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Clinical Efficacy and Safety Profile of Lurasidone Comparing with Risperidone: Randomized, Open Label, Clinical Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors VS, LR and TR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors JTR, EPK, MPK, MKS, TS, YY and BS managed the analyses of the study. Authors BN and MM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

There are diverse studies which afford evidences that risperidone is as effective as second generation antipsychotics in treating positive symptoms and more effective in treatment of negative symptoms. This study is intended to find the clinical efficacy and safety profile of lurasidone comparing with risperidone, a drug in common use nowadays. Patients aged between 18 to 60yrs, Patients with new onset of symptoms who fulfil the ICD-10 criteria for a primary diagnosis of schizophrenia and Patients having a total PANSS score of ≥80 including a score ≥4 (moderate) on two or more of positive subscale at baseline. Patients with acute exacerbation of schizophrenia who remained drug free for at least last 6 months also included. Demographic data of the patients were collected. Baseline investigations like BP, complete blood count, lipid profile, blood sugar, renal function test and liver function test were done. Severity of schizophrenia at baseline was

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assessed using positive and negative symptoms scale (PANSS). Patients were randomized by using computer generated random table in 1:1 ratio as group A and group B, with 25 patients in each group. The efficacy of group A and group B was analysed by applying rating scale Positive and negative syndrome scale (PANSS) at the end of 4 and 6 weeks. Adverse drug reactions were recorded and monitored by interviewing with patients, by physical examination and also by necessary lab investigations at the end of 6 weeks. Patients were insisted to maintain a diary to note any new occurrence of adverse drug reactions in between the follow up period. Suspected adverse drug reactions were documented in predesigned reporting form. In PANSS positive scale both groups had significant decrease in PANSS score both at week 4 and week 6 ($p<0.05$). Lurasidone is as equally efficacious as risperidone in reducing PANSS score, but produces less metabolic syndrome and other adverse effects than risperidone.

Keywords: Efficacy; lurasidone; positive and negative syndrome scale; risperidone; suspected adverse drug reactions.

1. INTRODUCTION

Schizophrenia is a type of functional psychoses in which severe personality changes and thought disorders occur with no evidence of organic cerebral damage. Although improvement is seen over a prolonged period of time for some patients, most of the patients experience some persisting symptoms despite treatment [1]. To prevent relapse, maintenance treatment with antipsychotic drugs is obligatory for most patients who have schizophrenia [2]. Antipsychotic drugs are the cornerstone for the treatment of schizophrenia. First-generation antipsychotics which mainly have dopamine D2 antagonist action, are effective against positive symptoms, but they are comparatively less beneficial in treating negative and associated mood symptoms [3]. In addition, the D2 antagonists frequently induce extrapyramidal side effects that are thought to reflect blockade of D2 receptors in the basal ganglia [4].

Second-generation antipsychotics, which commonly have combined 5- hydroxytryptamine 2A (5- HT2A) and D2 blocking activity, may offer greater improvement in negative symptoms [5] and have a more favorable tolerability profile with markedly reduced risk of extrapyramidal symptoms. However, several second-generation antipsychotics (e.g., clozapine, olanzapine) are associated with significant weight gain and metabolic dysfunction [6]. Most of the atypical antipsychotics have relatively high affinity for α_1 receptors, muscarinic receptors & H_1 receptors. Some of the atypical antipsychotics produce weight gain, sedation and impairment in cognitive function by acting at these receptors [7] Results from randomized, large, double-blind study showed that majority of chronic schizophrenia patients withdrawn their antipsychotic medications, because of either lack of efficacy of drug or intolerable adverse drug reactions [8]. In view of these drawbacks we need a drug with good clinical efficacy and lower or absent extrapyramidal and metabolic side effects. Lurasidone is an a typical antipsychotic drug recently approved in India apart from other countries for the treatment of schizophrenia. It blocks D_2, 5-HT_{2A} and 5-HT_7 receptors. It has partial agonistic activity on 5-HT_{1A} receptor but has no effect on H1 and muscarinic receptors. As it has negligible activity at H1 and 5- HT2C receptors, lurasidone may produce lesser incidence of weight gain. The sedation is little due to very minimal action on H1 receptors. [9] Risperidone is the second generation antipsychotic that gained approval of the Food and Drug Administration in 1994 and since then it is gaining rapid popularity. There are diverse studies which afford evidences that risperidone is as effective as second generation antipsychotics in treating positive symptoms and more effective in treatment of negative symptoms [10]. This study is intended to find the clinical efficacy and safety profile of lurasidone comparing with risperidone, a drug in common use nowadays.

2. Methodology

2.1 Study Type

Interventional clinical study.

2.2 Study Design

Randomized, Open label, prospective, comparative, clinical study.

2.3 Sample Size

Total of 50 patients (25 patients in each group).

2.4 Study Duration

From May 2019 to April 2020 (12 months).

2.5 Study Drug and Dosage

Lurasidone, starting dose 40 mg/day titrated up to 80 mg /day.

2.6 Study Place

Department of Psychiatry, Government Medical College Hospital, Ananthapuramu.

2.7 Inclusion Criteria

- Patients aged between 18 to 60 yrs.
- Patients with new onset of symptoms who fulfil the ICD-10 criteria for a primary diagnosis of schizophrenia.
- Patients having a total PANSS score of ≥80 including a score ≥4 (moderate) on two or more of positive subscale at baseline.
- Patients with acute exacerbation of schizophrenia who remained drug free for at least last 6 months also included.

2.8 Exclusion Criteria

- Pregnancy / Lactation.
- Patients with comorbid conditions like neurological, metabolic (including type I diabetes), pulmonary, cardiovascular, gastrointestinal and/or urological disorder.
- Patients with history of liver and renal disease.
- Patients with history of gastrointestinal surgery.
- Patients with history of neuroleptic malignant syndrome and active seizure disorder.
- Patients with evidence of tardive dyskinesia, dystonia or any other movement disorder.
- Patients with history of alcohol dependence.

2.9 Withdrawal Criteria

- Patients who develop severe extra pyramidal symptoms.
- Neuroleptic malignant syndrome.
- Severe drug intolerance.
- Patients requiring electro convulsive therapy for symptom control.

2.10 Schedule of Study Visit

2.10.1 Screening and recruitment

Patients who fulfill the inclusion criteria were enrolled for the study. Demographic data of the patients were collected. Baseline investigations like BP, complete blood count, lipid profile, blood sugar, renal function test and liver function test were done. Severity of schizophrenia at baseline was assessed using positive and negative symptoms scale (PANSS). Patients were randomized by using computer generated random table in 1:1 ratio as group A and group B, with 25 patients in each group.

2.10.2 Treatment protocol

2.10.2.1 Group A

Patients were given T. Lurasidone 40 mg/ day after night meal for 6 days followed by dose titration to a maximum of 80 mg/ day.

2.10.2.2 Group B

Patients were given T. Risperidone 4 mg/day after night meal for 3 days followed by dose titration to a maximum of 6 mg/ day.

2.10.2.3 Follow up

The efficacy of group A and group B was analysed by applying rating scale Positive and negative syndrome scale (PANSS) at the end of 4 and 6 weeks. Adverse drug reactions were recorded and monitored by interviewing with patients, by physical examination and also by necessary lab investigations at the end of 6 weeks. Patients were insisted to maintain a diary to note any new occurrence of adverse drug reactions in between the follow up period. Suspected adverse drug reactions were documented in predesigned reporting form.

2.10.3 Efficacy parameters

2.10.3.1 Primary endpoint

Mean change from baseline to Week 6 in PANSS total scores.

2.10.3.2 Secondary endpoints

- Proportion of responders (defined as 20% or greater improvement in PANSS total score from baseline at Week 4).

- Mean change from baseline to Week 4 and 6 in PANSS positive subscale.
- Mean change from baseline to Week 4 and 6 in PANSS negative subscale.

2.11 Positive and Negative Syndrome Scale (PANSS)

It is widely used in the study of antipsychotic therapy. To assess a patient using PANSS, an approximately 45-minute clinical interview was conducted. The patient was rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members. Of the 30 items included in the PANSS, 7 constitute a Positive Scale, 7 a Negative Scale, and the remaining 16 a General Psychopathology Scale. The scores for these scales were arrived at by summation of ratings across component items.

2.12 Statistical analysis

Statistical analysis was performed by standard statistical protocol using SPSS VERSION 21.0.

- Baseline characteristics of both the groups were tabulated by descriptive statistics (mean, standard deviation) and frequency table. The data obtained was coded and entered into Micro soft Excel Worksheet.
- The categorical data was expressed as rates, ratios and proportions.
- Comparison was done using chi- square test.
- The continuous data was expressed as mean ± standard deviation (SD) and comparison was done using independent sample 't'test, ANOVA.
- A probability ('p' value) of less than or equal to 0.05 was considered as statistically significant.

3. RESULTS

50 patients were enrolled for the study. They were randomly assigned in to 2 groups to receive lurasidone and risperidone through a computer generated random table. All the patients completed the study and the results were analysed.

Table 1. Baseline patient characteristics

Baseline characteristics	Lurasidone n (%)	Risperidone n (%)	n= 50	P-value
Age (in years)				
16-25	2(50%)	2(50%)	4	
26-35	6(32%)	13(68%)	19	
36-45	12(60%)	8(40%)	20	0.198
46-60	5(71%)	2(29%)	7	
Sex				
Male	15(55%)	12(45%)	27	
Female	10(43%)	13(57%)	23	0.395
Locality				
Rural	20(50%)	20(50%)	40	
Urban	5(50%)	5(50%)	10	1.000
Marital status				
Married	18(52%)	17(48%)	35	
Unmarried	7(46%)	8(54%)	15	0.758
Duration of Illness				
< 4 months	5(45%)	6(55%)	11	
4-6 months	3(60%)	2(40%)	5	
7-12 months	7(46%)	8(54%)	15	
> 1 year	10(53%)	9(47%)	19	0.938
Family history				
Yes	11(52%)	10(48%)	21	
No	14(49%)	15(51%)	29	0.774
Suicide attempt	9(56%)	7(44%)	1634	0.544
Yes no	16(47%)	18(53%)		

Table 2. Comparison of PANSS positive scale in both groups

Positive scale	Lurasidone (Mean±SD)	Risperidone (Mean±SD)	P-value
Baseline	33.48 ± 7.5	34.00 ± 7.2	0.805
Week 4	22.36 ± 6.2	22.00 ± 6.2	0.839
Week 6	16.04 ± 6.2	14.00 ± 9.9	0.206

Table 3. Comparison of PANSS negative scale in both groups

Negative scale	Lurasidone (Mean±SD)	Risperidone (Mean±SD)	P-value
Baseline	29.44 ± 6.52	28.92 ± 7.83	0.798
Week 4	20.08 ± 5.2	18.16 ± 6.16	0.241
Week 6	14.52 ± 5.5	13.04 ± 4.71	0.315

Table 4. Comparison of PANSS total score in both groups

PANSS total score	Lurasidone (Mean±SD)	Risperidone (Mean±SD)	P-value
Baseline	114.28 ± 17.1	105.96 ± 11.8	0.051
Week 4	72.20 ± 18.8	66.12 ± 20.34	0.279
Week 6	51.6 ± 18.4	46.96 ± 14.57	0.321

Table 5. Proportion of responders to treatment between groups

Responders to treatment - improvement in PANSS score			
Improvement	**Lurasidone**	**Risperidone**	**Total**
Responders	22	20	42
Non responders	3	5	8
P-value - 0.440			
Chi square test			
Non significant			

Table 6. Comparison of baseline metabolic parameters in both groups

Parameters	Lurasidone			Risperidone		
	Baseline	**6 weeks**	**P-value**	**Baseline**	**6 weeks**	**P-value**
Weight	58±14.4	59.44±14.17	0.002	62.44±13.52	64.52±13.57	0.001
BMI	21.85±4.61	21.85±4.68	0.001	23.01±4.85	23.81±4.81	0.001

- *A probability ('p' value) of less than or equal to 0.05 was considered as statistically significant.*

Table 7. Incidence of different ADR in both groups

ADR	Lurasidone(n)	Risperidone(n)	Total(n)
Akathisia	1	3	4
Insomnia	1	0	1
Amenorrhoea	0	3	3
Weight gain	6	10	10
Diabetes	0	3	3
Hypercholesterolemia	2	4	6
Hypertension	0	1	1
Nausea/vomiting	2	2	4
Dry mouth	0	2	2
Erectile dysfunction	1	0	1
Rigidity	1	2	3
Tremor	4	8	12
Sedation	3	5	8
Constipation	0	1	1
Dystonia	0	1	1

4. DISCUSSION

In our study 39 patients were in the 26 – 45 years age group. The higher prevalence of schizophrenia in this age group might be linked to stress factors as shown in study done by Castle et al [11]. There was no gender difference in this study which was in contradiction to the results of recent meta-analysis and systematic reviews which suggest that males were at higher risk for schizophrenia compared to females. Women tend to have a late onset which is presumed to be due to the effects of oestrogen on reduced sensitivity of D2 receptors in the central nervous system [12]. a survey done by FU L et al had shown higher prevalence in urban areas than in rural areas [13]. As our hospital is a tertiary care centre most of the rural population diagnosed with schizophrenia will be referred to government hospital. This may be the reason for higher prevalence in rural population. On analysing the marital status of our patients nearly 70% of them (18 in lurasidone and 17 in risperidone) were married and 30% were unmarried. This is in contrast with Li XJ et al study conducted in China [14]. Family history of schizophrenia was present in 21 patients in our study population. This is similar to study done by CarstenBøcker Pedersen et al among schizophrenia patients [15]. History of suicidal attempt was present in 16 patients in our study group. Studies so far done had not come to an agreement on suicide rates amongst patients with schizophrenia. The most widely cited lifetime suicide rate is 10%, as estimated by a review by Miles [16]. PANSS score was used to analyse the efficacy of the drugs in lurasidone and risperidone group. In PANSS positive scale both groups had significant decrease in PANSS score both at week 4 and week 6 ($p<0.05$). This was similar to the results obtained in study done by Liebermmenn. The improvement in positive symptoms in both groups is due to D2 receptor blockade along with other dopaminergic receptors like D1, D3, D4 [17]. There was no significant difference seen in PANSS positive scale between lurasidone and risperidone. Similarly negative PANSS scale showed significant decrease in PANSS score both at week 4 and week 6 in both the groups ($p<0.05$). The difference from baseline score to week 4, baseline to week 6, analysed by using student t test, yielded statistically significant reduction in PANSS score in both lurasidone and risperidone groups. There was no significant difference seen in PANSS negative scale between lurasidone and risperidone. The improvement in negative and cognitive symptoms in both the groups are due to blockade of 5HT2 receptors and increase in dopamine release in the prefrontal cortex by these drugs [18]. Only a few current treatment modalities had shown efficacy in this domain [19]. Lurasidone had efficacy equivalent to that of the risperidone in reducing both positive and negative symptoms [20]. Patients who had more than 20 % reduction in PANSS scale after four weeks of treatment were considered as responders to treatment. On comparing, lurasidone had an efficacy rate of 88% which was slightly more than that of risperidone (80%), but not statistically significant ($P>0.05$). On analysing the changes in metabolic parameters at baseline and week 6 in both the groups, there was significant increase in ($p< 0.05$) weight and body mass index (BMI) in both lurasidone and risperidone groups. A similar study done by Gupta et al, [21] reported that patients undergoing treatment with olanzapine were prone to develop metabolic syndrome as the drug induces weight gain after 16 weeks of treatment. But in our study, there was a significant weight gain at 4 weeks of treatment itself. The molecular mechanisms responsible for drug-induced weight gain have been hypothesized to be due to increase in leptin secretion [22] and interactions of antipsychotic drugs with several neurotransmitter receptors, including 5-HT(2A) and 5-HT(2C) serotonin receptors, H(1)-histamine receptors, alpha(1)- and alpha(2)-adrenergic receptors, and m3-muscarinic receptors. In our study around 76% of patients had some type of adverse reaction. There was no significant difference in incidence of adverse drug reaction between groups, but there was difference in type of adverse reaction between groups. The incidence of extrapyramidal side effects was higher in the risperidone group. Metabolic derangements like diabetes and dyslipidemia were also higher in risperidone group. Similarly, weight gain, tremors and sedation are the most frequently reported adverse effects in lurasidone group. This was similar to the study conducted by Peter JW et al which showed that the most common adverse effect in risperidone group were extrapyramidal disorder, akathesia, tremor and somnolence [23].

5. CONCLUSION

Lurasidone is as equally efficacious as risperidone in reducing PANSS score, but produces less metabolic syndrome and other adverse effects than risperidone.

CONSENT AND ETHICAL APPROVAL

The study was commenced after getting approval from the Institutional Ethics Committee. (IEC/BCP/Reddenna-2019/22)Written informed consent was obtained from all the patients included in this study, in their own vernacular language.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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