Placebo controlled study of Haloperidol in Schizophrenia.

Khan S.A[1*], Bhurgari G.R [2], Baig M.F[3]

Abstract:

Objective: The present study aimed to compare the efficacy and safety of haloperidol with placebo in first-episode schizophrenia.

Place and Time: The sample (*n*=64) was selected from the outpatient department of the Sir Cows Jee Jehangir Institute of Psychiatry Hyderabad (CJIP). The selected patients were admitted and randomly grouped (32) to receive haloperidol and placebo (multivitamin). This study was single blinded. Duration of study was three months from Jan 2011 to March 2011.

Results: Improvements in PANSS, PBRS score from baseline, by haloperidol week-1 2.6 ± 1.63, .67, by placebo 1 results showed < 0.05 siginificant. In week-2 3.14 ± 1.95, .74, by placebo 1.50 ± .71, 50, results showed <0.05 significant. In week-3 2.6 ± 1.63, .67 results showed <0.05 significant. In week-4 3.00 ± 1.58, .71. by placebo 1 results showed <0.05 significant. In week-5 2.50 ± 1.29, .65, by placebo 1 results showed >0.05 insignificant. In week-6 3.00 ± 1.58,.71, by placebo1 results showed >0.05 insignificant.

Conclusion: In patients with schizophrenia, haloperidol is better than placebo for disease improvement but increases the rates of parkinsonism, akathisia, and acute dystonias substantially.

Key Words: Psychosis, Schizophrenia, Haloperidol, Placebo, Akathesia, Dystonia.

Introduction:

Haloperidol was synthesized on the 11th of February 1958 at the Janssen Laboratories, in Belgium. Soon after its synthesis, haloperidol was administered to humans at the Liege hospital. The subsequent clinical studies confirmed that this new drug was particularly active against delusions and hallucinations. For many years, haloperidol had been widely used in western countries. Haloperidol is a typical antipsychotic. It is in the butyrophenone class of antipsychotic medications.

Concentrations of haloperidol under therapeutic conditions has been measured in human brain tissue. Concentrations in brain tissue are 10-30 times higher than the optimum serum concentrations in the treatment of schizophrenia. The estimated elimination half-life of the drug in brain tissue is 6.8 days. After two half-lives (about 2 weeks) there is still a considerable amount of haloperidol in brain tissue. Patients exposed to haloperidol cannot be considered to be free of residual effects of the drug for a number of weeks after withdrawal, even after acute treatment and even when the drug concentration is below the detection level in the blood. During long-term therapy with neuroleptic drugs, about 30% of patients develop tardive dyskinesia, which remains as a chronic disease after withdrawal of the drug in a substantial portion of the patients.

The removal of neuroleptic drugs from human brain tissue has been indirectly estimated through D_2 dopamine receptor occupancy in human patients by using postmortem D_2 receptor measurements, in vivo positron emission tomography (PET), and in vivo single photon emission computed tomography. In postmortem studies, high dissociation constant (K_d) values for the D_2 receptor reflect residual neuroleptic drug at the receptor. A decline of K_d values to control levels within 2 weeks after withdrawal of neuroleptic drugs has been reported for postmortem human brain putamen. In the PET examination of a single patient found that after withdrawal of oral haloperidol for up to 54 hours, there was a rapid fall in serum drug levels without a significant reduction in D_2 receptor occupancy. Withdrawal of depot preparations of fluphenazine decanoate and haloperidol decanoate resulted in high D_2 dopamine receptor occupancy for several months.

All antipsychotic drugs attach to the dopamine D_2 receptor, induce extrapyramidal signs and symptoms (EPS). They also, by binding to the D_2 receptor, elevate serum prolactin[5].

The D_2 dopamine receptor blockade was high in the temporal cortex with both haloperidol and atypical antipsychotics. The atypical, however, induced a significantly lower D_2 binding index than haloperidol in the thalamus and in the striatum. Results suggest that cortical D_2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher *in vivo* binding to the D_2 receptors in the cortex than in the basal ganglia is suggested[6].

as an indicator of favorable profile for a putative antipsychotic compound.

Material and Methods:

The sample (*n*=64) was selected from the outpatient department of the Sir Cows Jee Jehangir Institute of Psychiatry Hyderabad (CJIP), using the criteria described below.

1. Professor of Biochemistry
2. Professor of Pharmacology
3. Assistant Professor, Department of Pathology

Institute: Muhammad Medical College, Mirpurkhas.

.*=corresponding author :

Shams-ul- Arfeen Khan

Inclusion criteria:

5. The age of the subjects (males and females) was in the range of 20-60 years.
5. All subjects had paranoid schizophrenia.
6. The subjects had not have received any antipsychotic drug.
7. Informed consent was taken from the patient and/or a family member.

Exclusion criteria:

Patients with the following were excluded:

8. Co-morbid substance dependence, mood disorder, personality disorders
9. Evidence of organic conditions such as dementia and epilepsy.

The selected patients were admitted and randomly grouped (30 each) to receive haloperidol or placebo (multivitamin) therapy and the investigator was kept blind to the assignment. Three months from Jan-2011 to March 2011 was the duration of study. At baseline, along with a complete psychiatric history and physical examination, assessment in both the groups was done using the Positive and Negative Syndrome Scale (PANSS) and brief psychiatric rating scale for efficacy, and the Udvalg for Kliniske Undersogelser (UKU) side-effect rating scale for tolerability. The initial daily doses of haloperidol were 2 mg, respectively, which were subsequently increased as per the need, reaching a maximum daily dose of 15 mg for haloperidol at the end-point.

The patients were assessed at weekly intervals for 6 weeks using PANSS, which was the key measure of antipsychotic efficacy. The primary measure of efficacy was the percentage of patients showing clinical improvement defined as a 20% reduction from the baseline in the total PANSS score at the end-point.

The patients were also assessed every week till the end-point using the UKU side-effect rating scale. While no other antipsychotic treatment was allowed, EPS in both the groups were treated with the antiparkinsonian drug Kampro, as per the need.

Results:

Total 64 psychotic patients were included in the study; four did not follow the protocol of study. In table No1 showed Mean,Standard Deviation and Standard Error of Mean of total registered psychotic patients in haloperidol group 16.50 ± 9.37, 1.66, Male 10.5 ± 5.9, 1.32, Female 6.5 ± 3.60, 1.04, age between 20-39, 10.50 ± 5.9 1.32, and 40-60 6.50 ± 3.61, 1.04, married 13.50 ± 7.65, 1.50, unmarried 3.50 ± 1.87, .76, uneducated 10.50 ± 5.9, 1.32, weight of patients 40.78 ± 9.39, 1.6, shizophrenic 10.50 ± 5.9, 1.32, shizoaffective disorders 3.00 ± 1.58, .71 shizophreniform disorders 3.00 ± 1.58, .71, labour 10.50 ± 5.9 1.32, farmers 6.5 ± 3.61, 1.04, housewives 6.5 ± 3.61, 1.04. In placebo group showed 16.50 ± 9.37, 1.66, Male 10.5 ± 5.9, 1.32, Female 6.5 ± 3.60, 1.04, age between 20-39, 10.50 ± 5.9 1.32, and 40-60 6.50 ± 3.61, 1.04, married 13.50 ± 7.65, 1.50, unmarried 3.50 ± 1.87, .76, uneducated 10.50 ± 5.9, 1.32, weight of patients 40.78 ± 9.39, 1.6, shizophrenic 10.50 ± 5.9, 1.32, shizoaffective disorders 3.00 ± 1.58, .71 shizophreniform disorders 3.00 ± 1.58, .71, labour 10.50 ± 5.9 1.32, farmers 6.5 ± 3.61, 1.04, housewives 6.5 ± 3.61, 1.04 In table no-2 showed weekly improvements in PANSS, PBRS score from baseline, by haloperidol week-1 2.6 ± 1.63, .67, by placebo 1 results showed < 0.05 siginificant. In week-2 3.14 ± 1.95, .74, by placebo 1.50 ± .71, 50, results showed <0.05 significant. In week-3 2.6 ± 1.63, .67 results showed <0.05 significant. In week-4 3.00 ± 1.58, .71. by placebo 1 results showed <0.05 significant. In week-5 2.50 ± 1.29, .65, by placebo 1 results showed >0.05 insignificant. In week-6 3.00 ± 1.58,.71, by placebo1 results showed >0.05 insignificant.

In table-3 reactions showed by haloperidol tardive dyskinesia 6.6%, In placebo nil. akathesia 3.3% by placebo nil, dryness of mouth 3.3%, in placebo 3.3%, lethergy 3.3%, on placebo nil, trmors 6.6% were produced, in placebo nil.

Table -1: Demography of basic variables of participants in the study.

Variables	Haloperidol		Placebo	
	Mean±St.D	S.E. M	Mean±St.D	S.E. M
Number of Patients	16.50±9.38	1.66	16.50±9.38	1.66
Male	10.5±5.9	1.32	10.5±5.9	1.32
Female	6.5±3.60	1.04	6.5±3.60	1.04
Age-20-39	10.50±5.9	1.32	10.50±5.9	1.32
Age-40-60	6.50±3.61	1.04	6.50±3.61	1.04
Married	13.50±7.65	1.50	13.50±7.65	1.50
Unmarried	3.50±1.87	.76	3.50±1.87	.76
Educated	6.50±3.61	1.04	6.50±3.61	1.04
Uneducated	10.50±5.9	1.3	10.50±5.9	1.3
Weight of Patients	40.78±9.39	1.6	40.78±9.39	1.6
Schizophrenic	10.50±5.92	1.32	10.50±5.92	1.32
Schizoaffective disorders	3.00±1.58	.71	3.00±1.58	.71
Schizophreniform disorders	3.00±1.58	.71	3.00±1.58	.71

Figure-1: Demography of basic variables of participants in the study.

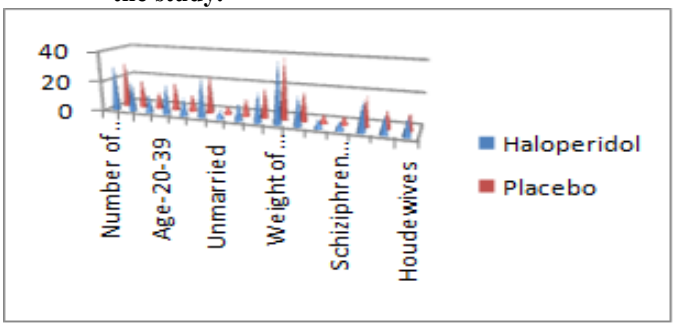


Table-2: Weekly improvements (in PANSS and PBRS score from baseline) in symptoms of psychosis by study drugs.

Weeks	Haloperidol		Placebo		P-value
Biostatistics	Mean±St.D	S.E.M	Mean± St.D	S.E.M	
Week-1	2.6±1.63	.67	1	NA	.04*
Week-2	3.14±1.95	.74	1.50±.71	.50	.02*
Week-3	2.67±1.63	.67	0	NA	.04*
Week-4	3.00±1.58	.71	1	NA	.08
Week-5	2.50±1.29	.65	1	NA	.15
Week-6	3.00±1.58	.71	1	NA	.08

Figure-2
Weekly improvements (in PANSS and PBRS score from baseline) in symptoms of psychosis by study drugs.

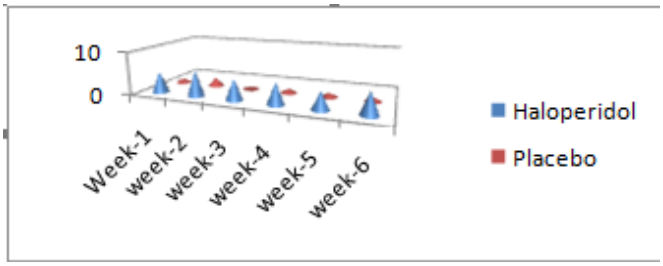
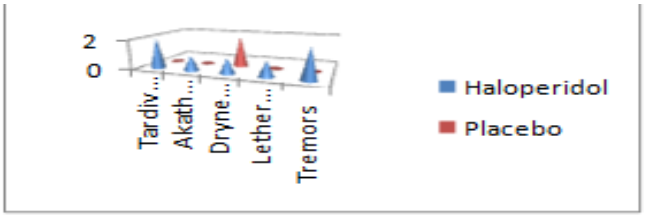


Table-3: Reactions occurred in the study.

Reactions	Haloperidol	Placebo
Tardive Dyskinesia	6.6%	0
Akathesia	3.3%	0
Dryness of mouth	3.3%	3.3%
Lethergy	3.3%	0
Tremors	6.6%	0

Figure-3: Reactions occurred in the study.

Occupation-labour	10.50±5.9	1.3	10.50±5.9	1.3
Farmers	6.5±3.61	1.04	6.5±3.61	1.04
Housewives	6.5±3.61	1.04	6.5±3.61	1.04



Discussion:

Our study matched with Devanger (1989)[7] in which oral haloperidol in doses of 1 to 5 mg daily improved target symptoms, confirmed by double blind ratings of videotaped interviews. Patients could not be maintained on more than 4 mg of haloperidol daily due to the severity of extrapyramidal side effects. Modified Mini-Mental State scores worsened while taking haloperidol, with only partial recovery in the final 4-week placebo phase. Severe extrapyramidal side effects and decline in cognitive function may compromise the efficacy of commonly used doses of neuroleptic drugs in patients with Alzheimer's disease.

This study consistant with the study of JoyCB (2001)[8] In patients with schizophrenia, haloperidol is better than placebo for global improvement but increases the rates of parkinsonism, akathisia, and acute dystonias substantially.

This study matched with he study of P.P. De Deyn (1999)[9] Severity of extrapyramidal symptoms with risperidone did not differ significantly from that of placebo and was less than that of haloperidol. A post hoc analysis showed significantly greater reductions in the BEHAVE-AD aggressiveness score with risperidone than haloperidol at week 12.

This study correlated with the study of Green (2006)[10] in which patients were less likely to discontinue treatment with olanzapine than with haloperidol: mean time (in days) in the study was significantly greater for those treated with olanzapine compared to haloperidol (322.09 vs. 230.38, $p<0.0085$). Moreover, remission rates were greater in patients treated with olanzapine as compared to those treated with haloperidol (57.25% vs. 43.94%, $p<0.036$). While extrapyramidal side effects were greater in those treated with haloperidol, weight gain, cholesterol level and liver function values were greater in patients treated with olanzapine.

This study contrast with study of Lieberman JA (2003)[11] as expected on the basis of previous studies, both olanzapine and haloperidol were effective in the acute reduction of psychopathological symptoms in this group of patients with first-episode psychosis

Our study correlated with the study of Siegfried Kasper (2003)[12] in which aripiprazole demonstrated long-term efficacy that was comparable or superior to haloperidol across all symptoms measures, including significantly greater improvements for PANSS negative subscale scores and MADRS total score ($p<0.05$). The time to discontinuation for any reason was significantly greater with aripiprazole than with haloperidol ($p=0.0001$).

Time to discontinuation due to adverse events or lack of efficacy was significantly greater with aripiprazole than with haloperidol ($p=0.0001$). Aripiprazole was associated with significantly lower scores on all extrapyramidal symptoms assessments than haloperidol ($p<0.001$).In our study haloperidol week-1 2.6 ± 1.63, .67, by placebo

1 results showed < 0.05 siginificant. In week-2 3.14 ± 1.95, .74, by placebo 1.50 ± .71, 50, results showed <0.05 significant. In week-3 2.6 ± 1.63, .67 results showed <0.05 significant. In week-4 3.00 ± 1.58, .71. by placebo 1 results showed <0.05 significant. But haloperidol produced tardive dyskinesia 6.6%, in placebo nil. Akathesia 3.3% by placebo nil, dryness of mouth 3.3%, in placebo 3.3%, lethergy 3.3%, on placebo nil, trmors 6.6% were produced, in placebo nil.

This study matched with study of K.J. Vijay Sagar (2005) [13] in this randomized, double-blind, 6-week study, though marked improvement of 56% vs 48% on the positive subscale and 39% vs 23% on the negative subscale of PANSS was recorded, for risperidone and haloperidol, respectively, there was no statistical difference between the two groups. Thus, our conclusion of equal efficacy is in concurrence with the results of others studies. Better efficacy with risperidone was recorded by some authors. However, in the general psychopathology subscale of PANSS and in terms of severity and global improvement on the CGI scale, risperidone showed more efficacy than haloperidol.

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