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Effects of hormone therapy on the clinical outcomes of endoscopic intervention in patients with endometriosis-related ureteral obstruction

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Purpose: We investigated whether endoscopic interventions, including laser endoureterotomy and balloon dilatation following hormone therapy, are a good choice to treat ureteral obstruction due to ureteral endometriosis instead of laparoscopic or open surgery.

Materials and Methods: Patients with ureteral obstruction due to endometriosis who underwent endoscopic intervention between 2004 and 2021 were reviewed. Patients with other causes of ureteral obstruction or previous ureteral surgery were excluded from the study. The primary endpoint was the 3-month success rate of endoscopic intervention with or without hormone therapy. Secondary endpoints were the success rate of endoscopic intervention between the hormone-treated and hormone-untreated groups at 6 months and the success rate according to the hormone therapy response of endometriosis at 3 and 6 months.

Results: Eighteen patients with 19 ureter units were evaluated in this study, including 12 patients receiving hormone therapy and six patients not receiving hormone therapy. Among patients receiving hormone therapy, one patient had bilateral ureteral obstruction. The success rate of endoscopic intervention was higher in patients who received hormone therapy than in those who did not receive hormone therapy three months after endoscopic intervention (76.9% vs. 0.0%, p=0.003). The same result was also found 6 months after endoscopic intervention (75.0% vs. 0.0%, p=0.005). In addition, the success rates were higher in the hormone-responsive group than in the non-responsive group (100.0% vs. 57.1%), although the difference was not statistically significant (p=0.122).

Conclusions: Ureteral obstruction caused by endometriosis can be effectively treated by endoscopic intervention with hormone therapy in select patients.

Keywords: Endometriosis; Hormones; Ureteral obstruction; Ureteroscopy

INTRODUCTION

Endometriosis is a chronic disease characterized by the growth of endometrial glands and stroma outside the endometrial cavity. It affects approximately 10% of women of reproductive age and can involve any organs [1]. Endometriosis can also invade the urinary tracts and accounts for 1% of endometriosis patients [2]. Ureteral endometriosis is a rare

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disease, accounting for approximately 10% of all urinary tract endometriosis [3,4]. Ureteral endometriosis can present with various symptoms, such as flank pain, hematuria, dysmenorrhea, dyspareunia. However, up to 50% are asymptomatic [5-8]. In addition, ureteral endometriosis can cause ureteral obstruction and loss of renal function in advanced stages [9].

There are several medical and surgical ways to treat ureteral endometriosis. The treatment modalities depend on the patient's symptoms, health, and location of the endometriosis [10]. Treatment includes both surgical and medical options. Surgery is performed to remove all abnormal endometriotic lesions and restore normal anatomical structures. Medical treatment is used to prevent disease from progression or recurrence depending on the pathogenesis of endometriosis [11].

In medical treatments, hormone therapy is crucial because hormones are related to the progression of endometriosis. Endometriosis can be controlled and eliminated through medical treatment based on its pathophysiology [11]. Hormone therapy includes contraceptives and gonadotropin-releasing hormone (GnRH) agonists and antagonists [11]. However, hormone therapy alone is not sufficient in cases involving deep tissues, such as ureteral endometriosis. Hormonal treatment prevents the proliferation of endometriotic tissue but does not resolve the fibrotic changes in the surrounding tissue caused by endometriotic tissue [12]. For this reason, surgical treatment, such as ureterolysis has been accepted as a good choice to remove all fibrotic tissue from the ureter. Ureteral reconstruction, including uretero-ureterostomy and ureteral reimplantation, has been used successfully to treat ureteral obstruction caused by endometriosis [12].

Endoscopic procedures, such as ureteral ballooning and endoureterotomy, have been used as the first line of treatment for ureteral strictures because they are cost-effective, show low morbidity and require a short hospital stay [13,14]. However, the success rate of endoscopic intervention is expected to be limited in cases of ureteral stricture due to uncontrolled progressive disease, including endometriosis. Theoretically, when endometriosis is effectively controlled by hormonal treatment, endoscopic intervention may play a role in ureteral obstruction caused by endometriosis. But no study has evaluated the role of hormone therapy in treating endometriosis with endoscopy.

In this study, we investigated the results of endoscopic intervention after hormone therapy as a first-line treatment for patients with ureteral endometriosis that obstructed the ureter.

MATERIALS AND METHODS

1. Study population

This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB no. 2022-05-161). All the study protocols were performed in accordance with the principles of the Declaration of Helsinki. Written informed patient consent was waived owing to the retrospective nature of study.

Patients who were diagnosed with ureteral obstruction due to endometriosis between January 2004 and December 2021 were included. All patients were diagnosed as endometriosis by experienced gynecologist with pathological or clinical findings including symptoms, physical examination, laboratory tests, image findings, and response to medical treatments. Patients with other causes of ureteral strictures or a history of ureteral surgery were excluded. Asymptomatic patients with nonfunctional kidneys were also excluded because of the difficulties in determining the surgical outcomes.

2. Data collection

The medical records of all patients were reviewed, and their clinical and pathological characteristics were evaluated. This included their age at surgery, hormone therapy for endometriosis, and stricture characteristics at surgery, such as the laterality, site, and length of the stricture; operation time; post-operative ureteral stent period; and period of the hospital stay.

All patients underwent abdominopelvic computed tomography (CT) or pelvic magnetic resonance imaging (MRI) to measure the burden of ureteral endometriosis, and diuretic renal scans to evaluate ureteral obstruction. Patients treated with hormone therapy underwent follow-up imaging to investigate their responses to hormone therapy.

3. Endoscopic intervention surgical technique

Endoscopic surgery includes endoureterotomy using Holmium:YAG laser and ureteral balloon dilatation. All patients were evaluated for laterality, location, and length of ureteral strictures with intra-operative retrograde pyelography. Balloon dilatation or endoureterotomy covered the entire stricture length. In cases of balloon dilatation, we used 6mm balloon catheter and inflated the ureteral balloon until the narrowed ureteral lumen was fully dilated on fluoroscopy. During endoureterotomy, ureteral strictures were incised with the full thickness of the ureter until the periureteral fat was exposed. In all cases, ureteral stents were placed after endoscopic intervention. Patients without postoperative com-

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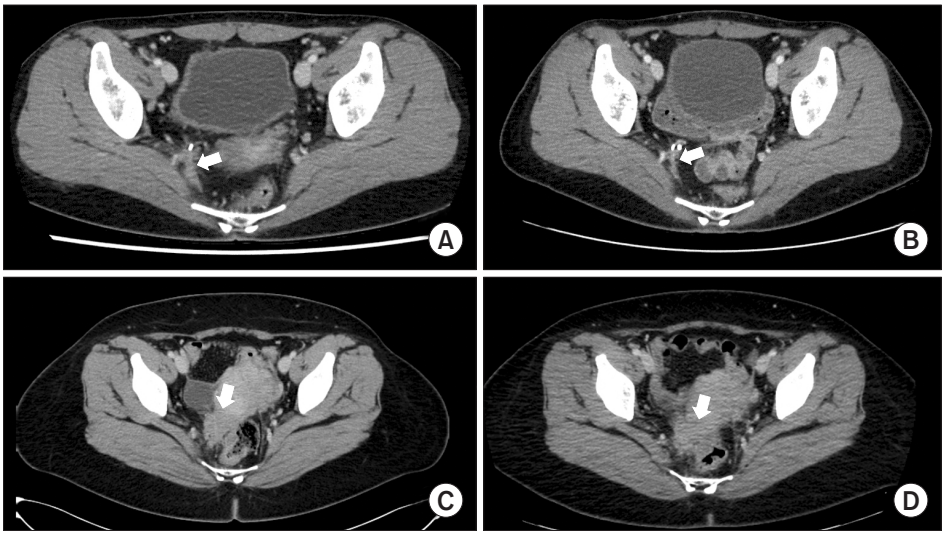

Fig. 1. Evaluation of hormone response (arrow) in patients with hormone therapy. Computed tomography (CT) images of hormone responsive patient before hormone therapy (A) and after hormone therapy (B). CT images of hormone non-responsive patient before hormone therapy (C) and after hormone therapy (D).

plications were discharged 1 or 2 days after surgery. Stents were removed 6 weeks after the endoscopic intervention.

4. Evaluation of clinical outcomes

After endoscopic ureterotomy, ureteral stents were maintained for 6 weeks and then removed. Subsequently, follow-up visits were made every 3 months with serum creatinine, urinalysis, and diuretic renal scan to evaluate ureteral patency. The primary endpoint of this study was the success rate of endoscopic intervention in the hormone-treated and hormone-untreated groups at 3 months. Successful endoscopic intervention was defined as a nonobstructive pattern on a diuretic renal scan and relief of patient's symptoms. Secondary endpoints included the success rate of endoscopic intervention between the hormone-treated and hormone-untreated group at 6 months and the success rate according to the hormone therapy response of endometriosis at 3 and 6 months. Patients were defined as responders when the maximal diameter of the endometriosis-encasing ureter was decreased by 30% or greater on CT or MRI, and non-responders were defined as a decrease of <30% (Fig. 1).

5. Statistical analysis

Continuous variables were expressed as median (range), and comparison between groups were performed using the Mann–Whitney U-test. Categorical variables are expressed as numbers and percentages, and statistical comparisons of the success rates for each group were performed using Fisher's exact test. And a p-value <0.05 was taken to indicate statistically significant differences. IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, NY, USA) was used for statistical analysis.

RESULTS

Thirty-three patients with thirty-four ureter units were diagnosed with ureteral obstruction secondary to ureteral endometriosis. In six units, endoscopic intervention was performed without hormone therapy. In twenty-eight ureter units, hormone therapy including GnRH agonist, antagonist, and oral contraceptive was done as the first treatment. Ureteral obstruction was resolved after hormone therapy in 15 of the 28 ureter units (53.6%). Thirteen of the 28 ureter units showed persistent ureteral obstruction even after hormonal treatment and required endoscopic intervention (Fig. 2).

The baseline characteristics of the patients who underwent endoscopic intervention with and without prior hormone therapy are shown in Table 1. The median age of the patients was 40 (30–52) years. The median stricture length was 2 (0.5–15) cm, and 42.1% (8 of 19 cases) had a stricture length of more than 2 cm. One ureter unit in the hormone-untreated group had a diffuse ureteral stricture, measuring approximately 15 cm. In patients receiving hormone therapy, median hormone treatment period was 2 (2–49) months. The median operation time was 29 (13–115) minutes. The median stent period was 42 (19–115) days, and the median hospital stay was 2 (1–8) days.

The success rate of endoscopic intervention with prior hormone therapy was significantly higher than that without prior hormone therapy (76.9% vs. 0%, p=0.003) 3 months after surgery. The success rate at 6 months was also significantly different between the two groups (75.0% vs. 0.0%, p=0.005; Table 2).

Among the 13 ureter units in which hormone therapy was performed before endoscopic intervention, the success rates at 3- and 6- month follow-up were higher in the hor-

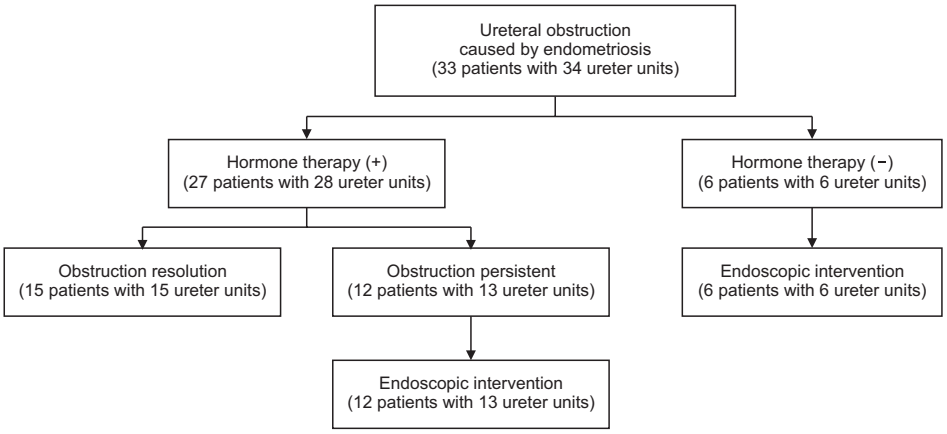

Fig. 2. Flow chart of study population.

Table 1. Baseline and perioperative characteristics

Characteristic	Hormone therapy		p-value
	(-) (n=6)	(+) (n=13)	
Age (y)	39 (32–52)	42.5 (30–51)	0.892
Previous ureteroscopic intervention	2 (33.3)	3 (23.1)	>0.999
Hormone therapy period (mo)	-	2 (2–49)	-
Stricture side (right:left)	5:1	5:8	>0.999
Stricture length (cm)	2.5 (1–15)	2 (0.5–3)	0.639
Stricture length >2 cm	3 (50.0)	5 (38.5)	>0.999
Stricture location	-	-	0.264
Upper	0 (0.0)	0 (0.0)	-
Mid	0 (0.0)	1 (7.7)	-
Low	5 (83.3)	12 (92.3)	-
Diffuse[a]	1 (16.7)	0 (0.0)	-
Operation time (min)	42 (19–115)	28 (13–35)	0.058
Ureteral stent diameter (Fr)	7 (6–14)	7 (6–7)	0.521
Ureteral stent period (d)	42.5 (21–55)	39 (19–115)	0.966
Hospital stay (d)	2 (1–8)	1 (1–2)	0.244

Values are presented as median (range) or number (%).
[a]:Stricture involving more than one ureteral segments.

Table 2. Success rate of endourologic management

Success	Hormone therapy		p-value
	(-) (n=6)	(+) (n=13)	
3-Month	0.0%	76.9%	0.003
6-Month	0.0%	75.0%[a]	0.005

[a]:n=12, one patient was excluded by loss to follow-up.

Table 3. Success rate of endourologic management, subgroup

Success	Hormone response		p-value
	(+) (n=6)	(-) (n=7)	
3-Month	100.0%	57.1%	0.122
6-Month	100.0%[a]	57.1%	0.159

[a]:n=5, one patient was excluded by loss to follow-up.

mone-responder group (100.0% vs. 57.1%), although the difference were not statistically significant (p=0.122 and p=0.159, respectively; Table 3).

Three ureter units in hormone non-responder group failed because of flank pain and nausea. In hormone-untreated group, three ureter units failed due to flank pain and another three ureter units failed due to progression of hydronephrosis and aggravation of ureteral obstruction. One of them eventually progressed to non-function kidney.

DISCUSSION

According to recent studies, the success rate of endoscopic intervention is 33% to 100% for balloon dilatation and 60% to 86% for endoureterotomy [15]. The success rate of endoscopic intervention for ureteral strictures depends on the causative

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disease. Unless the underlying etiology is controlled, ureteral strictures can recur. Therefore, it is very important to control the underlying disease before endoscopic intervention. Hormone therapy may be an effective way to prevent the progression of ureteral endometriosis.

A continuous supply of estrogen is required for the growth of endometriotic tissue, and a continuous supply of estradiol is also produced in the endometriotic tissue itself due to intrinsic aromatase activity [16]. It is also known that an increase in the resistance of endometriotic tissue to progesterone also affects the occurrence of endometriosis [17]. Hormone therapy, including GnRH agonists and antagonists and contraceptives, induces estrogen deprivation and causes decidualization of endometriotic tissue followed by the atrophy of endometriotic lesion [18]. A few papers have reported that hydronephrosis and symptoms were resolved by hormone therapy alone in patients with endometriosis-induced ureteral obstruction [19-21]. In the current study, hormone therapy was done in 28 cases as the first treatment of ureteral obstruction, and ureteral obstruction was resolved in 15 cases (53.6%).

Although hormonal treatment prevents the growth of endometriotic tissue, it has a limited role in resolving fibrotic tissue in endometriotic lesions [12]. This fibrotic tissue can persist even after hormonal treatment and distort the surrounding tissue, causing persistent ureteral obstruction [12,22]. In the current study, ureteral obstruction persisted even after hormone therapy in 13 cases, including 6 cases in which ureteral endometriotic tissue was markedly decreased on the follow-up imaging. We assumed that endourologic intervention would have a curative role in persistent ureteral obstruction after hormone therapy because the persistent stricture by the remnant fibrotic component could be resolved. In this study, the success rates of endoscopic intervention were 76.9% and 75.0% at 3- and 6-months follow-up, respectively. We also assumed that the role of endoscopic intervention would be very limited without proper hormone therapy because the endometriotic tissue would play a progressive role in extrinsic ureteral obstruction. In this study, the success rate of endoscopic intervention was 0% in the hormone-untreated group.

In several studies, endometriosis with larger fibrotic tissue components and less endometriotic tissue showed less volume reduction after hormone therapy [23]. In this study, the degree of volume reduction of endometriosis after hormone therapy was related with the success of endoscopic intervention. The hormone-responsive group, whose endometriosis decreased by more than 30% in diameter, showed a 100% success rate. However, in hormone-non-responsive patients who might have more fibrotic tissue components than the hormone-responsive group, the success rate was 57.1%. Interestingly, the success rate of the hormone non-response group is comparable with the success rate of endoscopic intervention in idiopathic ureteral strictures [13,15]. And it was still much higher than that in the hormone-untreated group in this study.

Some studies have found that hormones, such as estrogen, are associated with inflammatory reactions in endometriosis by stimulating macrophages in the endometriotic tissue [24]. In other studies, GnRH analogs were found to reduce inflammation [25-27]. Anti-inflammatory effects of hormone therapy along with mass-reductive effects may attribute to those favorable outcomes of endoscopic intervention. These data suggest that hormone therapy should be considered as the first treatment modality before surgical treatment for ureteral obstruction caused by endometriosis.

The current study had several limitations. First, this was a retrospective study in a small population conducted at a tertiary referral center, which raises concerns about selection bias. Second, the heterogeneity of the treatment modality could affect the success rate of endoscopic intervention. Generally, endoureterotomy using a holmium laser tends to provide a higher success rate than ureteral ballooning in ureteral strictures. In this study, the two procedures were not divided during the analysis because the number of enrollments in each group was small. However, even without dividing both surgeries, it was possible to confirm the prominent difference of the effectiveness of endoscopic intervention depending on neoadjuvant hormone therapy. Third, not all the patients were diagnosed as endometriosis by pathological confirm. In this study, 37% of patients were diagnosed by clinical findings. However, all patients were diagnosed as endometriosis by experienced gynecologists. Fourth, there were insufficient medical records for the duration of hormone therapy. Therefore, it was not possible to quantitatively investigate the optimal duration of hormone therapy before endoscopic intervention. This study seems to be valuable because, to the best of our knowledge, this is the first study to demonstrate the effect of hormone therapy on the success of endoscopic intervention in ureteral obstruction accompanied by endometriosis.

Hormone therapy before endoscopic intervention is important. This makes endoscopic intervention more successful.

CONCLUSIONS

In some select cases, hormone therapy alone can resolve ureteral obstruction caused by endometriosis. Endoscopic

intervention following hormone therapy could effectively resolve the ureteral obstruction that persisted even after hormone therapy. In patients with endometriosis-related ureteral obstruction, hormone therapy should be the first-line treatment before surgery.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Deok Hyun Han. Data acquisition: Jungyu Kim and Youngjun Boo. Statistical analysis: Jungyu Kim, Chung Un Lee, Kwang Jin Ko, and Jae Hoon Chung. Data analysis and interpretation: Hyun Hwan Sung, Minki Baek, and Deok Hyun Han. Drafting of the manuscript: Jungyu Kim. Critical revision of the manuscript: Jungyu Kim, Seong Soo Jeon, and Deok Hyun Han. Obtaining funding: Deok Hyun Han. Administrative, technical, or material support: Deok Hyun Han. Supervision: Deok Hyun Han. Approval of the final manuscript: Deok Hyun Han.

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