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Effect of Iloperidone on serum Prolactin in patients suffering from Schizophrenia

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Abstract: -

Background: Schizophrenia is a severe mental disease that is characterized by different psychopathological symptoms like disturbance of the affect, difficulty thinking or dysfunction of perception. Its lifetime prevalence is estimated at around 1%. It is well known that hyperprolactinaemia is a well documented side effect of most anti-psychotics. Hence this study was conducted to evaluate the elevation of serum prolactin levels in patients with schizophrenia on a latest second generation anti-psychotic Iloperidone.

Aim: The aim of this study was to investigate the changes in the levels and side effects of serum prolactin elevation in patients suffering from schizophrenia on treatment with atypical anti-psychotic Iloperidone.

Methods: This is an open labeled, prospective study on Fifty patients (30 men and 20 women), diagnosed with schizophrenia according to the DSM 5 (Diagnostic and statistical Manual of Mental Disorders 5th Edition) criteria on treatment with Iloperidone. This study was conducted in the department of Psychiatry, Bhaskar medical college and General Hospital. Serum Prolactin levels, and the side effects related to elevated serum prolactin were assessed. ANOVA was used for statistical analysis using SPSS 16 version.

Results: It was found that the majority of the study sample was in the age group of 21-30 years, male patients, belonging to Lower middle socio economic status, had their education till secondary level. The mean serum prolactin levels were increased from 12.95 ng/ml to 16.26 ng/ml at the end of three months. There was an increasing trend of serum prolactin levels in females and a reverse trend in males. Iloperidone increased the serum prolactin levels but did not cause any prolactin related side effects. It was found that use of Iloperidone in the higher age group did not increase serum prolactin levels even at the end of 90 days.

Conclusions: There is an elevation of serum prolactin with the usage of Iloperidone. Iloperidone at dose of 12-20mg/day is a safer and a better alternative treatment option for patients being treated on second generation anti-psychotics who are suffering from increase in serum prolactin and its adverse effects.

Key-words: Anti-psychotic; Iloperidone; Serum prolactin; Schizophrenia.

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Introduction

Schizophrenia is a severe mental disease that is characterized by different psychopathological symptoms like disturbance of the affect, difficulty thinking or dysfunction of perception. Its lifetime prevalence is estimated at around 1%[1]. Schizophrenia affects around 0.3–0.7% of people at some point in their life[2], or 24 million people worldwide as of 2011 (about one of every 285)[3]. The mean age of onset is between 25-35 years. Women present with schizophrenia 4-10 years after their male counterparts[4]. According to the W.H.O the prevalence and incidence is similar around the world.

The first drugs used in the treatment of schizophrenia were termed first – generation drugs or classical or typical drugs. They were efficacious in reducing positive symptoms like hallucinations and delusions. The limitation of these drugs however was the development of extrapyramidal symptoms (EPS). Clozapine is a neuroleptic which was introduced in 1960's and was later withdrawn due to its ability to cause agranulocytosis [5] was again reintroduced which brought a dramatic change in research expectations. Clozapine caused less EPS and showed efficacy in improving both positive and negative symptoms in patients refractory to first – generation antipsychotic drugs[6]. The reintroduction of clozapine along with the introduction of risperidone opened the door to atypical antipsychotics[7] also known as second generation anti-psychotic drugs (SGAs). Advances in the field of anti-psychotic drugs in the past 30 years have been important leading to the introduction of numerous SGAs. These agents have improved the quality of life of psychotic patients and contributed towards reducing the stigma[8] associated with the disease. After the introduction of new anti-psychotics in 1993, authorization for their use for the treatment of bipolar disorder came in 2003 the research efforts for these drugs showed a manifold increase[9].

It is well known that hyperprolactinaemia is a well documented side effect of most anti-psychotics[10,11]. They act by the blockade of the dopamine D2-receptors on the lactotrophs in the pituitary, the dopamine inhibiting effect on the prolactin release is more[12], leading to hyperprolactinaemia and hormonal side-effects such as menstrual disturbances, galactorrhoea in women and impotence in male[13,14,15,16]. In addition, previous studies show that hyperprolactinaemia due to anti-psychotic therapy is more common in women than in men, despite lower dosages in women[17,18,19]. In order to avoid the prolactin elevation and its side effects newer atypical anti-psychotics like Iloperidone have been tried in the recent times. Its efficacy in the treatment of schizophrenia which has been established in clinical trials along with a favorable safety profile[20,21] (e.g., lack of EPSE, akathisia, not likely to cause clinically significant prolactin elevation) and has the USFDA approval for use in patients suffering from schizophrenia in May 2009[22]. Hence our study is being conducted to evaluate the effect of Iloperidone on serum prolactin and its effects in patients suffering from schizophrenia.

Methods

This open labeled, prospective study was conducted at a tertiary care hospital in the out patient department of Psychiatry. Institutional ethics clearance was taken prior to the study. The sample size was taken as 50 patients and the period of study was from December 2014 to June 2015. Patients who were newly diagnosed, old patients who have discontinued medications for more than two weeks (wash out period of the medications) and suffering from Schizophrenia using the DSM 5 criteria (Diagnostic and statistical Manual of Mental Disorders 5th Edition) were included in the study. Age range is chosen from 20 to 50 years and are married in order to assess any sexual side effects of prolactin, however patients with medical complications,

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pregnancy, breastfeeding, developed any adverse events during the study have all been excluded. Informed consent was taken from the individual and the nature of the study and risks involved and the possible side effects are explained and a written consent is taken from the patient. Kuppuswamy scale was used for classification of the Socio Economic status. Patients have been kept on monotherapy of Iloperidone by the psychiatrist baseline investigation of serum prolactin at the beginning of the study and at the end of 1,2,3 months has been done and at each visit the side effects of elevated serum prolactin has been assessed. End point of the study is the successful completion of 90 days of monotherapy treatment with Iloperidone.

Results

Socio demographic data

Age distribution:

Majority of the patients were in the age range of 21 to 30 years which constitutes 40 percent of the study sample (20 patients). 17 patients were in the age group of 41-50 years and 13 patients were in the age group of 31-40 years (as shown in Table-1).

Table-1: Age Distribution

Age Groups (In Years)	Frequency	Percentage
21-30 Years	20	40
31-40 Years	13	26
41-50 Years	17	34
Total	50	100

Gender distribution:

Out of the total 50 subjects the male subjects were 30 (60%) and the female subjects were 20 (40%). (as shown in **Table -2**)

Table-2: Gender distribution

Gender	Frequency	Percent
Male	30	60.0
Female	20	40.0
Total	50	100.0

Education:

Majority of the patients were found in the secondary level of education followed by uneducated category. These two categories contributed to 68% of the study population (as shown in **Table-3**).

Table-3: Distribution frequency of educational qualifications

Education Level	Frequency	Percent
Uneducated	16	32.0
Primary Level	10	20.0
Secondary Level	18	36.0

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Graduate	6	12.0
Total	50	100.0

Socioeconomic status:

Just under half of the patients i.e. 48% were from the lower middle SES (Socio-economic Status). 15 (30%) of the subjects belonged to the lower SES. 24 (48%) belonged to the lower middle SES. 9 (18%) belonged to the middle SES and 2 (4%) belonged to the upper middle SES. (as shown in **Table-4**)

Table-4: Distribution frequency of socio economic status

Socio-economic status (SES)	Frequency	Percent
Lower SES	15	30.0
Lower Middle SES	24	48.0
Middle SES	9	18.0
Upper Middle SES	2	4.0
Total	50	100.0

Serum prolactin:

It was found that there was an increase in serum prolactin concentration during the course of the treatment. The mean and standard deviation in serum prolactin levels during the follow up are represented in **Table-5**. At baseline (serum prolactin 0 month) the mean was 12.95 and standard deviation (SD) was 4.88. At one month (serum prolactin 1month) the mean was 14.56 and SD was 4.74. At two months (serum prolactin 2 months) the mean was 15.41 and SD was 4.46. At the end i.e., there months (serum prolactin 3 months) the mean was 16.26 and SD was 4.36. There was gradual but significant increase in the mean values but the standard deviation decreased gradually. This indicates that the increase was only very minimal or not much increase was seen in each individual patient but on the whole when all the patients were considered together it showed an increase.

Table-5: Descriptive Statistics of Serum Prolactin

SERUM PROLACTIN in months	Mean	Std. Deviation	N	
SERUM PROLACTIN 0 Months	12.9568	4.88864	50	
SERUM PROLACTIN 1 Months	14.5684	4.74002	50	
SERUM PROLACTIN 2 Months	15.4136	4.46843	50	
SERUM PROLACTIN 3 Months	16.2692	4.36056	50	

A one-way repeated measured Analysis of variance (ANOVA) was conducted (as shown in **Table-6**) to evaluate the null hypothesis that there is no change in the participant's serum prolactin level when measured before, during and at the end of the study. The results of the ANOVA indicated a significant time effect, Wilk's lambda = 0.33, F = 31.56, $p < 0.01$ and $\eta^2 = 0.66$. Thus, there is significant evidence to reject the null hypothesis. Follow up comparisons indicated that the difference was significant, $p < 0.01$. There was

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significant increase in the levels overtime suggesting that the patient's serum prolactin levels were increasing as the treatment progressed.

Table-6: ANOVA for Serum Prolactin

Effect	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[c]
Pillai's Trace	0.668	31.561[b]	3.000	47.000	0.001	.668	94.684	1.000
Wilks' Lambda	0.332	31.561[b]	3.000	47.000	0.001	.668	94.684	1.000
Hotelling's Trace	2.015	31.561[b]	3.000	47.000	0.001	.668	94.684	1.000
Roy's Largest Root	2.015	31.561[b]	3.000	47.000	0.001	.668	94.684	1.000

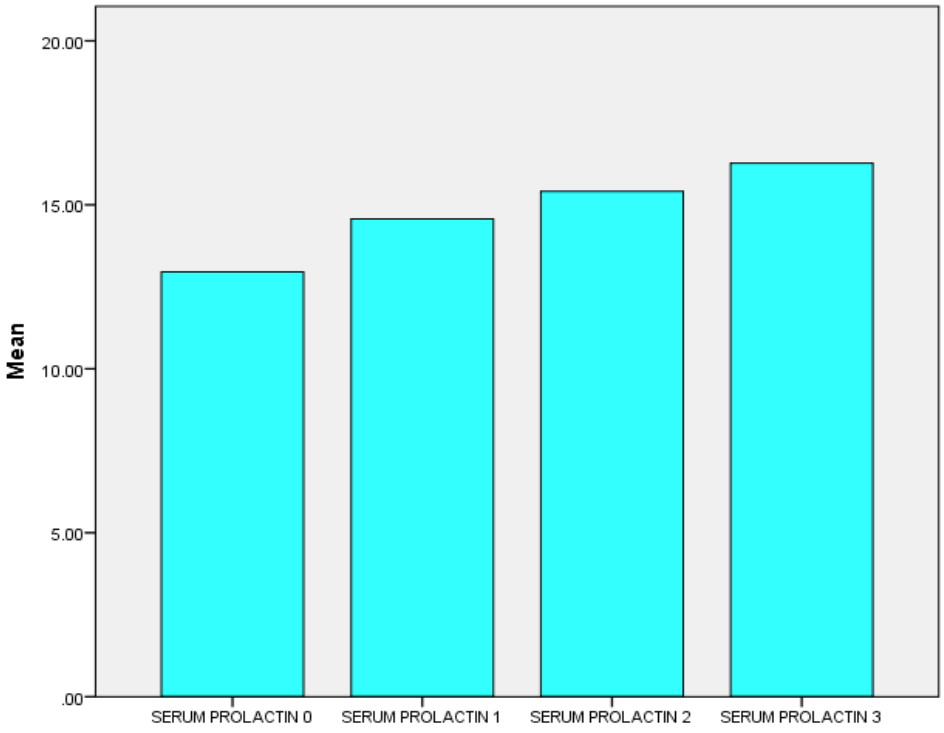
a. Design: Intercept Within Subjects Design: Serum Prolactin

b. Exact statistic

c. Computed using alpha = .05

Figure-1 depicts the bar diagram indicating an increase in serum prolactin levels overtime from around 12 ng/ml to around 16 ng/ml over a period of 90 days.

Figure-1: Bar diagram for serum prolactin



Side Effects of serum prolactin

Side effects like menstrual disturbances, galactorrhoea in women and impotence in male were explored for at the end of each month but there were none reported.

Dose range

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The average dose range in which Iloperidone used in this study was 12-20 mg/day.

Age range verses Serum prolactin

It was found that the age range of 41-50 years at the end of the 3 months of use of Iloperidone had so significant increase in serum prolactin levels. Hence, with increasing age the increase in serum prolactin level was found to be negligible. **(Table-7).**

Table-7: AGE * SERUM PROLACTIN at the end of 3 months

Age Range		SERUM PROLACTIN 3 range				Total
		9-12 ng/ml	13-16 ng/ml	17-20 ng/ml	21-24 ng/ml	
	21-30 Years	6	3	4	7	20
	31-40 Years	3	5	3	2	13
	41-50 Years	6	7	2	2	17
Total		15	15	9	11	50

Gender vs Serum prolactin

It has been observed that at the end of three months number of patients with higher range of serum prolactin levels had a decreasing trend in male population and with an increasing trend in female population. **(Table-8, Figure-2).**

Table-8: Sex * SERUM PROLACTIN 3 months

Sex		SERUM PROLACTIN 3 months range				Total
		9-12 ng/ml	13-16 ng/ml	17-20 ng/ml	21-24 ng/ml	
	Male	13	11	4	2	30
	Female	2	4	5	9	20
Total		15	15	9	11	50

Figure-2: SERUM PROLACTIN at 3 months

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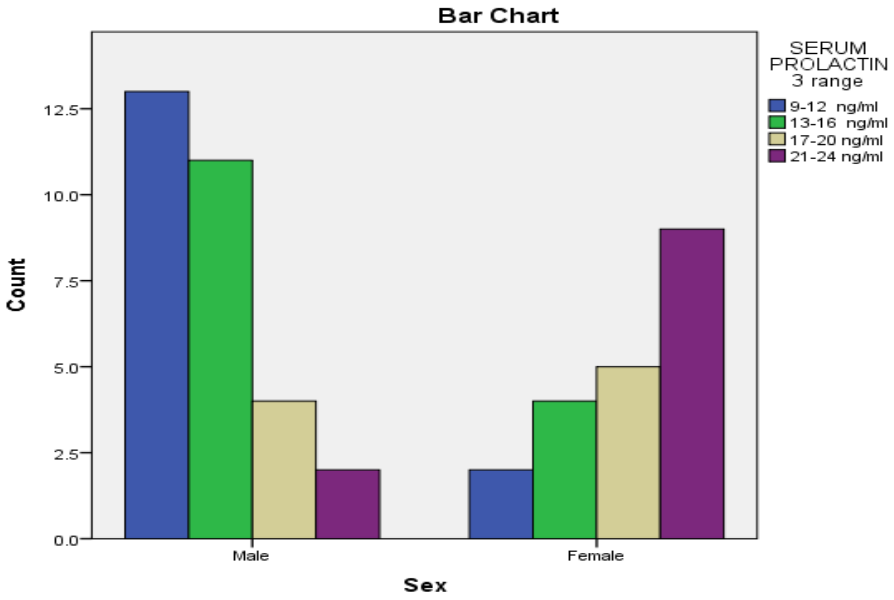

Discussion

In the study conducted here, it was found that Iloperidone above 12 mg/dl the serum prolactin (PRL) concentration started to increase slowly. The prolactin levels increased from a mean value of 12.95 at the beginning of the study to 16.26 at the end of the study period(3 months). This is in accordance with other studies were they found that there was a significant increase in prolactin concentration with $p<0.01$ as with other drugs that antagonize Dopamine type 2 receptiors (D2R), Iloperidone elevates PRL levels[23]. However, the effect of Iloperidone on PRL is reported to be low[24, 25, 26, 27] and transient with acute onset of treatment.[28] Short-term [29, 30] as well as long-term studies[31] showed PRL levels generally decrease or remain unchanged during Iloperidone treatment. However, there does appear to be a potential for PRL elevations in some subjects[29, 32, 33]. In a pooled analysis of three 6-week, prospective, randomized, multicenter, double-blind, placebo- and comparator-controlled trials (n = 1,943), patients were exposed to three dose ranges of Iloperidone (4–8, 10–16 and 20–24 mg/day). PRL levels were generally decreased after treatment with two Iloperidone dosages; least squares mean changes in PRL from baseline to endpoint were −38 and −23.1 ng/ml in patients receiving Iloperidone 4–8 and 10–16 mg/day, respectively. PRL levels were not available for the Iloperidone 20–24 mg/day group[30].

In our study, it was observed that in males there was a pattern of decrease in elevation of serum prolactin, where as there was an increase in the serum prolactin levels in females at the end of 90 days. Similar findings were reported in a study conducted by Kuruvilla *et.,al*[19].

In this study, though there was significant increase in serum prolactin level, there was not a single recorded case of galactorrhea. And the hyperprolactinemia was only profound when the dose was titrated to 12 mg/dl or above. However Arghya dutta *et al.*,[34] have reported a case of Iloperidone induced galactorrhea in a middle aged female. A 35 year old female with symptoms of schizophrenia was started with Iloperidone and dose was titrated from 1mg twice a day to 4 mg twice daily within a week. After three months of starting the treatment she developed galactorrhea and she missed her menstrual cycle. Serum Prolactin was estimated and found to be 31.70 ng/ml, which was way higher compared to the normal reference range (normal reference range for premenopausal female (4.79–23.3).

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Limitaions

- Though the total sample size is adequate male and female distribution of the total sample is uneven hence the serum prolactin elevation cannot be compared with each other.
- There was no comparator or a placebo involved to compare the findings.
- In this study sample high doses of Iloperidone was not used.

Conclusions

There is an elevation of serum prolactin with the usage of Iloperidone.

The elevation of serum prolactin was and from base line of 12.9 ng/ml a maximal increase at the end of 90 days to 16.2 ng/ml.

The level of increase in serum prolactin was not sufficient to cause any significant side effects of elevated serum prolactin.

Iloperidone increased the serum prolactin levels but did not cause any prolactin related side effects.

With increasing age, the increase in serum prolactin level was found to be negligible.

There was an increasing trend of serum prolactin levels in females and a reverse trend in males.

Hence, Iloperidone at dose of 12-20mg/day is a safer and a better alternative treatment option for patients being treated on second generation antipsychotics who are suffering from increase in serum prolactin and its adverse effects.

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