Original article

Prospective Randomized Study between Intravesical BCG and Mitomycin-C for Non-Muscle-Invasive Urothelial Carcinoma of Urinary-Bladder Post TURBT

Mondal HP[1], Yirang K[2], Mukhopadhyay C[3], Adhikary SS[4],Dutta B[5], Bhoj SS[6]

Abstract:

Background: Approximately 70% of urinary bladder cancer arenon muscle invasive at presentation. It is notorious for its high incidence and recurrence rate. The five-year recurrence rate varies between 30 and 60%. The intravesical treatment evolved out of need to prevent tumour recurrence after local surgical resection. ***Objectives:*** To compare intravesicalMitomycin C and BCG therapies in the prevention of recurrences and severity of their side effects. ***Materials and Methods:*** 40 patients with superficial bladder cancer were studied in urology unit of surgery department of North Bengal Medical College, Darjeeling from June, 2012 to May, 2013. They underwent transurethral resection of bladder tumour. Post operatively 19 patients were treated by intravesicalMitomycin C and 21 patients with BCG. Post intravesical therapy, patients were monitored 3 monthly for recurrence and side effects. ***Results:*** No recurrence was observed at the 3rd month follow up, two recurrences were observed at the end of 6th month in the Mitomycin C group. Regarding side effects, cystitis had no significant difference between the two groups but fever, hematuria and retention of urine were found significantly in BCG group during the study period. ***Conclusions:*** In the prevention of recurrences, intravesical Mitomycin C and BCG therapies have comparable efficacies at the end of 6 months. A further follow up period is required to see and compare the long term results. The incidence of the side effects although mild was much higher with intravesical BCG therapy.

Keywords: Non-muscle-invasive bladder cancer; Intravesical Mitomycin-C and BCG.

Bangladesh Journal of Medical Science Vol. 15 No. 01 January'16. Page : 74-77

Introduction:

Bladder is the second most common site for cancer in the genitourinary tract. It is the fourth most common carcinoma in men after prostate, lung and colorectal cancer, and the most common cancer in females[1].Superficial bladder cancer is a frequently encountered urological malignancy. About 70% are non-muscle invasive at presentation. Five-year recurrence rates for superficial bladder cancer vary between 30 and 66%. Risk factors for recurrence being initial presentation with more than one tumor as well as large (>3 cm), high grade, or superficially invasive (stage PT 1) tumors[2]. Treatment for superficial bladder cancer has undergone a revolution from repeated electrocoagulation in 1950s to intravesical chemotherapy using thiotepa in 1960s[3] and then to immunotherapy using BCG in the 1970s and 80s[4]. The intravesical treatment evolved out of need to prevent tumour recurrence after successful local surgical resection. For years various intravesical chemotherapeutic agents such as thiotepa, doxorubicin and mitomycin C have been the mainstay of therapy but, although they achieved short remissions, a net durable benefit was only apparent in 7 to 14% of patients[5,6]. This study has been conducted to deal with diagnosis, treatment and prevention of recurrences of bladder carcinoma.

1. Hari Pada Mondal, Associate Professor, Dept. of Surgery
2. Kapang Yirang, PGT, Dept. of Surgery
3. Chandranath Mukhopadhyay, RMO, Dept. of Surgery
4. Shyam Sundar Adhikary, RMO, Dept. of Radiotherapy
5. Biswajit Dutta, Associate Professor, Dept. of Urology
6. Sudhansu Sekhar Bhoj, Professor, Dept. of Surgery

North Bengal Medical College, Sushrutanagar, Darjeeling.

Corresponds to: Hari Pada Mondal, Bimala Bhawan, 3/1, Rajanikanta Sarani, Hakimpara, Siliguri, West Bengal, India. Pin-734001. **E-mail:** drhpmondal@gmail.com

Aims and objectives:

To study and compare the efficacy of intravesical chemotherapy (Mitomycin C) vs intravesical immunotherapy with Bacillus Calmette-Guerin(BCG) in prevention of recurrence of tumour in superficial bladder cancer patients following transurethral resection of bladder tumour (TURBT). To compare the side effects of Mitomycin C vs Bacillus Calmette- Guerin.

Materials and Methods:

Study population consisted of 40 patients with superficial bladder cancer treated in the dept. of Surgery, North Bengal Medical College and Hospital and in the urology unit during the period from June'2012 to May'2013. The study was ethically approved by the ethical Committee of North Bengal Medical College.

All patients suspected of having bladder tumour (active hematuria or history of hematuria), underwent detailed clinical examination and investigation like urinary cytology, ultrasonography, cystoscopy and biopsy. Once the diagnosis was confirmed, pH of urine, Mantoux test, contrast enhanced computerized tomographic scan of the abdomen and pelvis, intravenous and retrograde pyelography, ureteral cytology and urethroscopy whenever required was done for staging and to exclude other urinary tract pathology. Patients with stage Ta (Noninvasive papillary carcinoma) or T1(Tumour invading sub epithelial connective tissue) were subjected to TURBT under spinal or general anesthesia using Karl Storz urological endoscopic equipment. In the post –operative period these patients were randomly assigned to either the mitomycin C group or the BCG group for intra-vesical therapy. In Mitomycin C group, therapy was started after TURBT-40 mg dissolved in 50 ml saline intravesical for two hours, once a week, for 6 weeks.

In BCG group BCG (Danish 1331 strain) 120 mg in 50 ml of saline intravesical for two hours, once a week, for 6 weeks. Patients were catheterized and the drug solution administered through the catheter and the catheter is clamped, They were then asked to lie in various positions for 10 to 15 minutes each. At the end of one hour the catheter was unclamped and the bladder emptied.

Post intravesical therapy, patients were monitored 3 monthly with side effects if any, urinary cytology, cystoscopy and biopsy of suspicious lesion and ultrasonography of KUB region.

Results:

A total of 96 patients with active hematuria or history of hematuria were subjected to the preliminary test. 40 patients were found to be of superficial bladder cancer, 25 of invasive cancer and 31 were of non bladder cancer. 34 patients were male and 6 patients were female

Table 1: Patients characteristics

Patient	Mitomycin C group	BCG group
Male	16	18
Female	3	3
Total	19	21

Table 2 shows similarity with regard to the grade in both the two study arms.

Table2: Tumours of grade distribution in the study groups

Grade	Mitomycin C group	BCG group
1	17	19
2	2	2
Total	19	21

Table 3: Comparison of number of tumours in the two groups

Group	Single lesion	Two lesion	>2 lesion
Mitomycin C group	11	2	6
BCG group	14	2	5

During the 6 weeks of therapy, the patients were evaluated for side effects to the therapy. Side effects were seen more commonly in the BCG study group.

Table 4: Comparison of the side-effects in the two groups.

Side-effects	Mitomycin C group	BCG group
Cystitis	8 (out of 19)	12 (out of 21)
Fever	0 (out of 19)	6 (out of 21)
Hematuria	0 (out of 19)	4 (out of 21)
Retention of urine	0 (out of 19)	2 (out of 21)

Table 5: Age distribution of cases of carcinoma bladder

Age in years	31-40	41-50	51-60	61-70	71-80	81-90
No. of patients.	5	6	11	11	6	1

Peak incidence of carcinoma bladder was seen between 51 to 70 years of age group irrespective of sex of the patients.

Regarding recurrences none was observed at the 3rd month follow up, two recurrences were observed at the end of 6th month in the Mitomycin C group. The tumour recurrence observed was also of the same grade as that of preoperatively and therefore

Table 6: Recurrences in the follow up

Recurrences at 3rd month	Mitomycin C group	BCG group
Yes	0	0
No	19	21
Total	19	21

Recurrences at 6th month	Mitomycin C group	BCG group
Yes	2	o
No	17	21
Total	19	21

Table 7: Disease free percentage in follow up in previous studies

Follow up	At 6 months		At 12 months		At the end of the study	
Study group	MitomycinC	BCG group	MitomycinC	BCG group	MItomycinC	BCG group
DeBruyne et al(2 years)[7]	_	_	_	_	64	58
Rintala et al(2years)[8]	70	88	67	90	79	97
Lundholm et al (3years)[9]	90	90	58	65	34	49
Malmstrom et al(5years)[10]	90	90	55	65	34	47
Present study	90	100	_	_	_	_

no progression of disease was observed in the case.

Discussions:

Superficial bladder cancer has been notorious for a high recurrence rate. The intravesical treatment evolved out of need to prevent tumour recurrence after successful local surgical resection. Intravesical immunotherapy with agents such as BCG has become an important treatment modality, although there has been a difference of opinion with regards to its superiority over chemotherapeutic agents such as MitomycinC. In the present study Mitomycin C and BCG were compared with respect to efficacy of therapy in prevention of recurrences following definite TURBT in superficial bladder cancer and side effects to therapy.

In the previously conducted studies, the disease free percentage at the 6-month follow up varied from 70% to 90% for Mitomycin C and 88% to 90% for BCG following TURBT in superficial bladder cancer. The disease free percentage showed a downward trend over the years with results mostly being in favour of BCG.

In our study recurrence was observed in two cases at the 6-month follow up in the MitomycinC study group. No recurrences were observed in the BCG study group. There was no progression of the grade of the disease in recurrent tumour. A further period of follow up is required in our study to comment upon progression of disease and survival.

Side effects to therapy were observed in both the study groups. In our study, patients in the BCG study group had more local side effects (70%of the patients), which included cystitis, hematuria and acute retention of urine when compared to the MitomycinC group(40% of the patients).Witjes et al[11] in a study comparing MitomycinC(dosage-30mg) and BCG(dosage-120mg) reported cystitis in 36% of patients of MitomycinC group and 575 in the BCG group. These values are comparable to the values obtained in our study.Hematuria in our study was observed in four patients in the BCG group and no cases in MitomycinC group which is statistically significant ($p < 0.042$). Fever after BCG therapy was also statistically significant in comparison to MitomycinCtherapy.In the present study recurrence at 6 month was present in MitomycinC group and side effects are higher in the BCG group, but are mild and did not require any delay or stoppage of therapy.

Conclusions:

In the prevention of recurrences, intravesical MitomycinC and BCG therapies have a comparable efficacies at the end of 6 months follow up. A further follow up period is required to see and compare the long term results of MitomycinC and BCG therapies.

The incidence of the side effects although mild was much higher with intravesical BCG therapy when compared to intravesicalMitomycinC, thus leading to a poor patient compliance and follow up.

References:

1. Boring CC, Squires TS,Tong T. Cancer statistics-1995. *Cancer J Clin* 1995;**45**:2-8.
2. Lange P, DeBrune F, Frader Y, Narayan P. Symposium: Treating superficial bladder cancer. *ContempUrol* 1996;**8**:61-66.
3. Jone HC, Swinney J. Thiotepa in the treatment of tumours of the bladder. *Laccet* 1961;**2**:615-620. http://dx.doi.org/10.1016/s0140-6736(61)90304-x
4. Lamm DL, Thor DE, Harris SC. BCG Immunotherapy of superficial bladder cancer. *J Urol* 1980;**124**:38-45.
5. Pawinsky A, Sylvester A, Kurth KH. A combined analysisof European organization for research and treatment of cancer, and Medical Research Council: Randomized trials for the prophylactic treatment of stage TaT1 bladder cancer. *J Urol* 1996;**156**:1934-1942. http://dx.doi.org/10.1016/S0022-5347(01)65396-5
6. Lamm DL, Riggs DR,Traynelis CL, Nyeso UO. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long term course of superficial transitional cell carcinoma of the bladder. *J Urol* 1995;**153**:1444-1449. http://dx.doi.org/10.1016/S0022-5347(01)67427-5
7. DeBruyne FMG, DeJong WH Road J. BCG (RIVM) vsMitomycin C intravesical therapy in superficial bladder cancers. *Urology* 1998 Mar;**31**(3 Suppl):20 -25.
8. Rintala E, Janhianen K, Alfthan O. Intravesical chemotherapy(Mitomycin C) versus immunotherapy (BCG) in superficial bladder cancers. *EurUrol* 1991;**20**:19-25.
9. Lundholm C, Norlen BJ, Ekman P. A randomized prospective studt comparing long term intravesical instillations of MitomycinC and BCG in patients with superficial bladder cancer. *J Urol* 1996;**156**:372-381. http://dx.doi.org/10.1016/S0022-5347(01)65853-1
10. Er-Uno Malstrom, Hanswikstrom, Lundholm C. Five year follow up of randomized prospective study comparing Mitomycin C and BCG in patients with superficial bladder cancers. *J Urol* 1996;**161**:1124-1132. http://dx.doi.org/10.1016/S0022-5347(01)61607-0
11. Witjes JA, Debruyene FM, Van Aubel. Longterm follow up of an EORTC randomized prospective trial comparing intravesical BCG-RIVM and MMC in superficial bladder cancer. *Urology* 1998 Sep;**52**(3):403-410. http://dx.doi.org/10.1016/S0090-4295(98)00212-X