

# Effects of Thyrotropin-Releasing Hormone on Urethral Closure Pressure in Females with Voiding Dysfunction

HAJEBRAHIMI S\*, MADAEN SK, SHEIKHZADEH P

*Department of Urology, Imam Khomeini Hospital, Tabriz University of Medical Sciences, Tabriz, Iran*

## ABSTRACT

**Purpose:** To evaluate the effect of intravenous thyrotropin releasing hormone (TRH) on the urethral closure pressure (UCP).

**Materials and Methods:** Twenty-two female patients with either bladder outlet obstruction (BOO) or detrusor under activity were included in this study. They divided into two study and control groups randomly. Twelve patients in study group received 200 $\mu$ g of TRH intravenously and patients in control group received intravenous normal saline as placebo. Standard urethral pressure profilometry was performed before injection and after injection at 5, 10, 20 and 30 minutes. Functional profile length (FPL), maximum urethral closure pressure (MUCP), and urethral closure pressure at the proximal quarter of the FPL (1/4 FLP) and at the distal quarter of FPL (3/4 FLP) were measured in both groups.

**Results:** The mean age of the study and control groups were 41.61 $\pm$ 21.7 years and 43.59 $\pm$ 19 years respectively. The study and control groups included 5 BOO and 6 detrusor under activity and 4 BOO and 5 detrusor under activity respectively. The mean peak flow rate was 5.69 $\pm$ 8.4 ml/s in the study group and 6.31 $\pm$ 8.1 ml/s in control group. There wasn't significant difference between two groups. Mean maximum urethral closure pressure demonstrated no significant difference in two groups before and after TRH injection, but a marked reduction in 3/4 UCP and 3/4 FPL in patients after TRH injection was seen.

**Conclusion:** TRH injection significantly reduces the distal urethral pressure.

KEY WORDS: thyrotropin releasing hormone, urethral pressure profilometry, voiding dysfunction-underactive detrusor

## INTRODUCTION

Voiding dysfunction is a bladder emptying disorder and manifested with a complex of lower urinary tract symptoms. Voiding dysfunction is common in women so that 14% of females who seek urologic consults have lower urinary tract symptoms. However they would not be diagnosed until they come several times with serious sign and symptoms like recurrent urinary infections or urinary incontinence. Evaluation of voiding dysfunction in women and young girls in order

to prevent and treat urinary incontinence, retention, urinary tract infection and the renal injury caused by it, is an important matter.<sup>(1)</sup>

Several therapeutic methods have been proposed for these patients but the specific anatomy of female's outlet caused limitations in treatment options. Female's sphincter almost composed of skeletal muscle (slow-twitch) and an inner layer of smooth muscle which is predominant in the proximal part, but muscle fibers are arranged in an oblique and longitudinal manner and there is no well defined smooth muscle sphincter.

Therapeutic recommendations in evaluating voiding dysfunction in female especially in whom with detrusor hypocontractility are limited and any new information will be interesting.

Intravenous TRH as a diagnostic test for endocrine dysfunction, caused severe urgency in more than 1/3 of patients.<sup>(2)</sup> In another study on women with stress urinary incontinence, a marked reduction in UCP was seen after TRH injection.<sup>(3)</sup> So it seems that the primary response of lower urinary tract to TRH is the relaxation of urethra. This hypothesis encouraged us to study its effects on women with bladder hypocontractility or bladder outlet obstruction. Our aim was to evaluate the effects of intravenous TRH on UCP in a double-blinded placebo-controlled study.

If we can confirm that TRH or TRH like peptides can relax the female urethra, the long acting pharmacologic products can help these patients with detrusor hypocontractility in order to empty their bladder without using any other therapeutic methods such as CIC.

#### MATERIALS AND METHODS

In this clinical trial 22 female patients with either bladder outlet obstruction (BOO) or poor contraction of bladder (detrusor under activity), which were diagnosed based on uroflowmetry and pressure flow study (PFS), were included.

Patients with detrusor pressure less than 30 cm H<sub>2</sub>O in peak flow less than 10 ml/sec were diagnosed as underactive detrusor and patients with detrusor pressure more than 60 cmH<sub>2</sub>O in the same peak flow (<10 ml/sec) were diagnosed as BOO.

Patients with BOO caused by anatomic obstruction were excluded from the study. Patients were divided into two groups (study and control) randomly. Twelve patients in study group received 200 µgr intravenous TRH and the control group patients received intravenous normal saline as placebo. The Urethral pressure profile (UPP) was done before injection and 5, 10, 20, and 30 minutes after injection. The UPP test was done with a MMS 2000 urodynamic machine with software version 5.10 the converter 10 French from Gaotec model and a fluid with 1009 density was installed with a pump speed of 10mm/sec. The test was done in supine position.

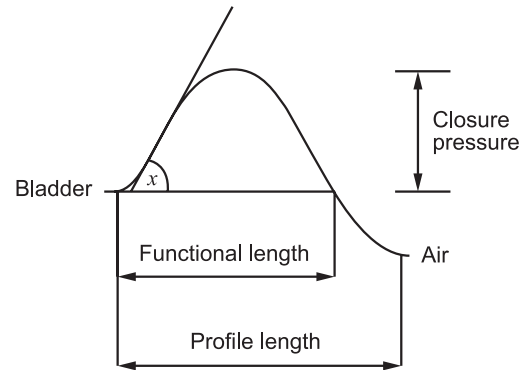


FIG. 1

At first the transducers were put in bladder completely and then pushed out with 30mm/s speed. The resting profile was recorded (fig. 1). The measured variables were: functional profile length (FPL), maximum urethral closure pressure (MUCP), and closure pressure at the proximal quarter of the FPL (1/4 UCP) and at the distal quarter of FPL (3/4 UCP). In addition, blood pressure (BP) and pulse rate (PR) of each group before and after TRH injection were measured. In this study we used Man-Whitney U-test for analysis.

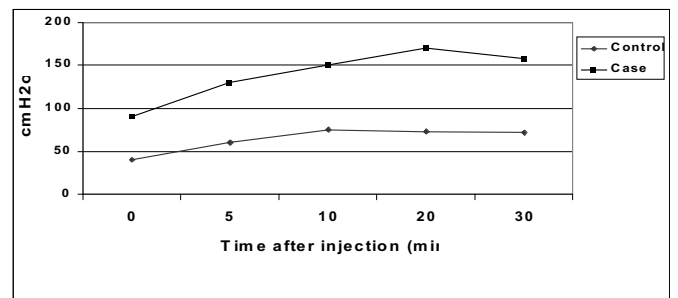


FIG. 2. Urethral closure pressure in 1/4 proximal of functional profile length, change from base in either group

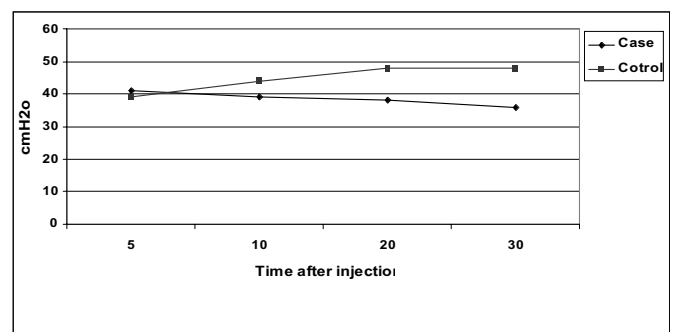


FIG. 3. Urethral closure pressure in 3/4 distal of functional profile length, change from base in either group

RESULTS

The mean age of each study and control group was 41.61±21.7 years and 43.59±19 years respectively. The study group included 6 patients with BOO and 6 with underactive detrusor and the control group included 5 patients with BOO and 5 with underactive detrusor (p=0.45). The mean peak flow rate in the study and control groups were 5.69±8.4 ml/s and 6.31±81 ml/s respectively. There wasn't any significant difference between the two groups (p=0.67).

The FPL and UCP measured for both groups before and after TRH injection have no significant differences (table 1). The results of urethral pressure profilometry (UPP) after injection are demonstrated in figures 2, 3, and 4.

A marked reduction in FPL and UCP in distal 3/4 of the urethra in the study group (after TRH injection) compared to the control group (after placebo injection) were seen (p=0.03) and (p=0.02) (fig. 3, 5). The maximum UCP 5 minutes after TRH injection in the study group was reduced but it has no significant statistical difference with control group (p=0.35) (fig. 4). In addition,

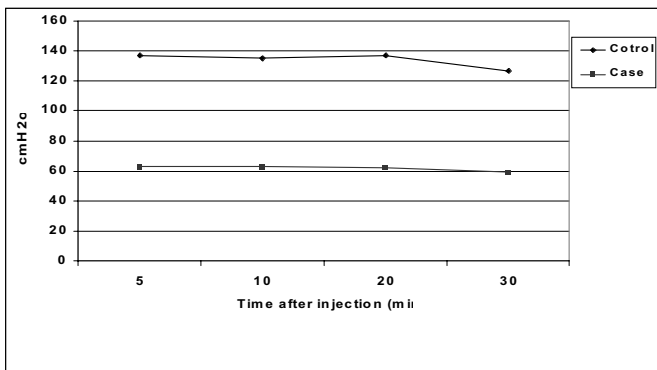


FIG. 4. Maximum urethral closure pressure, change from base in either group

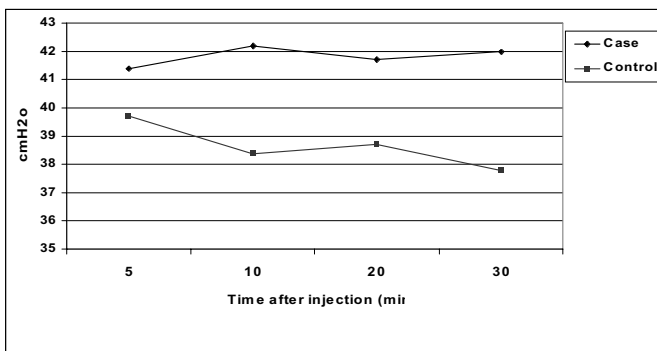


FIG. 5. Functional profile length, change from base in either group

TABLE 1. Mean urethral closure pressure and Functional profile length before injection

Measured Variables	Control Group	Study Group	P value
MUCP (cmH <sub>2</sub> O)	93.98±20.16	93.19±24.98	.35
FPL (cm)	3.96	3.13	.42
UCP in 30% FPL (cmH <sub>2</sub> O)	72.59±23	68.06±26.3	.29
UCP in 70% FPL (cmH <sub>2</sub> O)	31.92±21.06	38.03±21.64	.02

tion, a reduction in (1/4 UCP) 5 minutes after TRH injection in the study group was seen but there was no significant difference with the control group either (p=0.29) (fig. 2). After TRH injection no increased detrusor pressure was seen and there was no significant difference between two groups in urgency. Also no significant difference in BP and PR before and after TRH injection was seen (p=0.6).

DISCUSSION

Voiding dysfunction is a disorder in bladder emptying in persons who have no urologic problem. In these patients we have an increased activity of external sphincter during voiding which is trained as a habit and differs with detrusor sphincter dyssynergia which results from neurologic disorder or trauma. So terms, Pseudo-dyssynergia and Behavioral Voiding Dysfunction were used for explaining this problem.<sup>(6)</sup>

Diagnosis of female voiding dysfunction is an important matter because of its role in prevention and treatment of urinary incontinence, retention, and urinary tract infection and the subsequent renal injury. <sup>(1)</sup>

In spite of high incidence of voiding dysfunction in females, there are controversies on its etiology and diagnosis. Although many different therapeutic options may be propounded for these patients but the specific anatomy of female outlet is a limitation factor in this way. The female sphincter consists of slow-twitch skeletal muscles<sup>(7)</sup> and an inner layer of smooth muscle with a majority in proximal part, but these fibers are arranged in a longitudinal and oblique manner and there is no well defined smooth muscle sphincter.

Therapeutic options in females with voiding dysfunction especially with detrusor hypocontractility are limited. Drugs used in underactive detrusor treatment consist of betanecol chloride, distigmine bromide, and E2 and F2

prostaglandins that are overused, but studies shows that none of them can help in long term. In males with bladder outlet obstruction (diagnosed by urodynamic)  $\alpha$ -adrenergic blockers are helpful but such a problem in females is rare and it seems these agents (Phenoxybenzamin, Prazosin, and Indoramin) have limited value in treatment of female's urinary outlet obstruction.

$\alpha$ -Adrenergic blockers reduce the urine outgoing resistance by affecting proximal smooth muscle sphincter and have marginal effects on females. Therefore finding any drug, which affects skeletal muscle sphincter (which is the main part responsible for female's sphincter mechanism) will be important.

In a placebo-control trial, Trazosin ( $\alpha$ -blocker) was used for female with symptoms like prostatism but had no significant clinical effect.<sup>(11)</sup>

TRH can have a direct peripheral effect on urethral muscles or a central effect on neural control that can reduces the muscle tone.<sup>(10)</sup> So we can study its effects on UCP in females with underactive detrusor or BOO.

Abundance of TRH receptors and TRH like peptides in human's prostate indicates its peripheral effects.<sup>(9)</sup> Rosenthal reported urgency after TRH injection in a patient with total spinal cord injury and related it to TRH central effects.

Our study indicated that TRH has its maximum effect on UCP and FPL and the most significant alteration is in 3/4 UCP and FPL (fig. 2, 4).

Although the reason of different effects on distal and proximal parts of urethra is not clear, probably it indicates the openly effect of TRH on skeletal muscle of female urethra which is prevalent in the distal part. In addition, as it is shown in Table 1, although there is no significant statistical difference between the study and the control group in reduction in (1/4 UCP), compared to control group it is bending to lower pressure.

In our study we have no significant difference between the study and the control group in the amount of urgency, blood pressure, and pulse rate before and after TRH injection and there was not any other side effects such as nausea and headache. So we can know TRH as a low side effect drug.

In a study on the effect of TRH on muscular contraction of urogenital system in ten woman in comparison with normal saline as placebo, TRH

increased the pressure of urethra in all of them and increased vaginal pressure in seven, but none of them have any elevation in bladder pressure. On the other hand, the normal saline had no effect on all of them so we can conclude that TRH, by central or peripheral effect or both of them, can play a role in the start of skeletal contracture of urogenital system.<sup>(25)</sup>

In a study by Derek and coworkers in England, TRH injection caused reduction in UCP in females with voiding dysfunction.<sup>(10)</sup>

Therapeutic options in the management of female voiding dysfunction is limited, so any new drug would be welcome and if the effect of TRH or TRH like peptides on relaxation of female's urethra is confirmed, the pharmacological long acting products can help patients with underactive detrusor to empty their bladder without using any other therapeutic options like CIC or electrical stimulation of sacral nerve roots. Also patients with BOO have no need to undergo inconvenient therapeutic procedures like urethral dilatation or bladder neck incision that may cause urinary incontinence.

## CONCLUSION

In summary, TRH injection causes reduction in UCP (with the most effect on distal 3/4 of urethra) and knowing how it effects on urethra can open new ways in the evaluation of voiding dysfunction in women.

Voiding dysfunction in females is relatively common and almost 14% of patients who seek urologic consults have lower urinary tract symptoms, and even sever bladder emptying disorders may be normal from the patients' view and they won't come to clinic seeking treatment. This may cause irreversible injuries like renal failure. So examination, evaluation, and treatment of these patients are very important matters and developments in noninvasive therapeutic procedures could facilitate obtaining this purpose.

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