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Efficacy of Intranasal Buserelin for Preoperative Treatment of Uterine Leiomyomas

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ABSTRACT

Objective To study the efficacy of intranasal buserelin for preoperative treatment of uterine leiomyomas.

Design Open non-comparative study.

Setting Reproductive endocrine unit, Ramathibodi hospital.

Subjects Seventeen patients with symptomatic uterine leiomyomas.

Interventions All patients were treated with intranasal buserelin 900 ug/day for 12-16 weeks. Hysterectomy was performed within 2 weeks after discontinuation of buserelin treatment.

Main outcome measures Clinical symptoms, volume of uterine leiomyomas and adverse effects of the treatment.

Results Two patients were excluded from the study, one had severe headache four days after drug used, the other was lost to follow up with unknown reason. The mean volume of uterine leiomyoma decreased by 33% after 12 weeks of treatment from mean pretreatment volume of 274.94 ± 37.45 cm^3 to 182.46 ± 16.78 cm^3 ($P < 0.05$).

Nine of fifteen patients experienced more than 25% reduction in leiomyoma volume. Tumour related symptoms (dysmenorrhea, pelvic pain and pressure symptoms) decreased in all cases after 8 weeks of treatment.

Conclusion This preliminary results demonstrate the efficacy of intranasal buserelin in reduction of uterine leiomyoma and alleviation of clinical symptoms. The usefulness and cost-benefit of GnRH-a preoperative treatment of uterine leiomyoma should be evaluated further.

Key words : leiomyoma, GnRH-a

Uterine leiomyomas are the most common benign tumour of pelvic neoplasm. Although its aetiologic cause is unknown, many evidences have suggested that this tumour is estrogen dependent.[1,2] Continuous administration of gonadotropin releasing hormone agonist (GnRH-a) could suppress the gonadotropins and sex steroids production and subsequently reduce the growth of uterine leiomyomas.[1,2] After the first report of reduction of leiomyoma size by the GnRH-a therapy was published in 1983,[3] many studies have confirmed the reduction of leiomyoma volume and alleviation of tumour related symptoms.[4-11] Because the regrowth of tumour occurs rapidly after discontinuation of the drug using, so this therapy has been used as a preoperative treatment. In Thailand, GnRH-a has been available for several years, but no study of its efficacy for the treatment of uterine leiomyoma in Thai patients has been reported. Buserelin is a GnRH-a which glycine at position 6 and 10 of the natural GnRH molecule are replaced by D-serine and ethylamide respectively. Its potency is 20 times more than the natural GnRH.[9]

The objective of this report was to study the efficacy of intranasal buserelin for preoperative treatment of uterine leiomyomas in Thai women.

Materials and Methods

This study was open, non-comparative clinical trial. Seventeen patients with symptomatic leiomyomas were enrolled to the study. The inclusion criteria were as follows :

1) had uterine leiomyoma with related symptoms justified for surgical therapy.

2) had one leiomyoma at least more than 3 cm in diameter by ultrasound.

3) were not pregnant and not desirous of future pregnancies.

4) had haemoglobin equal to or more than 8 g/dL and had no serious infectious disease, history of depression, abnormal liver function and impaired renal function.

Each patient received intranasal buserelin (Suprefact E^R, Hoechst, Germany) 900 μg/day (300 μg x 3) for 12-16 weeks. The treatment was started in the first week of menstrual cycle. Patients were instructed to use the record form of buserelin administration. The size of largest leiomyoma was measured by abdominal ultrasound in three dimensions by two gynaecologists using 3.5 MHz transducer (Aloka SSD 1200, Tokyo, Japan) before treatment and every four weeks after treatment. The leiomyoma volume was calculated by formula $0.523 \times D_1 \times D_2 \times D_3$ (D_1, D_2, D_3 : diameter of leiomyoma in three dimensions). Serum estradiol (E_2) concentration was determined by using radioimmunoassay method before treatment and at 4, 8 weeks after treatment. Clinical symptoms and adverse effects were recorded every four weeks. An unpaired t - test was used to test the difference of leiomyoma volume between pretreatment and after treatment.

Results

Two patients were excluded from the study. One had severe headache four days after drug used and the symptom disappeared with discontinuation of drug administration, the other was lost to follow up after 8 weeks of treatment with unknown reason. Data of the remaining fifteen patients who completed the study were analysed. Table 1 showed patient characteristics. All patients were in the reproductive age. The mean body mass index (BMI) was 23.12 ± 0.77 kg/m^2 (range 19.13 - 28.30) .

Tumour reduction was observed in all but one patient. The mean volume of leiomyoma

decreased by 33% from pretreatment volume of 274.94 ± 33.45 cm^3 (range 91.58 - 695.28) to 182.46 ± 16.78 cm^3 (range 61.50 - 288.22) after 12 weeks of treatment (Fig. 1). Most patients (53.3%) experienced 25 - 50% reduction in leiomyoma volume, one had more than 50% reduction (Table 2). Patient symptoms such as pelvic pain (5 cases), dysmenorrhea (6 cases) and menorrhagia (9 cases) disappeared after 8 weeks of treatment (Table 3). Nevertheless, vaginal bleeding was observed in 2, 5 and 3 patients at the end of 4, 8 and 12 weeks respectively.

In 7 out of 15 patients, serum E_2 decreased to post-menopausal level. Of these, 3 patients decreased after 4 weeks of treatment and the other 4 occurred after 8 weeks. However, the mean serum estradiol before and during treatment did not differ significantly.

In one third of the patients, no gonadal suppression was observed during treatment. Despite of no gonadal suppression, tumour

Table 1. Patient characteristics

	Mean ± SEM	Range
Age (yr)	40.07 ± 1.20	28 - 46
Height (cm)	154.07 ± 1.39	149 - 168
Weight (kg)	54.89 ± 2.00	45 - 68
BMI (kg/m^2)	23.12 ± 0.77	19.13 - 28.30

SEM - standard error of mean

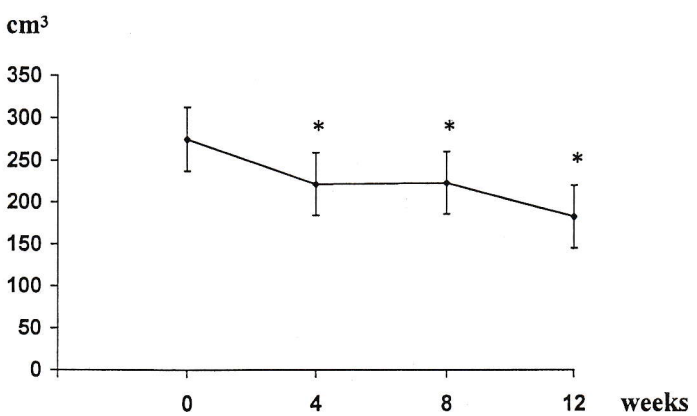

Fig. 1. Changes in volume of uterine leiomyoma during buserelin treatment.
* $P < 0.05$ as compared to pretreatment

Table 2. Number of patients in different degree of tumour reduction

Degree of tumour reduction	No.	%
< 0.1%	1	6.7
0.1 - 25%	5	33.3
25 - 50%	8	53.3
> 50%	1	6.7
Total	15	100.0

Table 3. Number of patients with uterine leiomyoma related symptoms

	Duration of treatment (weeks)			
	0	4	8	12
Pelvic pain	5	2	-	-
Dysmenorrhea	6	3	-	-
Menorrhagia	9	1	-	-
Vaginal bleeding	-	2	5	3

reduction occurred in 4 of 5 patients.

Two patients had hot flushes. No other adverse symptoms were reported in the fifteen patients.

Discussion

The result of this study confirms previous studies that GnRH-a effectively reduce volume of uterine leiomyoma in most patients. The reduction of mean volume of uterine leiomyoma was observed by 33%. The magnitude of tumour reduction in the present study is comparable to the others using intranasal buserelin in the same dose for 12 weeks of therapy.[6,10] However, the magnitude of volume reduction in this study is less than the others which have demonstrated the reduction of 44-50% after 3 months of subcutaneous long acting GnRH-a usage. [5,7,8,11] In the present study, 9 of 15 patients (60%) experienced more than 25% of volume reduction, and only one patient (6.7%) experienced more than 50% of volume reduction while Friedman et al[7] have demonstrated that 15 of 18 patients (83%) had more than 25% of volume reduction and 4 of 18 (22%) had more than 50% of volume reduction after using subcutaneous leuprolide acetate depot, long acting GnRH-a, for 12 weeks of therapy. These have shown that the efficacy of long acting GnRH-a is superior to the short acting one, which can be explained by the difference of bioavailability, especially absorption of two forms of the drugs. The absorption of intranasal buserelin is less than 5%, thus the serum drug concentration is so low.[12] The gonadal suppression is achieved more complete in long acting than short acting GnRH-a. Therefore, more reduction of tumour volume should be observed in the long acting one. The study of Friedman et al,[5] in which comparison of using subcutaneous and intranasal leuprolide in the treatment of uterine leiomyoma has demonstrated that significant reduction of tumour volume was achieved in the subcutaneous group, but no reduction of tumour volume was occurred in the intranasal group, can confirm the explanation.

Although only seven patients had serum E_2 concentration below 30 pg/ml, but tumour reduction was observed in 14 of 15 patients, especially 4 of 5 patients had tumour volume reduction despite of no gonadal suppression. So the gonadal suppression in different degree in most patients with the fluctuation of E_2 concentration during the treatment should be considered. This fluctuation of E_2 occurred promptly, rapidly, thus regrowth of leiomyoma was not observed, and caused no significant difference of mean serum E_2 concentration between pretreatment and during treatment. This is not comparable to the others which have demonstrated the complete gonadal suppression occurred at the end of 4 weeks of intranasal buserelin.[6,10] These results may be explained

in part by the difference of compliance of patients in each study. For long acting GnRH-a, E_2 concentration of all cases were decreased to post-menopausal level after 4 weeks of treatment with the reasons as described above.[5,7,8,11]

From this study, the reduction of tumour volume was observed despite the incomplete gonadal suppression. This indicates that the response of leiomyoma to GnRH-a does not necessitate absolutely severe hypoestrogenism and variation of individual sensitivity of leiomyoma that may be explained in part by additional factors which effect tumour growth and genetic factors.

The incidence of vaginal bleeding and adverse symptoms observed in this study were much less than the others.[5,7] This should be the advantage of the drug that all patients can tolerate with no more suffering during treatment. Because of reduction in leiomyoma volume, tumour related symptoms diminished and disappeared at the end of 8 weeks which is comparable to the previous reports.[10,11] This preliminary report demonstrated the efficacy of intranasal buserelin in reduction of uterine leiomyoma volume and alleviation of clinical symptoms in Thai patients. Preoperative GnRH-a administration may improve patient condition before surgery, may facilitate the surgical procedure and diminish blood loss during operation. However, the usefulness and cost-benefit of GnRH-a as a preoperative treatment of uterine leiomyoma should be evaluated further.

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