

## RESINIFERATOXIN FOR DETRUSOR INSTABILITY REFRACTORY TO ANTICHOLINERGICS

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### ABSTRACT

**Purpose:** We have evaluated the clinical and urodynamic effects of intravesical instillation of resiniferatoxin in patients with idiopathic detrusor instability refractory to anticholinergics.

**Materials and Methods:** There were 30 women, median age 56 years old with detrusor instability for over 6 months and a history of anticholinergic use with no response or intolerable collateral effects. A 50 nM solution of resiniferatoxin was prepared for intravesical instillation. All patients were evaluated for urinary symptoms, as well as for urodynamic assessments before and 30 days after instillation. Tolerability was analyzed during the instillation.

**Results:** A clinical improvement was observed in 30% of the patients with urinary urgency and in 33% of the patients with urge-incontinence. The mean maximum cystometric capacity before application was  $303.9 \pm 78.9$  and after application  $341 \pm 84.6$ . No significant difference was observed ( $p = 0.585$ ). The mean maximum amplitude of the contractions diminished from  $47.86 \pm 29.64$  to  $38.72 \pm 30.77$  ( $p = 0.002$ ).

**Conclusions:** Resiniferatoxin, in this concentration, proved to be useful in a small percentage of patients regarding clinical detrusor instability. Maximum amplitude of the involuntary contractions was significantly reduced and in 33% patients the involuntary contractions disappeared. Further studies with different concentrations are recommended.

**Key words:** bladder; urodynamics; urination disorders; bladder instillations; toxins  
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### INTRODUCTION

Detrusor instability (DI) is responsible for lower urinary tract symptoms and it is characterized by involuntary contractions of the detrusor during the filling phase of the bladder, during urodynamic assessment (1). These contractions have been attributed to neurogenic (2,3) or myogenic (4) alterations and, recently, the focus has been on C sensory fibers (2) and atropine (3) resistant parasympathetic transmitters. Anticholinergics have been used as first line treatment, despite the side effects (5). Recently, experimental studies have demonstrated that a substance isolated from the euphorbia species, a common cac-

tus found in Morocco, presents pharmacological activity in detrusor instability. It is known as resiniferatoxin (RTX), an analogue of capsaicin but a thousand times more potent (6). RTX seems to interfere in the non-myelinated C fibers responsible for the micturition reflex in patients with medullar lesions. It has very little effect on the myelinated delta A fibers present in the pelvis and responsible for transmitting sensorial information to the encephalic center in normal individuals (7). RTX has a homovanillylic ring in its structure its biological activity is able to treat some lower urinary tract functional disorders (8). Lastly, evidence exists indicating that involuntary detrusor contractions also depend on C fiber

mediated micturition reflex, since lidocaine instillation reduces these contractions (9). Lidocaine is a potent C fiber inhibitor and less potent in the case of A delta fibers. As this anesthetic improves involuntary contractions in patients with detrusor instability, it has been suggested that this type of nerve fiber contributes to the etiology of this disease (9).

RTX was effective in reducing the frequency, urgency and incontinence episodes in patients with detrusor hyperreflexia. As it did not produce anatomic dysreflexia episodes in spinal cord trauma patients, it proved to be a good alternative in such patients (10,11). Since RTX has been successfully used in patients with detrusor hyperreflexia, it could also be effective in the treatment of detrusor instability.

## MATERIALS AND METHODS

A prospective cohort study was conducted comprising 30 women, median age 56 years-old (age range 24 to 88) with urodynamic proven detrusor instability for more than 6 months and unsuccessful use of anticholinergics for at least 40 days or severe collateral effects. All the patients underwent urine test to rule out urinary tract infection. This study received the approval of the Hospital Ethics Committee for research in humans.

All patients underwent a work-up for DI that included history and physical examination, so that patients with neurological, cardiovascular, renal, hepatic and psychiatric disorders as well as those patients with malignant diseases or pregnant patients could be excluded from the study.

RTX was supplied in 1 mg packages by Sigma Company. They were diluted into 10  $\mu$ M stock solutions in pure ethanol and conserved in dark flasks at 4°C. This solution was then utilized to prepare the

required volumes in the following manner: 9.5 mL of pure ethanol, 90 mL of 0.9% saline solution and 0.5 mL of RTX, producing a 50 nM solution in 10% ethanol using the saline solution as a vehicle. This solution was prepared just before each instillation. A 14F Foley catheter was used for intravesical instillation of the medication and left in the bladder for 30 minutes. Patients were asked about pain and the intensity of these symptoms was analyzed using a visual analogical scale. Zero meaning no discomfort and 10 indicating unbearable sensation.

All patients were asked about urinary symptoms on the 30th day following the instillation.

Cystometry was performed before and 30 days after RTX instillation. The same researcher performed all the urodynamic tests. A double lumen 8F catheter (one lumen for saline infusion rate of 50 mL/min and other to measure the intravesical pressure) and a 4F rectal catheter-balloon to measure abdominal pressure were used.

The cystometric parameters evaluated were maximum cystometric capacity, maximum amplitude of the involuntary contractions and the presence of urgency or urinary leakage during these contractions.

The influence of intravesical instillation of RTX was accessed by comparing the results of the various parameters utilizing McNemar's test and the Wilcoxon rank sum test for non-parametric samples.  $P < 0.05$  was considered statistically significant.

## RESULTS

No significant difference was observed in urinary frequency after treatment. Nevertheless, in 3 cases, the condition worsened and an improvement was observed in 5 cases (Table-1).

**Table 1** – Resiniferatoxin effect on urinary frequency.

Frequency	Before	%	After	%
Once / 3 to 5 hours	8	26.66	12	40
Once / 2 hours	11	36.67	8	26.67
More than once/ 2 hours	11	36.67	10	33.33
Total	30	100	30	100

$p = 0.207$

**Table 2** – Resiniferatoxin effect on urgency.

Urgency	Before	%	After	%
No	3	10	12	40
Yes	27	90	18	60
Total	30	100	30	100

$p = 0.0077$

Urgency was present in 90% of the patients, and decrease to 60% after RTX instillation (Table-2).

Urge-incontinence was present in 83.33% of the patients, and decrease to 50% after RTX instillation (Table-3).

Resiniferatoxin instillation produced no significant changes in nocturia and enuresis.

Supra-pubic pain also did not improve significantly because 60% reported pain before treatment and 46.67% after treatment ( $p = 0.134$ ). The urodynamic examination before and after RTX treatment did not demonstrate significant alterations of urinary leakage during involuntary contractions ( $p = 0.077$ ).

Despite the fact, no statistically significant difference regarding maximum cystometric capacity was noted ( $p = 0.585$ ), this finding may be related to the fact that 6 patients presented reduction in bladder capacity post RTX instillation.

The histograms in Figure-1 demonstrate the distribution of the patients before and after RTX instillation for maximum cystometric capacity.

The mean maximum cystometric capacity pre-instillation was  $303.9 \pm 78.9$  and post instillation  $341 \pm 84.6$ .

There were significant differences between the maximum amplitude of the involuntary contrac-

tions before and after treatment. The mean pre-instillation was  $47.86 \pm 29.64$  cm H<sub>2</sub>O and post instillation was  $28.72 \pm 30.77$  cm H<sub>2</sub>O ( $p = 0.0002$ ). The mean reduction was 40%. In 33.33% the involuntary contractions disappeared.

The histograms of Figure-2 demonstrate the distribution of contraction amplitude before and after RTX.

## DISCUSSION

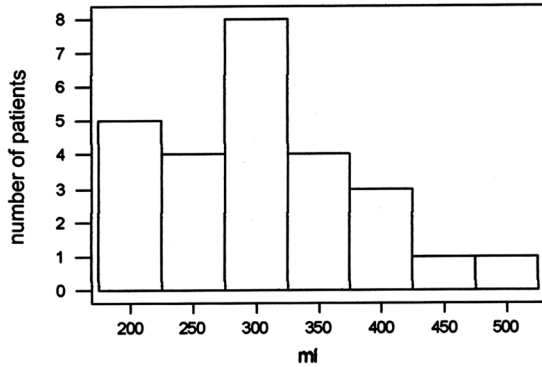
Resiniferatoxin is a potent agonist of type 1 vanilloid receptors in rats and humans (12). These receptors are localized on the dorsal ganglionar neurons (12). A study has demonstrated that the increase in bladder volume triggered the first contraction due to the attachment of RTX to the type 1 receptors in the C fibers (7). However, it is not known if desensitization or degeneration of the nerve endings of the bladder wall occurs. It was suggested that the C fibers were more responsible than the A delta fibers for the involuntary contractions. In normal individuals, desensitization of these fibers does not provoke any reaction (10), but finding out why sensorial information becomes preponderant in the C fibers may explain the physiopathology of idiopathic detrusor instability. The increased sensorial information in the C fibers could be provoked by the liberation of excessive bladder NGF (nerve growth factor) (13) musculature, also observed in infravesical obstruction. Although this study suggests the involvement of C fibers in the etiology of bladder instability, the existence of other abnormalities cannot be ignored, especially because the same improvement was not observed in the present study. The fact that the patients were extremely refractory to any type of treatment or presented bad results with any kind of proposed medi-

**Table 3**– Resiniferatoxin effect on urge-incontinence.

Urge-Incontinence	Before	%	After	%
No	5	16.67	15	50
Yes	25	83.33	15	50
Total	30	100	30	100

$p = 0.0044$

**A**



**B**

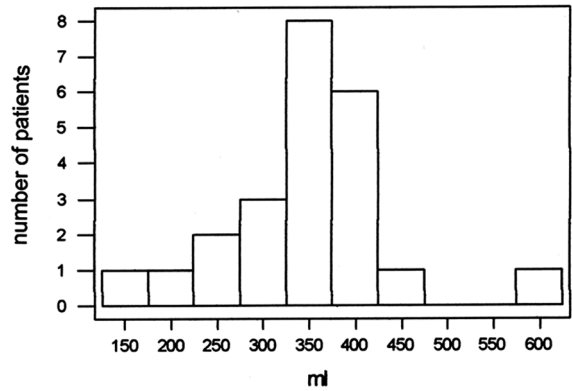
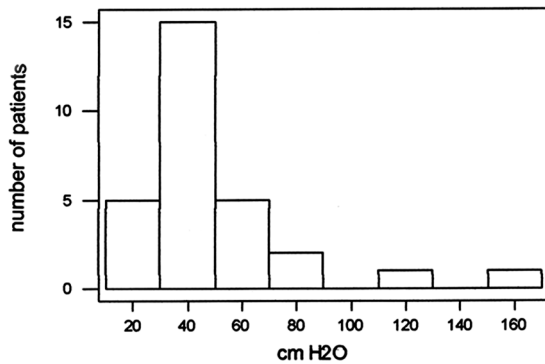


Figure 1 – Maximum cystometric capacity before (A) and after (B) resiniferatoxin instillation.

**A**



**B**

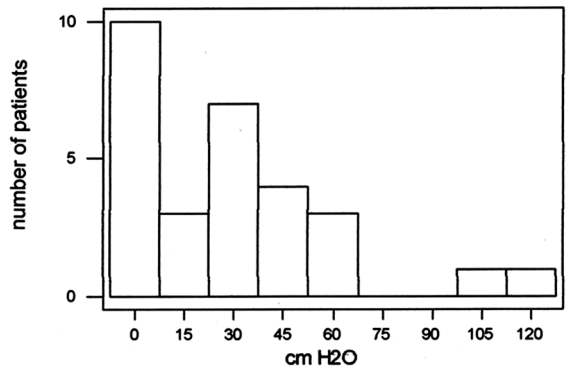


Figure 2 – Maximum involuntary contractions before (A) and after (B) resiniferatoxin instillation.

cation should obviously be taken into consideration. Nevertheless, partial improvement was observed with RTX, which reduced symptoms of urgency in up to 30% of the patients. The reason for the long-term effect of RTX is still unknown, but may involve the down-regulation mechanism of the C fiber receptors and of neuropeptides such as substance P and CGRP (14).

There is only one study in literature using RTX for DI (7). In that study a 50 nM solution of RTX was applied in 13 patients with DI and urodynamic were performed at 30 and 90 days after instillation. The maximum cystometric capacity and urinary volume at the first involuntary contraction were measured after instillation. The volume that triggered off the first contraction increased from a mean of  $170 \pm 109$  mL to

440 ± 130 mL during the first 30 days and 90 days. This increase was observed in 92% of a total of 11 women. The maximum cystometric capacity of the 11 patients (472 ± 139 mL) increased 30 days after instillation, returning to a volume above the initial volume (413 ± 153 mL) after 90 days. Our findings differ from that data because there was no difference in maximum cystometric capacity pre and post RTX. This may be partly because 6 patients presented reduced capacity after RTX. Silva's et al. (7) results showed an improvement in 91% of the incontinent patients, while in our study improvement was observed in only 33% of the patients, 30 days after instillation. The reason for these different findings is probably that our patients had more severe symptoms and were refractory to other treatments. Silva et al (7) used RTX as first line treatment in no refractory DI patients and this could be the reason of such difference. The urinary frequency also differed, it was 9.7 ± 3.2 times a day after 30 days decreasing in relation to the previous frequency, while in our study 73% of the patients reported that after instillation they urinated at least once every 2 hours. The urodynamic parameters in this present study did not demonstrate the significant change observed in the Silva's et al (7) study, with the exception of the amplitude of the involuntary contractions that decreased from 40 ± 28.86 to 28.72 ± 30.77 mL. This reduction was noticed in 25 patients.

These authors reported that there were no strong complaints during instillation and that the pain score was 3 on the same analogical scale, similar to the score in this study. Silva and collaborators (7) performed the RTX instillation with urodynamic control to verify the alterations caused and the innumerable phasic contractions of the detrusor that began slowly and became more spaced out at the end of the infusion. They reported that the RTX suppressed or diminished the involuntary contractions.

## CONCLUSIONS

Intravesical instillation of 50 nM RTX solution clinically improved a small percentage of patients. The maximum amplitude of the involuntary contractions diminished significantly, and in 33% patients the involuntary contractions disappeared.

Instillations were well tolerated with no interruption due to pain or discomfort. Further studies are recommended to access the role of RTX in this subset of patients.

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