

# Female Urology

## The efficacy and Safety of Intravesical Bacillus-Calmette-Guerin in the Treatment of Female Patients with Interstitial Cystitis: A double-blinded Prospective Placebo Controlled Study

IRANI D, HEIDARI M, KHEZRI AA

*Faghihi Hospital, Shiraz University Of Medical Sciences, Shiraz, Iran*

### ABSTRACT

**Purpose:** To evaluate the efficacy and safety of intravesical Bacillus Calmette-Gurein injection in the treatment of female patients with interstitial cystitis.

**Materials and Methods:** Thirty women meeting the National Institute of Arthritis, Diabetes, digestive and kidney diseases criteria for interstitial cystitis, were randomized in a double-blinded fashion in two groups each consisted of 15 patients to receive six, weekly instillation of 120 mg BCG vaccine of Iranian Institute of pastor or placebo. Periodic questionnaires on symptoms of interstitial cystitis, voiding diaries, bladder capacity at first desire to void, and maximum bladder capacity were obtained. Adverse events were closely monitored during the treatment and follow-up phases of the study. Subjective and objective baseline values were compared with the follow-up data.

**Results:** With a mean follow-up of 24 (range 6 to 33) months 11 out of 15 (73%) in BCG group, and 3 out of 15 (20%) in placebo group responded to the treatment ( $p < 0.002$ ). Responders were defined the patients with more than 40% improvement in the symptoms of interstitial cystitis. The global improvement in symptoms and signs of interstitial cystitis was 62%. Adverse events were similar in both groups, mostly irritative in nature and no significant systemic event was noted. BCG did not worsen interstitial cystitis symptoms.

**Conclusion:** We concluded that intravesical BCG is safe, effective, available, and inexpensive with relatively durable results in the treatment of interstitial cystitis.

**KEY WORDS:** interstitial cystitis, BCG vaccine, immunotherapy

### Introduction

Interstitial cystitis is a chronic disabling disease presenting with irritative symptoms, pain, and sterile urine. It was described for the first time by Hunner in 1915.<sup>(1)</sup> Although near a hundred years have been passed from then, the etiology and definite treatment is unknown. A series of various causes have been suggested including mast cell related inflammation, infection, and immunologic

system alteration.<sup>(1)</sup> Zeidman et al reported the experience of effective Bacillus Calmette-Guerin (BCG) intravesical installation in 1994.

They selected five patients with resistant interstitial cystitis as candidates for a 6-week therapy with intravesical installation of BCG and observed significant improvement in bladder capacity ( $p=0.027$ ), daytime frequency ( $p=0.013$ ), nocturnal frequency ( $p=0.019$ ), and pain and bladder discomfort ( $p=0.031$ ).<sup>(2)</sup> Zeidman's interest was attracted

to BCG when he found that its installation into bladders with suspected tumors led to improvement of symptoms which were later defined to be due to interstitial cystitis.<sup>(2,3)</sup> BCG vaccine is FDA approved and produced by Pastor Institute in Iran with a low cost and acceptable availability; thus we decided to try the efficacy and safety of BCG vaccine on interstitial cystitis in the patients referred to educational medical centers of Shiraz University of Medical Sciences.

### Materials and Methods

This study was designed as a double-blinded randomized controlled trial at Shiraz University of Medical Sciences' hospitals to be done from January 1999 to September 2002. Thirty patients who met NIDDK diagnostic criteria were selected from among 150 females with irritative symptoms and bladder pain, after performing cystoscopy under anesthesia, bladder hydrodistention, and other preliminary evaluations. They were randomly assigned into the study and control groups, each containing 15 patients, based on the prediction of 15% response to the treatment vs. 20% response in the control group, the study power of 80%, and error of 5%.<sup>(2-5)</sup>

The excluding criteria were immunocompromising conditions, steroids, Warfarin, or immunosuppressant administration, pregnancy, vesicoureteral reflux, a history of intravesical installation in the last 3 months, positive HIV serology, positive cutaneous PPD, and males due to the risk of catheterization.<sup>(3,4)</sup>

Primary evaluations consisted of history and physical examination, complete blood count, biochemical HIV serologic test, cutaneous PPD test, chest x-ray, cystography, cystoscopy, bladder hydrodistention, and bladder capacity measurement. Bladder biopsy would be done if tumor was suspected or in some particular conditions.

A general questionnaire was filled before and after (during the study) the intervention in which vaginal or urethral pain, pelvic pain, painful intercourse, urgency, dysuria, feeling of healthy, sleep status, life quality,<sup>(6)</sup> and validated questions of Viscontin University about interstitial cystitis symptoms,<sup>(7)</sup> day time urination profile, the average volume of the bladder that induces fullness, and the average tolerable urine volume were included.

Also, patients with involuntary contraction of the bladder or the ones responded to anticholinergic medications were excluded in this study.

Routine cystometry was not performed in all the patients in order to minimize the research costs and physicians' intervention.

Thirty patients who had positive hydrodistention and glomerulization in more than 75% of bladder mucosa under general anesthesia and met the NIDDK criteria for interstitial cystitis, were randomly assigned into two groups each contained 15 patients. They received intravesical installation of 120 mg of BCG vaccine or 50 cc of normal saline (as placebo) through foley catheter for six weeks. Vials of placebo with similar appearance were produced.

Consecutive cases were selected to received either the placebo or BCG, Vials nominated blindly as drugs A and B. The staff who were involved with the therapy were blind to the drugs type and nominating the drugs and listing the patients were done by a third person not enrolled in the study. In case of severe fever or a serious complication the patient would be excluded from the blind procedure to be treated for BCG complications. The patients were informed about the details of placebo controlled design of the study and their written consent was taken before the study. Also charges were omitted. They were asked to maintain the solution in the bladder for two hours and change the position every 15 minutes.

In case of inconvenience the bladder would be emptied temporarily and the contents would be installed again. An emergency telephone number was available to contact if any probable complications occurred over the first three days of treatment. Follow-up after 1,2,3, and 6 months was done when the 6-week therapy period finished. The last follow-up was performed at least six months later. The study remained double-blinded until the end of the follow-up. The comparison of the symptoms and signs before and after the treatment was done preceding the revealing of the groups.

According to Parson, over 40% improvement of valid scores of Wisconsin University for interstitial cystitis were considered as response to the treatment. This was selected as a criterion to evaluate other symptoms.<sup>(8)</sup>

Patients were asked to show the severity of the symptoms before and after the treatment on a graded 10 cm rulers.

Statistic analysis was done by Mann-Whitney U signed rank test using SPSS software.

### Results

Demographic characteristics of the two group were similar with no significant statistic difference. These parameters are demonstrated in table 1. Changes in primary symptoms and signs were evaluated during 1,2,3, and 6 months follow-ups.

**TABLE 1.** *The comparison of symptoms and signs of the patients receive BCG and placebo*

Variable	BCG group	Placebo group	P value
Patients	15	15	1
Age (year)	40.8±13.96	36±12.84	0.529
Disease (year)	9.4±5.98	6.8±5.5	0.315
Urination per day (times)	14.6±4.35	12.7±5.25	0.218
Urination per night (centimeter)	4.9±1.19	4.2±1.31	0.218
Urgency (centimeter)	5.45±1.11	5.6±1.14	0.315
Dysuria (centimeter)	5.56±1.1	5.51±1.16	0.971
Painful intercourse (centimeter)	5.32±0.93	4.89±0.9	0.393
Pelvic pain (centimeter)	4.88±1.2	4.76±0.95	0.853
Valid scores of Wisconsin University for interstitial cystitis (No.)	31.2±8.5	25.4±6.7	0.105
Feeling well (centimeter)	4.66±8.5	4.98±0.95	0.393
Sleep (centimeter)	4.7±1.3	4.5±1	0.393
Bladder volume in the first feeling of urination (cc)	57±243.52	62.2±27.61	0.796
Maximum tolerable bladder capacity (cc)	187±81.79	183±61.1	0.796
Score of 36 graded questions of life quality (No.)	53±4.3	54±3.75	0.165

Eleven out of 15 patients who received BCG vaccine (73%,  $p<0.002$ ) responded to the treatment, compared to 3 out of 15 in the control group (20%,  $p<0.05$ ).

The mean two year follow-up showed that of 11 patients improved with BCG installation 7 (63.6%) did not required any excessive therapy in order to control the symptoms. The overall improvement was 62% ( $p<0.05$ ).

Frequency and nocturia reduced by 33.5% and 40%, respectively, in the BCG group, while no considerable change was observed in the control group. Some of the other symptoms and signs in BCG group vs. control group improved as follows: dysuria 75% vs. 42%, urgency 42% vs. 24.3%, painful coitus 61% vs. 13.4%, pelvic pain 65% vs. 22%, appropriate sleep 63% vs. 17%, and feeling healthy 51% vs. 18%.

Improvement of valid scores of Wisconsin University for interstitial cystitis was achieved 56% vs. 16.5%. Life quality (FS 36) increased by 63% vs. 16%. Mean bladder capacity at the first feeling of fullness increased approximately by 27 cc (47%) vs. 7 cc (9.6%). Maximum tolerable volume increased by a mean of 53 cc (70%) in BCG group compared to 13 cc (21%) in control group.

**TABLE 2.** *The comparison of symptoms and signs of the patients enrolled in BCG and placebo groups 24 months after the treatment*

Variable	BCG group	Placebo group	P value
Interstitial cystitis validated score of the University of Viscontine (No.)	16.6±11.45	21.2±7.69	0.143
Urination per day (times)	9.7±4.39	12.2±3.55	0.123
Urination per night (centimeter)	2.9±1.91	3.9±1.52	0.19
Dysuria (centimeter)	2.59±2.31	5.16±1.22	0.015
Urgency (centimeter)	3.39±2.23	4.74±1.3	0.165
Painful intercourse (centimeter)	2.59±1.86	4.23±1.46	0.009
Pelvic pain (centimeter)	2.32±2.15	4.61±0.99	0.015
Sleep (centimeter)	2.3±1.4	4.2±0.7	0.016
Feeling well (centimeter)	2.27±2	4.49±0.83	0.019
Bladder volume in the first feeling of urination (cc)	85±35.35	68.5±27.6	0.529
Maximum tolerable bladder capacity (cc)	240.5±93.7	196.5±61.8	0.165
Score of 36 graded questions of life quality (No.)	31.2±8.05	57.6±8.15	0.001

**TABLE 3.** *Mean differences in the symptoms between the two groups after 24 months*

Variable	Mean±SD	P value
Interstitial cystitis validated score of the University of Viscontine (No.)	9.4±8.59	0.003
Urination per day (times)	2.7±3.18	0.001
Urination per night (centimeter)	1.15±1.59	0.023
Dysuria (centimeter)	1.66±1.79	0.002
Urgency (centimeter)	1.23±1.49	0.002
Painful intercourse (centimeter)	1.94±1.76	0.001
Pelvic pain (centimeter)	1.35±1.40	0.002
Feeling well (centimeter)	1.39±1.40	0.015
Bladder volume in the first feeling of urination (cc)	16.7±15.06	0.002
Maximum tolerable bladder capacity (cc)	-35.25±28.75	0.001
Score of 36 graded questions of life quality (No.)	-14.9±14.73	0.0001

Differences between the two group and P values are presented in tables 2 and 3.

Analysis of the results in the control group did not reveal any statistically meaningful changes in symptoms and signs of interstitial cystitis neither before the study, nor during or after then ( $p>0.1$ ). No complication interrupted the double-blinded design of the study and all patients were cooperative and with high compliance.

### Discussion

BCG vaccine has been used widespread in bladder cancer for 20 years. The first investigation was reported in 1970 showing its efficacy in the treatment of bladder tumors.<sup>(9,10)</sup>

Although BCG therapeutic mechanism is still unknown, mediating and adjusting the immune system has been suggested. As a whole its efficacy has been proved by Peter and it is easy to administer.<sup>(3,4,11)</sup>

Why BCG vaccine is effective in interstitial Cystitis? BCG is a strong stimulator of the immune system and some evidence indicate that interstitial cystitis is an autoimmune disease.<sup>(11-19)</sup> Presence of abnormal HLA in bladder mucosa provides this fact. It seems that a type of immune reaction occurring in the bladder wall causes increased activity of type II T helper cells compared to type Is, leading to tissue injury. BCG vaccine induces the activity of type I T helper cells, so that it regulates the adjustment of type II ones and protection of the tissues.<sup>(12,18)</sup>

These patients have Interleukin-6 in their urine, six times as much as normal individuals and the severity of the disease is directly related to the amount of IL-6. BCG vaccine can reduce IL-6.<sup>(17-19)</sup>

Interstitial cystitis is associated with low amounts of nitric oxide (NO) in the urine and BCG is a strong stimulator of NO secretion in the urine, so that it may have a role in the treatment.<sup>(20)</sup>

Eventually, BCG may lower the sensitivity of sensory neuron fibers and consequently reduce pain and increase urinary reservoir.<sup>(3,4)</sup>

Sixty two percent of our respective patients responded to BCG installation that is comparable with Zeidman findings (75%) and Peter's studies (60% and 70%).<sup>(2-4)</sup>

In this study patients who had a bladder capacity of lower than 250 cc under general anesthesia and severe symptoms, did not respond to the treatment properly. However, BCG installation did not yield any case of aggravating symptoms.

### Conclusion

This study showed that intravesical injection of BCG vaccine is an effective, safe, and cost-effective treatment of interstitial cystitis which is easily available and durable.

### References

1. Hunner GL. A rare type of bladder ulcer in women: report of cases. *Boston Med Surg J* 1915; 172: 660-664.
2. Zeidman EJ, Helfrick B, Pollard C, et al. *Bacillus Calmette-Guerin Immunotherapy for refractory interstitial cystitis*. *Urology* 1994; 43: 121-124.
3. Peters K, Diokno A, Steninerd B, et al. The efficacy of intravesical Tice strain BCG in the treatment of interstitial cystitis: A double-blind, prospective, placebo controlled trial. *J Urol* 1997; 157: 2090-2994.
4. Peters KM, Diokno AC, Steninerd B, et al. The efficacy of intravesical Tice strain BCG in the treatment of interstitial cystitis. Long-term follow up. *J Urol* 1997; 159: 1483-1487.
5. Gillenwater JY, Wein A J. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis. *J Urol* 1988; 140: 203-206.
6. Ware JE, Sherbourne CD. The MOS 36 item short-form health survey (SF 36): I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-476.
7. Keller ML, McCarthy DO, Neider RS. Measurement of symptoms of interstitial cystitis. *Urol Clin N Amer* 1994; 21: 67-70.
8. Parsons CL, Benson G, Childs S, et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. *J Urol* 1993; 150: 845-848.
9. Morales A, Eidinger D, Bruce AW. Intracavitary BCG in the treatment of superficial bladder tumors. *J Urol* 1976; 116: 180-190.
10. Akaza H, Hinotsu S. BCG in treatment of existing papillary bladder cancer and carcinoma in situ of the bladder. Four year results. The Bladder Cancer BCG Study Group. *Cancer* 1995; 75: 552-555.
11. Liebert M, Wedemeyer G, Stein JA. Evidence of urothelial cell activation in interstitial cystitis. *J Urol* 1993; 149: 470-475.
12. Christmas TJ, Bottazzo GF. Abnormal urothelial HLA-DR expression in interstitial cystitis. *Clin EXP Immunol* 1992; 87: 450-454.
13. Silk MR. Bladder antibodies in interstitial cystitis. *J Urol* 1970; 103: 307-309.
14. Joustra B, Karrenbeld A, Mensink H. Specific autoantibodies in interstitial cystitis patients suggest an autoimmune etiology. *J Urol* 1996; (part 2) 155: 431 A- abstract 483.
15. Keay S, Zhang CO, Trifillis AL. Urine autoantibodies in interstitial cystitis. *J Urol* 1997; 157: 1083-1087.
16. Ochs RI, Muro Y, Chan EKL. Autoantibodies to DFS70 in patients with interstitial cystitis or ectopic dermatitis (abstract). *International Research Symposium on Interstitial Cystitis, Washington DC; 1997. p. 80.*
17. Mosmann TR, Moore KW. The role of IL10 in the cross regulation of TH1 and TH2 responses. *Immunol Today* 1997; 12: A 49.
18. Bohle A, Nowc CH, Ulmer AJ, et al. Elevation of cytokines IL1, IL2 and TNF in the urine of patient after BCG immunotherapy. *J Urol* 1990; 144: 59-62.
19. Erickson DR. Urine marker of interstitial cystitis. *Urol* 2001; 57: 15-21.
20. Smith SD, Wheeler MA, Foster HE, et al. Improvement in interstitial cystitis symptom scores during treatment with oral 1- argentine. *J Urol* 1997; 158: 703-707.