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Comparison between risperidone, an atypical antipsychotic agent and haloperidol, a conventional agent used to treat schizophrenia

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Abstract: An observational and comparative study was conducted to compare the functional outcome between the patients treated with conventional antipsychotic agent haloperidol and atypical antipsychotic agent, Risperidone (Risperidal). A total of 32 patients were included in the study with established schizophrenia according to (DSM iv). The data was processed on SSPE 10th version. The primary outcome measure was the improvement of negative symptoms of schizophrenia and secondary outcome measure was to observe the superiority of the atypical drug Risperidone over conventional agent haloperidol regarding side effects. Patients were assessed at baseline, 2nd and 8th week, using four tools of assessment. For treatment group receiving haloperidol mean was 47.2 ± 11.50 at 8th week and for Risperidone treatment group mean was 43±14.68. The P values for all the parameters in the Clozapine group were significant as compared to haloperidol.

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INTRODUCTION

The terms antipsychotic, neuroleptic or major tranquilizer are applied to drugs that are used in the treatment of psychosis beneficial1. They have effects on mood and thought, but carry the risk of producing side effects that mimic neurological diseases[2] The main indication of antipsychotic drugs is Schizophrenia, a particular kind of psychosis, characterized by a clear sensorium but a marked thinking disturbance .recent classification of schizophrenia, which correlates with responsiveness to drug therapy, is the separation of symptoms into positive and negative symptoms[3].

Psychosis is condition in which the individuals lose contact with reality. Positive symptoms include delusions, hallucinations, marked thought disorders and bizarre behaviour. Negative symptoms include social withdrawal, poverty of speech, attention impairment and difficulty in interpersonal relationship. The limitations of conventional antipsychotic have prompted a search for new agent with greater efficacy (particularly against negative symptoms) and fewer side effects. One promising strategy has been to investigate agent that block both dopamine and serotonin receptors.

The role of serotonin in schizophrenia has been proposed in 1954[4]. The newer atypical antipsychotichave the neuropharmacological properties of being effective against emotional with drawl and other negative symptoms of schizophrenia with clear efficacy compared with agents against positive symptoms of delusion5. The antipsychotic drugs had great impact in the treatment of psychosis in general and schizophrenia in particular. Newer or atypical antipsychotic drugs include Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone and Amisulphride. These antipsychotic have become the most commonly employed agents for the treatment of psychotic disorders in many countries[6].

The term "Atypical" has been used to designate there relative freedom from risks of adverseextra pyramidal syndromes (EPS) including akathesia, dystonia, parkinsonism and Tradive Dyskinesia (TD) or tradive dystonia, compared with older, potent anitidopaminergic type antipsychotic.[7]The advent of atypical antipsychotic has revolutionized the treatment of psychosis in the elderly. The general Psychiatric literature indicates that the atypical agents areas efficacious in reducing positive symptoms as the conventional agents; more efficacious against negative symptoms, and to have a much more benign adverse effect profile[8] The currently marketed atypical agents are cloazpine , risperidone, Olanzapine and quetiapine. These drugs are available in the US and UK and a number of other countries worldwide. The essential feature of an atypical antipsychotic is less acute extra pyramidal symptoms, especially dystonia associated with therapy as compared with a typical antipsychotic like haloperidol. The atypical agents differ in pharmacology with the addition of serotonin 5HT2 antagonism to the traditional D2 antagonistic effects and therefore classified pharmacologically as serotonin dopamine antagonists[9.] these agents are associated with lower incidence of extrapyramidal side effects and better efficacy for negative symptoms) The newest serotonin –dopamine antagonist is Risperidone .which potently blocks both serotonin 5HT2 and dopamine D2 receptors.[10]

Results of open and controlled trials with Risperidone have demonstrated that Risperidone optimal doses are more effective than Haloperidol in reducing both positive and negative symptoms of Schizophrenia and causes fewer extrapyramidal symptoms than conventional antipsychotic agents. Rispridone as high binding affinity to both serotonin and dopamine receptors. Results of pilot studies of psychotic patients in Europe indicates that Risperidone is an antipsychotic agent that is less likely than conventional agents cause extra pyramidal side effects., compared to Haloperidol was more effective (low score on Brief Psychiatric Rating Scale(BPRS) at end points) than either Haloperidol or placebo.

MATERIALS AND METHODS

This is an observational and comparative study conducted on patients suffering from schizophrenia. The duration of study was 8 weeks; sampling was done through systematic randomization. All selected patients were divided into four groups, having eight patients in each group using a conventional agent and an atypical agent.

Inclusion criteria

Patients fulfilling the criteria of (DSM IV) having schizophrenia according to international classification of diseases.

Exclusion criteria

Patients having concomitant physical morbidity along with schizophrenia. The primary purpose of this study was to determine if Risperidone was superior to Haloperidol in improving overall psychopathology. The analysis was done on intent-to-treat basis. The patient entered in the study was assessed at baseline, for 2 weeks and data were processed on SSPE version 10, adequately tabulated and statistical analysis was done. Following drugs and corresponding doses were used:

Haloperidol

Trade name; Serenace, dose=50-60mg in divided doses.

Risperidone

Trade name; Risperidal, dose=2-1 mg in divided doses.

Instruments

Brief psychiatric rating scale (BPRS).

This instrument has 16 items each scored on a seven points scale. For example, absent, minimal, mild, moderate, moderate-severe, severe, and extreme. The items include anxiety, emotional withdrawal (autism), depressive mood, guilt feeling etc. There are criteria to define the symptomatology items but not the severity ratings. It is suitable for rating of sever psychiatric illness but not minor disorders.

Positive and negative syndrome rating scale (PANSS)

This scale rates blunted effect, poor rapport, social withdraw difficulty in abstract and stereo typed thinking and lack of spontaneity. A thirty minutes interview is required. It has seven items for positive symptoms and seven items for negative symptom and scoring is the same as in BPRS.

Extra pyramidal symptom rating scale (EPSRS)

On this scale, quantitative rating of the symptoms of Parkinsonism, dystonia and dyskinesia is done. It has twelve items each scored on four points scale.

Quality of life questionnaire (WHO QOL-BREF)

Quality of life is a general term applied to the totality of physical, psychological and social functioning. It is determined by physical impairment, emotional reaction, personality, illness etc. QOL scale requires great deal of concentration and responsibility and assessed very carefully as involves many diverse aspects and is laborious. It has 26 items each scored on five-point scale. Increase in total count means an improvement in the symptoms and hence in the quality of life.

RESULTS AND DISCUSSION

The currently popular term “Atypical” was introduced to differentiate the antipsychotic from the classic or “Typical” antipsychotic (narcoleptics)[11] defined atypical antipsychotic as drug with 1.) decreased or absent acute EPS and tardive dyskinesia: 2.) increased symptoms; and 3.) decreased or absent capacity to elevate prolactin[12.] The concept of atypical antipsychotic is equivocal and still changing with the development of new compounds and discovery of their clinical features. Further to the hetero drugs and the difficulty of establishing a common definition the term “Atypical” should be replaced by “Novel” antipsychotic. But this term is also not precise. However, an important part of the definition must be the low or absent liability for producing EPS[13].

The negative symptoms of schizophrenia included the spectrum of impoverished effects. Logia, abolition, anhedonia and decreased attention. Early studies found that negative symptoms were resistant to treatment[14].

Receptor systems involved in antipsychotic treatment

Our current understanding of the etiology of schizophrenia suggests the presence of a multifactorial genetic deficit, which can be triggered

by perinatal environment factors. These processes result in neuronal defect. The best regarded hypotheses of abnormal neurotransmitter function include the dopaminergic, serotonergic (5- HT)[15] and glutamatergic system, apparently linked to the therapeutic antipsychotic effect of antipsychotic drugs. Several possible definitions of atypical antipsychotic have been proposed that, in the addition to producing fewer EPS, atypical antipsychotic have the following clinical characteristics: 1.) greater efficacy in the treatment of overall schizophrenic psychopathology among those nonrespective to typical antipsychotic: 2.) great negative symptoms efficacy and: 3.) less perturbation of serum prolactin[16].

Risperidone

Risperidone, a Benzioxazole deriviative,is the first of this new class of centrally acting serotonin – dopamine receptor antagonists[17]it has great affinity for serotonin 5 – HT2receptors, and is also potent inhibitor of dopanmine – D2 receptors. Risperidone has been found to improve positive, negative and affective symptoms in chronic psychotic patients in both open and single blind, placebo controlled studies[18]and in double bling studies [19]using Haloperidol as standard reference treatment.

As with many conventional neuroleptics, the weight gain associated with risperidone may be problematic, but more so for some patients than others.

One reason for such weight gain is quite likely to be simply that patients are getting better, they have an enhanced sense of well-being and greater organizationin self-care matters. There is some evidence that antagonism at 5HT uptake inhibitors; for example is known to be anorectic[20] probably weight gain reaches a plateau, if it is confirmed than it would present less of a problem.

The low incidence of extrapyramidal side effects associated with short term use may have a bearing on subsequent Tardive dyskinesia development .Several investigations suggested that one of the risk factors for the later development of Tardive dyskinesia is the earlier emergence of other extrapyramidal side effects [21] it might therefore follow that drugs like Risperidone, which have low propensities to cause extrapyramidal side effects during acute or early treatment, will be less likely to cause Tardive dyskinesia when used over prolonged maintenance periods.

Risperidone is well tolerated at recommended therapeutic doses, produce few extrapyramidal symptoms compared with Haloperidol, and does not appear to have any risk causing Agranulocytosis as seen in some percentage of patients receiving Clozapine.

In present work risperidone and other atypical agents like clozapine and olanzapine were found to be superior over Haloperidol. clinical trials with Risperidone demonstrate , a Canadian data of the North American study compared Risperidone, doses of 2,6,10and 16mg/d was superior to Haloperidol 20mg /d improving negative e symptoms. These studies suggest that the negative symptom efficacy, with atypical antipsychotic Risperidone is explained by reduced EPS liability.

EPS were evaluated at each visit using Extrapyramidal Symptom Rating Scale (ESRS) [22](Chouinard et al, 1979, 1980)which consists of a questionnaire to evaluate the subjective effects of EPS detailed clinical evaluation of parkinsonism, dystonia, dyskinesia.

The mean changes in PANSS total score and subtotal scores from base line to end point. the total PANSS score showed a significantly ($P \leq 0.05$)greater mean changes versus baseline in the Risperidone group 4mg,8mg,and 16mg groups than in group receiving Risperidone 1 mg. The effects of both Risperidone 4mg and 8mg were significantly ($P<0.05$) better than those of Risperidone 1mg, while Risperidone 4mg, was also significantly ($P<0.05$) better than Halperidol.

On the positive subscale of PANSS, five other treatment groups showed better effects than that receiving Risperidone 1mg.on the negative subscale, the changes versus baseline in the six treatment groups were not statistically different at end point, but there was a greater magnitude of response in the Risperidone 4mg ,8mg,and 16mg groups.

Table 1: Brief Psychiatric Rating Scale (BPRS) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	BPRS Scores (Mean±SD)			P-Value	
		Baseline	2nd weeks	8th weeks	BL-2wks	BL-8wks
Haloperidol	8	42.6±12.6	49.8±11.50	47.2±11.50	0.249	0.544
Resperidone	8	52.6±18.60	43.6 14.68	43.6±14.68	0.975	0.147

Table 2: Positive and Negative syndrome Scale (PANSS) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	PANSS Scores (Mean±SD)			P-Value	
		Baseline	2nd weeks	8th weeks	BL-2wks	BL-8wks
Haloperidol	8	83.7±24.09	94.0±17.43	91.0±19.57	0.176	0.483
Resperidone	8	98.7±34.90	92.0±28.65	76.6±30.02	0.469	0.156

Table 3: Improvement in Extra pyramidal rating scale (EPSRS) according to treatment at baseline, 2nd week and 8th weeks BPRS.

Treatment Group	Subjects	EPSRS Scores (Mean±SD)			P-Value	
		Baseline	2nd weeks	8th weeks	BL-2wks	BL-8wks
Haloperidol	8	21.1±6.45	19.8±6.49	18.4±6.16	0.420	0.204
Resperidone	8	20.4±3.34	19.7±4.80	16.5±4.57	0.644	0.010

Table 4: Quality of life BREF (Who-QOL-BREF) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	Who-QOL-BREF Scores (Mean±SD)			P-Value	
		Baseline	2nd weeks	8th weeks	BL-2wks	BL-8wks
Haloperidol	8	66.8±6.45	75.2±11.55	74.4±14.18	0.068	0.134
Resperidone	8	73.2±3.34	76.8±11.81	79.0±8.20	0.412	0.283

The result of this study has shown that, in patients with chronic schizophrenia, the optimal antipsychotic effects of Risperidone are seen at doses of 4mg or 8mg daily. In the higher dose groups of 12 mg and 17mg, the therapeutic effect was lower than the effect of 4mg and 7mg, so a bell shaped response emerges for the therapeutic effect as a function of dose. Pair wise comparison of the change versus baseline on the PANSS, and BPRS total score at end point showed no significant changes between Risperidone1mg and Haloperidol, while Risperidone doses of 4mg,8mg and 16mg had significantly greater beneficial effects than Risperidone 1mg.and higher doses resulted in significantly more patients having a 20% decrease in BPRS total score. The results in Risperidone 4mg and 8 mg groups were better than those observed in Haloperidol group on all primary and secondary efficacy parameters.

A clinically relevant advantage of Risperidone over Haloperidol is its low propensity to induce dystonic symptoms; Haloperidol induced significantly more dystonic symptoms than any of the five Risperidone treatment groups. Since dystonia is extremely disturbing for the patient, this side effect is one of the major drawbacks of conventional neuroleptic treatment and reason for non compliance.[23]Similarly with acathesia, shift to maximum score was higher under Halperidol than under all risperidone regimens.

A relative lack of acathesia may also help the patient in accepting antipsychotic treatment, since this symptom has been reported as being more difficult to endure than any other of the symptoms for which the patient was originally treated, is very resistant to treatment[24] and is strongly associated with depressing response to neuroleptics[25].

The results from this study have demonstrated that optimal dose of Risperidone for maximal efficacy and minimal occurrence of EPS appear to be in range of 4 mg to 8 mg daily. At these doses, Risperidone was effective in producing beneficial effect son negative, positive and affective symptoms as well as being more effective overall than Haloperidol. After placebo washout the occurrence of dystonia, acathesia, Parkinsonism was lower with Risperidone than with Haloperidol. This was reflected in the fact that significantly fewer patients required anti parkinson therapy with Risperidone 4mg and 8mg.

Risperidone showing benefits in treatment group at 8 weeks as compared to Haloperidol. Mean changes shows improvement in risperidone treatment group whereas haloperidol treated patients remained essentially unchanged at end point, the difference in changes from baseline was marginally significant. Reduction in BPRS total score was also seen with Risperidone in the 8th week .the doses of risperidone used were 6mg, 8mg and 10mg (Table 1).

The p-value is significant in the risperidone treatment group as compared to the older antipsychotic agent Haloperidol. This superiority develops after the patient has been exposed to to adequate dose regimen. Table 3 shows the Extrapyramidal symptom rating scale. At lower doses risperidone produces lower EPS and risk is definitely lower. Quality of Life BREF (WHO-QOL-BREF) show changes and improvement by all antipsychotic drugs (Table 4).

CONCLUSION

Present study suggests that atypical antipsychotic like Risperidone has lower incidence of EPS than the conventional agent Haloperidol.We can speculate that Haloperidol has far more adverse effects and higher incidence of EPS and TD than Risperidone which, in low doses, has lower risk of EPS .Both Risperidone and Olanzapine reduced the severity of already present TD. Also show beneficial effects in patients with psychosis and Parkinson's disease as compared to Haloperidol.

REFERENCES

1. American Psychiatric Association. DSM II Diagnostic and statistical manual of mental disorder. 3rd. Washington, DC: American Psychiatric Association, 1987.
2. Andreason NC. Symptoms, signs,, and diagnosis of schizophrenia. *Lancet* , 1999; 346: 477-481.
3. Andreason NC. Negative symptoms in schizophrenia: Definition and relaxibility. *Arch. Gen. Psychaian*., 1982; 39: 748-788.
4. Woolley DW and Shaw E. A biochemical and pharmacological suggestion about certain mental disorders. *Proc. Natl. Acad. Sci*., 1954; 40: 228-231.
5. Barnes TRE and McPhilips MA. Novel antipsychotics, extrapyramidal side effects and tardive dyskinesia. *Int. Clin. Psychopharmacol*., 1989; 13: S49-57.
6. Baldessarini RJ and Tarzai FI. Brain dopamine receptor: a prime on their current status, basic and clinical. *Harv. Rev. Psychiatr.*, 1996; 3: 301-325.
7. Annabel L, Chouinard and Ross-Chouinard A. The relationship between neuroleptic-induced parkinsonism and tardive dyskinesia. *Biolpsychiatry*, 1991; 29: 210S-329S.
8. Alder A, Angrist B and Reiter S. Neuroleptic induced akathesia a review psychopharmacology (Berl), 1989; 42: 874-878.
9. Keks NA. Impact of newer antipsychotics on outcome sin schizophrenia. *Clin. Ther*., 1997; 19: 148-158.
10. Leysen JE, Janssen PMF and Schotte A. Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and vivo in relation to pharmacological and clinical effects: role of 5HT2 receptors. *Psychopharmacology*, 1993; 112: 40-54.
11. Bustillo JR, Buchanan RW, Irish D and Breier A. Differential effects of clozapine on weight: a controlled study. *Am. J. Psychiatr*., 1996; 153: 817- 819.
12. Jeste DV, Lacro JP and Nguyen HA. Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. *J. Am. Geriatr. Soc*., 1999; 47: 716-719.
13. Coryell WH, Kelly MW and Perry PJ. Haloperidol plasma levels in acute clinical change in schizophrenia. *J. Clin. Psychopharmacol*., 1190; 10: 397-402.
14. Jardemark K, Wadenberg ML, Grillner P and Svensson TH. Dopamine D3 and D4 receptor antagonists in the treatment of schizophrenia. *Curr. Opin. Investig. Drugs*, 2002; 3: 101-105.
15. Morera AL, Barreiro P and Cano Munoz JL. Risperidone and clozapine combination for the treatment of refractory schizophrenia. Acta. Psychiatr. Scand., 1999; 99: 305-307.
16. Janssen PAJ, Miemegeers CJE, Awouters F, Sdhelekens KHL, Megens AAHP and Meert TF. Pharmacology of risperidone (R64 766) a new antipsychotic with serotonin S2 and Dopamine D2 antagonist properties. J. Pharmacol. Exp. Ther., 1988; 244: 685-695.
17. Chouinard G and Kapola LA. Phase IV multi centre clinical study of risperidone in the treatment outpatients with schizophrenia. Can. J. Psychiatr., 1998; 43: 1018-1025.
18. Borison RL, Rathiraja AP and Diamond BI. Resperidone: Clinical safety and efficacy in schizophrenia. Psychopharmacol. Bull., 1992; 28: 213-218.
19. Fontaine KR, Heo M and Harrigan EP. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. Psychiatr. Res., 2001; 101: 277-288.
20. Casey DE. Motor and mental aspects of extra pyramidal symptoms. Int. Clin. Psychopharmacol., 1999; 10: 847-853.
21. Cohen LJ. Risperidone. *Pharmacotherapy*, 1992; 14: 253-265.
22. Mac Ewan GW, Labelle A, Beauclair L and Arnott WA. Canadian multicentre placebo controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J. Clin. Psychopharmacol., 1993; 13: 25-40.
23. Chouinard G and Kapola LA. Phase IV multi centre clinical study of risperidone in the treatment outpatients with schizophrenia. Can. J. Psychiatr., 1998; 43: 1018-1025.
24. Van Putten T, May PR and Marder SR. Subjective response to antipsychotic drugs. Arch. Gen. Psychiatr., 1981; 38: 188-190.
25. Grant S and Fitton A. Risperidone. A Review of its Pharmacology and Therapeutic Potential in the Treatment of Schizophrenia. *Drugs*, 1994; 48: 253-265.