased significantly after CRT compared to TAU. This finding gives support to the hypothesis
that a cognitive intervention could be affected symptoms of schizophrenia. The efficacy for negative symptoms is more than positive symptoms. (α= 0/05 vs. α = 0/001). Several studies

are now demonstrated declining symptoms in patients with schizophrenia. Lecardeur and et.al (2009), Wykes and et.al(2007), Penades and et.al (2006), Combz and et. al (2006), Doolatshahi and et. al (2004) demonstrated congruent results (6-8-9-10-19) but most of these studies report no changes in positive symptoms. (10-20)

Results showed Group CRT for cognitive deficits is associated with negative and positive symptoms with a high effectiveness (p<0/001) but there is not enough evidence for behavioral function. These behavioral functioning effects are extremely important in a group that is known to be socially isolated. Although the effect may be the result of no special task on behavioral deficits, it is also highly likely that there was a short time for generalizing cognitive changes to behavioral functioning. This would need to be formally tested by follow- up studies.

However, it was clear that group participants were engaged in the process of group discussion about their cognitive performance. This chance to practice their cognitive ability had previously reduced their negative symptoms is likely to have an impact on their positive symptoms outside the manual of herapy. There wasn't any special intervention for positive symptoms. It seems that patients would have been involved to the same extent with any other topic.

These results suggest that some positive changes are possible for people using CRT principles within a goup setting. But the results did not follow the pattern suggested by the previous less well controlled studies. A variety of explanations were investigated. (21-22)

The third hypothesis of research confirmed. A tentative conclusion is that CRT lead to improvement of cognitive function in all cognitive domain; orientation, attention, memory, language, structural ability, calculation and reasoning. The result of the study are consisted with the recently published o CRT for schizophrenia. Findings of Lecardeur and et.al (2009), Frango and et.al (2008), Wykes, Newton and et.al (2007), Wykes, Reeder and et.al (2007), Favrod and at.al (2006), Combz and et.al (2006) Penades and et.al (2006) and Doolatshahi and et. al (2004) (6- 8-9-10-17-19-21-22).

Improvement in language ability (comprehension, repetition and naming) and constructive abilities is ore than other functioning (a= 0/001). We applied cognistat for cognitive abilities and previous studies applied other limited measurement, threfore, it needs more research to confirm the benefits of language abilities. The structure of manual and tasks which involve language would cause the improvement.

Whether improvement in one cognitive deficit can generalize to other deficits? This is a question wich needs more detailed research.

his treatment is not effective for behavioral performance although the most important item is improvement in behavioral function and social adjustability.

This finding is criticism to CRT. It is effective for cognitive function but finally we look for better social and behavioral life. Turkington, Kingdon and Weiden (2006) believe the short term efficacy of CT(23).

Green and et.al (2000) believe that cognitive deficits, specially memory deficits lead to occupational ad social drop outs and dysfunctions everlasts through the lifespan. (24).

Pammatter, Junghan and Brenner(2006) concluded from a meta-analysis, cognitive remediation leads to short-term improvements in cognitive functioning. These benefits seem to be accompanied by slight improvement in social functioning (25).

There are some evidence for behavioral improvement as result of cognitive improvement. (6-8-9-19-20).

However, previous researches suggest long term intervention, this research showed effectiveness of a 2months intervention efficacy. Intensity can maximize learning and overcome memory problems. Intensive intervention is more applicable for those patients who comes and

As the last point, successfully intervention and the consequences is related to cultural adaptation.

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