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Original Research Article

Comparison of therapeutic effects of monotherapy of chlorpromazine, risperidone and their combination in newly diagnosed schizophrenic patients

Tarun Vijaywargia*

Department of Pharmacology, Jhalawar Medical College and Associated group of Hospitals, Jhalawar, Rajasthan, India

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***Correspondence to:**
Dr. Tarun Vijaywargia,
Email: tarunvijaywari76@yahoo.com

ABSTRACT

Background: This study evaluates and compares how negative and positive symptoms of schizophrenia were influenced with monotherapy with a first-generation anti-psychotic medication (Chlorpromazine) and a second generation anti-psychotic medication (Risperidone) and by their combination, both of which are commonly used in clinical psychiatric practice.
Methods: It was randomized, double-blind, controlled clinical study performed in Indian newly diagnosed schizophrenic patients in the Department of psychiatry from Feb 2003 to March 2004. Patients 18 (eighteen) patients aged 20 to 60 years diagnosed schizophrenics according to ICD-10 Criteria who visited in outpatient department of psychiatry during study period. Three groups of 6 Patient each, group-1 - was treated with oral Chlorpromazine 100 mg 12 hly, group -2 - was treated with oral Risperidone 2mg 12 hly group 3 -was treated with combination of oral Chlorpromazine 100mg 12 hly + oral Risperidone 2 mg 12 hly. How symptomatology in schizophrenic patients affected, is measured by applying various validated psychiatric scales like Brief psychiatric Rating Score (BPRS), Scale for assessment of positive symptom(SAPS), and Scale for Assessment of Negative Symptoms (SANS).
Results: the study showed that the combination therapy of oral Chlorpromazine 100 mg 12 hly + Risperidone 2mg 12 hly had reduced the overall beneficial effects which were achieved with monotherapy of both the drugs.
Conclusions: In this study, the therapeutic effects of combination of oral Chlorpromazine 100 mg 12 hly + Risperidone 2 mg 12 hly found to be reduced on positive symptoms and negative symptoms of schizophrenia, assessed on SAPS and SANS scoring scales when compared with beneficial effects which were achieved with monotherapy of both the drugs.

Keywords: Chlorpromazine and risperidone, Schizophrenia, Testosterone

INTRODUCTION

Psychosis is a symptom of mental illnesses characterized by a distorted or nonexistent sense of reality. Psychotic disorders have different etiologies, each of which demands a unique treatment approach. Schizophrenia is generally a chronic disorder that during active phase presents with delusions, hallucination, disorganized speech and disorganized behavior (known as positive symptoms) or negative symptoms such as flat affect (reduction in the range and intensity of emotional expression), Avolition (reduction, difficulty, or inability to initiate and persist in goal-directed behavior) and Alogia (poverty of speech).[1] The diagnosis is made schizophrenia when these symptoms of active disease present for more than 1 month.[2] The current Pathophysiology of schizophrenia that is also utilized in clinical practice is that there is excessive dopaminergic neurotransmission in the associative striatum that leads to the positive symptoms of psychosis. Blockade of dopamine receptors of D2 type (60 to 75%) controls positive symptoms of schizophrenia as done by 1st and 2nd generation anti-psychotic agents. It is also found that dopaminergic hypoactivity in mesocortical area produces negative symptoms of schizophrenia (first

generation agents produce anhedonia (inability to feel pleasure, a negative symptom, most probably due to D2 receptor blockade).[3] Antagonism of 5-HT2a receptor by 2nd generation agents (e.g. clozapine) in Meso-cortical (pre-frontal) area is important in reducing negative symptoms.[4] Low-potency 1st generation agents such as chlorpromazine are not commonly used due to the high affinities for H1, M1, and α1 receptors that result in undesirable effects (sedation, anticholinergic properties, and orthostasis). Concerns regarding QTc prolongation further limit their clinical usefulness. The 1st generation low potency agents are useful as they are less likely to produce EPS side effects as they usually not produce excessive D2 blockade in low doses (e.g. 100mg 12 hly). Risperidone, a commonly used drug in clinical psychiatric practice, a 2nd generation anti-psychotic drug that potently antagonize the 5HT2A receptor while possessing less affinity for D2 receptors than 1st generation typical antipsychotic agents, resulting in antipsychotic efficacy with lower potential for extrapyramidal side effects.[5] In clinical practice both these drugs are used from long time in varying dosage as monotherapy.[6] In the recent years there has been an increase in the use of antipsychotic polypharmacy, although there are a variety of factors but poor response to monotherapy is the main cause but unfortunately there is no high quality evidence supporting antipsychotic polypharmacy for treatment resistant patients.[7] This study probes weather in some cases of schizophrenia if monotherapy either with 1st or 2nd generation agents not shows good therapeutic effect than in such cases the use of anti-psychotic combination therapy proved to beneficial for the patient or not i.e. weather non-evidence based use of antipsychotic polypharmacy in psychiatric clinical practice is supported by planned RCTs (evidence based medicine).

METHODS

Patients diagnosed as schizophrenic with no associated mental or medical disease and who fall into all exclusion and inclusion criteria for the clinical interaction study.

Semi structured proforma of patient consisting of:

- Biodata of patient
- History of illness
- Mental status and sex status
- General and physical examination notes
- Follow-up scales
- Adverse effect profile

Parameters/scales of diagnosis and grading the psychosis - 4 types - as under (Source: Lyerly SB: Handbook of Psychiatric Rating Scale, Ed. 2, National Institute of Mental Health, Bethesda, 1973)

- BPRS (Brief Psychiatric Rating Scale) - 1
- SAPS (Scale of Assessment of Positive Symptoms) - 2
- SANS (Scale of Assessment of Negative Symptoms) - 3
- ICD-10 Classification for Diagnosis of Schizophrenia- 4 (Source: WHO: The ICD-10 classification of mental and behavioral disorders: Clinical Descriptions and Diagnostic Guidelines, WHO, Geneva, 1992)

Drugs and their dosage form. It includes:

- Tablet Chlorpromazine 100mg - Sun pharmaceuticals, Ahmedabad
- Tablet Risperidone (SIZODON) 2mg - Sun Pharmaceuticals, Ahmedabad

Sphygmomanometer (Diamond), stethoscope (Littman), weighing machine.

Patient signed informed consent form.

Method of human exploratory clinical trial

Objective was to study the change in therapeutic effectiveness of chlorpromazine monotherapy, Risperidone monotherapy in schizophrenic patients when given in combination in newly diagnosed schizophrenic patients.

It was randomized, double-blinded, and controlled (conventional treatment only). The study was conducted on 18 schizophrenic patients.

The study was conducted in collaboration with department of psychiatry, division of internal medicine, M.Y. Hospital, Indore and Department of Pharmacology, M.G.M. Medical College, Indore between Feb 2003 to March 2004 and followed the Good Clinical Practice guidelines (ICH).

Grouping of sample population

It depends upon therapeutic intervention. Groups are described in Table 1.

Table 1: Grouping of therapeutic interventions.

Study group	n	Treatment given (route, drug, formulation, dose, frequency and duration)
A	6	Oral tab. CPZ 100 mg Twice a dayx28 days.
B	6	Oral tab. Risperidone 2mg twice a dayx28 days.
c	6	Oral tab. CPZ 100mg Twice a day + oral tab. Risperidone 2mg twice a day x 28 days.

CPZ - Chlorpromazine, RIS - Risperidone, n = no. of patients in study arm

Follow up

The follow up of patients was done in the OPD on regular/periodic basis (every 7th day from start of study). Those cases who failed to come at the trial center were given follow-up at their homes.

Design of study

This trial was conducted in collaboration with department of psychiatry, in M.Y.H Hospital, Indore. The cases of schizophrenia are selected according to "selection criteria" which is mentioned below:

Inclusion criteria

Age-20 to 60 years schizophrenic patients diagnosed by ICD-10 Diagnostic Criteria

Exclusion criteria

- Patients who have any other physical or mental illness than schizophrenia,
- Pregnant or nursing women
- Decreased hepatic or renal function.

Conduct of trial

The antipsychotic medications used in this study is chlorpromazine and Risperidone, the dose decided for Chlorpromazine was 100mg twice daily and for Risperidone 2mg twice daily. The total duration of study was 28 days. The protocol and informed consent were approved by the regional ethics committee. Written informed consent was obtained for all patients. Patients are randomized according to Random Table and given Treatment by an independent contributor who did not know the nature and protocol of study to ensure proper double blinding.

As per the design of study stipulated fixed dose of anti-psychotic medication were given orally for 28 days uninterruptedly in the OPD of psychiatry. The patients were instructed to come at OPD every 7th day along with relatives for interrogations regarding medications and symptomatology of illness during the follow-up phase of the study.

The duration of follow-up was done every 7th day till the end of study (i.e. 28 days).

The diagnosis of schizophrenia is made by ICD-10 classification, while the alteration in signs and symptoms of the illness following medication was monitored weekly by BPRS, SAPS, and SANS psychiatric rating scales.[8,9] During follow-up along with the assessment of psychiatric symptoms, adverse reactions of administered drugs are also watched and along with that patients certain physiological parameter like blood pressure, pulse and weight are also monitored.

These follow-up scales and criteria of ICD-10 are satisfied by conducting interview with patient and their relatives. Each symptom and its severity are assessed by putting some questions in front of patient and members of his/her family. The presence of psychiatrist facilitates diagnosis and assessment of severity of illness.

Outcome and statistical analysis

Primary efficacy outcome measure was reduction of score of different psychiatric scoring scales BPRS (Brief Psychiatric Rating Scale), SAPS (Scale for assessment of positive symptoms, and SANS (Scale for Assessment of Negative Symptoms Paired't' test is used for determining level of significance (p value) of intervention.

RESULTS

It is evident from the table that CPZ 200mg/day/OS for 3 weeks caused reduction in psychiatric symptoms by 24% to 28% in different psychiatric scales (Table 2).

Table 2: Effect of chlorpromazine 200mg orally per day on four different psychiatric scoring scales in schizophrenic patients.

Patient no.	BPRS		SAPS		SANS	
	Pre-treatment score	3rd week post CPZ treatment score	Pre-treatment score	3rd week post CPZ treatment score	Pre-treatment score	3rd week post CPZ treatment score
1	57	43	111	88	59	43
2	82	56	141	106	114	87
3	72	56	103	75	115	86
4	66	56	138	110	35	25
5	70	61	143	111	104	79
6	55	31	61	39	104	75
Total	402	303	697	529	531	395
% red. in score	24.62%		24.00%		25.61%	

Table 3: Effect of risperidone 4mg orally per day on four different psychiatric scoring scales in schizophrenic patients.

Patient no.	BPRS		SAPS		SANS	
	Pre-treatment score	3rd week post RIS treatment score	Pre-treatment score	3rd week post RIS treatment score	Pre-treatment score	3rd week post RIS treatment score
1	73	59	126	104	111	81
2	64	54	89	62	109	76
3	52	43	121	70	63	47
4	52	39	100	75	56	34
5	66	40	100	54	103	73
6	54	29	120	84	48	39
Total	361	264	656	449	490	350
% red. in score	26.86%		31.59%		28.57%	

Table 4: Effect of chlorpromazine 100mg orally per day and risperidone 2mg orally per day on four different psychiatric scoring scales in schizophrenic patients.

Patient no.	BPRS		SAPS		SANS	
	Pre-treatment score	3rd week post CPZ + RIS treatment score	Pre-treatment score	3rd week post CPZ + RIS treatment score	Pre-treatment score	3rd week post CPZ + RIS treatment score
1	65	45	99	60	113	74
2	57	42	119	96	69	60
3	82	67	143	126	104	74
4	70	60	124	113	43	39
5	53	43	108	76	67	61
6	66	52	100	86	103	89
Total	393	309	693	557	499	397
% red. in score	21.37%		19.62%		20.44%	

Table 5: Effect of oral chlorpromazine 200mg/day 12hly for 3 weeks in schizophrenic patients.

Treatment Group-A	% Reduction in BPRS Score			% Reduction in SAPS Score			% Reduction in SANS Score		
	% reduction	't' value	P value (level of significance)	% reduction	't' value	P value (level of significance)	% reduction	't' value	P value (level of significance)
CPZ 200 mg only (Control)	24.68%	3.96	<0.02	24%	27.47	<0.001	25.6%	7.165	<0.001

p and t-value

It is evident from the table that Risperidone 4mg orally per day for 3 weeks caused reduction in psychiatric symptoms by 26% to 33% in different psychiatric scales (Table 3).

It is evident from the table that Risperidone 2mg and Chlorpromazine 100mg orally per day for 3 weeks caused reduction in psychiatric symptoms by 19% to 22% in different psychiatric scales (Table 4).

It is evident from the table CPZ 200 12hly produce improvement in both negative and positive symptoms of schizophrenia as evident from % reduction in SAPS and SANS score and reduction level in negative symptomology is more (25.6%) is more as compared to positive symptomology is more (24%) (Table 5).

It is evident from the table that Risperidone 2mg 12hly produce improvement in both negative and positive symptoms of schizophrenia as evident from % reduction in SAPS and SANS score and reduction level in positive symptomology (31.59%) is more as compared to negative symptomology (28.57) (Table 6).

It is evident from the table that Risperidone 2mg + CPZ 100mg daily 12 hly for 3 weeks 12hly produce improvement in both negative and positive symptoms of

schizophrenia as evident from % reduction in SAPS and SANS score and reduction level in positive symptomology (21%) is more as compared to negative symptomology (20.44%) (Table 7).

Table 6: Effect of oral risperidone 2mg/day 12 hly for 3 weeks in schizophrenic patients.

Treatment Group- C	% Reduction in BPRS Score			% Reduction in SAPS Score			% Reduction in SANS Score		
	% reduction	't' value	P value (level of significance)	% reduction	't' value	P value (level of significance)	% reduction	't' value	P value (level of significance)
Risperidone 4mg only (Control)	26.86%	5.69	<0.01	31.59%	7.187	<0.001	28.57%	5.85	<0.01

p and t-value

Table 7: Effects of oral risperidone 2mg + CPZ 100mg daily 12 hly for 3 weeks.

Treatment Group- E	% Reduction in BPRS Score			% Reduction in SAPS Score			% Reduction in SANS Score		
	% reduction	't' value	P value (level of significance)	% reduction	't' value	P value (level of significance)	% reduction	't' value	P value (level of significance)
Risperidone 2mg + CPZ 100 only (Control)	21.37%	9.15	<0.001	21%	5.34	<0.01	20.44	3.11	<0.05

p and t-value

Table 8: Effect of CPZ, risperidone and their combination in schizophrenic patients on BPRS, SAPS, and SANS.

Treatment group	N	BPRS (Total of Group) Max. Score = 648			SAPS (Total of Group) Max. Score = 1050			SANS (Total of Group) Max. Score = 720		
		Pre-treat-ment score (Group Total)	3 weeks post-treat-ment score (Group Total)	% reduction in score	Pre-treatment score (Group Total)	3 weeks post-treatment score (Group Total)	% reduction in score	Pre-treat-ment score (Grou p total)	3 weeks post-treat-ment score (Group total)	% reduction in score
CPZ 200mg only	6 (3-M) (3-F)	402	303	24.68%	697	529	24%	531	395	25.6%
Risperidone 4mg only	6 (3-M) (3-F)	361	264	26.86%	656	449	31.59%	490	350	28.57%
CPZ 100mg + Ris. 2mg only	6 (3-M) (3-F)	393	309	21.37%	693	547	21.06%	499	397	20.44%

BPRS - Brief Psychiatry Rating Scale, SAP - Scale for Assessment of Positive Symptoms, SANS - Scale for Assessment of Negative Symptoms, Red. - Reduction, RIS - Risperidone, CPZ - Chlorpromazine

It is evident from the table that CPZ and Risperidone both reduce the psychiatric manifestations in Schizophrenia and the combination proved to be less effective in reducing effects of both positive and negative symptoms as compared to monotherapy with CPZ and RIS (Table 8).

$$\%\,\text{red. in score} = \frac{\text{Post treatment Score} - \text{Pre treatment Score}}{\text{Pretreatment Score}} \times 100$$

Of the 18 patients randomized, there were no dropouts, all patients complied with treatment. No patient had taken any other treatment than given in this trial. Statistical analysis was done for all 18 patients on primary outcome measures. Out of 18 patients included in study 9 were female and other 9 were male. Average mean age of females was 36 year and males mean age was 40 years. All patients completed the study according to protocol. Base line and after treatment score on different psychiatric scale of all treatment group was given in Table 8. No significant adverse effects were reported in any patient in any treatment group. In the study, Chlorpromazine + Risperidone treated group was compared with

Chlorpromazine monotherapy treatment group and Risperidone monotherapy treated group. It was observed in the scale which measures overall psychiatric manifestations i.e. BPRS (Brief Psychiatric Rating Scale) that there is reduction in improvement in schizophrenic patients by chlorpromazine + Risperidone treatment as compared to monotherapy of both drugs. When CPZ group is compared with CPZ + RIS group than it is found that the reduction in improvement in negative symptomology (25.6% → 20.44%) is more as compared to reduction in improvement in positive symptomology (24.0%→ 21.06%). On the other hand, when RIS group is compared with CPZ + RIS group than it is found that the reduction in improvement in negative symptomology (28.57%→ 20.44%) is less as compared to reduction in improvement in positive symptomology (31.59%→ 21.37%).

DISCUSSION

All psychiatric trials always have a subjective element inherent in them. In this study every effort has been made to overcoming this shortcoming by use of standardized psychiatric scales and questionnaires, involvement of a qualified and experienced senior clinical psychiatrist and Pharmacologist of a reputed Government Medical College and for funding the trial no industries are involved and conflict of interest is kept nil. Chlorpromazine (CPZ) in 1st generation anti-psychotic drugs and Risperidone in 2nd generation anti-psychotic drugs remain one of the most common drugs used for people with schizophrenia worldwide as monotherapy, and a benchmark against which other treatments can be evaluated.[10] The makers and marketers of antipsychotics have sponsored many comparative studies, but research has shown that the sponsor's drug is frequently found to be superior.[7] Similarly as already mentioned In introduction of this study there no high quality evidence supporting anti-psychotic polypharmacy.[7] In psychiatric clinical practice hit and trial method is very commonly practiced, the psychiatrist uses multiple anti-psychotic drugs without any reliable data from authentic randomized clinical trial or relying of biased studies which are industry sponsored rather than studies funded by government agencies.[7,11] The current RCT was designed in such a way that the effect of anti-psychotic monotherapy on symptomology of schizophrenia with representative drugs from 1st generation and 2nd generation anti-psychotic classes are simultaneously compared with their combination in new cases of schizophrenia (new cases were taken to avoid bias of residual effect of any drug therapy received by patient on brain neurotransmission and cellular signalling). This design of RCT simplify the comparison of data emerged from study and their direct application in to the clinical psychiatric practice. The data emerged from well-planned clinical studies proves that the therapeutic decisions which were taken by the physician (based on personal experience) for the betterment of patient health sometimes goes wrong as reflected in this clinical study which shows that combination therapy of anti-psychotics commonly used in chronic resistant cases of schizophrenia found to be inferior when compared to monotherapy alone. The small sample size, short duration of study and limited dose range used may be the limitation of this study which can be obviate with designing a large trial with multiple dose range and that can be combined with the study of cellular, molecular and other factors that runs behind the therapeutic inferiority of anti-psychotic polypharmacy when compared with monotherapy.

CONCLUSION

In this clinical study therapeutic effect on positive and negative symptom of schizophrenia by combination therapy with CPZ + RIS treatment group is compared with CPZ monotherapy treated group and RIS monotherapy treatment group and drug combination (CPZ + RIS) proved to be antagonistic which is shown as reduction in improvement in positive and negative symptom of schizophrenia when compared to their monotherapy (CPZ or RIS) alone.

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