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*Original Article*

# An open, randomized, comparative study of efficacy and safety of risperidone and haloperidol in schizophrenia

**Tamrakar SM[1], Nepal MK[2], Koirala NR[3], Sharma VD[4], Gurung CK[5], Adhikari SR[6]**
[1]Consultant Psychiatrist, Norvic International Hospital, [2]Professor and Head, [3]Associate Professor, [4]Associate Professor, Department of Psychiatry and Mental Health, IOM, TUTH, [5]Professor, Department of Epidemiology, Institute of Medicine, T.U., [6]Lecturer, Kathmandu Medical College, Sinamangal, Kathmandu

**Abstract**

**Objectives:** In the last decade there have been numerous randomized controlled trials comparing the efficacy and safety of second generation antipsychotics and conventional antipsychotics in the treatment of schizophrenia, but most of them have been conducted in the western population. This study compared the efficacy and safety of risperidone versus haloperidol in the Nepalese context, in order to add on to the very few literatures available on this topic in the South East Asia region and compare them.

**Methods:** Patients with the diagnosis of schizophrenia were randomly assigned to receive risperidone 4-6 milligrams (mg) per day and haloperidol 10-20 mg per day, and were followed up for 6 weeks. Assessment were done on the day of the diagnostic interview and days 7, 14, 28 and 42 (end point). During the assessment periods Positive and Negative Syndrome Scale (PANSS) was administered to monitor the progress in psychopathology and Udvalg for Kliniske Undersogelser (UKU) side effects rating scale was applied to rate the treatment emergent adverse effects.

**Results:** Both risperidone and haloperidol were associated with substantial baseline- to- endpoint reduction in symptom severity. After one week of treatment, the improvement in schizophrenia with risperidone was significantly better than haloperidol in terms of PANSS- total Score (-45.4 versus –29.5), negative subscale score (-14.3 versus -6.68) and general psychopathology subscale score (-20.9 versus –13.7). At the end point of the study, the benefit was maintained in total score (-52.1 versus –43.1), though the negative subscale score still showed tendency for greater improvement in psychopathology with risperidone. The side effects profile did not show significant differences except in extrapyramidal symptoms. Thirty-eight percent of risperidone treated patients had to resort to anti-parkinsonian treatment compared to 78% in haloperidol treatment group.

**Conclusion:** Similar to the studies in the western countries, Asia and Indian subcontinent, both risperidone and haloperidol were effective in the reduction of psychopathological symptoms in this group of Nepalese population with the diagnosis of schizophrenia. However, risperidone was quicker and better then haloperidol and risperidone had a better safety profile. This is important, because extrapyramidal side effects of neuroleptics are responsible for non-compliance and increased cost in terms of us of anti-parkinsonian medication.

**Key words**: schizophrenia, antipsychotic, risperidone, haloperidol, positive and negative syndrome scale (PANSS).

In 'Dementia Praecox and Pathophysiology (1919)', Kraepelin had described two principal pathophysiological process occurring in dementia praecox. The first one was a weakening of emotional activities that permanently formed the mainsprings of volition, and the second consisted of loosening of the inner unity of activities, intellect, emotions and volition, in themselves and amongst one another. They respectively provided a conceptual framework for the negative and positive symptoms of schizophrenia[1], which was formulated by Crow and his colleagues[2,3] in the form of type I and type II schizophrenia.

Today, very few disagree to the heterogeneity in schizophrenia and in this regard those domains of symptoms are well recognized[4-12]. The recently added third category includes disorganized speech, behaviour and poor attention. The negative symptoms include blunting of affect, poverty of speech, anhedonia and loss of volition[13].

**Correspondence**
Dr. Sharad Man Tamrakar
Consultant Psychiatrist,
Norvic International Hospital,
Thapathali, Kathmandu
Email: sharadman@hotmail.com

Negative symptoms have been consistently associated with psychopathological severity and poor social functioning[13,14,15,16,17,18,19]. One advantage of considering negative symptoms in relation to social functioning is that these symptoms are fairly specific to schizophrenia[9].

Negative symptoms occur only infrequently in other psychotic disorders[20] and when they occur outside schizophrenia (e.g. affective psychosis) they have little prognostic value[21]. They do not appear to endure except in schizophrenia[21] and their presence during non-acute phase adds to their prognostic importance[14].

Negative symptoms are associated with most measures of illness severity, which are, earlier age at onset, poor neuroleptic response, and increased likelihood of premorbid schizoid or schizotypal personality disorders. Stable (versus unstable) negative symptoms in adulthood are associated with poorer premorbid social relationships, as well as with poorer pre-onset adjustment problems and worse post-onset outcomes[19]. The presence of negative symptoms at illness onset predicts social disability at three years after first hospitalization[22]. Bellack et al.[23] found that negative schizophrenics were most impaired on social skill, social adjustment scale and quality of life (QOL) scale, followed in order by non-negative schizophrenics, affective disorder patients and non-patient controls. Solinski et al.[24] found that negative symptoms exerted an effect on interview performance, which indirectly influenced employability. Jackson and his colleagues[16] reported that the group of schizophrenics with the least negative symptoms exhibited the best social skills performance.

So the modern descriptions have given increasing importance to negative and cognitive symptoms in the diagnosis and treatment of schizophrenia[12]. So it is not surprising that not only were negative symptoms included for the first time as criterion for diagnosis in DSM-IV, but atypical medications for schizophrenia, such as clozapine, risperidone, and olanzapine have been purported to have specific effects on negative symptoms and cognitive functions.

In the modern psychopharmacology, two broad groups of antipsychotic drugs are recognized-conventional antipsychotics (CAPs) and second generation antipsychotics[25]. Before any antipsychotic can be accepted as useful, its relative merits in comparison with existing drugs must be carefully assessed. Haloperidol is a CAP whose beneficial effects have been ascribed to its ability to inhibit D2 receptors, and the induction of parkinsonian symptoms has been attributed to their blockade of dopamine receptors in the nigrostriatal pathology.

Clozapine is a prototype second generation antipsychotic, whose use is limited by some fatal side effects.

Risperidone is the second generation antipsychotic that gained approval of the Food and Drug Administration in 1994 and since than is gaining rapid popularity. There are various studies which provide evidences that risperidone is as effective as CAP in treating positive symptoms and more effective in treatment of negative symptoms. Risperidone is found to be more tolerable in most trials and has led to better outcome, in terms of better rehabilitation, drop in in-patients, crisis utilization, increased vocational training, increased compliance and medication visits, decreased hospitalization, with overall decrease in indirect health care costs, which offsets the direct acquision cost leading to stabilization at a lower level of health care expenditure.

All the beneficial effects of risperidone have been reported mostly in western literature and as yet have not been trailed in the Nepalese context.

In spite of the overall benefit, another issue raised against the use of atypical antipsychotic is the cost-factor. Risperidone from different pharmaceuticals have varying costs. A report by Koirala et al.[26], which compared the minimum monthly cost of different antipsychotics showed that chlorpromazine was the cheapest. But the relative cost for both risperidone and haloperidol was similar (relative cost of 1.3 in both compared to chlorpromazine). In this estimation the cost of other drugs which are commonly co-prescribed like benzodiazepines, anti-parkinsonian agents and propranolol have not been taken into account. Many studies have shown increased use of anti-parkinsonian medication in haloperidol group compared to risperidone group[27]. Therefore, the higher prevalence of use of additional medicines with haloperidol might indirectly increase the overall cost of treatment compared to risperidone.

The purpose of this study was to make a clinical comparison of conventional antipsychotics and second generation antipsychotics in terms of efficacy and tolerability in the context of Nepalese population. The secondary purpose of the study was to observe the difference in the use of additional anti-parkinsonian drugs in the two experimental groups,

so that it could give an estimation of extra indirect costs.

**Materials and methods**

The objectives of the study were to compare the efficacy of risperidone & haloperidol in managing positive and negative symptoms, compare the side-effect profile, and the frequency of use of anti-parkinsonian medications. It was an open, randomized, prospective study. It included patients diagnosed as schizophrenia according to ICD-10, Diagnostic Criteria for Research (WHO, 1992). It included patients between 18 to 45 years of age, and patient with comorbid psychiatric and medical illnesses were excluded.

A total of forty five patients fulfilling the criteria between January 1, 2002 and June 30, 2002 were enrolled in the study. The subjects were randomized to either risperidone 4 mg per day or haloperidol 10 mg per day alternatively. Patients were either drug naive or given one week wash out period if they were on oral neuroleptic medication, or four weeks wash out period if on depot preparation.

If the patients developed extrapyramidal symptoms (EPS), anti-parkinsonian medicine was started and the particular type was recorded. Lorazepam was allowed if needed for the stabilization of the patient and for disturbed sleep. According to the clinical response and tolerability of side effects increments in doses were allowed up to 6mg in risperidone group and 20 mg in the haloperidol group. Assessments were done on day 0 in which socio-demographic profile was obtained, and Positive and Negative Syndrome Scale (PANSS)[28] and Clinical Global Impression (CGI) (Gay et al., 1987) were applied. Subsequent assessments were done on days 7, 14, 28 and 42, when CGI, PANSS and Udvalg for Kliniske Undersogelser (UKU) side effects rating scale were applied.

The collected data were analyzed through the computer software-Statistical Package for Social Sciences (SPSS) version 10.0. Chi-square test was utilized to compare the significant difference between the socio-demographic variables of the 2 groups, as well as between those who were enrolled versus drop outs. For quantitative variables t-test was used, and Analysis of Variance (ANONA) was used to assess the variations of psychopathology over the time course of treatment.

**Results**

***Subject Characteristics***

A total of 36 patients completed the study and were equally divided among both groups. In the risperidone group the average age was 27.28 years (SD=4.38) with 66% male and 56% were unmarried. In the haloperidol group the average age was 28.67 years (SD=4.16) with 56% male and 44% of the total being unmarried. Apart from these the comparison according to religion, cast, occupation, and education did not show significant differences between the two medication groups.

At the baseline assessment with positive and negative syndrome scale, the mean score of risperidone was 88.17 (SD=15.70) and of haloperidol was 88.56 (SD=13.56). The t-test value for the differences between the means was 0.080 (p=0.937) (Table 1).

**Table 1:** The baseline scores (Day-0) of both drug groups

| PANSS scale | | Risperidone N=18 | Haloperidol N=18 | t-test |
|---|---|---|---|---|
| **Total score** | Mean | 88.17 | 88.56 | **P=0.937 (NS)** |
| | S.D. | 15.70 | 13.35 | |
| | SE mean | 3.70 | 3.15 | |
| **Positive score** | Mean | 21.44 | 25.22 | **P=0.096 (NS)** |
| | S.D. | 6.90 | 6.32 | |
| | SE mean | 1.63 | 1.49 | |
| **Negative score** | Mean | 25.06 | 26.56 | **P=0.734 (NS)** |
| | S.D. | 14.87 | 11.09 | |
| | SE mean | 3.51 | 2.61 | |
| **General Psychopathology (GPS) score** | Mean | 42.39 | 37.56 | **P=0.116 (NS)** |
| | S.D. | 10.06 | 7.73 | |
| | SE mean | 2.37 | 1.82 | |

Similarly in PANSS –positive scale, mean in risperidone was 21.44 (SD=6.90) and in haloperidol was 25.22 (SD=6.32). T-value for the difference in mean was 1.734 (p=0.096). Similarly, no significant differences were noted in negative and general psychopathology (GPS) scales at baseline.

Thus the two groups undergoing the treatment were homogeneous with respect to psychopathology severity as well as in socio- demographic profile so that the effect of medication can be compared reliably between the two groups.

***Efficacy***

The analysis of improvement was made in terms of difference in the scores at various periods of assessments from the baseline which is called 'gain'. The gains are in negative values, because less severe the psychopathology, lesser the scores on the rating scale.

The gain in psychopathology are shown in tables- 2, 3, 4 and 5.

Table 2 shows that, at week 1 the gain in risperidone was –45.44 (SD=11.94) and in haloperidol group it was - 29.50 (SD=14.05). The t-value for the difference in gain gives p=0.001. Thus the difference was significant at week one. Subsequently, at weeks 2 and 4 the gains were not significantly different, only to be significantly different at the sixth week, which was the end point of the study. At the endpoint gain in risperidone was – 52.11 (SD=12.20) and for haloperidol it was – 43.17 (SD = 12.64) and it was significant with p value of 0.038.

Table 3 shows that there were no significant differences in gain in the positive sub scale scores at any point in time. Regarding change in negative and general psychopathology sub scales the gain was significantly better with risperidone in the first week only.

**Table 2:** Mean Change of score (gain) on PANSS-Total scale from baseline during time course of treatment

| Time in study | Statistic | Risperidone(N=18) | Haloperidol (N=18) | t-test |
|---|---|---|---|---|
| **At Week 1** | Mean | -45.44 | -29.50 | P=0.001** |
| | SD | 11.94 | 14.05 | |
| | SE | 2.81 | 3.31 | |
| **At Week 2** | Mean | -48.94 | -42.00 | P=0.256(NS) |
| | SD | 12.69 | 22.01 | |
| | SE | 2.99 | 5.19 | |
| **At Week 4** | Mean | -51.17 | -47.67 | P=0.487(NS) |
| | SD | 13.41 | 16.31 | |
| | SE | 3.16 | 3.84 | |
| **At Week 6** | Mean | -52.11 | -43.17 | P=0.038** |
| | SD | 12.20 | 12.64 | |
| | SE | 2.87 | 2.98 | |

**Table 3:** Mean Change of score (gain) on PANSS-Positive subscale from baseline during time course of treatment

| Time in study | Statistic | Risperidone(N=18) | Haloperidol (N=18) | t-test |
|---|---|---|---|---|
| At Week 1 | Mean | -10.28 | -9.11 | **P=0.536(NS)** |
| | SD | 6.46 | 4.56 | |
| | SE | 1.52 | 1.08 | |
| At Week 2 | Mean | -11.44 | -12.11 | **P=0.744(NS)** |
| | SD | 7.11 | 4.84 | |
| | SE | 1.67 | 1.14 | |
| At Week 4 | Mean | -11.61 | -11.89 | **P=0.882(NS)** |
| | SD | 6.85 | 3.80 | |
| | SE | 1.62 | 0.90 | |
| At Week 6 | Mean | -12.39 | -12.18 | **P=0.909(NS)** |
| | SD | 6.81 | 3.71 | |
| | SE | 1.61 | 0.90 | |

***Safety***

The UKU side effects rating scale compares the side effects in four dimensions. Significant between-treatment differences in the incidents of side effects were seen only in the 'neurologic' side effects group (Table-6) and non in 'psychological', 'autonomic' and 'others' side-effect group, though there was a tendency for increased side effects in the haloperidol group.

Among the neurologic adverse effects, extrapyramidal symptoms were most prominent. The incidence of rigidity, tremor and hypokinesia/ akinesia were 22.2%, 22.2% and 11.1% respectively and in haloperidol were 77.8%, 66.7% and 16.7% respectively. Significant between treatment differences could not be obtained in dystonia and akathisia, though increased numbers were seen in the risperidone group. No occurrence of hyperkinesia was witnessed in both the groups.

Another paradigm of looking at the safety profile is the use of anti-extrapyramidal syndrome (anti-EPS) treatment. Table-7 shows that 38.9% (N=7) patients had to resort to use of thrihexyphenidyl at some point in the study. In the haloperidol groups, on the other hand, 77.8% had to use anti-EPS medication. Chi-square revealed a value of 5.31, which yields p=0.018 ($p<0.05$). This implies that use of anti-EPS medication is significantly more prevalent in haloperidol compared to risperidone.

**Table 4:** Mean Change of score (gain) on PANSS-Negative subscale from baseline during time course of treatment

| Time in study | Statistic | Risperidone (N=18) | Haloperidol (N=18) | t-test |
|---|---|---|---|---|
| **At Week 1** | Mean | -14.39 | -6.68 | **P=0.013**** |
| | SD | 11.21 | 4.60 | |
| | SE | 2.64 | 1.08 | |
| **At Week 2** | Mean | -15.61 | -14.00 | **P=0.710(NS)** |
| | SD | 13.02 | 12.72 | |
| | SE | 3.06 | 2.99 | |
| **At Week 4** | Mean | -16.89 | -16.44 | **P=0.918(NS)** |
| | SD | 14.17 | 11.31 | |
| | SE | 3.34 | 2.67 | |
| **At Week 6** | Mean | -17.06 | -13.00 | **P=0.316(NS)** |
| | SD | 14.17 | 9.11 | |
| | SE | 3.34 | 2.15 | |

**Table 5:** Mean Change of scores (gain) on PANSS-General Psychopathology subscale (GPS) from baseline during time course of treatment

| Time in study | Statistic | Risperidone(N=18) | Haloperidol (N=18) | t-test |
|---|---|---|---|---|
| **At Week 1** | Mean | -20.94 | -13.67 | **P=0.019**** |
| | SD | 8.00 | 9.67 | |
| | SE | 1.87 | 2.28 | |
| **At Week 2** | Mean | -22.39 | -16.89 | **P=0.091(NS)** |
| | SD | 9.65 | 9.34 | |
| | SE | 2.27 | 2.20 | |
| **At Week 4** | Mean | -23.17 | -20.11 | **P=0.275(NS)** |
| | SD | 9.08 | 7.33 | |
| | SE | 2.14 | 1.73 | |
| **At Week 6** | Mean | -23.50 | -20.11 | **P=0.220(NS)** |
| | SD | 8.87 | 7.33 | |
| | SE | 2.09 | 1.73 | |

**Table 6:** Neurologic Side effects of the groups and the significance of their differences

| Category | Symptoms | Risperidone | | Haloperidol | | χ2-test |
|---|---|---|---|---|---|---|
| | | Absent | Present | Absent | Present | |
| 2.1 | Dystonia | 15(83.3%) | 3(16.7%) | 12(66.7%) | 6(33.3%) | P=0.443(NS) |
| 2.2 | Rigidity | 14(77.8%) | 4(22.2%) | 4(22.2%) | 14(77.8%) | P=.001(S) |
| 2.3 | Hypokinesia/Akinesia | 16(88.9%) | 2(11.1%) | 15(83.3%) | 3(16.7%) | P=0.026(S) |
| 2.4 | Hyperkinesia | 18(100%) | 0(0%) | 18(100%) | 0(0%) | (NS) |
| 2.5 | Tremor | 14(77.8%) | 4(22.2%) | 6(33.3%) | 12(66.7%) | P=0.007(S) |
| 2.6 | Akathisia | 15(83.3%) | 3(16.7%) | 14(77.8%) | 4(22.2%) | P=1.00(NS) |
| 2.7 | Epileptic Seizures | 18(100%) | 0(0%) | 18(100%) | 0(0%) | (NS) |
| 2.8 | Paraesthesias | 17(94.4%) | 1(5.6%) | 14(77.8%) | 4(22.2%) | P=0.388(NS) |

**Table 7:** The use of anti-extrapyramidal syndrome (EPS) medication in both groups during the study period and the significance of differences

| Medicine | | Use of anti-EPS | | Total | χ2-test |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Risperidone | N | 7 | 11 | 18 | P=0.018** |
| | % | 38.9 | 61.1 | 100.0 | |
| Haloperidol | N | 14 | 4 | 18 | |
| | % | 77.8 | 22.2 | 100.0 | |
| Total | N | 21 | 15 | 36 | |
| | % | 58.3 | 41.7 | 100.0 | |

**Discussion**

Few people would disagree to the fact that between seventh and ninth decade of the last century haloperidol enjoyed the position as prototype antipsychotic drug and others were compared against it, so much so that hyperdopaminergic hypothesis was the only doctrine guiding the treatment of schizophrenia.

Along with widespread use of haloperidol, the concept of schizophrenia as heterogeneous disease process started evolving and the assessment of dimensions and consequences of schizophrenia spread from 'symptoms' level to 'behavioral disturbances' to the 'social functioning' and the subjective quality of life (QOL). The paradigm shift in the place of treatment moved from asylum to massive social and community integration in the stable phase[29]. Parallely, serious limitations of haloperidol (and other CAPs) soon started surfacing, because, though the acute phase was manageable, there were substantial lack of improvement in quality of life, social functioning, community rehabilitation and long term prognosis.

The negative symptoms and extra pyramidal side effects of neuroleptics have been consistently associated with psychopathological severity, poorer prognosis and poor social functioning[16].

The introduction of serotonin dopamine antagonists (SDAs) has fulfilled a substantial number of shortcomings of conventional antipsychotic agents and risperidone has earned an acceptable position in this regard.

The results of the present study also carry those promises to a large extent. In the current study, both treatments produced substantial and significant with-in treatment group reduction in psychopathology from baseline by sixth week. Although, statistically significant difference was found only on the PANSS –total score, there was tendency for greater gain, i.e. improvement, in negative subscale score in the risperidone group compared to haloperidol. However, in terms of positive and GPS scores there were no significant differences in gain at the end point.

As far as the improvement after first week is concerned, there was significant difference in gain between risperidone and haloperidol in total, negative and GPS subscales. Thus it can be deducted that risperidone has a quicker onset of action then

haloperidol and a greater tendency to attenuate the negative symptoms right from the beginning. This makes psychosocial rehabilitation achievable from the beginning.

The results of this study are consistent with many previous studies in the west as well as in Asia and India. In the Canadian study[30], the results showed that risperidone was more efficacious and onset of action was quicker. Others studies[31,32] have also given similar results. There is one study[33] which doesn't show a significant difference, but the author still reported a trend in favour of risperidone. There too was a quicker onset of antipsychotic activity than haloperidol. The mean age of the subjects was 39 years, which is higher than this study and this may be a confounding factor in the outcome.

One Asian study by Min et al.[34] and an open Indian trial by Shrivastav and Gupta[35] also reported better profile with risperidone.

In the treatment with antipsychotic molecules, the side effect profile is as important as the efficacy, because the short term and long term outcomes of the drug might make the patient worse than the disease itself. Amongst other things, the neurological effects are most important, as Van Putten and associates (1990) have suggested a 'psychotoxic' effects to explain the psychological reaction associates with the drug induced symptoms, which 'insisted patients on leaving the hospital against medical advice.'

In the present study, the category of neurological side effects clearly showed a preponderance of haloperidol in almost all the side effects, except for hyperkinesia factor, which was absent in both the groups.

There is also remarkable consistency in the results of EPS and the use of anti-parkinsonian medication. These results are again consistent with many other trials. Notably, in the Canadian study, a greater percentage of patients assigned to haloperidol (71.4%) required anti-parkinsonian medication compared to risperidone (31%) and Placebo (27%). Similar treatment emergent outcomes were found another studies[31],[36] moreover, two studies have specifically reported anti-dyskinetic effects of risperidone[33, 30].

**Conclusion**

The results of the study demonstrate the response of a Nepalese citizen with the diagnosis of schizophrenia to conventional and second generation (atypical antipsychotic) drugs.

The typical patient was a 27 years old male, of Hindu religion, Brahmin caste, educated up to secondary level, with the family income between NRs.5, 000 and NRs.10, 000.

Risperidone (4-6mg) was beneficial than haloperidol (10-20 mg) in the improvement of overall total, positive and negative symptoms of schizophrenia. The onset of action was also quicker with risperidone compared to haloperidol.

Risperidone caused less extrapyramidal side effects and was better tolerated than haloperidol. The adjunctive use of anti-parkinsonian medication was lesser in risperidone than in haloperidol. Though it is not the primary objective of the study, it could be extrapolated that, the less use of anti-parkinsonian medication with risperidone may directly reduce the overall cost in the mid-term and long-term treatment of schizophrenia. This is because in the present Nepalese market, the cost of risperidone is not different from haloperidol.

Also, the better and quicker action of risperidone on negative and cognitive symptoms may lead to better improvement in social functioning, vocational rehabilitation, occupational functioning, interpersonal relationships and quality of life. This might, more importantly, reduce the indirect cost of treating schizophrenia in the long-term basis.

Thus risperidone may be a more effective, safer and cost-effective drug than haloperidol in the treatment of schizophrenia in the Nepalese population as well.

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