

Intravesical Bacillus Calmette-Guerin for Treatment of Refractory Interstitial Cystitis

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Introduction: The aim of this study was to examine the efficacy and safety of intravesical Bacillus Calmette-Guerin (BCG) in the treatment of refractory interstitial cystitis (IC).

Materials and Methods: Thirteen patients with refractory IC were enrolled in the study. They were scheduled to receive 6 weekly courses of treatment with intravesical BCG. Variables including the frequency, nocturia, urgency, pelvic pain, dyspareunia, dysuria, IC symptom index, IC problem index, and average voided volume were assessed every 6 months after the BCG therapy.

Results: Thirteen patients received the complete course of intravesical BCG therapy. Twenty-four months after the treatment a mean improvement of 51.9% was seen in frequency ($P = .001$), 43.2% in nocturia ($P = .002$), 28.7% in urgency ($P = .004$), 43.1% in pelvic pain ($P = .001$), 58.3% in dyspareunia ($P = .003$), 6.5% in dysuria ($P = .16$), 57.7% in the O'Leary-Sant IC symptom index ($P = .001$), and 61.8% in the O'Leary-Sant IC problem index ($P = .001$) scores. A significant improvement was seen in the mean average voided volume at the 24th follow-up month (89.5%; $P = .001$).

Conclusion: Intravesical BCG is a relatively effective treatment in patients with refractory IC. Its efficacy seems to be modest and lasts for at least 24 months in majority of the patients. It is also safe and well tolerated.

Keywords: bacillus Calmette-Guerin, interstitial cystitis, urinary tract symptoms, treatment

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INTRODUCTION

Interstitial cystitis (IC) is a chronic pelvic pain syndrome with no specific identifiable cause. Its symptoms include variable combinations of referring pain to the bladder, frequency, and urgency.⁽¹⁾ Interstitial cystitis is annoying and affects the quality of life in many patients.

Despite many therapeutic approaches, the improvement remains suboptimal and the efficacy of these treatment modalities are unknown.⁽²⁾ Some evidence suggests that defects in the regulations of the immune system including an imbalance of type 1/type 2 helper T cells may play a role in the pathophysiology of the

disease.⁽³⁾ It has been shown that intravesical bacillus Calmette-Guerin (BCG) stimulates the type 1 helper T-cell cytokine profile and therefore, alleviate the symptoms of IC.^(4,5) We designed this clinical trial to determine the efficacy and safety of intravesical BCG in the treatment of refractory IC.

MATERIALS AND METHODS

Between January 2002 and December 2004, patients presented with refractory IC were evaluated in a prospective study at Sina Hospital in Tehran, Iran. Initial evaluation, including medical history, physical examination, and laboratory studies

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(urinalysis, urine culture, urine cytology, purified protein derivative [PPD] skin test, cystoscopy, potassium chloride test, and biopsy), were performed. Patients who met the symptom criteria of the National Institute of Diabetes, Digestive, and Kidney diseases (NIDDK) for interstitial cystitis were selected.⁽⁶⁾ Hunner's ulcer was reported in none of them, but all had glomerulations after cystoscopic hydrodistension. Patients with persistent symptoms for 3 years despite treatment were selected. Their symptoms were refractory to hydrodistension, oral treatments (amitriptyline and/or hydroxyzine), and intravesical dimethyl sulfoxide. Voiding diaries (for determining the frequency, nocturia, and average voided volume) and a visual analog scale self-administered questionnaire (zero to 5 scores) for assessment of pain, urgency, dyspareunia, and dysuria were recorded before the treatment and during the follow-up.⁽⁷⁾ O'Leary-Sant questionnaire was used for determining the symptom and problem indexes.⁽⁸⁾ The quality of life was determined by a global quality of life question on patients' feeling about their urinary condition scored from zero to 6, corresponding to "delighted" to "terrible," respectively.⁽⁹⁾

A total of 15 women were enrolled in the study and intravesical BCG therapy (Tice strain, 120 mg) was planned for them. Informed consent was obtained from all patients. When the 6-week instillations were completed, the patients returned for follow-up every 6 months, up to the 30th postoperative month. They were asked to rate their symptoms before and after the treatment. Clinical responders were defined as those whose symptoms improved 50% or greater.⁽¹⁰⁾ The subjects were instructed to report any adverse event since the first instillation of BCG.

Differences in scores between the baseline and follow-up times were analyzed using the –Wilcoxon signed rank test.

RESULTS

All patients were women and their median age was 27 years (range, 20 to 57 years). Of 15 women, 13 received all the courses of intravesical BCG therapy. For 1 patient, BCG was not started initially and for 1 another, BCG therapy was discontinued due to the side effects. The patients' characteristics are shown in Table 1.

Three patients were followed up for 30 months and the 10 remainders were visited up to the 24th month. Table 2 shows the efficacy of the treatment with BCG according to the visual analogue scales, O'Leary-Sant questionnaire, and the voided volume.

Table 1. Patients' Characteristics Before Treatment*

| Characteristics | Values |
|-------------------------------|--------------|
| Age | 31.8 ± 10.8 |
| Frequency | 14.0 ± 2.7 |
| Nocturia | 3.8 ± 0.7 |
| Urgency score | 4.1 ± 0.6 |
| Pain score | 4.2 ± 0.7 |
| Dyspareunia score | 2.5 ± 1.4 |
| Dysuria score | 1.5 ± 1.3 |
| O'Leary-Sant IC symptom index | 13.7 ± 2.3 |
| O'Leary-Sant IC problem index | 12.5 ± 1.7 |
| Average voided volume, mL | 115.4 ± 15.1 |
| Overall quality of life | unhappy† |

*Values are demonstrated as means ± standard deviations. IC indicates interstitial cystitis.

†The median score for quality of life was 5, indicating "unhappy."

Table 2. Patients' Characteristics After Treatment With Intravesical BCG*

| Characteristics | Postoperative Months | | | | |
|-------------------------------|----------------------|--------------|--------------|--------------|-------------|
| | 6 | 12 | 18 | 24 | 30† |
| Frequency | 6.1 ± 1.2 | 5.9 ± 1.1 | 6.4 ± 1.3 | 6.7 ± 1.4 | 7.0 ± 2.0 |
| Nocturia | 1.9 ± 0.7 | 1.4 ± 0.7 | 1.4 ± 0.7 | 2.1 ± 0.5 | 2.7 ± 0.6 |
| Urgency score | 2.7 ± 0.6 | 2.4 ± 0.7 | 2.5 ± 0.7 | 2.9 ± 0.7 | 2.7 ± 0.6 |
| Pain score | 2.6 ± 0.8 | 1.9 ± 0.6 | 2.1 ± 0.6 | 2.4 ± 0.7 | 2.7 ± 0.6 |
| Dyspareunia score | 1.2 ± 1.0 | 1.0 ± 1.0 | 1.1 ± 0.9 | 1.2 ± 1.0 | 2.3 ± 0.6 |
| Dysuria score | 1.2 ± 1.1 | 1.0 ± 1.0 | 1.2 ± 1.1 | 1.3 ± 1.1 | 2.0 ± 1.0 |
| O'Leary-Sant IC symptom index | 7.7 ± 1.1 | 6.7 ± 1.3 | 6.5 ± 1.1 | 6.8 ± 1.2 | 7.7 ± 1.5 |
| O'Leary-Sant IC problem index | 5.9 ± 1.1 | 4.9 ± 1.1 | 4.7 ± 1.1 | 5.0 ± 0.9 | 4.7 ± 0.7 |
| Average voided volume, mL | 210.8 ± 30.1 | 233.9 ± 23.6 | 228.5 ± 28.5 | 214.6 ± 29.9 | 246.7 ± 5.8 |

*Values are demonstrated as means ± standard deviations.

†Three patients were assessed at the 30th month.

Table 3. Improvement in Scores of Symptoms and Indicators*

| Characteristics | Postoperative Months | | |
|-------------------------------|----------------------|-------------|-------|
| | 12 | 24 | 30 |
| Frequency | 57.9 (.001) | 51.9 (.001) | 55.9 |
| Nocturia | 63.1 (.001) | 43.2 (.002) | 38.3 |
| Urgency score | 41.5 (.001) | 28.7 (.004) | 36.7 |
| Pain score | 55.4 (.001) | 43.1 (.001) | 43.3 |
| Dyspareunia score | 65.2 (.003) | 58.3 (.003) | 36.1 |
| Dysuria score | 32.4 (.01) | 6.5 (.16) | 0 |
| O'Leary-Sant IC symptom index | 56.1 (.002) | 57.7 (.001) | 49.3 |
| O'Leary-Sant IC problem index | 56.9 (.001) | 61.8 (.001) | 53.6 |
| Average voided volume, mL | 106.1 (.001) | 89.5 (.001) | 125.5 |

*Values are percents in proportion to the scores in the baseline and those in parentheses are *P* values.

At the 12- and 24-month follow-ups, the number of patients who responded to the treatments (50% improvement or greater) were 13 (100%) and 11 (84.6%) for frequency, 11 (84.6%) and 8 (61.5%) for nocturia, 6 (46.2%) and 3 (23.1%) for urgency, 11 (84.6%) and 6 (46.2%) for pain, 3 (23.1%) and zero for dysuria, 8 (61.5%) and 8 (61.5%) for dyspareunia, 12 (92.3%) and 12 (92.3%) for average voided volume, 11 (84.6%) and 10 (76.9%) for the O'Leary-Sant IC symptom index, and 12 (92.3%) and 12 (92.3%) for the O'Leary-Sant IC problem index, respectively. Table 3 demonstrates the improvement in the scores, and the Figure shows the mean scores. The quality of life changed from “unhappy” to “mostly satisfied” in the majority of the patients (median scores 5 in the baseline and 2 in the 12- and 24-months follow-ups).

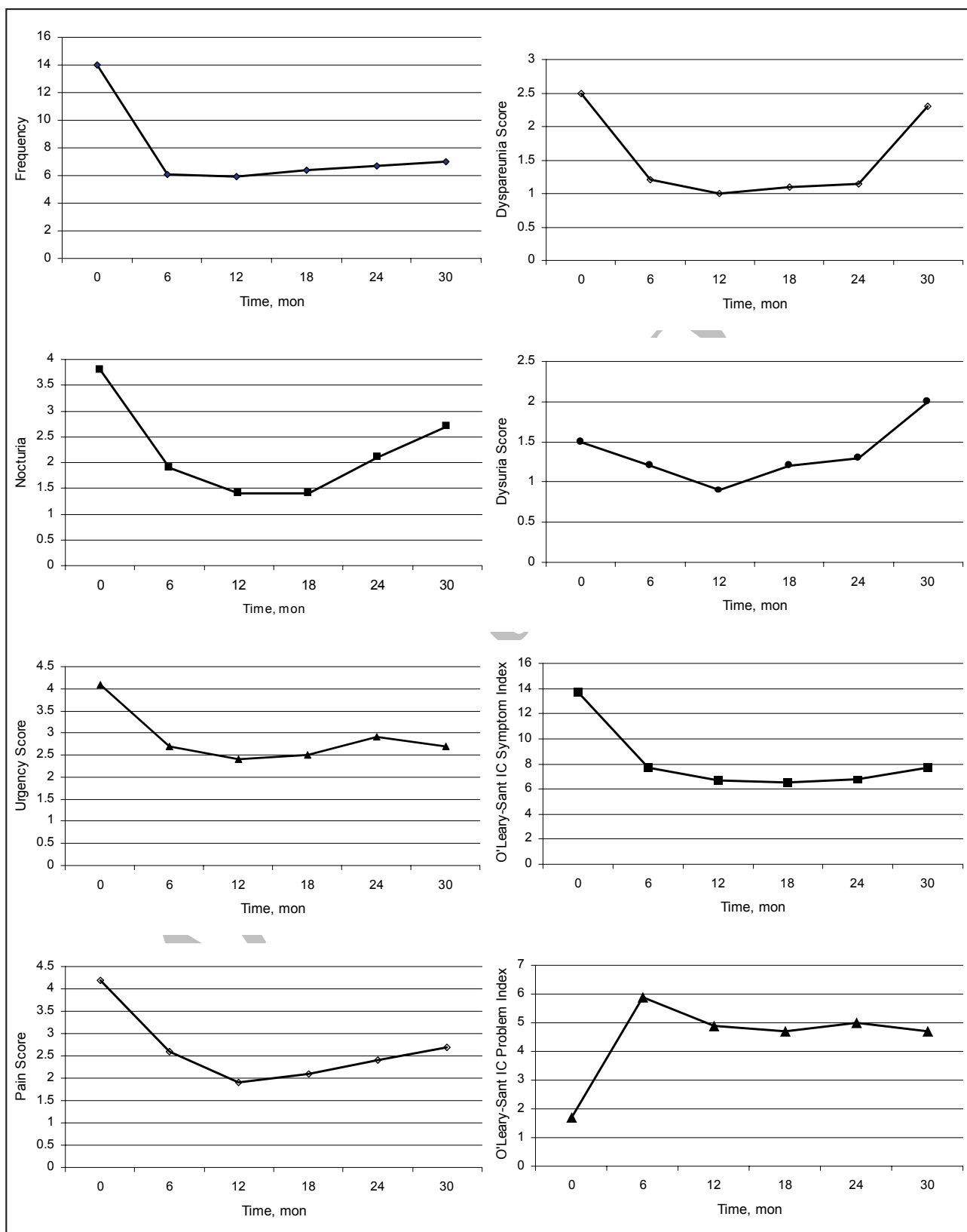
Patients tolerated the 6 courses of BCG therapy fairly well. Self-limited flu-like syndrome, a minor complication of BCG therapy, was reported in 3 patients. One of the patients did not complete the therapy course due to the BCG complications including fatigue, malaise, nausea, arthralgia, and low-grade fever and chills at the 4th week of the treatment. Tests for tuberculosis were negative in all patients.

DISCUSSION

Intravesical BCG is a novel therapy for the treatment of IC. Although this therapy has been used for years in the treatment of bladder cancer, its exact mechanism of action is unknown. Bacillus Calmette-Guerin is a strong stimulus of the immune system in the bladder and it is suggested that in some patients, IC may be an autoimmune disease.⁽¹⁰⁻¹²⁾

Some evidence has shown IC as a type 2 helper T-cell-mediated disease. In addition, it was reported that the urine of these patients had a 5-fold increment in the production of interleukin-6 (IL-6).⁽¹³⁾ Interleukin-6 is a known stimulus of the type 2 helper T-cell response and the degree of its elevation correlates with the symptoms of the patient. Furthermore, inhibitors of IL-2, which stimulate a type 1 helper T-cell response, were found in the urine of these patients.⁽¹⁴⁾ A type 1 T-helper cell response is thought to be beneficial, because it downregulates the inappropriate type 2 T-helper cell-driven responses that may cause immunopathologic problems. Bacillus Calmette-Guerin stimulates the type 1 T-helper cell response causing the remarkable elevation of IL-1, IL-2, interferon- γ , and tumor necrosis factor- α .^(15,16) Thus, the efficacy of BCG in the treatment of IC may be due to the stimulation of the type 1 T-helper cell response allowing the destruction of stressed immunogenic cells and promoting reparative conditions. Correcting the underlying abnormal immunologic problem may be the reason of the effectiveness of intravesical BCG in the treatment of IC and may explain the long-term improvement of the symptoms.⁽¹⁰⁾ Additionally, a probable association of IC with a low level of nitric oxide in the urine has been proposed. Increasing nitric oxide in the urine was shown to result in an improvement in the symptoms.⁽¹⁷⁾

Intravesical BCG is also known to be a potent stimulator for urinary nitric oxide in patients with bladder cancer.⁽¹⁸⁾ Morcos and colleagues showed that BCG induced the formation of nitric oxide in the bladder with no evidence of systemic nitric oxide formation.⁽¹⁹⁾ Increased production of nitric oxide in the bladder is probably due to the induction of



Changes in the symptom scores in patients with refractory interstitial cystitis after BCG therapy.

nitric oxide synthase activity in the urothelial cells. This finding is another potential etiology for the effectiveness of intravesical BCG in the treatment of IC.⁽¹⁰⁾ In 1997, a prospective double-blind study on intravesical BCG demonstrated a 60% response rate with BCG in comparison with the response rate of 27% with placebo.⁽⁵⁾ In a 24- to 33-month follow-up report, 8 of the 9 responders continued to respond favorably and BCG did not worsen the symptoms in nonresponders.⁽¹⁰⁾ These results are in contrast with the study of Peeker and coworkers.⁽²⁰⁾ However, their report has been criticized because of the study design and lack of adequate follow-up for BCG therapy.⁽²¹⁾ The study of Lane and associates indicated that intravesical Tice strain BCG could have a short-term effect on IC patients which was not durable with longer follow-ups. Management of these patients usually requires adjuvant therapy after the initial treatment.⁽²²⁾ Mayer and colleagues compared intravesical BCG and placebo instillations in patients with refractory IC. The response rates were 21% for BCG and 12% for placebo ($P = .06$). Small improvements were observed in the 24-hour voiding diary, pain, urgency, and validated IC symptom indexes; however, these differences were not statistically significant.⁽²³⁾

Our study showed that the efficacy of treatment with intravesical BCG in IC patients seems to especially improve the average voided volume. It should be mentioned that this study was performed in a small population of IC patients and the efficacy of this treatment in long-term setting is not clear, either.

CONCLUSION

Intravesical BCG is a relatively effective treatment in refractory IC patients. Its efficacy seems to be modest and durable for at least 24 months in the majority of the patients. It is also safe and well tolerated.

CONFLICT OF INTEREST

None declared.

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