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Original Article: Clinical Investigation

On- and post-treatment symptom relief by repeated instillations of heparin and alkalized lidocaine in interstitial cystitis

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Abbreviations & Acronyms
AVV = average voided volume
DMSO = dimethyl sulfoxide
FVC = frequency volume chart
GAG = glycosaminoglycan
GRA = global response assessment
HBS = hypersensitive bladder syndrome
IC = interstitial cystitis
NGF = nerve growth factor
NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases
NSAIDs = non-steroidal anti-inflammatory drugs
NUIC = non-ulcer type IC
OSSI/OSPI = O'Leary and Sant's symptom index and problem index
UF = urinary frequency
UIC = ulcer type interstitial cystitis
VAS = visual analog scale (for pain)

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Objectives: To examine outcomes of intravesical instillations of heparin and alkalized lidocaine in patients with interstitial cystitis.

Methods: Patients with interstitial cystitis refractory to conventional therapies were given a solution of 20 000 U heparin, 5 mL 4% lidocaine and 25 mL 7% sodium bicarbonate, intravesically, weekly for 12 weeks consecutively. The treatment was regarded as "effective", when patients rated "slightly improved" or "better" on a seven-graded scale of global response assessment. Other assessment measures included O'Leary and Sant's symptom index and problem index, visual analog scale for pain, and frequency volume chart variables.

Results: A total of 32 patients were enrolled in the study. The average age was 63.3 years. All participants had received hydrodistension 2.2 times on average, and fulfilled National Institute of Diabetes and Digestive and Kidney Diseases criteria. The therapy was effective in 60.0% of the patients at the fourth instillation, in 76.7% at the last instillation, and 90.0%, 46.7% and 16.7% at 1, 2 and 6 months after the last instillation, respectively. Most of other assessment measures improved significantly at the fourth instillation and further beyond until the end of therapy. On termination of therapy, the efficacy gradually diminished, yet mostly maintained statistical significance by 2 months post-instillation. No severe adverse events occurred.

Conclusions: A 12-week course of weekly intravesical instillations of heparin combined with alkalized lidocaine is safe and effective in relieving symptoms in interstitial cystitis patients. The effect of the treatment is maintained for 6 months. Further studies are required to optimize the number of instillations and maintenance intervals in order to maximize the therapeutic potential of simple or combined instillations in the management of interstitial cystitis.

Key words: heparin, interstitial cystitis, intravesical instillation, lidocaine.

Introduction

IC is characterized by a particular symptom complex with no identifiable causes.[1] The symptom complex, HBS, is defined as bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain.[2] No current treatments have a significant impact on symptoms over time, and as a result, patients are subject to numerous treatment modalities; from invasive to holistic therapies.[3–5]

One of the possible etiologies for IC is chronic and persistent deficiency of the GAG layer, which allows penetration of urine into the interstitial layer of the bladder, thereby causing inflammatory reactions.[6,7] Heparin, a family of sulfated polysaccharide resembling GAG, is believed to bind the defect of the GAG layer on bladder surface. According to the previous reports, intravesical heparin therapy is effective in approximately half of the patients; however, it cannot produce immediate relief of IC symptoms.[7] In contrast, immediate symptom relief can be attained by intravesical lidocaine therapy. The safety and

improved absorption of alkalized lidocaine was confirmed in IC patients, although the effects of alkalized lidocaine disappear within a few days.[8] Combination of heparin and alkalized lidocaine successfully attained immediate and sustained improvement; however, the patients were followed only for 2 weeks post-treatment, and backgrounds (i.e. age, sex, with or without ulcer) predictive of favorable response have not been explored.[9]

We tested the efficacy of 12-weekly intravesical instillations of a combination of heparin and alkalized lidocaine in patients with IC, and evaluated therapeutic outcomes up to 6 months after the last instillation. In addition, we examined the difference in therapeutic response according to their backgrounds.

Methods

Patients

Patients with IC refractory to conventional therapies were enrolled in the study. IC was diagnosed by three conditions: (i) lower urinary symptoms, such as urinary frequency, bladder hypersensitivity and/or bladder pain; (ii) bladder pathology proven endoscopically by Hunner's ulcer and/or mucosal bleeding after over-distension; and (iii) exclusion of confusable diseases, such as infection, malignancy or calculi of the urinary tract.[2] According to cystoscopic findings on hydrodistension, patients were categorized into two groups; UIC and NUIC. Symptoms were assessed by OSSI/OSPI. Scores six or more for both indices, despite present therapies (i.e. hydrodistension or oral drugs), were required for enrolment. At enrolment, patients' age at therapy, age at onset of IC, duration of IC symptoms, sex, number of hydrodistensions undergone before the therapy and distended bladder volume at the primary hydrodistension were recorded. Patients with an allergy to lidocaine, continuous macrohematuria, active urinary tract infection and hemorrhagic diathesis were excluded.

The protocol of the study was approved by our Institutional Review Board (#2205), and was fully explained to the patients before a written informed consent was obtained.

Therapeutic protocol

All patients were intravesically given a solution of 20 000 U heparin (Ajinomoto, Tokyo, Japan), 5 mL 4% lidocaine (Astrazeneca, Osaka, Japan) and 25 mL 7% sodium bicarbonate (Otsuka, Tokyo, Japan) weekly for 12 weeks consecutively at our outpatient clinic using an 8-Fr urethral catheter. The acidity of the solution was pH 7.5. At each treatment, patients voided before instillation, and were instructed to hold urine for 30 min after instillation. The solution was prepared under sterile conditions immediately before every instillation. Adverse events were monitored by urinalysis and interviewing patients.

Table 1 Patients' demographics

No. (male/female)	32 (3/29)
Mean age (years)	63.3 ± 13.8 (range 35–82)
Age at onset of IC (years)	60.0 ± 14.4 (range 25–74)
Duration of IC (years)	4.7 ± 3.5 (range 1–13)
Type of IC (UIC/NUIC)	17/15
Past treatment	
Hydrodistension	32 2.21 times on average (range 1–7)
Distended bladder volume at primary hydrodistension (mL)	570.0 ± 230.0 (range 200–1200)
DMSO instillation	10
Medicine	
Suplatast tosilate	18
Tricyclic antidepressant	11
NSAIDs	14
Others	6

Evaluation items

We used GRA as the primary outcome measure. Participants rated their symptoms on a seven-grade scale ranging from markedly worse (–3) to markedly improved (+3) compared with the baseline. Efficacy was classified as "effective" when participants reported slight (+1) to marked improvement (+3) on the GRA, otherwise efficacy was considered to be "not effective" or as "symptom recurrence" if it was during the follow-up period.[10]

Other assessments included OSSI/OSPI, VAS for pain and FVC variables. The efficacy was evaluated after the first, fourth and 12th instillations, and 1, 2 and 6 months after the last instillation. Withdrawal from the study without completing the treatment course was counted as drop-out.

Statistical analysis

Therapeutic outcomes were compared with the baseline values. For its skewed distribution, signed Wilcoxon's rank sum test for paired samples was carried out to compare the values of average voided volume, daytime urinary frequency and nocturnal urinary frequency. For other variables, Wilcoxon's signed rank test was used. Patients' background factors associated with therapeutic efficacy at the fourth instillation and 2 months post-therapy were examined by χ^2-test and Fisher's exact test. $P < 0.05$ was considered significant. All calculations were carried out with SPSS, version 18.0 (SPSS, Chicago, IL, USA).

Results

A total of 32 participants (29 women and 3 men) were enrolled in the study (Table 1). The mean age was 63.3 years (range 35–82 years). All participants were compatible with the NIDDK criteria.[11] Of them, 17 were categorized as UIC, and 15 as NUIC. All patients had received hydrodistension

Table 2 Global therapeutic response ($n = 30$)

	During therapy			Post-therapy		
	Week 1	Week 4	Week 12	1 Month	2 Months	6 Months
Responders†	10	18	23	27	14	5
Non-responders‡	20	12	7	3	16	25
Response rate (%)	33.3	60.0	76.7	90.0	46.7	16.7

†GRA: +1, +2 or +3. ‡GRA: 0, −1, −2 or −3.

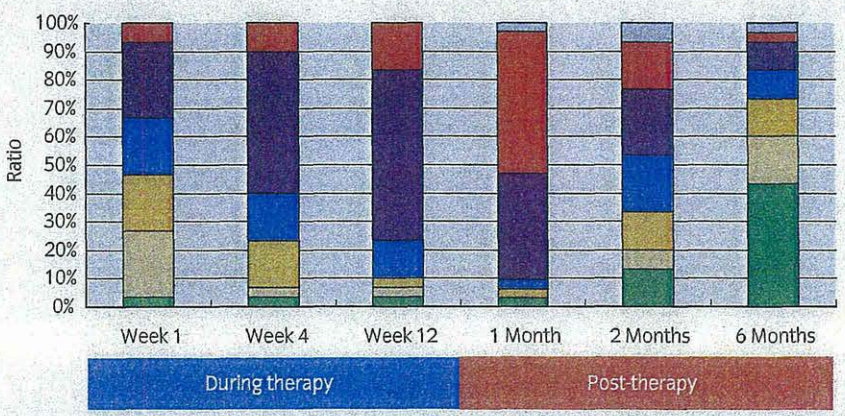

Fig. 1 Global response assessment for efficacy of heparin and alkalized lidocaine instillation. Patients with IC refractory to conventional therapies received a solution of 20 000 U heparin, 5 mL 4% lidocaine, and 25 mL 7% sodium bicarbonate intravesically weekly for 12 weeks consecutively. The patients were followed up at 1, 2 and 6 months post-instillation without further treatment. The efficacy was graded as "marked improved" (GRA +3), "moderately improved" (GRA +2), "slightly improved" (GRA+1), "no change" (GRA 0), "slightly worsened" (GRA −1), "moderately worsened" (GRA −2) or "marked worsened" (GRA −3). ■, GRA = +3; ■, GRA = +2; ■, GRA = +1; ■, GRA = 0; ■, GRA = −1; ■, GRA = −2; ■, GRA = −3.

at least once before instillation, with 2.2 times on average (range 1–7). Prior treatments included suplatast tosilate ($n = 18$), tricyclic antidepressant ($n = 11$), DMSO instillation ($n = 10$) and/or NSAIDs ($n = 14$). A total of 30 patients completed the treatment protocol and post-treatment follow up to 6 months, whereas two patients discontinued the therapy because of symptoms worsening at the fourth or sixth instillation.

According to GRA, responders gradually increased with advancement of the therapy (Table 2, Fig. 1); the response rate was 33.3% after the first instillation, 60.0% after the fourth and 76.7% after the 12th, and 90.0% 1 month after the last instillation. On the termination of instillation, the rate declined to 46.7% at 2 months and 16.7% at 6 months. Post-hoc analysis indicated ulcer type IC, onset age younger than 60 years and bladder volume at primary hydrodistension less than 500 mL as prognostic factors for better therapeutic response at the fourth instillation (Table 3); however, no factors were identified for efficacy at 2 months post-therapy. Other variables showed significant improvement during the therapy (Table 4). OSPI reached a significant level of improvement as early as at the fourth instillation ($P = 0.033$), and it was pronounced at the 12th instillation ($P < 0.001$). VAS for pain showed a significant reduction after the fourth instillation from the baseline ($P = 0.024$) and thereafter. Average voided volume significantly increased from the fourth therapy ($P = 0.029$). Urinary frequency decreased significantly at the fourth therapy for daytime frequency ($P = 0.003$) and for night-time frequency ($P = 0.001$). During post-therapy follow up, all the variables showed gradual deterioration with time; however, significant improvement lasted until 2 months after the termination of instillation. There was no significant difference at 6 months after the last instillation, except for nocturnal frequency, compared with the baseline.

As for side-effects of the therapy, no adverse events requiring additional intervention were observed. Two patients discontinued the therapy because of poor benefit. Minor side-effects included bladder pain ($n = 18$), gross hematuria ($n = 4$) and urinary tract infection ($n = 3$), all of which were self-limited. Gross hematuria was observed only on the day of instillation and not associated with systemic coagulation disorder (data not shown).

Additionally, 70% of patients reported slight bladder discomfort lasting for approximately 1 day every time after the administration, which also could be tolerated and decreased

Table 3 Univariate analysis of overall response factors at fourth therapy and 2 months post-treatment

	Univariate analysis					
	Fourth therapy			2 months post-treatment		
	OR	CI (95%)	*P*-value	OR	CI (95%)	*P*-value
Ulcer						
Ulcer/non-ulcer	8.250	1.154–59.003	0.039*	1.167	0.224–6.081	0.855
Sex						
Male/female	4.667	0.352–61.831	0.269	0.750	0.541–1.040	0.217
Age						
≥65 years/<65 years	0.500	0.087–2.886	0.657	1.250	0.233–6.715	0.795
Age at onset						
≥60 years/<60 years	0.121	0.017–0.867	0.039*	0.857	0.164–4.467	0.855
Duration of IC						
≥5 years/<5 years	1.500	0.266–8.449	0.685	1.167	0.224–8.081	0.855
Distended bladder volume						
≥500 mL/<500 mL	0.083	0.011–0.641	0.023*	1.250	0.233–6.715	0.795
Past hydrodistension						
≥2/once	0.686	0.119–3.963	0.673	2.4	0.444–12.980	0.414

*P-value <0.05.

Table 4 Therapeutic effects by symptom measures (mean ± SD, $n = 30$)

	Baseline	During therapy			Post-therapy		
		Week 1	Week 4	Week 12	1 Month	2 Months	6 Months
OSSI	13.4 ± 3.7	12.9 ± 3.4	10.9 ± 3.9	8.3 ± 3.6**	8.8 ± 4.0**	9.4 ± 4.4*	9.3 ± 5.3
OSPI	11.8 ± 4.2	11.5 ± 4.0	8.6 ± 4.2*	6.9 ± 3.3**	6.5 ± 3.6**	7.0 ± 3.9**	7.1 ± 4.5
VAS	5.8 ± 2.7	5.5 ± 2.4	3.4 ± 2.4**	3.5 ± 2.5*	3.3 ± 2.3**	3.8 ± 2.9*	3.5 ± 2.7
AVV1 (mL)	93.8 ± 65.5	108.2 ± 61.6	130.3 ± 61.8*	143.9 ± 72.9*	129.8 ± 66.4**	106.1 ± 72.4	118.6 ± 102.9
UF2 (day)	27.1 ± 36.6	19.3 ± 13.4**	14.4 ± 3.7**	13.4 ± 4.6**	14.6 ± 4.5**	15.1 ± 4.2*	15.0 ± 6.5
UF2 (night)	4.3 ± 2.7	3.6 ± 2.8**	2.7 ± 2.0**	2.3 ± 2.4*	2.3 ± 1.6**	2.1 ± 1.4*	2.0 ± 1.3*

*$P < 0.05$ versus baseline, **$P < 0.005$ versus baseline.

with continuation of the therapy. This discomfort was not related to therapeutic effect (data not shown).

Discussion

Intravesical therapy with a combination of heparin and alkalized lidocaine was first reported by Parsons.[9] The solution consisting of 40 000 U of heparin, 8 mL 2% lidocaine and 3 mL 8.4% sodium bicarbonate was given three times per week for 2 weeks. At the initial administration of the solution, 94% of patients (33 of 35 patients) reported immediate relief of both pain and urgency. However, patients were followed until 48 h after the last therapy, when 80% of them reported sustained relief of the symptoms. Another study by Welk used 10 000 U of heparin, 8 mL 2% lidocaine and 4 mL 8.4% of sodium bicarbonate for 23 female IC patients complaining of dyspareunia.[12] Patients were treated with the solution three times per week for 3 weeks. Three weeks after the therapy, 65% of patients reported a successful outcome of IC symptoms. Most of the efficacy parameters, including OSSI, OSPI, frequency, voided volume, Pelvic Pain Urgency Frequency score and Female Sexual Function Index pain domain score, showed significant improvement, supporting the effectiveness of the therapy. A double-blind, crossover, placebo-controlled trial showed that a single instillation of the solution can provide significant and immediate relief of IC symptoms up to 12 h.[13] These three studies demonstrated well the short-term efficacy, especially for pain, of intravesical therapy with a combination of heparin and alkalized lidocaine. However, they presented little data for outcomes post-administration.

Based on previous studies and the short-term efficacy of heparin instillation, we carried out the present study to assess the long-term outcomes of combined instillations, confirming the efficacy comparable with three previous studies. According to GRA, responders increased with advancement of the therapy; 33.3% after the first therapy, 60.0% at the fourth therapy and 76.7% at the 12th therapy. Once improved, there was no deterioration in efficacy during therapy. At the

first week, all the parameters showed slight improvement, yet not at a significant level, whereas Parsons and Welk reported quicker responses to the therapy. The reason for the difference might be because of the difference in the study design; the previous two studies gave the solution three times per week, whereas ours was given weekly. We designed the interval according to the capacity of our outpatients' clinic and patients' convenience. However, almost all of the parameters reached a significant level of improvement at the fourth instillation. No specific backgrounds were identified as predictive factors, although patients with the ulcer type of IC, younger onset age and smaller bladder volume at primary hydrodistension were likely to be better off earlier. As these factors are related to the ulcer type of IC, the subtyping might be responsible for the responsive difference. During the post-instillation period, the response rate was maximized (90.0%) at 1 month, 46.7% at 2 months and 16.7% at 6 months; the therapeutic effect lasted an average of 4.1 months after the last therapy. Other parameters similarly showed slight deterioration. These facts suggest that repeated administration of the solution could recover the damaged GAG layer of the bladder mucosa, and that the recovery deteriorates in due time. In other words, the current therapy would not be a curative, but palliative, treatment for IC. Also suggested is the necessity for regular maintenance therapy, with 1–4 months as a possible interval.

The therapy was well tolerated. A common side-effect was bladder discomfort after instillation, which occurred to 60.0% of patients after every instillation. Two patients discontinued the therapy because of worsening symptoms, amplified with instillation. The bladder discomfort might be explained by catheterization, alkalinity of the solution, stimulation of bladder mucosa by agents and/or natural course of the disease. Though discomfort itself might not affect the therapeutic effect, it should be solved by further study. Another adverse event was gross hematuria; however, it was self-limited and observed only on the day of instillation.

The limitations of the present study should be mentioned. It was a single-armed, open-label trial with a small number of patients. The efficacy of a single agent, heparin or lidocaine, remained unevaluated; heparin instillation alone might be effective.[13] In addition, the therapeutic outcomes were assessed by subjective questionnaires, but not by objective measures, such as urine NGF level.[14] Further studies should be explored to determine: (i) composition of the solution; (ii) duration of induction therapy; (iii) interval of maintenance therapy; and (iv) therapeutic assessment by objective outcome measures.

Twelve weekly intravesical instillations of heparin combined with alkalized lidocaine safely achieved symptom relief in most IC patients, which diminished in 6 months post-treatment. Younger age and the presence of ulcers are predictive of a quicker response. Further studies are required to optimize the patient selection, the number of instillations and the maintenance interval to maximize the therapeutic potential of this therapy in controlling IC symptoms.

Conflict of interest

None declared.

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実践マニュアル

膀胱のボツリヌス毒素療法

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はじめに

ボツリヌス毒素（ボツリヌストキシン，Botulinum toxin: BTX）は自然界で最も高い生物活性を有するとされる神経毒であり，ごく少量の摂取で呼吸筋麻痺による死を招きうることが知られ，第二次大戦中は生物兵器として研究された歴史をもつ。1980年にAlan B. Scottが斜視に対するボツリヌス毒素療法の治療成績を報告[1]してから，その臨床応用は広がりをみせ，近年では神経因性および非神経因性の過活動膀胱，間質性膀胱炎など泌尿器科領域でもその有用性が報告されつつある。

過活動膀胱（尿意切迫症状を主症状として頻尿，切迫性尿失禁を伴うことのある症候群）はきわめて一般的な病態で，本邦でも患者数が810万人に上るとされている[2]。治療として抗コリン薬が第一選択とされているが，十分な量の抗コリン薬を用いても症状が改善しない，もしくは口内乾燥などの副作用により内服の継続が困難な症例もある。

間質性膀胱炎は，膀胱痛，頻尿，尿意切迫感，下腹部違和感などを主徴とする原因不明の膀胱の慢性炎症疾患で，疾患の定義が確立されていない。そのためにその患者数などの実態は明らかになっていないが，類似の症状を呈するのは人口の5%程度という報告もあり，決してまれな疾患ではない。しかし，有効な治療法が少ないのが現状である[3]。

これらの難治症例に対する治療の一選択肢として，近年ボツリヌス毒素膀胱壁内注入療法が注目されている。本稿では，自験例での経験も交えて，膀胱のボツリヌス毒素療法について説明する。

ボツリヌス毒素（BTX）

BTXは1987年に*Clostridium botulinum*の産物として同定された[4]。ヒトに対する薬理学的活性を有するA，B，E，F，G型と非活性型のC，D型が存在する。現在，A型ボツリヌス毒素（BTX-A）とB型ボツリヌス毒素（BTX-B）が臨床で利用されている[5]。BTX-Aは末梢の神経筋接合部における神経終末内でのアセチルコリン放出作用により神経筋伝達を阻害し，筋弛緩作用をもたらす。BTX-Aは2つのHeavy chain，Light chainから成る。Heavy chainはシナプス前領域でprotein receptor（synaptic vesicle protein）とganglioside coreceptorの認識にかかわる。Light chainは神経終末にあるSNARE（*N*-ethylmaleimide sensitive attachment protein receptors）の1つであるSNAP25（synaptosome-associated protein 25 kDa）に結合する[5]。

排尿の知覚に関する神経線維としては，A線維，C線維が知られている。A線維は主に膀胱壁の伸展知覚に関与する。C線維は正常の排尿状態では顕著な働きを示さないが，侵害刺激の知覚に重要な役割を果たす。C線維に発現している受容体としては，神経成長因子（nerve growth factor: NGF）に対するtrk-A受容体，サブスタンスPとニューロキニンAに対するニューロキニン受容体，カプサイシンに対するバニロイド受容体，ATPに対するプリン受容体が知られている[6]。BTX-Aは，知覚神経からのグルタミン酸，サブスタンスP，NGFの放出を抑制する，膀胱上皮細胞からのATP分泌を抑制するなどの作用を有し，C線維からの知覚神経路を遮断するとされている[7]。

医療用のBTXとしてはBOTOX（Allergan Inc.,

Irvine, California, USA), Dysport (Ipsen Inc., Slough, UK), Xeomin (Merz Inc., Frankfurt, Germany) などの商品名で販売されている。本邦ではボトックス® (グラクソ・スミスクライン株式会社が販売) が眼瞼痙攣, 片側顔面痙攣, 痙性斜頸, 上肢痙縮, 下肢痙縮, 2歳以上の小児脳性麻痺患者における下肢痙縮に伴う尖足, 重度の原発性腋窩多汗症の治療にすでに保険適用となっており, 臨床の場で痙攣, 筋硬直を取り除く目的で使用されている。なお, 本薬の所持には「二種病原体等の所持等における必要な手続き等」として厚生労働省に書類を提出する必要がある。

膀胱疾患のボツリヌス毒素療法

近年, 諸外国では泌尿器科領域において基礎・臨床の両面でBTX-Aの膀胱壁内注入療法の有用性・安全性が報告されている[6-18]。2011年には米国食品医薬品局 (FDA) によってBOTOXが脊髄疾患などに伴う神経因性膀胱への適応を追加承認されているが, 2013年5月現在, 本邦では膀胱疾患に対する保険適用はないのが現状である。

1. 用量設定

BTX-Aの致死量は2,000～3,000単位であるとされるが, 膀胱疾患における使用量の100～300単位は, 重篤な副作用の報告がなく, 安全性には問題ないと考えられる。

BTX-Aの膀胱壁内注入療法は1999年より行われ, BTX-A 100～300単位の投与量が一般的となっている。2000～2007年までの論文で発表されている副作用としては, 870例のうち一過性の尿閉により間欠的自己導尿が必要になった症例9%, 排尿困難7.6%, 尿路感染症4.9%, 血尿, 局所痛, 排尿痛などの局所症状が4.3%, その他として発熱, てんかん発作, 風邪様症状, 混乱がそれぞれ1例に認められている。

臨床での有効性・安全性は動物実験データから勘案しても妥当と考えられる。たとえば, ラット (200～300 g) にBTX-Aを2～3単位 (10単位/kg) 膀胱内注入した実験において, 膀胱容量は対照群に比べ1～1.5倍になり効果は2カ月間継続し, またBTX-Aに起因する合併症は認めなかった[11]。同様に, ラット (250～300 g) にBTX-Aを膀胱内に50単位 (200単位/kg), 尿道に30単位 (100単位/kg) 注入しアセチルコリン放出能を調べた実験においても副作用を認めていない[12]。また, 薬物動態についてであるが, ラットに125I-BTX-Aを筋肉内単回投与したときの血漿中濃度は, 2時間後に最高値として投与量の3%が認められ, 24時間後には1%であった。筋肉内には84%を認めたが, 24時間後には5%に減少し, 消失半減期は約10時間と推定された。また, 投与後24時間以内に60%が尿中排泄された。

相互作用として筋弛緩薬 (ツボクラリン, ダントロレンナトリウム), 筋弛緩作用を有する薬剤 (スペクチノマイシン, アミノグリコシド, ポリペプチド系抗菌薬, テトラサイクリン系抗菌薬, 抗コリン薬, ベンゾジアゼピン系薬剤, ベンザミド系薬剤) が筋弛緩作用を増強するおそれがあり, 併用注意となっている。

2. 治療にあたって

膀胱疾患に対するボツリヌス毒素療法は, 内視鏡下に膀胱壁内に注入する方法がもっぱら行われている。施設によるが, 東京大学泌尿器科では, 2泊3日の入院のうえで手術室で麻酔下にて行っている。治療については保険適用外の治療であるため, 倫理委員会の審査・承認を受けたうえで原則自費診療の形で行う。また, BTX-Aは適用外使用となるため海外からの輸入が必要である。なお, 残った薬剤の廃棄に際しては, アンプルやBTXと接触した機器を含めて0.5%次亜塩素酸ナトリウム溶液と混和して失活させる必要がある。

注入にあたって, 専用の器械があるわけではなく, 施設によって用いている器械は異なる。当科では, 操作用膀胱鏡にコラーゲン注入針 (23G) を用いていた。過活動膀胱の場合はさほど問題にならなかったが, 間質性膀胱炎の場合, 組織が脆弱で穿刺に伴う出血で視野の確保が困難になることから, 最近は27Gの内視鏡穿刺針を用いている (図1)。

BTX-Aは, 治療直前に調製して投与する。東京大学ではBTX-A100単位を生理食塩水15 mLに溶解して投与しているが, 薬剤自体が無色透明のため, そのままだと注入部位が判然としない。そのため, 調

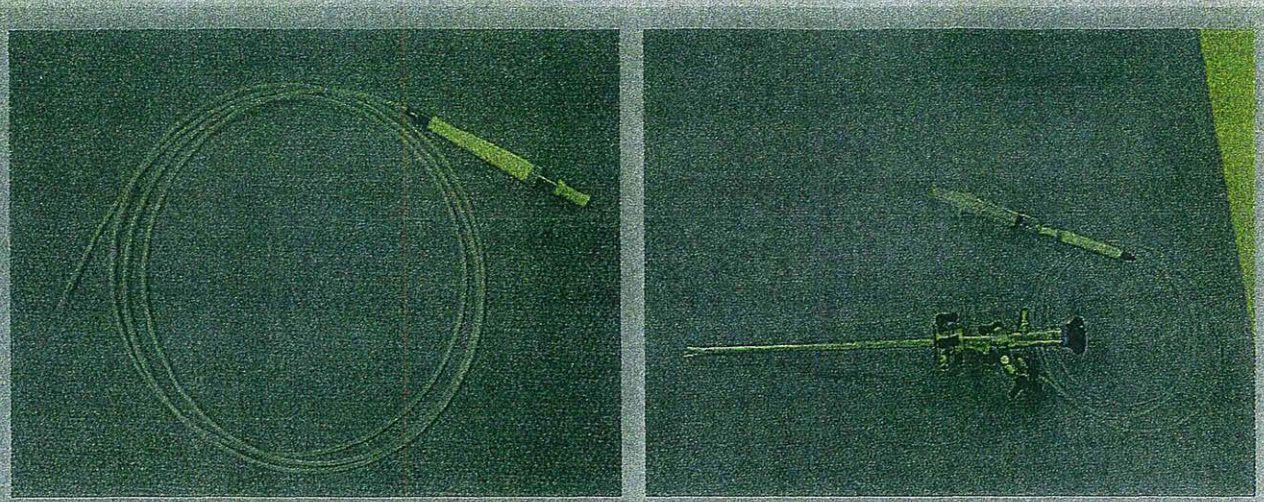

図1　ボツリヌス毒素注入用器具
当科では左の内視鏡用穿刺針（25G）を右のように操作用膀胱鏡の操作用チャンネルに通して，ボツリヌス毒素を注入している。

図2　ボツリヌス毒素の注入
写真ではわかりにくいが，注入部位は粘膜下がインジゴカルミンの青色で周囲と判別しやすくなる。

製したBTX-A溶液に0.1 mL程度のインジゴカルミンを添加して青色とし，注入部位が判然とするようにしている（**図2**）。

注入部位については，決められた方法はないが，通常は膀胱全体に満遍なく注入し，排尿筋に十分薬剤が行き渡るようにする（**図3**）。ただし，間質性膀胱炎の場合は，排尿筋の弛緩より疼痛などの知覚を抑制することが重要であり，骨盤神経叢に近い膀胱三角部を中心に注入するようにしている[18]（**図4**）。

治療に際して特別な処置を患者に行う必要はないが，尿閉のリスクが高い症例については，尿閉となった場合の対応（α_1ブロッカー，自己導尿など）をあらかじめ考慮する必要がある。

神経因性膀胱に対する治療効果

神経因性膀胱に対する最初のBTX-A膀胱壁内注入療法は，2000年Schurchらにより報告されている[19]。最近の比較的症例数の多い200例の神経因性膀胱に対するBTX-A 300単位膀胱壁内注入療法の結果では，最大膀胱容量の増大，73%の症例で自己導尿の離脱，抗コリン薬併用不要などの効果を認め，約6カ月間効果の持続を認めた。

国内では最近，仙石，岡村らの報告がある[20]。対象は脊髄損傷患者9例（男：女=7：2）で，BTX-A 200単位を膀胱に30カ所注入した。最大膀胱容量は126 mLから263 mL，不随意収縮圧は83.5 cmH_2Oから23.8 cmH_2O，1日尿失禁回数は4.9回から1.1回，1日導尿回数は10回から7.9回，1回導尿量は97.7 mLから184 mL，ICIQ-SF（International Consultation on Incontinence Questionnaire-Short Form）での尿失禁による生活困窮度（0～10）が7.1から1.1と著明な改善を認めている。BTX-Aによる有害事象も認めていない。

非神経因性膀胱に対する治療効果

1999年より過活動膀胱に対するボツリヌス毒素膀胱壁内注入療法が報告されている。症例数30～200の報告においてBTX-Aの使用量200～300単位で，術前排尿量との比較にて1回排尿量が70～80%増加する，尿意切迫感の消失（70%），昼間排尿回数の減少率約50%，夜間平均排尿回数減少（4回から1.5回）

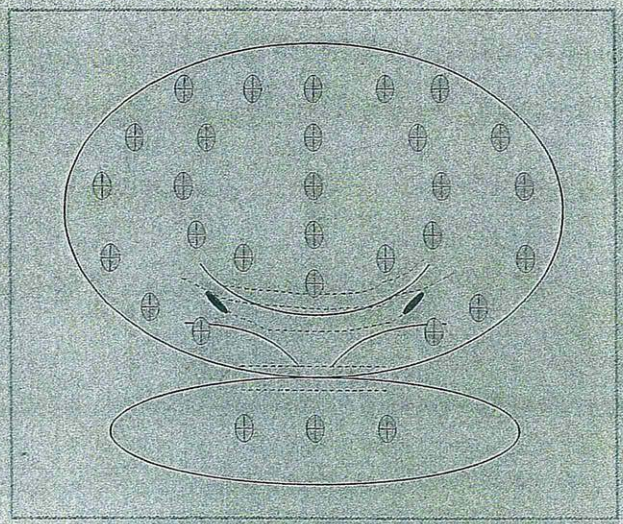

図3　神経因性膀胱，非神経因性膀胱におけるボツリヌス毒素の注入部位

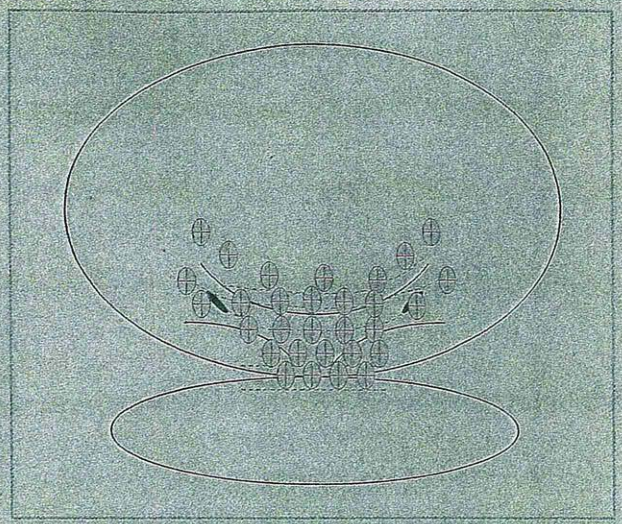

図4　間質性膀胱炎におけるボツリヌス毒素の注入部位

などの効果を認めている。効果持続期間は3～6カ月とされている。最近の無作為化二重盲検比較対照試験[21]では，抗コリン薬に対して治療抵抗性の過活動膀胱患者で，1日尿失禁量が100 g以上の22症例（プラセボ群7例，BTX-A群15例）が対象となった。治療群には，BTX-A 200または300単位を三角部を除く8～10カ所に注入した。BTX-A治療群は1日尿失禁回数が7.9回から3.4回，1日パッド使用数は4.4回から2.2回，1日尿失禁量は346 gから190 gと改善したのに対し，プラセボ群では著変が認められなかった。副作用として血尿，尿路感染症，残尿量の増加（25 mLから107 mL）を認めている。

東京大学でも難治性過活動膀胱患者に対してボツリヌス毒素膀胱壁内注入療法を行っており，術後1カ月において77%の症例で尿失禁の改善を認め，主要下部尿路症状質問票，過活動膀胱症状質問票でも有意な改善を認めている。

間質性膀胱炎に対する治療効果

間質性膀胱炎に対するBTX-A注入療法の報告は，2004年にSmithらが13例に対するBTX-A 200～300単位の注入療法をはじめて報告している[17]。それによると，間質性膀胱炎の症状スコア・問題スコア（Interstitial Cystitis Symptom Index，Interstitial Cystitis Problem Index），および疼痛スコア（Visual Analogue Scale）の改善，最大排尿量の増加を認めている。近年の間質性膀胱炎に対するボツリヌス毒素療法の結果もおおむね同様の結果を示し[15,16]，また，Kuoらは治療が有効であった症例では治療前に比べて治療後の尿中のNGF値が有意に低下していることを報告しており[22]，間質性膀胱炎の症状をコントロールする一つの有効手段と考えられる。

東京大学でも2011年より間質性膀胱炎患者を対象に本治療を行っており，有効例では自覚症状の改善，排尿回数の有意な減少を認めている。ただし，過活動膀胱の場合と同様，治療効果は平均5カ月程度であり，今後は反復投与についても検討していく必要がある。

副作用とその対応

副作用および使用上の注意であるが，2000～2007年半に「非神経因性過活動膀胱に対するBTX-A膀胱壁内注入」に関して発表されている論文上での副作用は，332例のうち間欠導尿が必要になった症例は18例（5.4%），排尿困難・排尿痛・血尿などの手術に伴う一過性の症状が46例（13.8%），尿路感染症が29例（8.7%）であった。膀胱の筋肉の収縮力低下により排尿困難を生じる可能性がある。

他の疾患でBTX-Aを使用した場合は，嘔気，頭痛，などがそれぞれ1～3%に認められている。また，まれな重篤な合併症として，呼吸困難および筋無力症や，因果関係が不明な心筋梗塞，死亡例の報告がある。全世界では，現在までに数百万例に及ぶBTX-Aの治療が行われているが，2008年1月23日付けで米

国の消費者団体Public Citizenが「さまざまな疾患に対してBOTOXを使用した結果658例の有害事象が報告され，そのうち12症例（うち1例が膀胱壁内注入）が嚥下障害，誤嚥性肺炎により死亡したとの記録が米国FDAにある」と発表した。しかし，これまでの調査ではBTX-Aによる治療と死亡との因果関係がはっきりしているわけではない。

一方，本邦においては，痙性斜頸の治験時に死亡例が1例報告されている。また，眼瞼痙攣6,526例，片側顔面痙攣8,457例，痙性斜頸2,132例における使用成績調査の結果では，本剤との因果関係が完全には否定されない死亡例が3例報告されている。しかし，いずれの症例も情報不足などにより被疑薬と死亡との因果関係は評価できていない。

泌尿器科領域でBTX-Aを用いる場合，誤嚥の可能性のある症例を除外基準に設ければ，米国の消費者団体が指摘しているような嚥下障害，誤嚥性肺炎になる可能性はきわめて低いと考えられる。

おわりに

かいつまんでではあるが，膀胱疾患のボツリヌス毒素療法の概要について述べさせていただいた。まだ，泌尿器科領域では保険適用となっておらず，治療を行ううえでは制約が多く，また基本的に対症療法であることには変わりないが，抗コリン薬抵抗性の過活動膀胱や間質性膀胱炎のなかには本治療でQOLが著しく改善する場合があるのも事実である。適応症例を十分に吟味し，適正に治療を行えば，安全な優れた治療法であると考えられる。

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