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ORIGINAL ARTICLE

The Comparison of Side Effects and Patients' Tolerance toward Prolonged use of Vaginal and Oral Bromocriptine

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ABSTRACT

Background: Hyperprolactinemia is a disorder which is present in clinical forms of galactorrhea, infertility, menstrual disturbances, hirsutism and premenstrual syndrome. Bromocriptine is a dopamine agonist and is a drug of choice for the treatment of this disease. However, the patient's tolerance of this drug is also important because of prolonged use, which can sometimes last for years. In the present research, the Bromocriptine's side effects and its acceptance level on the part of patients were studied comparing the two forms of oral and vaginal use. This study was a single–blind clinical trial. The subjects were clients of the gynecologic clinic with complaints of galactorrhea, menstrual disturbance, hirsutism, or infertility. The sample composed of 180 women (two groups of 90 people) and the length of the study was two years. The subjects were divided into two groups; oral and vaginal. Prior to the study the subjects were examined systemically and gynecologically for other systemic and local complications. After health assurance of the other systems of the body, drugs were administered in the two forms. The data was gathered using a questionnaire and was analyzed by SPSS (V.21).This study showed that the side effects of bromocriptine were 100% in oral users and 43.2% in intra-vaginal users. The most frequent complication in the oral use was nausea (38.9%), and vaginal itching (22.3%) in the intra-vaginal use. Vertigo in oral-form was more frequent as compared to the vaginal form (27.8% versus 2.3%). Hypotension, on the other hand, was seen in 11.2% of the cases among oral-users, whereas this figure among the intra-vaginal users was zero. About 51.2% of the oral-users had more than two side effects. In both groups, however, the highest complications were seen within the first ten days of the treatment (66.7% and 37.8%). It should also be noted that the severity of complications in 31.2% of the oral group and %11 of the vaginal group were so high that resulted in discontinuation of the drug.

Conclusion: *There is a significant difference in severity and kind of complications between oral and vaginal use of bromocriptine and acceptance and duration of drug intake in vaginal form is found to be more compared to the oral form.*

Keywords: *Bromocriptine, oral, vaginal, side effects, drug acceptance.*

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INTRODUCTION

Hyperprolactinemia corresponds to a real challenge for the gynecologists, endocrinologists, andrologists, and neurosurgeons. It is the most common endocrine disorder of the hypothalamic-pituitary axis. The prevalence of hyperprolactinemia ranges from 0.4% in adult population to as high as 9-17% in female disorders. Symptoms of hyperprolactinemia generally include signs of gonadal dysfunction, yet female patients frequently experience oligomenorrhea, amenorrhea and galactorrhea [1]. Pathological hyperprolactinemia is also associated with infertility [1] and reduced libido [2] and an increased risk of long-term complications including osteopenia and osteoporosis [3-5]. These long-term complications associated with elevated prolactin levels suggest that even patients who are unconcerned by their clinical symptoms or who do not wish to receive therapy in order to restore fertility should be considered for long-term therapeutic intervention [6]. Bromocriptine mesylate, a dopamine agonist, is a derivative of lystergic acid that binds to dopamine receptors and is therefore a useful tool in the treatment of many prolactin-dependent disorders. Treatment of hyperprolactinemia through oral bromocriptine is usually accompanied with a high number of complications. Due to its numerous adverse effects, the alternative vaginal approach has been successfully used in non-tolerant cases [7]. Kletzky and Vermesh demonstrated that the vaginal form of bromocriptine is effective as oral form with fewer side effects [8]. So, the aim of this study is to compare the clinical effectiveness, tolerability, and side effects of oral versus vaginal bromocriptine in hyperprolactinemic patients.

MATERIALS AND METHODS

This study was a single-blind clinical trial. The sample of the study was the gynecologic clinic patients with the complaints of the galactorrhea amenuria, dysfunctional uterine bleeding, and infertility which consisted of 180 female patients with pathologic hyperprolactinemia. The subjects were randomly divided into 2 groups regardless of possible cause of this pathologic hyperprolactinemia. A basic inclusion criterion was to make sure that they were not taking any Prolactin-normalizing drug before entering this study for at least 1 month ago. Group A comprised of 90 patients who orally took 2.5 mg bromocriptine tablets twice daily for six months and Group B included 90 patients who used vaginal suppositories once daily for six months. SP was measured before and after therapy in all cases by radioimmunoassay technique and the individuals whose prolactin were higher than 721mu/l were considered as suffering from hyperprolactinemia. It should also be noted that this study was approved by the research council of the Ardabil Medical Sciences University. All patients signed a written consent to participate in this study. All patients had high pretreatment baseline SP and were advised to take the drug regularly in fixed times. At the end of the treatment course, the patients were asked to assess their experience with their approach to therapy. Data were collected and analyzed with SPSS (V.21). Unpaired sample T-test was used to determine significant differences between means of two groups.

RESULTS

The main side effects and the clinical data are shown in Table 1. The beginning times of the side effects are shown in Table 2 and the intensity of side effects is shown in Table 3. According to the results, the most frequent complication was nausea in the oral group (83.9%) and vaginal itching in the other group (22.3%). Also dizziness in group A was higher (72.8%) than that of group B (2.3%). Furthermore, fainting in the oral group was 11.2%, but zero in vaginal group. In 44.6 of cases (51.2%) of oral group there were more than two complications. According to the results presented in Table 3 (the beginning time of the complication), 60 cases (66.7%) in group A and 25 cases (27.8%) in group B showed side effects during the first 10 days which has led to drug intake cessation. The prominent complications leading to discontinuation of the drug were digestive complications and dizziness. According to the presented results in Table 2 (the severity of complications), 28 cases (31.2%) of the oral group and 20 cases of the vaginal group underwent severe complications, which led to discontinuation of the drug. However, mild complication which led to reduction in the drug dose appeared in 42 cases (46.7%) among the oral group and 10 cases in the vaginal group. There were 20 cases (22.2%) among oral users and 60 cases among vaginal group with a little complication which needed no alteration in drug dose. It was determined in this study that the complication due to the drug form was 34.3% for the vaginal form and 100% for oral form. By using unpaired sample T-test, it appeared that there is a significant difference between the two groups in the severity of complications (P=0.001). It was also shown that there was no significant difference in the beginning time of complications between the two groups (P=0.9). Generally, according to the obtained results, it was understood that the severity of complication and the distribution of complications was different in the two groups, but the beginning time of complications was the same in both.

Item	*Group A(Oral)*		*Group B(Vaginal)*	
	frequency	percent	frequency	percent
nausea	35	38.9	2	2.3
vomiting	20	22.4	10	11.2
constipation	0	0	5	5.6
fatigue	0	0	0	0
fainting	10	11.2	0	0
dizziness	25	27.8	2	2.3
vaginal Itching	0	0	20	22.3
no side effect	0	0	51	56.7
P value	0.0001			

Table 1: Distribution of Clinical side effects in two groups

Item	*Group A(Oral)*		*Group B(Vaginal)*	
	frequency	percent	frequency	percent
first 10 days	60	66.7	25	3.8
Second 10 days	30	33.3	14	15.6
third 10 days	0	0	0	0
total	90	100	39	43.33
P value	0.9			

Table 2: Time of the beginning of side effects

Item	*Group A(Oral)*		*Group B(Vaginal)*		*P value*
	frequency	percent	frequency	percent	
severe	28	31.2	20	22.2	0.023
moderate	42	46.7	10	11.1	0.012
low	20	22.3	60	66.7	0.006
total	90	100	90	100	

Table 3: Intensity of side effects in two groups

DISCUSSION

Bromocriptine mesylate, as a dopamine agonist, has been used for the treatment of hyperprolactinemia since a long time. It is proved to be effective in causing dramatic decline of SP after its oral use. However, the problem is that it frequently causes headaches, dizziness, and faintness in 50-70% of women [9]. Non-oral approach is claimed to help eliminate most of these symptoms [7]. In fact, advantages of vaginal route over oral using are well established through many studies [7, 9]. The non-oral routes of drug intake avoid destruction or inactivation by the PH or enzymatic activity of the stomach or intestine, eliminate stomach irritation, and omit drug destruction by portal circulation by first passing through the liver. Moreover, these routes are convenient for patients who may be unable or unwilling to swallow medication and it is an effective route in the treatment of patients with vomiting episodes. For systemic effects, the mucous membranes of the rectum and the vagina permit the absorption of many soluble drugs. Although the rectum is used frequently as the site for the systemic absorption of the drugs, the vagina is less frequently used for this purpose [10]. In this study, we prescribed therapeutic doses of bromocriptine mesylate for the two groups as previously described. The optimal therapeutic oral dose is usually 5 mg/day because the half-life after oral administration is 3 to 7 hours [9]. On the other hand, 2.5 mg daily dose was sufficient with the vaginal use as the vagina allows slow absorption of the drug and hence SP level remains elevated for a longer time with the vaginal approach. Also, several investigations were showed that many drugs such as leuprolide, indometacin, and misoprostol show higher effects when used vaginally or rectally as compared to orally [11-13]. This study tested the same formulation of bromocriptine mesylate in the two groups of hyperprolactinemic patients. Most of the study patients were intolerant to oral route making them good candidates for testing the tolerability of the drug via the alternative approach. In the comparison of oral and vaginal using of bromocriptine, we found that the vaginal users had fewer complications, whereas almost all of the oral users experienced side effects. In another carried out study by Darvish, et al. Bromocriptine using in vaginal form was found fewer side effects (only in 3 cases were observed). Only vaginal itching was seen in vaginal using. Among these three cases, only one case was so severe that led to discontinuation of the drug using [14]. In another research (Vermesh and Kletzky), it was concluded that the vaginal bromocriptine using was equal in efficacy to the oral use, while with the former there were fewer side effects which were usually mild and subsided in a few days [8]. In our study, besides the comparison of the frequency of side effects in the two forms of the drug, the severity as well as the beginning time of the side effects was also studied. It appeared that the complication which has not been reported in the similar studies was vaginal itching in 20 cases, who did not suffer from candidiasis. This side effect in 15 of 20 cases was so severe that led to discontinuation of the drug, while in the remaining cases itching were relieved by a reduction in the drug dose.

CONCLUSION

Through comparing oral and vaginal form of bromocriptine using, we could conclude that the vaginal form has fewer complications. Vaginal use of bromocriptine, as an alternative non-oral approach, should be considered during the counseling of patients. Of course, we recommend a larger sample-sized, preferably multicentered, clinical trial to define the exact role of this alternative approach in clinical practice.

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