

# The effectiveness of vaginal lisuride in the treatment of hyperprolactinemia

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## Abstract

**Background:** hyperprolactinemia is a disorder which may be represented clinically by one or more of the following: galactorrhea ,infertility , oligmenorrhea , amenorrhea, luteal phase defect and hirsutisim, lisuride drug was recently used vaginally in the treatment of hyperprolactinemia to decrease the side effects by its use orally .

**Patients & Methods:** An interventional study conducted over a period of one year from October 2011 to October 2012 , in Al-Yarmok Teaching Hospital ,50 patients presented with one or more of the following symptoms, abnormal menstrual cycle(amenorrhea,oligmenorrhea), infertility(unovulatory), galactorrhea. All the 50 patients with elevated prolactin level were received lisuride (dopergin) 0.2 mg vaginally at bed time and continued for 12 weeks ,serum prolactin was measured at 8,12 weeks with monitoring of ovulation by serial U/S.

**Results:** The study include fifty patients with mean age was 27.2years  $\pm$ SD7.01 ,and there mean weight was 62.1kg  $\pm$ SD9.08

All 50 patients had elevated serum prolactin level with mean 66.1ng/ml  $\pm$ SD 15.5,at the end of the treatment the range of serum prolactin level between 6-17ng/ml  $\pm$  SD2.9 , which was significantly lower than pre treatment level  $P = 0.0001$  At the end of the treatment 86% achieved regular cycle , Ovulation occur in significant number of patients p value  $< 0.01$ , (37.5%) of them get pregnancy .less side effect compared to oral lisurid

**Conclusion:** Vaginal lisurid is an effective drug used for the treatment of hyperprolactinemia to avoid the discontinuation of the drug because of its side effect, when given orally.

**Keywords:** lisurid ,hyperprolactinemia, infertility

## INTRODUCTION

Hyperprolactinemia represents a real challenge for the gynecologists ,endocrinologist and neurosurgeon(1). Hyperprolactinaemia is the presence of abnormally high levels of prolactin in the blood. Normal levels are less than 500 mIU/L [20 ng/mL or ug/L] for women. Prolactin is a peptide hormone produced by the anterior pituitary gland that is primarily associated with lactation and plays a vital role in breast development during pregnancy(2). hyperprolactinemia is a disorder which may be represented clinically by one or more of the following :galactorrhea ,infertility , oligmenorrhea ,premenstrual tension syndrome, amenorrhea, luteal phase defect and hirsutisim (3) In men it has been reported to cause hypogonadism , impotence and loss of

libido(4). Hyperprolactinemia may result from a prolactin secreting adenoma(5) or from a non-functioning disconnection, tumour in the region of the hypothalamus or pituitary, which disrupts inhibitor influence of dopamine on prolactin secretion. Hyperprolactinemia could also occur because of hypothyroidism, polycystic ovarian syndrome and several drugs, i.e. the dopaminergic antagonists like phenothiazines, domperidone and metoclopramide (6) .The standard primary treatment is the dopamine agonist (7) . The two most commonly prescribed drugs in the treatment of hyperprolactinemia are bromocriptine and cabergoline. Both medications are dopamine receptor agonists and share many characteristics and adverse Effects (8) Cabergoline, in particular, probably is more effective and causes fewer

adverse effects than bromocriptine. However, it is much more expensive. Cabergoline is often used in patients who cannot tolerate the adverse effects of bromocriptine or in those who do not respond to bromocriptine(9,10).

Lisuride (dopergin) is a potent dopamine agonist initially used as a prolactin-lowering compound, it is well tolerated and no particular toxicity has been reported, It has a high affinity for the dopamine D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors, as well as serotonin 5-HT<sub>1A</sub> (hydroxytryptamine<sub>1A</sub>) (11) and 5-HT<sub>2A/C</sub> receptors.(12) lisuride was developed later on and assumed to have less side effects than other dopamine agonist drugs although it was not free of it (13).

The study was conducted aiming to assess the effectiveness of vaginal lisuride in treatment of hyperprolactinemia.

## PATIENTS AND METHODS

This study conducted over a period of one year from October 2011 to October 2012 in Al-Yarmok Teaching Hospital, included patients presented with one or more of the following symptoms, abnormal menstrual cycle (amenorrhea, oligmenorrhea), infertility (unovulatory), galactorrhea, with hyperprolactinemia.

Verbal consent was taken from all patients, complete history including menstrual, reproductive, medical history of chronic illness and drug history was taken from each patient. general examination, abdominal, pelvic and vaginal examination performed. BMI was calculated.

All the patient did hormonal assay include FSH, LH, testosterone, Thyroid function test (T<sub>3</sub>, T<sub>4</sub>, TSH) and Serum prolactin level which was measured by ELISA test system, the kit of Monobind Inc USA, the normal level of prolactin ranged between 1.2-19.5 ng/ml.

For all the patients abdominal and pelvic U/S were performed.

56 patients with elevated prolactin level, 50 patients complete this study, 6 patients excluded. Patients with abnormal thyroid functions test, PCOS, or under the effect of any medication that may cause elevation of prolactin level and patient with vaginal infection, were excluded from this study.

All the 50 patients received lisuride (dopergin) 0.2 mg vaginally at bed time and continued for 12 weeks, serum prolactin was measured at 8, 12 weeks with monitoring of ovulation by serial U/S.

Lisuride discontinued once pregnancy confirmed. Descriptive statistic like mean, standard deviation were

used together with analytic statistic like chi-square, P value of <0.05 was considered as significant.

## RESULT

The study include fifty patients with an age ranged between 16-40 years with mean 27.2 years  $\pm$ SD 7.01, and their weight range between 50-75 kg with mean 62.1 kg  $\pm$ SD 9.08. All 50 patients had elevated prolactin level which was ranged between 50-105 ng/ml with mean 66.1 ng/ml  $\pm$ SD 15.5. 31 patients with unovulatory infertility, 37 with oligmenorrhea, 8 with amenorrhea, 8 with galactorrhea, as shown in table 1.

The level of serum prolactin starting to decline gradually and the duration that need to reach the normal level did not depend on the value of serum prolactin prior to treatment, at the end of the treatment the range of serum prolactin level between 6-17 ng/ml  $\pm$ SD 2.9, which was significantly lower than pre treatment level P = 0.0001. Most of the patients at the beginning of the study complaining from more than one symptom, irregular cycle (amenorrhea, oligmenorrhea), galactorrhea and/or infertility. After the end of the treatment only 7 patients out of 45 (37 oligmenorrhea & 8 amenorrhea) failed to achieve regular cycle p value <0.01. At the end of the study 43 patients had regular cycle.

Ovulation occur in significant number of patients p value < 0.01, it was achieved in 24 patient out of 31 (77.4%), 9 of them get pregnancy (37.5%) and 7 only failed to get pregnancy or ovulation (22.6%). Galactorrhea stopped in all patient except in one (12.5%).

## DISCUSSION

Lisuride a dopamine agonist used for the treatment of hyperprolactinemia orally but there are often side effect that may lead to discontinuation of the treatment, because the vagina provide an acidic environment which is important for the absorption of the lisuride, we studied the effectiveness of vaginal lisuride and its side effects.

In this study there was significant fall in the level of serum prolactin during treatment period from (66.1  $\pm$  15.5) to (9.9  $\pm$  2.8) this agree with the study done by Diaa El-Mowafi et al where the serum prolactin decline from (72.7  $\pm$  23.7) ng/ml to (12.0  $\pm$  5.7)<sup>(14)</sup>.

Since the normal menstruation is a complex process that requires many things to happen properly and at the correct time with the proper hormone levels, Significant number of patients return to normal menstrual cycle (38) patients (84.4%) when the serum prolactin return to its normal level.

There was no study that deal with the regularity of the menstrual cycle with vaginal lisurid ,but it agree with study done by Atef M.Darwish et al who use bromocriptine vaginally and found that 2.5mg daily dose was sufficient with the vaginal route as the vagina allows slow absorption of the drug while 5mg daily dose was needed with oral route <sup>(15)</sup> .

80% of patients had restored regular menstrual cycle according to the study done by Dececco by using lisuride orally .<sup>(16)</sup>

Galactorrhea had been stopped in 98% ( 7 out of 8,) similar result had reported by Khairunisa et al 94.7% after use of lisuride orally<sup>(17)</sup> and all the patients with galactorrhea included in Diaa El-Mowafi et al study were improved<sup>(14)</sup> .

At the end of this study 24 patients out of 31 ovulated (77.4)% ,similar result found by Diaa El-Mowafi et al study<sup>(14)</sup> .

Pregnancy rate in our study (37.5%), lower rate (35.7%), reported by Diaa El-Mowafi et al study<sup>(14)</sup> .but higher

rate was reported (42.4%) ,after 3 months of oral lisuride use by Scholz and Horowski<sup>(18)</sup>.

The non oral routes of administration of drugs avoid destruction or inactivation by the gastric acidity ,eliminate stomach irritation ,and omit drug destruction by portal circulation <sup>(19)</sup>.

The side effects from use of lisuride vaginally was frequent , nausea occur in 46% of the patient but still lower than the study done by Esraa H. Humadi by using lisuride orally 60% , dizziness occur in 24% ,30% respectively ,headache 16% in both studies <sup>(20)</sup>.

In this study the discontinuation of the treatment only 2% (only 1 patient can't tolerate the drug the drug and it is lower than the study of Murat et al where discontinuation observed in 10%(2 out of 20 patients) due to orthostatic collapse and severe vomiting <sup>(21)</sup>.

So in conclusion the use of lisuride vaginally can avoid the side effect that lead to discontinuation of the drug in addition it had the same efficacy if compared with oral use.

**Table 1. The Frequency of Clinical features of patient with hyperprolactinemia before/after treatment with Vaginal Lisurid**

Clinical feature (Clinical complaints)	Patients number (%) before the treatment	Patients number (%) after the treatment	Percent of improvement (%)	Chi square P value Significance
Un ovulatory infertility	31(62)	7(14)	48	30.3 P value <0.01 Significant
Oligomenorheoa	37(74)	6(12)	62	73.92 P vlaue <0.01 Significant
Amenorheoa	8(16)	1(2)	14	1.16 P value >0.05 (No rejection for Null hypothesis)
Regular menstrual cycle	5(10)	43(86)	76	288.8 P value <0.01 Significant
Galactorheoa	8(16)	1(2)	14	1.16 P value >0.05 (No rejection for Null hypothesis)

**Table 2. Side effects of vaginal lisuride and their frequency**

Side effect	No of patient	%
Nausea &vomiting	23	46
Dizziness	12	24
Headache	8	16
Vaginal discharge	2	4
Vaginal soreness	5	10
Discontinuation of treatment	1	2

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