comunicação breve

Randomized controlled trial of occupational therapy in patients with treatment-resistant schizophrenia

Estudo aleatorizado e controlado empregando a terapia ocupacional em pacientes com esquizofrenia refratária a tratamento antipsicótico

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Abstract

Objective: It is well established that the combination of psychopharmacological treatment and psychosocial interventions, such as psychotherapy, family orientation and occupational therapy (OT), represent the best strategy for treating patients with schizophrenia. However, in terms of treatment-resistant schizophrenia (TRS) almost only psychopharmacological treatments are available and psychosocial interventions such as OT had not proved to be effective. The aim of this study is to investigate if OT is effective when added to a psychopharmacological treatment in TRS.

Methods: Two groups of patients with TRS were compared: The experimental group (EG) received psychopharmacological treatment with clozapine plus sessions of occupational therapy (OT) and the control group (CG) received only clozapine. The Scale for Interactive Observation in Occupational Therapy (EOITO) was employed to evaluate the outcome. The duration of the study was 6 months and patients were rated at baseline and monthly totaling 7 assessments. EOITO was independently applied by two occupational therapists with high reliability rates (Kappa=0.90, p=0.001). Repeated measures of analyses of variance and the evaluation of the standardized effect sizes were used for statistical analyses.

Results: The EG showed that the OT intervention was effective along the whole period of observation, mainly from the 4th month to the end of the study.

Conclusions: In patients with TRS the combination of OT and clozapine showed to be more effective than the use of clozapine alone. OT may represent an additional therapeutic option for patients with TRS.

Keywords Schizophrenia.Treatment-resistant schizophrenia. Occupational therapy. Scale of interactive observation in occupational therapy (EOITO).

Resumo

Objetivo: Já está bem estabelecido que a forma de intervenção mais eficaz no tratamento de pacientes com esquizofrenia consiste na combinação de tratamento psicofarmacológico com intervenções psicosssociais. No caso da esquizofrenia refratária a tratamento antipsicótico (ERTA), a terapêutica concentra-se quase que exclusivamente nos tratamentos farmacológicos, não havendo evidências de que as intervenções psicossociais sejam eficazes. O presente estudo procura investigar o efeito da Terapia Ocupacional (TO) como possível potencializadora do tratamento psicofarmacológico da ERTA.

Método: Foram comparados dois grupos de pacientes com ERTA: O grupo Experimental (GE) recebeu tratamento psicofarmacológico com clozapina e TO e Grupo Controle (GC), apenas tratamento psicofarmacológico. Foi utilizada a Escala de Observação Interativa de Terapia Ocupacional (EOITO) para avaliar a evolução do processo terapêutico. O estudo teve duração de 6 meses e cada paciente foi avaliado em sete tempos diferentes (avaliação inicial e seis avaliações mensais). A EOITO foi aplicada independentemente por dois terapeutas ocupacionais, com altos índices de confiabilidade (Kappa= 0,90, p=0,001). A análise estatística utilizada foi a análise repetida de variância e a comparação dos tamanhos de efeito padronizados.

Resultados: O cálculo dos tamanhos de efeito mostrou de modo consistente que o GE beneficiou-se da intervenção da TO ao longo de todo período de observação, sendo que os maiores tamanhos de efeito ocorreram a partir do quarto mês.

None financial support and conflict of interests.
Recieved on 28/2/2002. Reviewed on 28/6 and 2/9/2002. Approved on 7/11/2002.

Conclusões: A combinação de TO com clozapina mostrou-se mais efetiva do que o uso de clozapina isoladamente na evolução dos pacientes com esquizofrenia refratária a tratamento antipsicótico. A TO pode representar uma alternativa adicional no arsenal terapêutico da ERTA.

Descritores Esquizofrenia. Esquizofrenia resistente a tratamento antipsicótico. Terapia ocupacional. Escala de observação interativa de terapia ocupacional.

Introduction

There is evidence suggesting that the most efficient way to treat schizophrenic patients consists in the combination of psychopharmacological treatment and psychosocial interventions such as psychotherapy, family therapy and occupational therapy (TO).[1]

It has been already established that 30% of schizophrenic patients are non-responsive to a conventional neuroleptic treatment and their disorder is called treatment-resistant schizophrenia (TRS)[2] being clozapine the medication of choice for the treatment of these patients.[3]

However, some authors suggest that the combination of psychosocial interventions and antipsychotics is more effective in the treatment of refractory patients.[4] In fact, there is evidence that this combination be really effective in TRS. Hellewell et al,[5] in a review about the alternatives to treat refractory schizophrenia, noted that, besides the strategy of prescribing clozapine, its combination with a psychosocial intervention modifies widely the outcome.

Recent research of the literature using Medline showed that, except for cognitive-behavioral therapy, there are no controlled studies assessing the efficacy of combining the several forms of psychosocial interventions with a pharmacological treatment of TRS, although it is known that in the clinical practice this combination is largely employed.[6]

We define a psychosocial approach as any intervention aimed at inserting the subject in the social environment based on a non-psychopharmacological treatment. OT's clinic aims mainly at the social (re)insertion using the daily routine as an organizing axis.[7] This triadic relationship (therapist-patient-activity) creates the conditions to develop an environment in which subjects experience learning and the possibility of applying their resources, in which a pathological space can be transformed into one of creative and structured development, thus enabling patients to deal differently with their limitations and to improve their social interaction.[8]

In the treatment of schizophrenic patients, the use of activities in OT has also a pedagogic aspect, enabling them to learn from its development, to face up with the possibilities and limitations of materials and processes, to develop or utilize specific skills, to experience several situations, which could be transported from the therapeutical setting to the external activities. [8]

There is no literature about the intervention of OT in patients with TRS. Based on the need of interventions to complement the psychopharmacological treatment of patients with refractory schizophrenia, our study aims at verifying if OT enhances the pharmacological treatment of TRS by comparing two groups of patients: the experimental group (EG), which in this study received a psychopharmacological treatment and OT intervention, and a second one called control (CG), which received only psychopharmacological treatment. These patients' outcome was assessed with the Scale of Interactive Observation in Occupational Therapy (EOITO) which is an instrument derived from the Scale for Interactive Observation of Psychiatric Inpatients (EOIPPI)[9] and adapted for OT situations.

Methods

This study was performed in the ambulatory of Treatment-Resistant Schizophrenia (Proerta) of the Program of Schizophrenia (PROJESQ) of the Psychiatric Institute of the Clinical Hospital of the Medical School of the University of São Paulo (HCFMUSP). The study was approved by the Ethics Committee of the HCFMUSP for Analysis of Research Projects (CAPPesq) and patients and/or family members signed the Informed Consent.

Patients were defined as having TRS if they met Kane et al criteria,[10] which has the following dimensions:

Historic

The patient should have persistent psychotic symptoms for the last five years, although having received treatment with, at least, three antipsychotics, of two different chemical classes, at different times, having achieved doses equivalent to 1000 mg or more of chlorpromazine, for six weeks.

Current

The patient should have a punctuation of at least 45 points in the Brief Psychiatry Rating Scale (BPRS), 27 points in the BPRS anchored version[11] and in this scale should have reached a punctuation from 3 to 4 in the following: Conceptual Disorganization, Hallucinatory Behaviors, Suspiciousness and Delusions. The BPRS is a scale that has been extensively used in the PROJESQ and has mean reliability levels near to 0.75 (intraclass correlation coefficient)[12] Besides, it should have 4 points ('moderately mentally ill') in the global impression scale (CGI).[13]

Prospective

Incapacity of decreasing the BPRS score in at least 20% compared to the initial observation or incapacity of decreasing the

CGI to less than 3 ('mildly mentally ill'), after a treatment with up to 20 mg/day of haloperidol, for six weeks.

Twenty-six patients were studied and randomized to each group. The randomization was performed through allotment, that is, only after it we knew whether the patient would go to the EG, where they received a combined intervention of OT and clozapine or to the CG, where they received only clozapine.

In OT groups, free choice of activities was used and the dynamics of the group were: group of activities and group activity. In the group of activities patients perform individual activities and the axis of the relationship is preferentially with the therapist. In the group activity, patients develop a common activity, as a whole, enabling richer and more varied exchanges between themselves and between them and the therapist.[7] From a group or individual event, the occupational therapist can make an interpretation which is not traditionally communicated but translated to the patient/group by means of an intervention.[14]

Outcome assessments were performed during the therapeutic process through the EOITO,[15] a 14-item scale, divided in four factors: performance of the activity; psychotic symptoms; social interaction and personal care. Each item is assessed according to three severity levels (0, 1 and 2), which are mutually exclusive within each item and which indicate in increasing order the severity of the pathological manifestations. In items related to the expression of desirable behaviors the graduations imply: spontaneous occurrence (grade 0), occurrence after stimulation (grade 1), or non-occurrence even after stimulation (grade 2). The scale is interactively applied and in the case of items related to inadequate behaviors, the assessment stimulates the confrontation of these behaviors or the observation of environmental variables which favor them. In these items the grades involve absence of behavior (grade 0), presence in certain conditions or susceptible to confrontation (grade 1), and constant presence or irreducible to confrontation (grade 2).

As already said, the main feature of this scale is that the assessment is not based only in the observation of behaviors but implies the interaction between the evaluator and the patient (participant observation). Evaluators were trained by the author of the scale and the calculation of the items' reliability applied at the beginning of the study (baseline) has revealed a mean KAPPA of 0.90 (p=0.001).

In the EG and CG groups the application of the scale was performed by two previously trained occupational therapists. Each patient was assessed in 7 different times (baseline and monthly, during 6 months), and the EOITO was applied at intervals of 15 days in both groups. In the CG, the performing of activities item was excluded as obviously could not be assessed.

The statistical analysis was based on the intent-to-treat, using the method of the last observation carried forward, and analyses of all patients who started the study were performed and only of those who completed it (completer analysis).[16] The differences between the group of patients with combined therapy (EG) and the control group (CG) were assessed through the variance analysis for repeated measures and through the statistics of standardized effect sizes (g).[17,18] This measure assesses the clinically significant difference between the CG and EG groups with the following formula: ME- MC/ dp EC, being 'ME' and 'MC' the means of the groups EG and CG, and 'dpEC', their combined standard deviation. This denominator has the following formula: $\{[(nE-1)(sE)^2 + (nC-1)(sC)^2]/[nE+nc-2]\}$,$^{1/2}$ being n the number of subjects, s^2 the variance, and ½ the square root of the expression. The sign of the effect size depends on the tested hypothesis that, in the current study, was: the experimental group < group, that is, the benefit of the OT would be expressed by a lower severity in the EOITO. Therefore, the 'minus' sign means the confirmation of the hypothesis, that is, that the EG has reached lower values in the EOITO and, in the opposite case, higher values expressed by the positive sign. The effect sizes were calculated through the pro-

Table 1 - Demographic data [frequencies, means (standard deviations)] of patients who started the study: comparison between the Control Group (CG) and the Experimental Group (EG).

	CG	EG	Statistical test	P
Gender	10 males 2 females	9 males 5 females	Chi-square=1.192[b]	0.27
Current Age	36.58 (6.60)	33.71 (6.90)	t=1.07	0.29
Disease's age of onset	19.67 (7.43)	20.93 (4.91)	t=-0.51	0.60
Duration	16.92 (8.60)	12.79 (5.44)	t=1.48	0.15
Number of admissions	5.08 (4.38)	3.08 (2.47)	t=1.42	0.16
Schooling (number of years)	8.17 (2.59)	9.64 (3.34)	t=-1.24	0.22

t= student's t test; p= statistical significance; CG= control group; EG= experimental group.

Table 2 - Demographic data [frequencies, means (standard deviations)] of patients who completed the study: comparison between the Control Group (CG) and the Experimental Group (EG).

	CG	EG	Statistical test	P
Gender	9 males 2 females	4 males 3 females	Chi-square=1.3	0.26
Current Age	36.2 (6.8)	31 (5.10)	t =1.8	0.1
Disease's age of onset	19.7 (7.8)	17.9 (1.9)	t =0.6	0.6
Duration	16.6 (8.9)	13.2 (4.0)	t=0.9	0.4
Number of admissions	4.7 (4.4)	3.9 (2.6)	t=0.5	0.6
Schooling (number of years)	8.4 (2.6)	8. (3.1)	t=-0.5	0.9

t= student's t test; p= statistical significance; CG= control group; EG= experimental group.

grams DSTAT 1.10[19] and SPSS for Windows version 10.0.

Results

We show in tables 1 and 2 the demographic variables of CG and EG groups, which started and completed the study and we can note that they are comparable, as there were no statistically significant differences regarding gender, age, age of onset, duration, number of admissions and schooling years.

In the case of the repeated analysis of variance, as the EOITO's means at the beginning of the study (baseline) were significantly different between CG and EG (t=2.9 p=0.008), they were used as covariates and, therefore, months from 2 to 7 were analyzed. In table 3 we present the results of this analysis which shows a statistically significant difference between CG and EG (F=5.129, p=0.033).

The analysis of all initially included patients (i.e., on an intent-to-treat basis) shows that patients progressively benefited from OT intervention and patients who completed the study have also benefited, although the effect sizes were slightly lower as can be seen in tables 4 and 5, illustrated by the graph.

Of note, the high number of withdrawals (8/26: 30%), a very common fact in clinical studies, particularly in cases of schizophrenia which is notoriously difficult to be managed. On the other hand, the application of the method of the last observation carried forward enables us to infer that if patients had remained they would have benefited from the intervention.

Regarding patients who completed the study, the comparison between EOITO's total means (sum of 14 items) at the study's beginning was also non-significant in the initial time [experimental =(4.1 (3), control =6(2); t=1.5, p=0.2)]. The calculation of effect sizes shows that the experimental group benefited consistently from OT interventions, and the greatest effect sizes occurred at the treatment's end [Table 2]. The graph shows that effect sizes started to grow from time 4 onwards and the drop in time 5 could be explained by the suicide of a patient, what affected intensely the experimental group.

Discussion

In this study we could evidence that OT intervention combined with appropriate medications was associated to an improvement in the patients' condition, according to the factors measured by the EOITO, mainly in terms of occupational performance and interpersonal relationships. We also verified that OT is a therapeutic which provides medium and long-term results, due to its nature which establishes a dynamic between the therapist-patient-activity elements.There is clear evidence that patients with schizophrenia have an intense impairment of the executive functions, what Kraepelin called "loss of the main springs of the volition".[20] This deficit is defined nowadays as the "negative syndrome" of schizophrenia[21] and, regarding TRS, this syndrome appears with great intensity. Thus, it is possible that the use of OT as a complementary treatment enables an improvement of the patients' executive functions.

Table 3 - Results of the analysis of variance –repeated measures.

Source	Sum of squares	Degrees of Freedom	Mean squares	F	P
Intersection	95.263	1	95.263	7.865	0.010
Baseline EOITO mean (covariate)	217.661	1	217.661	17.969	0.001
Factor: CG or EG	62.128	1	62.128	5.129	0.033
Error	278.595	23	12.113		

CG= control group; EG= experimental group, F= result of the test; p = significance.

Table 4 - Total means (standard deviations), magnitudes of effect sizes (d) and respective statistical significances (p) of EOITO values obtained in the different times points of the study of all patients.

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
CG	6.13	5.63	6.17	6.83	7.00	6.33	6.58
N=12	(2.09)	(3.27)	(3.31)	(2.66)	(2.38)	(2.58)	(2.81)
E	3.75	3.43	3.93	3.57	4.14	3.18	3.07
N=14	(2.08)	(1.49)	(1.45)	(1.37)	(1.6)	(1.48)	(1.89)
Magnitude of the effect (d)	-1.11	-0.86	-0.87	-1.3	-1.31	-1.48	-1.44
Significance (p)	0.01	0.04	0.04	0.0001	0.003	0.001	0.001

CG= Control group; EG= Experimental group.

Table 5 - Total means (standard deviation), magnitudes of effect sizes (d) and respective statistical significances (p) of EOITO values obtained in the different times of the study in patients who completed the study.

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
CG	5.95	5.23	5.82	6.55	6.73	6	6.27
N=11	(2.10)	(3.11)	(3.23)	(2.58)	(2.30)	(2.42)	(2.72)
EG	4.14	3.50	4.50	3.79	4.93	3	2.97
N=7	(2.97)	(2.14)	(1.93)	(1.93)	(2.42)	(2.10)	(2.71)
Magnitude of the effect (d)	-0.70	-0.59	-0.44	-1.11	-0.73	-1.23	-1.22
Significance (p)	0.16	0.23	0.36	0.03	0.15	0.02	0.02

CG= Control group; EG= Experimental group.

As far as we know, there are no randomized and controlled studies of application of OT as was the case of current study. However, its conclusions are limited by the sample's size and by the number of withdrawals, what indicates the need of further similar studies, with greater samples and with a lower rate of withdrawals to allow the replication of the findings of this study.

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