Original Article

Effect of the intravesical resiniferatoxin instillation evaluated by the ice provocative urodynamic study

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Study design: Prospective urodynamic investigation before and after intravesical resiniferatoxin instillation treatment.

Objective: To evaluate the effectiveness of intravesical resiniferatoxin instillation for the treatment of neurogenic detrusor overactivity (NDO), using conventional and ice provocative urodynamic studies to monitor the activity of the unmyelinated C-fiber.

Setting: Spinal Cord Injury Unit, Yonsei Rehabilitation Hospital, Seoul, Korea.

Methods: A measure of 100 ml of resiniferatoxin solution, at a concentration of 100 nM diluted in 10% ethanol, was intravesically instilled into the bladder of 15 spinal cord injury patients with NDO. Conventional and ice provocative urodynamic studies were performed to evaluate the change in the involuntary detrusor activity, reflex volume, maximal bladder capacity, compliance, maximal detrusor pressure and reflex volume ratio 7 days before and 30 days after the instillation.

Results: Before the intravesical resiniferatoxin instillation, all patients exhibited NDO in both the conventional and ice provocative urodynamic studies, with a mean reflex volume ratio of 0.45 ± 0.22 . There was no significant change in the maximal bladder capacity, compliance and maximal detrusor pressure at the follow-up urodynamic study, but the reflex volume ratio was significantly increased ($P < 0.05$) after the intravesical resiniferatoxin instillation. Among the 15 patients, three (20%) showed complete and nine (60%) partial suppression of the unmyelinated C-fiber activities.

Conclusion: Intravesical resiniferatoxin instillation was partially controlled by the unmyelinated C-fiber activities, which were estimated by an ice provocative urodynamic study. Therefore, further studies on the optimal dosage and accurate indications for resiniferatoxin instillation are required.

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Keywords: neurogenic detrusor overactivity; resiniferatoxin; ice provocative urodynamic study

Introduction

Neurogenic detrusor overactivity (NDO)¹ is usually observed in suprasacral spinal cord lesions. This condition results in urinary incontinence and high pressure of voiding, with subsequent upper urinary tract damage. Its management has focused on reduction of the intravesical pressure and maintenance of adequate compliance and bladder capacity.² To achieve these therapeutic goals, oral medications, such as oxybutynin, propiverin or tolterodine, clean intermittent catheterization, electrical therapy or surgical approaches have been tried.^{3,4} However, some patients cannot be

controlled by oral medications, despite maximal dosages, and some cannot tolerate the side effects,^{5,6} such as a dry mouth, visual disturbance or constipation, at any dosage. Recently, to minimize the side effects of anticholinergics, intravesical instillations, such as oxybutynin^{7,8} or vanilloids,⁹ have been tried.

Of these, vanilloids, unmyelinated C-fiber blockers (capsaicin or resiniferatoxin), have been tried, but the effects of the treatment are equivocal.¹⁰ The rationale of Fowler *et al.*,⁵ to initiate the intravesical vanilloid instillations in spinal cord-injured patients with NDO, was based on the study of de Groat *et al.*¹¹ He explained that vanilloids have a suppressive action that is selective to the unmyelinated C-fibers, which are taught to become predominant in reflex contractions of the bladder

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after a spinal cord injury.¹² Theoretically, the use of C-fiber blockers results in suppression of the afferent C-fiber activity at the voiding reflex arc and can partially suppress NDO, so the use of the intravesical vanilloid may be desired after confirmation of abnormal unmyelinated C-fiber activity in spinal cord-injured patients.

In 1957, Bors and Blinn¹³ reported that rapid filling of the bladder with ice water caused an immediate detrusor contraction in patients with an upper motor neuron lesion. The cooling reflex originates from the cold-sensitive receptors (afferent from the unmyelinated C-fiber) in the bladder and urethral wall, as the receptors are different from the bladder mechanoreceptors (afferent from myelinated A δ -fiber) that drive the normal micturition reflex.¹⁴ Therefore, the ice water test has been used as a simple valuable supplement to routine cystometry in spinal cord-injured patients,¹⁵ Shin *et al*¹⁶ has also suggested that the urodynamic study using normal saline below 4°C was a useful provocative maneuver¹ for evaluation of the cold-sensitive receptor via the afferent C-fiber in NDO.

Therefore, the purpose of this study was to assess the effectiveness of intravesical resiniferatoxin instillation for the treatment of NDO mediated by abnormal unmyelinated C-fiber activation, as confirmed by an ice provocative urodynamic study.

Patients and methods

Patients

From 2002 to 2003, 15 spinal cord-injured patients were admitted to Yonsei Rehabilitation Hospital. Those with a urinary tract infection, lithiasis, malignancy or

vesicoureteral reflux after cystographic examination were excluded. On admission, 10 patients were classified¹⁷ as neurologically complete (ASIA A) and five as ASIA B (Table 1). There were 11 males and four females, with an average age of 27.2 years. The subjects underwent conventional and ice provocative urodynamic studies to confirm NDO. During the study, the drugs previously prescribed to the patients remained unchanged. The age, gender, voiding method, prescribed drugs and duration of rehabilitative treatments of the subjects after injury were evaluated (Table 1).

Methods

The ethics committee of Yonsei University College of Medicine approved the protocol for this study, and all patients gave their personal informed consent to participate in the trial.

Synthetic resiniferatoxin was prepared by the Pharmacy Department. A measure of 100 ml of resiniferatoxin (Sigma, St Louis, MO, USA) solution, at a concentration of 100 nM, was diluted in 10% ethanol.^{9,18} This solution was prepared immediately before each instillation to decrease contact of the resiniferatoxin with the plastic container. It was then instilled into the bladder at an infusion rate of 30 ml/min, without anesthesia, after catheterization with a 16 F Foley catheter and evacuation of residual urine, and left in place for 30 min with Foley clamping. The investigator observed any side effects during this procedure.

At 7 days before the intravesical resiniferatoxin instillation, conventional and ice provocative urodynamic studies were performed with a Duet urodynamic

Table 1 General characteristics of subjects

Case	Sex/age (years)	Injury level (ASIA scale)	Injury duration (mos)	Voiding method	Medications
1	M/32	T10 (A)	6	CIC	No
2	M/46	T3 (A)	246	CIC	No
3	F/24	C6 (A)	6	CIC	No
4	M/33	C6 (A)	6	CIC	Oxybutynin 30 mg, Propiverin HCl 40 mg
5	M/43	C5 (B)	7	CIC	No
6	M/48	L3 (B)	6	CIC	No
7	M/27	C8 (A)	7	Foley	Oxybutynin 25 mg, Propiverin HCl 20 mg
8	F/60	C6 (B)	7	CIC	Oxybutynin 5 mg, Propiverin HCl 40 mg
9	M/27	C7 (A)	8	CIC	Oxybutynin 15 mg
10	F/27	T8 (A)	35	CIC	Oxybutynin 20 mg, Propiverin HCl 10 mg
11	M/31	C6 (A)	46	CIC	Oxybutynin 30 mg, Propiverin HCl 10 mg
12	F/48	C4 (A)	6	Foley	Oxybutynin 20 mg, Propiverin HCl 20 mg
13	M/53	T1 (B)	6	CIC	No
14	M/42	C4 (B)	6	CIC	No
15	M/53	C6 (A)	10	CIC	No

mos = months; CIC = clean intermittent catheterization; Foley = Foley indwelling catheterization

machine (Dantec, Denmark), and the maximal bladder capacity, compliance, maximal detrusor pressure and reflex volume¹⁹ (the volume at which involuntary detrusor contractions began to appear) were measured during the filling phase. A conventional urodynamic study was performed by infusion of normal saline at a room temperature, and an ice provocative urodynamic study by infusion of normal saline below 4°C, at an infusion rate of 30 ml/min, through a double lumen catheter, with a pressure sensor device placed in the rectum measuring the abdominal pressure. The bladder volume was measured until an abrupt rise in detrusor pressure during the filling phase, and then this volume divided by a detrusor pressure calculated compliance. All the patients underwent the same urodynamic studies 30 days after the intravesical resiniferatoxin instillation. The unmyelinated C-fiber activities were confirmed when the reflex volume (RVc) at the ice provocative urodynamic study was smaller than the reflex volume (RVw) by the conventional urodynamic study, the so-called RV ratio (RVc/RVw) being <1.0.¹⁶

Clinical assessments of the volume of each catheterization, functional bladder capacity and each volume of incontinence were record in a urinary diary, 7 days before and 30 days after the resiniferatoxin instillation. For statistical analysis, the SPSS statistical program, version 10.0 for windows, and paired sample *T*-test was used. Statistical significance was defined as *P*<0.05.

Results

Before the intravesical resiniferatoxin instillation

Before the intravesical resiniferatoxin instillation, all 15 patients exhibited detrusor overactivities in the conventional urodynamic study. The mean maximal bladder capacity, compliance, maximal detrusor pressure and RVw were 363.9 ± 110.9 ml, 20.8 ± 12.4 ml/cm H₂O, 55.8 ± 21.5 cm H₂O, and 247.4 ± 93.8 ml, respectively (Table 2). In the ice provocative urodynamic study, all patients exhibited unmyelinated C-fiber activity (ie the RV ratio was <1.0 in the all patients), with a mean RVc and RV ratio of 111.5 ± 61.3 and 0.45 ± 0.22 ml, respectively (Table 3).

After the intravesical resiniferatoxin instillation

Clinically, the mean functional bladder capacity and volume of each catheterization increased from 280 ± 93.4 to 322 ± 102.7 ml and from 250.5 ± 123.8 to 305.3 ± 171.9 ml, respectively, and the mean volume of incontinence decreased from 220 ± 68.6 to 180 ± 56.5 ml after the instillation; however, these parameters were not statistically significant.

In the conventional urodynamic study, the involuntary detrusor contractions did not disappear in all cases. The mean maximal bladder capacity and maximal detrusor pressure also decreased from 363.9 to 337.5 ml and from 55.8 to 47.8 cm H₂O, respectively, and the mean compliance increased from 20.8 to

Table 2 Results of the conventional urodynamic study before the intravesical resiniferatoxin instillation

Case	Maximal bladder capacity (ml)	Compliance (ml/cm H ₂ O)	Maximal detrusor pressure (cm H ₂ O)	RVw (ml)
1	225	14	65	210
2	452	13.3	53	411
3	457	20	37	237
4	450	28	32	280
5	450	46.9	55	375
6	450	14.1	83	296
7	450	6	74	350
8	450	28.2	24	169
9	158	5.8	74	123
10	250	11	37	124
11	183	10.1	62	172
12	304	41.5	42	249
13	380	18.3	82	120
14	450	30.6	29	275
15	350	24.6	88	320

RVw = reflex volume in the conventional urodynamic study

Table 3 Reflex volume and reflex volume ratio in the conventional and ice provocative urodynamic studies before the intravesical resiniferatoxin instillation

Case	RVw (ml)	RVc (ml)	Reflex volume ratio
1	210	85	0.40
2	411	146	0.36
3	237	150	0.63
4	280	210	0.75
5	375	50	0.13
6	296	42	0.14
7	350	161	0.46
8	169	140	0.83
9	123	23	0.19
10	124	73	0.59
11	172	120	0.70
12	249	103	0.41
13	120	41	0.34
14	275	102	0.37
15	320	226	0.71

RVw = reflex volume in the conventional urodynamic study; RVc = reflex volume in the ice provocative urodynamic study

29.9 ml/cm H₂O, but there were no statistically significant changes (Table 4).

However, the activities of the unmyelinated C-fibers were significantly changed after the instillation. The mean RVw changed from 254.1 to 236.9 ml, but without statistical significance. However, the mean RVc and RV ratio were significantly increased, from 111.5 to 180.7 ml (*P*<0.05) and from 0.45 to 0.76 ml (*P*<0.05), respectively. Among the 15 cases, the RV ratio was above 1.0 in three cases, indicating the complete suppression of the unmyelinated C-fiber activities. In addition, the RV

Table 4 Comparison of conventional urodynamic results before and after the intravesical resiniferatoxin instillation

Case	Maximal bladder capacity (ml)		Compliance (ml/cm H ₂ O)		Pdet-max (cm H ₂ O)	
	Before	After	Before	After	Before	After
1	225	167	14	12.7	65	48
2	452	262	13.3	14	53	39
3	457	460	20	47.3	37	54
4	450	450	28	32	32	34
5	450	452	46.9	47.5	55	48
6	450	300	14.1	18.7	83	79
7	450	456	6	10.1	74	44
8	450	320	28.2	33.8	24	25
9	158	120	5.8	1.8	74	28
10	250	210	11	10.7	37	44
11	183	220	10.1	17.4	62	55
12	304	450	41.5	112.5	42	8
13	380	450	18.3	15.8	82	85
14	450	295	30.6	14	29	84
15	350	450	24.6	61.4	88	42
Mean (SD)	363.9 (110.9)	337.5 (122.0)	20.8 (12.4)	29.9 (28.4)	55.8 (21.5)	47.8 (21.7)

Pdet-max = maximal detrusor pressure

Table 5 Comparison of reflex volume and reflex volume ratio between before and after the intravesical resiniferatoxin instillation

Case	Before resiniferatoxin instillation			After resiniferatoxin instillation		
	RV _w	RV _c	RV ratio	RV _w	RV _c	RV ratio
1	210	85	0.40	161	100	0.62
2	411	146	0.36	262	374	1.43
3	237	150	0.63	284	124	0.44
4	280	210	0.75	304	180	0.59
5	375	50	0.13	402	85	0.21
6	296	42	0.14	187	98	0.52
7	350	161	0.46	356	336	0.94
8	169	140	0.83	203	307	1.51
9	123	23	0.19	40	22	0.55
10	124	73	0.59	110	68	0.62
11	172	120	0.70	184	109	0.59
12	249	103	0.41	292	303	1.04
13	120	41	0.19	158	123	0.78
14	275	102	0.37	180	115	0.64
15	320	226	0.71	430	367	0.85
Mean (SD)	254.1 (87.5)	111.5 (61.3)	0.45 (0.22)	236.9 (108.8)	180.7* (120.6)	0.76* (0.35)

RV_w = reflex volume in the conventional urodynamic study; RV_c = reflex volume in the ice provocative urodynamic study; RV ratio = reflex volume ratio (RV_w/RV_c)**P* < 0.05

ratios were increased in nine cases, indicating the partial suppression of the unmyelinated C-fiber activities, and the RV ratios were decreased in three cases (Table 5).

Discussion

Bladder afferent pathways consist of small, myelinated Aδ- and unmyelinated C-fibers. Aδ-fibers transmit signals mainly from mechanoreceptors, which detect

bladder fullness or wall tension, while the C-fibers mainly detect noxious signals and initiate nociceptive sensations. In spinal cord-injured patients, NDO is based on a spinal reflex arc, involving small unmyelinated C-fibers, which become relevant after disconnection of the bladder from a higher center.²⁰ de Groat *et al*¹¹ initially showed that C-fibers take over as the afferent pathway of the voiding reflex after a spinal cord injury. This seems to be a considerable reorganization of

the reflex connections in the spinal cord following the interruption of descending pathways from the brain, and this new reflex pathway can be blocked by vanilloids, such as capsaicin or resiniferatoxin.

The vanilloids are neurotoxins that selectively desensitize the unmyelinated C-fiber afferent neurons that may be responsible for the signals triggering detrusor overactivity.^{10,21} The rationale of Fowler *et al*,²² to initiate intravesical vanilloid instillation in patients with NDO of spinal origin, was the same as in the study of de Groat *et al*,¹¹ and more recently, resiniferatoxin was instilled for the treatment of NDO refractory to oral medications. However, the efficacy of treatment with resiniferatoxin may be different among institutions.¹⁰ The reason for these differences in the efficacy of treatment may be due to the lack of precise evaluations of the changes from the abnormal unmyelinated C-fiber activity. Therefore, in our study, an ice provocative urodynamic study, which could monitor the abnormal unmyelinated C-fiber activity, by stimulation of the nociceptor in NDO before and after resiniferatoxin instillation, was designed and used.

Since Bors *et al*¹³ reported that the bladder cooling reflex caused immediate involuntary detrusor contraction in patients with spinal cord injury, the ice water test has been used as a simple valuable method in the evaluation of NDO. However, some patients with detrusor sphincter dyssynergia might show a positive nonleakage ice water test²³ (no fluid leakage despite detrusor contraction to cold stimulation). Stöhrer *et al*¹⁹ defined the reflex volume as: the volume for which involuntary detrusor contractions began to appear. Using conventional urodynamic studies, the reflex volume (RVw) stimulated by mechanoreceptor can be measured, whereas the reflex volume (RVc) stimulated by nociceptor can be measured using ice provocative urodynamic studies. According to Geirsson *et al*,²⁴ the reflex volume for the bladder cooling reflex was below that needed to elicit a reflex volume in patients with a mechanoreceptor-induced micturition contraction. This implied that the RVc was usually smaller than the RVw, namely, the reflex volume ratio (RVc/RVw) was always less than unity. If the threshold of the RVc was to become larger than the threshold of the RVw after blockage of the nociceptive afferent, the reflex volume ratio may be changed to more than 1.0. Therefore, it could be supposed that the activity of unmyelinated C-fibers could be measured by the reflex volume ratio.

In our study, the instillation of 100 nM of resiniferatoxin, diluted in 10% ethanol, showed statistically significant increases in the mean RVc and RV ratio, from 111.5 to 180.7 ml ($P < 0.05$) and from 0.45 to 0.76 ml ($P < 0.05$), respectively, but there was no significant changes in the RVw. Such a result suggested that intravesical resiniferatoxin suppressed abnormal unmyelinated C-fibers in NDO. Among the 15 patients, three (20%) showed complete suppression and nine (60%) partial suppression of the C-fiber activity, but there was no change in the three other patients (20%) after instillation. In the conventional urodynamic study,

the involuntary detrusor contractions did not disappear in all cases, and there were no significant changes in the mean maximal bladder capacity, compliance or maximal bladder pressure after instillation. These findings imply that even if intravesical resiniferatoxin had an effect on the suppression of abnormal unmyelinated C-fiber activity, it could not completely suppress all the involuntary detrusor contractions. This can be explained by the abnormal C-fiber activation not being uniquely attributable to NDO. Therefore, other pathophysiologic mechanisms, including abnormal unmyelinated C-fiber activation, may be involved for the induction of NDO.

Rivas *et al*²⁵ reported that 0.5 or 1 μ M resiniferatoxin could improve the bladder capacity due to NDO, compared to Silva *et al*'s¹⁸ report that 50 or 100 nM resiniferatoxin was effective. Watanabe *et al*²⁶ supposed that more than a 50 nM concentration of resiniferatoxin was favorable for a therapeutic effect. In recent studies,^{9,18,27} resiniferatoxin, as low as 100 nmol/l (compared with 1 mmol/l capsaicin), induced full desensitization and was much less irritating to the bladder afferents. In our study, even with 100 nM of resiniferatoxin, it was not effective for complete suppression. There is no consensus on the ideal dose for the treatment of NDO, and the optimal concentration for a therapeutic effect, without serious side effects, remains to be clearly defined. Therefore, further study will be necessary to determine the optimal dosage, for which ice provocative urodynamic study could be helpful in the estimation of the abnormal unmyelinated C-fiber activity.

A limitation to this study was that neither the long-term effect of intravesical resiniferatoxin could not be observed nor the effect on NDO evaluated, when abnormal unmyelinated C-fiber activity was not detected in the ice provocative urodynamic study. Therefore, further studies will be required.

Conclusion

Intravesical resiniferatoxin instillation for the treatment of NDO, as confirmed by ice provocative (nociceptor stimulation) urodynamic study, could partially control abnormal unmyelinated C-fiber activity, but the partial suppression of abnormal unmyelinated C-fiber activity was not in concordance with the improvement in bladder functions due to the incomplete exploration of the mechanism for the development of NDO. Therefore, further studies on other pathophysiologic mechanisms of NDO, including unmyelinated C-fiber stimulation, accurate indications and the optimal concentration of resiniferatoxin instillation, are needed.

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