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A Randomized Controlled Trial of Bacillus Calmette-Guerin and Botulinum Toxin-A for the Treatment of Refractory Interstitial Cystitis

Abd Elhameed El-Bahnasy, Yasser A. Farahat*, Mohamad El-Bendary*, Mohamad R. Taha*, Mahmoud El-Damhogy*,*
Sherif Mourad†
*Urology Department, Tanta University Hospital, Tanta, Egypt; †Urology Department, Ain Shams University, Cario, Egypt
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ABSTRACT

INTRODUCTION: Interstitial cystitis (IC) primarily occurs in middle-aged women, with a female to male ratio of 9:1. Currently, IC therapy is inadequate with only 2 treatments approved by the Food and Drug Administration: oral pentosan polysulphate and dimethyl sulfoxide (DMSO) bladder instillation. Several researchers have evaluated the efficacy of intravesical bacillus Calmette-Guerin (BCG) instillation for the treatment of IC with promising results. On the other hand, botulinum toxin-A (BTX-A) has gained widespread acceptance for the treatment of bladder overactivity, detrusor-sphincter dyssenergia, and IC. The present work is designated to evaluate the use of intravesical BCG instillation versus intravesical injection of BTX-A in patients with IC.

PATIENTS AND METHODS: We randomly divided 36 patients who met the National Institutes of Health-National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) criteria for IC and reported at least moderate pain and frequency for a minimum of 6 months into 2 groups (cases 1,3,5,etc vs. cases 2,4,6,etc). The first group (Group I) received the standard 6 weeks of intravesical BCG instillations. The other subjects (Group II) received an intravesical injection of 300 units of BTX-A. The patients were followed at routine intervals with questionnaires and voiding diaries. Adverse events were closely monitored in the treatment and follow-up phases of the study.

RESULTS: During the follow-up period (23 weeks and 22 weeks, respectively), 11 of 16 (68.75%) patients in Group I and 14 of 16 (87.50%) patients in Group II continued to have an excellent response in all parameters measured. The global interstitial cystitis survey improved 71% in Group I and 92% in Group II; daily voids decreased 31% and 68%, nocturia improved 54% and 100%, pelvic pain decreased 81% and 96%, urgency decreased 71% and 100%, and dysuria decreased 82% and 92%, respectively. The patients in Group II showed a statistically significant improvement in all parameters compared to Group I.

CONCLUSION: Although the safety profile of BCG is acceptable, its response rate for treatment of intractable IC was poorer in relation to BTX-A. On the other hand, though BTX-A has not yet been approved by the FDA, clinical trials have proved intravesical injection of BTX-A to be a safe and effective therapy for treatment of intractable IC within a 22-week follow-up period.

KEYWORDS: Interstitial cystitis (IC), Bacillus Calmette-Guerin (BCG), Botulinum toxin (BTX-A)

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A Randomized Controlled Trial of Bacillus Calmette-Guerin and Botulinum Toxin-A for the Treatment of Refractory Interstitial Cystitis

CORRESPONDENCE: Yasser A. Farahat, Urology Department,

Tanta University Hospital, Tanta, Egypt,

yasserafarhat@yahoo.com

INTRODUCTION

Interstitial cystitis (IC) is a chronic, debilitating condition characterized by pelvic pain, urinary urgency, and urinary frequency. It affects an estimated 700,000 to 1 million people in the United States, most of them women [1]. Actual prevalence may be significantly higher because of the lack of diagnostic criteria appropriate for clinical use. The strict diagnostic criteria developed for the research setting by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have been shown to miss 60% of cases [2].

IC has been classified into the classic and non-ulcer types based on cystoscopic findings. Classic IC, also called Hunner's ulcer, is found in 5%-20% of patients with IC and is characterized by observable bladder ulcerations after hydrodilatation. Non-ulcer IC, also called early IC, is characterized by glomerulation and petechia formation after hydrodilatation under anesthesia [3].

Intravesical administration of immune modulators is a widely accepted treatment for IC at the present time. Several intravesical agents have already been approved by the Food and Drug Administration (FDA) for treatment of IC, such as dimethyl sulphoxide, hyaluronic acid, heparin, and some anti-inflammatory agents [4,5].

Bacillus Calmette-Guerin (BCG) has been used for more than 20 years for treatment of superficial bladder carcinoma. It is proposed to exert its tumor prophylaxis by modulating the immune system. The interest in BCG for treating IC began in 1994 when Zeidman *et al.* [6] used BCG on a patient with IC misdiagnosed as having superficial bladder tumor. Interestingly, at the end of BCG course, the error of diagnosis was discovered, and the IC symptoms were resolved. Others have tried to test BCG in a prospective study for the treatment of refractory cases with IC [7].

Botulinum toxin-A (BTX-A), a presynaptic neuromuscular blocking agent, has gained widespread acceptance for treatment of bladder overactivity, detrusor-sphincter dyssenergia, and IC [8]. The therapeutic value of BTX-A stems from its ability to inhibit acetylcholine release and correct focal dystonia when injected into the muscle [9,10].

The present work was designated to prospectively evaluate and compare the efficacy as well as the safety of intravesical BCG instillation versus intravesical injection of BTX-A in subjects with intractable IC or painful bladder syndrome (PBS).

PATIENTS AND METHODS

We randomly divided 36 female patients who met the NIDDK criteria for IC/PBS and reported at least moderate pain and frequency for a minimum of 6 months into 2 groups (Group I = cases 1,3,5,etc and Group II = cases 2,4,6,etc).

Eligible participants were at least 18 years old with a self-reported urinary frequency of 11 or more. On a 0-9 Likert scale, all participants recorded a 4 or higher for pelvic pain, bladder pain (dysuria), and urgency for at least 6 months [11] and were required to give written consent.

Exclusion criteria included patients with vesicoureteral reflux, immunocompromised patients, and patients on concomitant steroids or anticoagulant therapies, as well as pregnant patients.

The initial evaluation included medical history, physical examination, laboratory evaluation (urine analysis and culture, renal function tests, and complete blood picture), radiological study (plain x-ray on urinary tract, abdominal ultrasound, and cystogram), filling cystometry, and cystourethroscopy. Data was collected before treatment and every 4 weeks throughout the study period.

Patients in Group I (18 cases) were subjected to intravesical BCG administration in the form of weekly instillations of 5×10^8 colony forming units for 6 weeks, the recommended dose for patients with superficial bladder carcinoma. Reconstitution was performed with 1 ml sterile saline and dilution with 50 ml saline for intravesical instillation. The patients were instructed to retain the solution for 2 hours while changing their position in bed to assure contacting most of the bladder mucosa with the drug.

Patients in Group II (18 cases) were treated with intravesical injections of BTX-A under local anesthesia in the form of intraurethral 2% lidocaine jell and intravesical 2% lidocaine on 100 ml saline for 10 minutes. Using a rigid cystoscope and a 25-gauge disposable injection needle, 300 units of BTX-A diluted in 30 ml of preservative-free saline were injected submucosally into the superficial muscles at 30 sites within the bladder (Figure 1). The injection sites included the lateral

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Figure 1. A case of IC showing bladder peticheal hemmorrhage (upper) and cystoscopic injection of BTX-A submucosally into the superficial muscle (lower)
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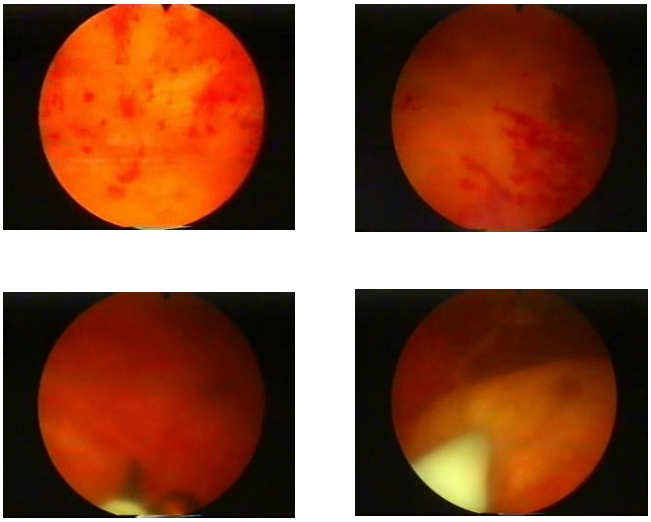

bladder walls, anterior bladder wall, posterior bladder wall, bladder base, and trigone. All cases received perioperative oral antibiotics.

During the study, 4 cases were excluded. In Group II, 2 patients discontinued follow-up visits from the 3rd and 12th weeks, respectively. A third case discontinued the BCG therapy because of severe hemorrhagic cystitis. The fourth patient (from Group I) was diagnosed as having superficial transitional cell carcinoma at the 6th week of follow-up and was transferred to the uro-oncology unit.

The final outcome was evaluated via 2 components. First, we looked at the participants' Global Response Assessment (GRA) [7] at the end of the study (23 weeks for Group I and 22 weeks for Group II). The GRA asked subjects to rate symptoms compared with the baseline on a 7-point centered scale of markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, and markedly improved. Successful responders were defined as those reporting moderate or marked improvement on the GRA.

The second component of the assessment included the 24-hour voiding diary parameters of diurnal and nocturnal frequency and pain, urgency, and dysuria recorded on a Likert scale from 0-9.

RESULTS

During the follow-up period, there was significant improvement of basal IC symptom diaries in both groups compared to the pretreatment data. Diurnal frequency decreased from the pretreatment average of 16 to 11.50 ± 2.338 in Group I (a 31% improvement) and 5.277 ± 1.138 in Group II (a 68% improvement). Furthermore, nocturnal frequency significantly improved in BCG patients by 54% and reached normal nocturnal frequency among BTX-A cases (a 100% improvement). Pelvic pain was the most distressing complaint among IC patients, with a pretreatment Likert scale score of around 5.5, but improved significantly to 1.0556 ± 0.771 (an 81% improvement) in Group I and 0.222 ± 0.403 in Group II (a 96% improvement). Urgency was completely cured among BTX-A patients during the whole follow-up period, while it improved significantly ($P < 0.005$) among BCG cases during the same period by 71%. Moreover, pretreatment dysuria improved significantly in both groups by 82% and 92%, respectively. The complete results for both groups can be found in Table 1 and Figure 2.

The timing of improvement was different between the 2 groups. Patients in Group I started to show improvement in their overall symptoms after 2 weeks with maximum improvement at the end of the fourth week. Patients in Group II showed immediate improvement at the first week with maximum improvement at the tenth day after the injection. From then on, only marginal changes in the symptoms were noticed with no significant change.

At the end of the study (22-23 weeks), a total of 11 of 16 (68.75%) patients in Group I and 14 of 16 (87.50%) in Group II continued to have excellent responses in all the parameters tested. Furthermore, the global interstitial cystitis survey improved by 71% and 92%, respectively.

Regarding complications, 1 case in Group I stopped treatment because of severe hemorrhagic cystitis. Otherwise, no major complications were reported among patients in the 2 groups. Out of the 36 patients, 5 (31%) in Group I and 3 (18%) in Group II had dysuria immediately after treatment, persisting for 3 to 4 weeks. Among those 8 patients, urinary tract infection was documented in 3 (2 in Group I and 1 in Group II). Their symptoms were controlled by urinary antibiotics and nonsteroidal antiinflammatory analgesics, and none required

any narcotics. The other 5 patients had their symptoms controlled by nonsteroidal anti-inflammatory agents only.

DISCUSSION

The cause of IC is unknown, but evidence suggests that immune system dysregulation with an imbalance of Th1 and Th2 cells may have a role in the pathophysiology [12]. Currently, there is increasing support for the hypothesis of neurogenic inflammation, which activates bladder afferent nerves and provokes bladder pain and a hypersensitive bladder [13].

Current IC therapy is inadequate with only 2 treatments approved by the FDA: oral pentosan polysulphate and dimethyl sulphoxide (DMSO) bladder instillation. However, many IC cases show either transient or no response to both lines of treatment as patients continue to suffer [7]. As such, researchers continue to look for a more suitable option that may offer IC patients a more effective and persistent treatment.

BCG has been used extensively to treat superficial bladder carcinoma for more than 20 years. The use of BCG in the treatment of IC aims to modulate immunologic and allergic responses in the IC bladder wall [12]. In fact, the actual mechanism of action of BCG is not yet clear even after all the years of its use for treatment of superficial bladder carcinoma. Peters *et al.* [14] reported a 60% favorable response rate in IC cases after treatment with BCG. In long-term follow-up, 89% of those patients who responded favorably after the 6-week BCG treatment continued to have an excellent response at 24 to 33 months [15].

In the present series, we used intravesical BCG instillation in 16 cases with a follow-up to 23 weeks. We reported statistically significant improvement of diurnal frequency by 31% and nocturnal frequency by 54%, as well as an 81% increase in the control rate of pelvic pain. Furthermore, urgency and dysuria decreased by 71% and 82%, and the global interstitial cystitis survey improved by 71%. Moreover, 11 of 16 of the BCG cases continued to have excellent responses in all parameters after the study period, and all the subjects stopped any use of narcotics.

BTX-A has been used for years for different conditions with somatic and autonomic motor disorders [16]. The efficacy of BTX-A in bladder overactivity may result from an inhibitory effect on the detrusor muscle. The inhibitory effect of BTX-A is not only limited to the acetylcholine release, but it also impairs ATP release in isolated bladder tissue [17]. We have been using a dose of 300 units of BTX-A to treat cases of bladder overactivity for the last 3 years with no serious side effects. We choose the dose of 300 units again for this study, as it is still inside the safety margin of the drug, and we believe that it may enhance the expected response of patients with IC. On using BTX-A for treatment of intractable IC in Group II, we reported an excellent response in all parameters (87.5%) during 22 weeks of follow-up. Diurnal frequency improved by 68%, and nocturnal frequency returned to normal (a 100% response). Pelvic pain was resolved in 96% of patients, and urgency improved by 71%, while dysuria was resolved in 100% of patients. Similar results were reported Smith *et al.*

Table 1. Basal and posttreatment (22-23 weeks) symptom scores of the patients (± SD)
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	Group	Basal data	Posttreatment	*t*	*P*	Improvement
Frequency	Group I	16.666 ± 3.198	11.50 ± 2.338	5.804	< 0.005	31%
	Group II	16.833 ± 2.613	5.277 ± 1.138	16.819	< 0.005	68%
Nocturia	Group I	6.056 ± 6.056	2.778 ± 1.078	8.828	< 0.005	54%
	Group II	6.333 ± 1.821	0.277 ± 0.478	12.652	< 0.001	100%
Pelvic pain	Group I	5.444 ± 1.263	1.0556 ± 0.771	10.618	< 0.005	81%
	Group II	5.833 ± 1.390	0.222 ± 0.403	16.765	< 0.001	96%
Urgency	Group I	6.388 ± 1.314	1.833 ± 1.024	12.531	< 0.005	71%
	Group II	6.444 ± 1.030	0.055 ± 0.250	27.701	< 0.001	100%
Dysuria	Group I	4.888 ± 1.454	0.888 ± 0.718	10.549	< 0.005	82%
	Group II	4.833 ± 1.204	0.389 ± 0.50	12.225	< 0.005	92%

There is higher significant improvement in all parameters in Group II (BTX- A) compared to Group I (BCG) ($P < 0.005$)

[18] with a 69% improvement in subjective symptoms, a 71% improvement in the symptom index, a 69% improvement in the problem index, and a 79% improvement of bladder pain. In another study, Kuo [19] used suburothelial injections of BTX-A to treat 10 women with IC, and improved results were reported in 7 patients. All patients with therapeutic effects had dysuria after treatment.

The effect of BTX-A on IC patients was further confirmed by Giannantoni *et al.* [20], who treated 14 patients with injections of 200 units of BTX-A in 20 mL saline at 20 sites in the trigone and bladder base. They reported 12 (85.7%) patients with subjective improvement at 1 and 3 months, scores on the visual analog scale (VAS) decreased, frequency decreased, and bladder capacity increased significantly. Dysuria was reported in 2 patients, and they required intermittent clean catheterization.

Zermann *et al.* [21] examined the use of BTX-A injections in 11 patients with chronic prostatic pain. Following injection of 200 units of BTX-A, 9 out of the 11 patients reported subjective pain relief. In addition, significant decreases in postvoid residual urine and increases in the flow rate were observed. Their explanation for this outcome was that, by deceasing pelvic floor muscle tone, BTX-A not only facilitates detrusor muscle activity and improves voiding efficiency, but it may also diminish pain sensations.

A recent multi-center, randomized, double-blind, placebo-controlled trial of intravesical BCG for the treatment of refractory IC has shown different results. Among 265 patients who received BCG or a placebo and were followed-up for 34 weeks, the response rate was 12% for the placebo and 21% for BCG (P = 0.062). Only marginal statistical significance was observed in the secondary outcomes (voiding diary, pain, urgency, and IC symptom index). Although the safety profile was acceptable, intravesical BCG treatment was considered ineffective in treatment of refractory IC. These results encourage researchers to find a better treatment for the specific group of patients with refractory IC who fail to respond to the available lines of treatment [7].

Looking at the overall results in the present study, both BCG and BTX-A have favorable outcomes when used for treatment of patients with IC. However, analysis of the data shows that BTX-A is clearly more favorable, as it alleviates nocturia and urgency in all patients. Also, the rate of frequency of micturition was decreased by more than double among the patients treated by BTX-A when compared to BCG patients (68% vs. 31%). As such, the use of BTX-A may open the way for the treatment of refractory cases of IC with acceptable outcomes.

CONCLUSIONS

Although the safety profile of BCG is acceptable, its response rate for treatment of intractable IC was poorer in relation to BTX-A. On the other hand, though BTX-A has not yet been approved by the FDA, clinical trials have proven the intravesical injection of BTX-A to be a safe and effective treatment for intractable IC within a 22-week follow-up period. However, long term follow-up is required to test the persistence of the improvement and the requirements for repeated treatment.

Figure 2. There is significant improvement of all symptoms in both groups at the end of the study (right). Moreover, we reported higher significant improvement in all parameters in Group II (BTX-A) compared to Group I (BCG) ($P < 0.005$) (left).

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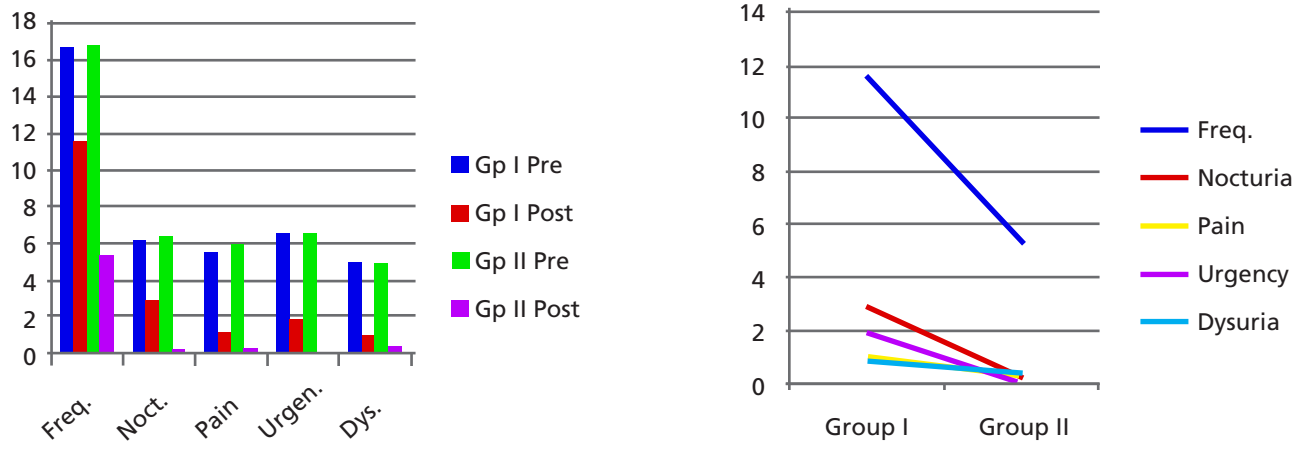

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