Buserelin Acetate Implants in the Treatment of Pain in Endometriosis

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Abstract

Objective : To examine the treatment of pain in endometriosis by buserelin acetate implants.

Design : Fourteen patients with laparoscopically confirmed pelvic endometriosis were included in the study. All presented with severe dysmenorrhea with or without deep dyspareunia and pelvic pain. Buserelin acetate 6.6 mg. Implants were injected subcutaneously in the lateral region of the anterior abdominal wall, 3 doses every 8 weeks in group 1 (n=7) and 2 doses every 12 weeks in group 2 (n=7). Bone mineral density (BMD) was measured at the lumbar spine by dual energy X-ray absorptiometry (DEXA) before initiation of treatment and 1 year after. Symptoms, pelvic examination, ultrasonogram and serum estradiol were recorded every 4 weeks until two regular menses were established.

Results : All the painful symptoms were relieved and eventually disappeared in every patient within 4-6 weeks. Mean duration of amenorrhea in group 1 (408.4±47.7 days) was significantly longer than group 2 (331.3±22.4 days), $p < 0.01$. Mean duration of first observed side effects was 2.7±1.6 weeks. Hot flushes were the most common side effects. Serum estradiol levels were below 15 pg/ml in all patients and there were no significant differences between the two groups during amenorrhea. There was significant bone loss in both groups, 6.49±4.90 per cent in group 1 and 7.71±5.67 per cent in group 2. However, there were no significant differences between the two groups for lumbar BMD before and after treatment.

Conclusion : Buserelin acetate implants are effective in the treatment of pain in endometriosis. These implants should have an important clinical application when chronic treatment is indicated. Further study is needed to design how this preparation should be used to minimize the adverse effects.

Key word : Endometriosis, Buserelin Acetate Implants

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Gonadotrophin releasing hormone agonists (GnRHa) are widely used in the treatment of endometriosis[1,2]. Although the regression of endometriosis, pregnancy rates and recurrence rates are independent of the route of administration and dosage of GnRHa, patient compliance, amenorrhea rates and subjective improvement are better with depot preparations with high dosages [3]. Most GnRHa have been designed with a biological efficacy of four weeks. Treatment with these monthly GnRHa are usually limited to six months because of effects on bone loss, which appears to be reversible after this relatively short period[4,5]. The subcutaneous implant mode has been found to be very effective in suppression of ovarian hormone secretion longer than 2 months [6]. Previous studies found that patient acceptibility was even better with the longer depo preparation[7] and suggested that this implant should have an important clinical application where chronic treatment is indicated[6]. The use of these longer-acting preparations would be advantageous in the treatment of pain in endometriosis.

Buserelin acetate implant is a GnRHa implant designed to be effective for 2-3 months. The length of time taken for ovarian function to recommence varies considerably between 79-290 days with a single injection[6]. This study aimed at examining the treatment of pain in endometriosis by buserelin acetate implants.

MATERIAL AND METHOD

Fourteen patients with laparoscopically confirmed pelvic endometriosis diagnosed between October 1997 and October 1998 were included in the study. All patients presented with severe dysmenorrhea with or without deep dyspareunia and pelvic pain and had regular menstrual cycles prior to treatment. None had ever been treated by hormonal therapy or planned to conceive in the next one or two years. All had minimal to mild endometriosis by revised American Society for Reproductive Medicine classification. Buserelin acetate 6.6 mg implants were injected subcutaneously in the lateral region of the anterior abdominal wall every 8 weeks, 3 doses in group 1 (n=7, aged 29.3±6.1 years) and every 12 weeks, 2 doses in group 2 (n=7, aged 28.9±1.7 years). Bone mineral density (BMD) was measured at the lumbar spine by dual energy X-ray absorptiometry (Lunar CO., Madison, WI) before initiation of treatment and 1 year after. Symptoms, pelvic examination, ultrasonogram and serum estradiol were recorded every 4 weeks until two regular menses were established.

Data are presented as their means±SEM. Statistical analysis was performed with a significant level of $P<0.05$.

RESULTS

Table 1 gives the clinical data of both groups. There were no significant differences between the two groups for age, height, weight and body mass index (BMI).

All the painful symptoms were relieved and eventually disappeared in all patients within 4-6 weeks and they remained pain-free or only had some abdominal discomforts during amenorrheic periods. Four patients in group 1 had no or mild dysmenorrhea during the first two return cycles. Others had mild to moderate dysmenorrhea which required analgesics. Five patients in group 2 had no or mild dysmenorrhea during this time, while another two had mild to moderate dysmenorrhea.

Table 1. Clinical data.

Group	n	Age (yrs)	BMI (kg/m^2)
1	7	29.3 ± 6.1	19.9 ± 2.0
2	7	28.9 ± 1.7	19.0 ± 2.1

Table 2. Mean serum estradiol during amenorrheic period (pg/ml).

Group	Estradiol level (weeks after first injection)								
	4	8	12	16	20	24	28	32	36
1 (n=7)	2.89	4.39	4.82	4.71	5.39	4.56	5.21	4.37	4.71
2 (n=7)	2.59	5.09	4.53	3.57	4.64	6.21	4.28	3.75	3.28

Table 3. Bone mineral density (BMD) and bone loss (%).

Group	BMD (g/cm^2)		Bone loss (%)
	Before	After	
1	1.034 ± 0.117	0.967 ± 0.123	6.49 ± 4.90
2	1.180 ± 0.210	1.093 ± 0.211	7.71 ± 5.67

Mean duration of the first observed side effect was 2.7±1.6 weeks. Hot flushes were the most common side effects and occurred in 6 out of 7 in both groups, but only 1 in each group needed short term medication. Hot flushes resolved with the return of cycles. Other side effects were mood change, hair falling out, dry skin, decreased libido, vaginal dryness, headache, insomnia and musculoskeletal symptoms. All patients tolerated these symptoms and none left the study because of side effects.

All women were amenorrhoeic during the period of ovarian suppression, except one instance of painless light breakthrough bleeding in 2 patients of both groups. Mean duration of amenorrhea in group 1 (408.4±47.7 days) was significantly longer than in group 2 (331.3±22.4 days), $p<0.01$. Amenorrhea was well correlated with serum estradiol levels. Serum estradiol is shown in Table 2. There were no significant differences between the two groups for estradiol levels during amenorrheic periods.

Bone mineral densities are shown in Table 3. There were no significant differences between the two groups for lumbar BMD before and after treatment. Bone loss at one year after first injection was significant in each group, however, there were no significant differences in bone loss between the two groups.

DISCUSSION

The present results confirm the efficacy of this injectable long-acting implant for ovarian suppression[6,8,9]. All painful symptoms were relieved or disappeared in only 4-6 weeks which corresponded to the very low serum estradiol levels below 15 pg/ml in all patients during amenorrheic periods. According to the estrogen threshold hypothesis[10,11], the treatment of symptomatic endometriosis required the suppression of estradiol below approximately 40 pg/ml. Vasomotor symptoms begin at estradiol level of about 40 pg/ml and significant loss in BMD does not occur until the estradiol level is below approximately 20 pg/ml. In this study, profound ovarian suppression occurred in only 4 weeks after the first injection. Estradiol levels fell below 15 pg/ml in all patients with mean serum estradiol levels of only 2.59-6.21 pg/ml. These levels remained in almost all patients during amenorrheic periods, so significant bone loss would be expected.

Mean duration of amenorrhea in group 1 (408.4±47.7 days) was significantly longer than group 2 (331.3±22.4 days), $p<0.01$. This implies the longer ovarian suppression in group 1 as expected. Menses returned 282.4±47.7 days (232-348 days) after the last injection in group 1 and 247.3±22.4 days (212-279 days) in group 2. Compared to other 6 monthly GnRHa injections which reported 83.8±29.1 days return of menstruation[12], these regimens of implants may be considered inappropriate for the treatment of endometriosis associated with infertility, where predictable return to ovulation is required. However, for the treatment of pain-associated endometriosis which is a chronic condition, this may be one of the most effective ones. These implants have profound ovarian suppression with longer duration than other types of depo forms of GnRHa. The major concern is the effects of a long duration of ovarian suppression on bone mass. There was significant bone loss in both groups, 6.49±4.90 per cent in group 1 and 7.71±5.67 per cent in group 2, but there was no difference between the two groups. However, there could be further bone loss in both groups due to further ovarian suppression beyond the measured period. With the other GnRHa treatments, BMD decreased by 4-12 per cent over the first treatment period of 3-6 months [13], BMD recovered over the subsequent few months and may ultimately normalize.

Generally GnRHa therapy appears to offer several advantages in the treatment of pain-related endometriosis, but the duration of such therapy is limited by metabolic and, to a lesser extent, clinical side effects. Add-back hormonal therapy appears to be effective in attenuating the observed bone loss and in reducing the adverse clinical signs and symptoms of hypoestrogenism without reducing symptomatic benefits[14,15].

Buserelin implants exert the very long duration of profound ovarian suppression, so it is very effective in the treatment of pain-related endometriosis. To lessen the extent of adverse effects on BMD, hormone replacement may be started from the beginning of the treatment. This should allow "long-term" therapy of pain-related endometriosis in patients who do not require fertility by these implants.

Most adverse effects of treatment in this study were the result of hypoestrogenemia. Most symptoms were mild and needed no specific treatment. Hot flushes were the most common side effect. Mean duration of first observed side effect was very short (2.7±1.6 weeks), which implies the rapid ovarian suppression of these implants. All obverse symptoms resolved with the return of cycles.

SUMMARY

Buserelin acetate implants are effective in the treatment of pain in endometriosis. These implants should have an important clinical application when chronic treatment is indicated. Add-back hormone replacement therapy may be started at the same time as GnRH agonist treatment in all women treated for pain related to endometriosis. Further study is needed to decide how this preparation should be used to minimize the adverse effects.

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การใช้ยาบูเซอเรลิน อะซิเตทชนิดฝังในการรักษาอาการปวดในภาวะเยื่อบุโพรงมดลูกเจริญผิดที่

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วัตถุประสงค์ : เพื่อศึกษาการรักษาอาการปวดในภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ด้วยบูเซอเรลิน อะซิเตทชนิดฝัง

วิธีการศึกษา : ผู้ป่วย 14 ราย ได้รับการวินิจฉัยว่าเป็นภาวะเยื่อบุโพรงมดลูกเจริญผิดที่โดยการตรวจผ่านกล้องส่องช่องท้อง ผู้ป่วยทุกรายมีอาการปวดระดูขั้นรุนแรง โดยอาจพบร่วมกับอาการปวดขณะร่วมเพศหรือการปวดอุ้งเชิงกรานเรื้อรัง แบ่งผู้ป่วยแบบสุ่มเป็น 2 กลุ่ม กลุ่มละ 7 ราย กลุ่มแรกได้รับยาบูเซอเรลิน อะซิเตท 6.6 มิลลิกรัม ชนิดฝัง ทุก 8 สัปดาห์ จำนวน 3 ครั้ง กลุ่มที่สอง ทุก 12 สัปดาห์จำนวน 2 ครั้ง ติดตามผู้ป่วยทุก 4 สัปดาห์ โดยการซักประวัติ ตรวจร่างกาย การตรวจด้วยคลื่นเสียงความถี่สูงเมื่อจำเป็นและตรวจระดับฮอร์โมนเอสตราไดออล จนกว่าผู้ป่วยจะมีระดูสม่ำเสมอ 2 ครั้ง ตรวจความหนาแน่นของกระดูก (BMD) เมื่อเริ่มและ 1 ปี หลังจากเริ่มการรักษา

ผลการศึกษา : อาการปวดทั้งหมดดีขึ้น และหายไปเกือบทั้งหมดในผู้ป่วยทุกรายภายใน 4-6 สัปดาห์ ระยะการขาดระดูในผู้ป่วยกลุ่มแรก (408.4±47.7 วัน) นานกว่ากลุ่มที่สอง (331.3±22.4) อย่างมีนัยสำคัญ ($p<0.01$) อาการข้างเคียงที่พบบ่อยที่สุด คือ hot flush ระดับฮอร์โมนเอสตราไดออล ลดลงต่ำกว่า 15 pg/ml ในผู้ป่วยทุกรายระหว่างการขาดระดู แต่ไม่แตกต่างกันอย่างมีนัยสำคัญระหว่าง 2 กลุ่ม มีการสูญเสียมวลกระดูกอย่างมีนัยสำคัญทั้ง 2 กลุ่ม (6.49±4.90% ในกลุ่มแรกและ 7.71±5.67% ในกลุ่มที่สอง) แต่ไม่แตกต่างกันระหว่าง 2 กลุ่ม ทั้งก่อนและหลังรักษา

สรุป : บูเซอเรลิน อะซิเตทมีประสิทธิภาพดีในการรักษาอาการปวดในภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ และน่าจะนำไปใช้ได้ดีในการรักษาระยะยาว อย่างไรก็ตามต้องมีการศึกษาเพิ่มเติมเพื่อปรับวิธีการใช้ให้มีผลข้างเคียงน้อยที่สุด

คำสำคัญ : ภาวะเยื่อบุโพรงมดลูกเจริญผิดที่, บูเซอเรลิน อะซิเตทชนิดฝัง

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