COMPARATIVE STUDY OF EFFICACY BETWEEN RISPERIDONE AND HALOPERIDOL IN DRUG NAIVE ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

M. Mohana Lakshmi, R. Saravana Jothi, W. J. Alexander Gnanadurai, K. Jeevitha, Jyosna B., B. Kalamathi

1Assistant Professor, Department of Pharmacology, Stanley Medical College, Chennai.
2Associate Professor, Department of Psychiatry, Stanley Medical College, Chennai.
3Professor and HOD, Department of Psychiatry, Stanley Medical College, Chennai.
4Junior Resident, Department of Psychiatry, Stanley Medical College, Chennai.
5Junior Resident, Department of Psychiatry, Stanley Medical College, Chennai.
6Assistant Professor, Department of Pharmacology, Stanley Medical College, Chennai.

ABSTRACT

BACKGROUND
To compare the efficacy between risperidone and haloperidol in drug naïve acute and transient psychotic disorder patients attending Government Stanley Medical College Hospital by assessing the mean changes in PANSS total score from start to end of treatment.

MATERIALS AND METHODS
Patients (n=60) diagnosed as drug naïve acute and transient psychosis as per DSM-TR criteria & age between 18-60 years are recruited and randomly allocated into group A (n=30) Risperidone tab 4 mg daily & group B (n=30) Haloperidol tab 5 mg daily as decided by the treating psychiatric consultant, for the period of 3 months after obtaining informed consent by the patients family members.

RESULTS
The mean value for total PANSS score at the start of the study was 57.57 and reduced to 39.42 in Risperidone group; while in Haloperidol group the mean reduced from 81.00 to 57.06 with the p value of 0.012* (statistically significant at 5 level).

CONCLUSION
This study showed marked reduction in PANSS in drug naïve psychiatric patients with 60% of patients achieving primary outcome with Haloperidol and 73% of patients achieving primary outcome with Risperidone, however patients in Haloperidol group with initial high PANSS score showed marked reduction at the end of study.

KEYWORDS
ATPD, PANSS, Drug Naïve Psychosis.


BACKGROUND
Acute Transient Psychotic Disorder (ATPD-ICD-10) or Brief Psychotic Disorder (DSM-5) refers to a syndrome characterized by:1

1. Change of the disorder from a non-psychotic to clearly psychotic state
2. Has an onset of more than 48 hrs. but less than 2 weeks with full recovery within three months (a few days or weeks)
3. Acute onset of delusions, hallucinations, incomprehensible or incoherent speech or any combination of these.
4. With eventual full return to premorbid levels of functioning.
5. The disturbance is not better explained by mood disorders with psychotic features or schizophrenia spectrum disorder or substance use or another medical condition.
6. Presence of associated acute stress (bereavement, job loss, psychological trauma) is mostly seen.2

In her study, ‘Diagnostic stability of Acute Transient Psychotic Disorders in Developing country settings: An overview. Mental illness’, Shubham Mehta has found that the incidence of acute and transient psychotic disorders is ten times higher in developing countries; incidence is 2 times higher in women; annual incidence rates per 10,000 were 0.49 in men and 0.88 in women in developing countries.
People with a first psychotic episode tend to present late for medical attention, often initiated by others, not by patients themselves. Patients who experience intolerable symptoms (distressing delusions or voices) often seek medical help. The risk of suicide is highest in these patients ("the critical period") interventions are most fruitful during this time. Any discontinuation in treatment due to side effects or delayed response to the drugs can predispose the patient to enter schizophrenia spectrum.

Present pharmacogenomic literature suggests that the alleles modulating the specific side effects like tardive dyskinesia may be different in the Indian population as compared to elsewhere. Similar studies when extended to efficacy profile may also find unique differences. This motivated us to pursue a study on efficacy profile in our population.

Current trends in the treatment of ATPD or Drug naïve psychosis involves administration of an antipsychotic with or without concomitant benzodiazepines (typical or atypical) and an anticholinergic. In this study we compare the efficacy of two well-known and widely used drugs: Haloperidol and Risperidone.

**Risperidone**
Risperidone is an antipsychotic that is a potent antagonist at 5-HT2a and D2 receptors. It also demonstrates relatively high affinity for alpha1 and H1 receptors but low affinity for beta-adrenergic or muscarinic receptors. Preclinical studies such as those done by Mc Donald LM et al indicate that while risperidone is approximately equipotent to haloperidol at D2 antagonism, it is several times less potent than haloperidol at inducing catalepsy. Mean peak plasma concentration occurred in about 1 hour. The apparent half-life of risperidone depends on extensive or poor metabolizing capacity of the liver.

**Haloperidol**
Haloperidol is a butyrophenone derivative with antipsychotic properties that is highly effective against the positive symptoms like delusions and hallucinations. It has a marked tendency to provoke extra pyramidal effects and has relatively weak alpha-adrenolytic properties. It may also exhibit hypothermic and anorexiant effects and potentiate the action of barbiturates, general anaesthetics, and other CNS depressant drugs. The mechanism of action of haloperidol has been attributed to the inhibition of the transport mechanism of cerebral monoamines, particularly by blocking the impulse transmission in dopaminergic neurons as quoted in Mc Donald LM et al study. Peak plasma levels of haloperidol occur within 2 to 6 hours of oral dosing and about 20 minutes after I.M. administration.

Schizophrenic patients receive Risperidone 4-6 mg bd or haloperidol 5-10 mg bd along with trihexyphenidyl 2 mg bd; during stabilization phase pts receive Risperidone 4 mg bd and haloperidol 5 mg bd along with trihexyphenidyl; during the maintenance phase pts receive lesser doses according to the degree of improvement.

In our study clinical assessment and drug response in ATPD patients are done by using, PANSS (Positive and Negative Symptom Scale). Here the efficacy of the drugs has been compared using PANSS score.

**PANSS (Positive and Negative Symptom Scale)**
It was developed out of the need for a well operationalized method for assessing the symptoms in psychotic patients. It is a 30 points scale, where 7 constitute a positive scale, 7 a negative scale and the remaining 16 a general psychopathology scale. The potential ranges are 7 to 49 for the positive and negative scales and 16 to 112 for general psychopathology scales. A reduction in the PANSS to a score of =30 is taken as efficacy.

As ethnicity plays a role in the treatment outcome, the results of similar studies in Western population cannot be standardized for Indian people. Only very few Indian studies have been done in ATPD so far, hence this subject became the topic of interest to us.

**Aim**
To compare the efficacy between Risperidone and Haloperidol in drug naïve Acute Transient Psychotic Disorders patients attending Government Stanley Medical College Hospital by assessing the mean changes in PANSS total score from start to end of treatment.

**MATERIALS AND METHODS**

**Sample**

**Inclusion Criteria**

Newly diagnosed psychotic disorder patients aged between 18-60 years attending psychiatric OPD, Stanley medical college hospital, diagnosed as drug naïve acute and transient psychosis as per DSM-5 criteria for the period of 1st January 2016 - 30th June 2016 were recruited for the study after obtaining informed consent from the patient's attenders. The study was conducted after Regional Ethical Committee approval.

**Exclusion Criteria**

Patients hypersensitive to Risperidone & Haloperidol, contraindication to Risperidone or Haloperidol usage as per patient's medical history, patients with liver & renal disorders, patients already exposed to antipsychotic drugs,
Pregnant women, patient’s family members who are not willing to give informed consent were excluded from the study.

**Methods**

It is a prospective, Randomized, Comparative, Open labelled, parallel grouped study. The participants were randomly allocated into group A & group B as decided by the treating psychiatric consultant after informed consent by the patient’s family members (eligible proxy).

- Group A: Risperidone tab 4 mg daily.
- Group B: Haloperidol tab 5 mg daily.

Both groups were supplemented initially with lorazepam/diazepam, anticholinergics and followed up for 3 months.

**Primary Outcome**

Recovery from Acute Transient Psychosis is assessed by reduction in the PANSS scale. A reduction in the PANSS to a score of 30 is taken as efficacy in this study. Recovery time varies; in some patients it occurs within a few days or few weeks and if responsive, definitely by three months. If patient persists with the illness even after 3 months, then he is considered as schizophrenic & treated accordingly.

**Statistical Analysis**

Done by group statistics, paired sample test and Levene’s test for equality of variances. Analysis was done at the onset of the study, end of 2nd week, 4th week, 2nd month and 3rd month.

**RESULTS**

The study spanned for a period of 6 months to get the target sample number. 40 patients in Risperidone group and 38 patients in Haloperidol group were enrolled in the study. At the end of first month, 8 patients in Risperidone group and 4 patients in Haloperidol group lost follow up. Remaining 2 patients in Risperidone group, 4 patients in Haloperidol group wanted to go to native place and hence lost follow up.

**Demographic Profile**

<table>
<thead>
<tr>
<th>Marital status</th>
<th>Haloperidol (No. &amp; %)</th>
<th>Risperidone (No. &amp; %)</th>
</tr>
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<tbody>
<tr>
<td>Single</td>
<td>10 (33.3)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Married</td>
<td>13 (43.3)</td>
<td>17 (56.6)</td>
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<tr>
<td>Separated</td>
<td>6 (36.6)</td>
<td>6 (36.6)</td>
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</table>

<table>
<thead>
<tr>
<th>Family H/O mental illness</th>
<th>Haloperidol (No. &amp; %)</th>
<th>Risperidone (No. &amp; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>11 (36.6)</td>
<td>11 (36.6)</td>
</tr>
<tr>
<td>No</td>
<td>19 (63.3)</td>
<td>19 (63.3)</td>
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</table>

**Table 1. Socio-demographic Features between Haloperidol and Risperidone Group**

The mean age was 30 yrs. as 85% of patients were between the age of 20-40 years and the sample included more women (67%) than men (33%). The majority were degree holders (35%) and with primary education (26%) when compared to uneducated (17%) and high school education (22%). Up to 50% were unemployed and 25% each were self-employed and students. Of the 60 patients most of them belonged to lower socioeconomic status and the rest belonged to lower middle (20%) and upper middle class (13%). Among the participants, 50% were married whereas 28% were single and 22% were separated. 37% had family history of mental illnesses.

As shown in Figure 1, out of 30 patients treated with risperidone, 6 (20%) of them showed earliest improvement in their PANSS score at the end of 2nd week. By 4th week, 5 (17%) showed improvement. At the end of 2nd month 23% (7) responded. At the end of 3rd month, 13% (4) felt better. 27% (8) patients never responded even at the end of the 3rd month.

As demonstrated in Figure 2, 10% (3) responded by the end of 2nd week; 13% (4) by the end of 4th week; 20% (6) by end of 2nd month and 17% (5) by the end of 3rd month. Among 30 patients 12 (40%) did not respond to haloperidol even at the end of 3rd month.
While assessing PANSS at the start of the visit we found 70% of patients had positive and general symptoms, 16.7% of patients had negative and general symptoms and 13.3% had combination of positive, negative and general symptoms in both the groups.

Statistical Analysis Done by Group Statistics, Paired Sample Test, Levene’s Test for Equality of Variances.

<table>
<thead>
<tr>
<th>Group</th>
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<th>Haloperidol</th>
<th>P value</th>
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<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>P 0</td>
<td>18.72</td>
<td>7.63</td>
<td>24.76</td>
</tr>
<tr>
<td>N 0</td>
<td>17.44</td>
<td>9.68</td>
<td>25.56</td>
</tr>
<tr>
<td>G 0</td>
<td>36.73</td>
<td>13.96</td>
<td>52.70</td>
</tr>
<tr>
<td>Total</td>
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<td></td>
</tr>
<tr>
<td>PANSS</td>
<td>57.57</td>
<td>18.39</td>
<td>81.00</td>
</tr>
<tr>
<td>P 2</td>
<td>15.80</td>
<td>7.05</td>
<td>20.68</td>
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<tr>
<td>N 2</td>
<td>15.56</td>
<td>9.59</td>
<td>21.78</td>
</tr>
<tr>
<td>G 2</td>
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<tr>
<td>N 4</td>
<td>15.29</td>
<td>5.59</td>
<td>19.67</td>
</tr>
<tr>
<td>G 4</td>
<td>26.71</td>
<td>10.88</td>
<td>38.19</td>
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<td>PANSS</td>
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<td>P 2 month</td>
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<td>5.79</td>
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<tr>
<td>N 2 month</td>
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<td>16.78</td>
</tr>
<tr>
<td>G 2 month</td>
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<td>Total</td>
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<tr>
<td>PANSS</td>
<td>40.74</td>
<td>15.30</td>
<td>58.35</td>
</tr>
<tr>
<td>P 3 month</td>
<td>12.40</td>
<td>3.63</td>
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<tr>
<td>N 3 month</td>
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<tr>
<td>PANSS</td>
<td>39.42</td>
<td>12.78</td>
<td>57.06</td>
</tr>
</tbody>
</table>

Table 2. Statistical Analysis Done by Group Statistics, Paired Sample Test, Levene’s Test for Equality of Variances

Figure 2. Response Rate % in Haloperidol Group

Figure 3. Comparison of the Time taken for Response of the Two Groups

When a graph comparing the percentage of patients and their time taken for response of the two groups was plotted it showed that earliest signs of improvement were seen in group A and late peaking in response was seen in group B. [Figure 3].

Figure 4. Comparison of the % of Patients and Time taken for Response of the Two Groups
The maximum initial PANSS score in Risperidone group were as follows: 36- positive symptom score, 36-negative symptom score and 65-general symptom score and the least scores were 6, 6 and 12 respectively for positive, negative and general symptoms.

In Risperidone group, the P0 (positive symptom score at 0 visit) mean reduced from 18.72 to 12.40 at the end of 3rd month (P3). Negative symptom mean N0 reduced from 24.46 to 19.69 at the end of 3rd month (P3). Negative symptom Mean N0 reduced from 25.56 to 16.29 at the end of study (N3) and that of General symptom mean reduced from 52.70 to 35.88 at the end of the study (G3).

Earliest recovery by 2nd week was achieved by 6 patients in Risperidone group and out of 30 patients, 22 (72%) achieved efficacy outcome within 3 months with the p value of < 0.05* and 8 (28%) patients failed to achieve reduction in total PANSS of <30. Earliest recovery by 2nd week was achieved by 3 patients in Haloperidol group and out of 30 patients, 18 (60%) achieved efficacy outcome within 3 months and 12 (40%) patients failed to achieve reduction in total PANSS of <30 even at the end of 3 months.

The mean value for presence of positive symptoms at the start of the study was 18.72 and reduced to 12.40 in Risperidone group; while in Haloperidol group the mean reduced from 24.76 to 19.69 with the p value of 0.014* (statistically significant at 5 level)

The mean value for presence of negative symptoms at the start of the study was 17.40 and reduced to 12.67 in Risperidone group; while in Haloperidol group the mean reduced from 25.56 to 16.29 with the p value of 0.483 (statistically not significant)

The mean value for presence of general symptoms at the start of the study was 36.73 and reduced to 25.92 in Risperidone group; while in Haloperidol group the mean reduced from 52.70 to 35.88 with the p value of 0.044* (statistically significant at 5 level).

DISCUSSION
In this study, we sought to compare the efficacy of two of the most widely used drugs used in the first line management of ATPD: Haloperidol and Risperidone by charting the PANSS score at the start of the study and at the end of 3 months. As shown in Figure 6, the group B patients on haloperidol who initially had PANSS mean score of 81 showed a mean score of 57.06 at the end of 3rd month (mean score difference of 24). Whereas, group A patients who were on risperidone, at the start of the study had a mean PANSS score of 57.57 and at the end of 3rd month had 39.42 (difference in mean score of 18). This demonstrates that haloperidol causes marked reduction in PANSS score despite its lower response rate clinically [Table 2]. On the other hand risperidone causes rapid improvement and greater adherance to treatment but its change in mean and negative symptoms in the study was 57.57 and reduced to 39.42 in Risperidone group; while in Haloperidol group the mean reduced from 81.00 to 57.06 with the p value of 0.012* (statistically significant at 5 level).

Positive and negative symptom score reduction achieved in both the groups were comparable but they are not statistically significant in this study.

![Figure 5. PANSS Pattern Efficacy Comparison](image)

![Figure 6. Total PANSS at the start and at the end of the study between Risperidone and Haloperidol Groups](image)

![Figure 7. Total PANSS Reduction between Risperidone and Haloperidol Groups](image)
PANSS score is lesser than haloperidol. This discrepancy can be because of better side effect profile and hence better adherence to risperidone.

Previous similar studies showed Risperidone is at least as (and possibly slightly more) effective than typical antipsychotics drugs (chiefly haloperidol).

It has a low incidence of EPS and may be more acceptable to patients with psychosis.\textsuperscript{10} Whether risperidone offers any advantages over the other atypical anti-psychotics is yet to be established.

Another study by Pratim Chaudhry et al\textsuperscript{11} concludes that Risperidone at 4 mg/ day has an overall therapeutic activity comparable to Haloperidol 15 mg/day, on outcome of clinical symptomatology at short term in first episode Acute and transient psychotic disorder, with Risperidone holding a more efficacious and early onset of action on some of the positive & negative symptoms in comparison to Haloperidol.

Patients who present with a first episode of psychosis pose many challenges to psychiatry. While some morbidity from schizophrenia is probably not modifiable once acute psychosis has occurred, the best management of this stage of illness nevertheless holds the promise of improving long-term outcomes. We feel that risperidone may represent a potentially useful first line antipsychotic agent in the treatment of Acute Psychosis in their first episodes.

**Limitations of this study**
Sample size could have been larger. The initial PANSS score of both the groups were not uniform, even subgroup analysis of the initial PANSS score were highly variable. Some patients had either only one positive or negative symptom, some patients had marked no symptoms in general scaling. There is no uniformity in symptom presentation in the subjects recruited for this study.

**CONCLUSION**
This study showed marked reduction in PANSS in drug naïve psychiatric patients with 60% of patients achieving primary outcome with Haloperidol and 73% of patients achieving primary outcome in Risperidone group, however patients in Haloperidol group with initial high PANSS score showed marked reduction at the end of study.

**REFERENCES**