

A COMPARATIVE STUDY BETWEEN SINGLE DOSE & MULTIPLE DOSES OF MITOMYCIN-C IN THE MANAGEMENT OF TRANSITIONAL CELL CARCINOMA OF URINARY BLADDER

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Abstract

Objectives: To find out the efficacy of post TURBT immediate single dose adjuvant intravesical Mitomycin C therapy in comparison with multi-dose regimen of Mitomycin C therapy in the management of superficial transitional cell carcinoma of the urinary bladder.

Methods: Total 76 patients of bladder mass were included in the study who had undergone transurethral resection followed by immediate single instillation of Mitomycin C. After availability of histopathological examination report of resected tumor, those fulfill the selection criteria were randomized into two groups. One group (Group A) was the odd numbers of the patients who already received immediate single intravesical instillation of Mitomycin C and another group (Group B) even number of the patients who received single dose of intravesical instillation of Mitomycin C immediately with additional 5 instillations (1 week interval for 5 weeks) and in whom prospective follow-up could be completed within next 12 months

Results: The effect of single intravesical instillation of 40 mg of Mitomycin C (Group A) within 24 hours of TURBT with that of multiple doses (six doses) of Mitomycin C (Group B) in similar dose was insignificant.

Conclusion: The efficacy of MMC single dose was similar to MMC multi-dose regimen with insignificant difference of side effect among the two groups (0% versus 6.25%).

Keyword: TURBT, Urinary Bladder Tumor, Recurrent Bladder Tumor, MMC, Grade (high, low, intermediate).

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Introduction:

Bladder cancer is the second most common cancer of the genitourinary tract and transitional cell carcinoma (TCC) accounts for more than 90% of bladder cancers[1].

Common risk factors for bladder cancer are smoking, occupational exposure such as textile, tobacco factory, environmental pollutions, arsenic poisoning, chronic analgesic abuse, artificial sweeteners, chronic UTI, cyclophosphamide and pelvic irradiation[2].

On average 70% of bladder cancers are non-muscle invasive or superficial which may be confined to the mucosa (Ta) or invading the lamina propria (T1)[3]. Among the superficial cancer group, approximately 70% present as Ta lesions, 20% as T1 lesions and 10% as carcinoma in situ (CIS or Tis lesions).

Low grade Ta lesions recurred at a rate of 50% - 70% and have a 5% chance of progression where are high grade T1 lesions recurred in more than 80% of cases and progress to a higher stage in 50% of cases within 3 years[4].

The diagnosis of bladder cancer ultimately depends on cystoscopic examination and histologic evaluation of the resected tissue[5]. Transurethral resection of bladder tumour (TURBT) is the first and gold standard treatment option for superficial bladder cancer. The quality of the initial TURBT specimen is extremely important[6]. The pathologic report should specify the grade of the lesion and the depth of tumour invasion into the bladder wall and give information on whether the lamina propria and muscle are present in the specimen[7]. So a complete and correct TUR is essential for the prognosis of the patient[8].

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Intravesical adjuvant chemotherapy and immunotherapy can be used to prevent recurrence following TURBT of NMIBC[9]. Intravesical chemotherapeutic agents are Thiotepa, Mitomycin C, Doxorubicin, Epirubicin, Valrubicin and Gemcitabine. Immunomodulatory agents are Bacillus Calmette-Guérin (BCG), Interferon’s 3[10].

Recently, Mitomycin C has been commonly used in a perioperative fashion delivered intravesically immediately after TURBT (or in some studies within 24 hours postoperatively). Several randomized trials and recent meta-analyses have demonstrated a relative-risk reduction with a single perioperative dose of Mitomycin C in patients with nonmuscle invasive urothelial carcinoma with both low- and high-risk features[11].

The present study aims at observing the results of immediate single dose and multi-dose regimen of Intravesical Mitomycin C in the management of superficial bladder cancer after TURBT. After completion of the study it may be possible to recommend simple, cheaper and effective Intravesical chemotherapy regimen after transurethral resection of superficial bladder cancer to control the recurrence.

Method:

A hospital based quasi-experimental study was conducted in the Department of Urology of Sir Salimullah Medical College Mitford Hospital Dhaka from January 2013 to December 2014, on patient with superficial urinary bladder cancer managed by transurethral resection of Bladder tumour (TURBT). Total 76 patients of bladder mass were included in the study who had undergone transurethral resection followed by immediate single instillation of Mitomycin C. Tissue sent for histopathological examination. All the patients received single dose of intravesical Mitomycin C therapy within 24 hours of TURBT. After availability of histopathological examination report of resected tumor and tumor base, those fulfill the selection criteria & who agreed to

participate in the study was randomized into two groups. Sixteen (16) patients were excluded from the study, of them 11 patients due to histopathological report of muscle invasiveness & 5 patients were excluded due to irregular follow up. One group (Group A) was the even numbers of the patients who already received immediate single intravesical instillation of Mitomycin C and another group (Group B) odd number of the patients who received single dose of intravesical instillation of Mitomycin C immediately with additional 5 instillations (1 week interval for 5 weeks). In this way thirty (30) patients were selected as Mitomycin-C immediate single dose group (Group A) and thirty (30) patients were selected as Mitomycin-C multi-dose group (Group B).

Result:

A total of 60 cases with superficial urinary bladder cancer managed by transurethral resection of Bladder tumour (TURBT). All the patients received single dose of intravesical Mitomycin C therapy within 24 hours of TURBT, thirty (30) patients were selected as Mitomycin-C immediate single dose group (Group A) and thirty (30) patients were selected as Mitomycin-C multi-dose group (Group B).

No statistically significant difference found regarding age, sex, tumour size, number, grade, stage and side effect as well as recurrence at 3rd, 6th and 12th month follow up between group A and group B.

Table I
Recurrence status at 3rd month of follow up cystoscopy

Modality of Rx group	Total no. of cystoscopy	No. of recurrence
Group A	30	0
Group B	30	0

Table II
Distribution of recurrence status at 6th month among the respondents of follow up cystoscopy.

Modality of Rx group	Not recurred		Recurred		Total No. (%)	P value
	No	(%)	No	(%)		
Group-A	26	(86.67)	4	(13.33)	30(50)	0.689
Group-B	27	(90)	3	(10.00)	30(50)	

Data were analyzed using **Chi-square (χ^2) Test.**

Table III*Distribution of recurrences of the superficial bladder cancer seen at 12th month of follow up cystoscopy.*

Modality of Rx group	Not recurred		Recurred		Total No	P value
	No	(%)	No	(%)		
Group-A	25	(83.33)	5	(16.67)	30 (50)	0.962
Group-B	26	(86.67)	4	(13.33)	30 (50)	

Data were analyzed using **Chi-square (c²) Test**.

Discussion:

Superficial transitional cell carcinoma of urinary bladder (Non-muscle-invasive bladder cancer) is characterized by a favorable biological behavior. Their high recurrence rate leads to a reduction in quality of life because they require repeated treatments and periodic check up. Superficial tumors can progress to muscle-invasive tumors, with the consequent threat for specific survival. Therefore, the use of intravesical treatments would be justified by a two-fold goal: to reduce the rate of recurrence and to prevent disease progression¹¹.

The overall rate of recurrence is estimated to be 60-90% and the rate of progression is 10-30%. The probability of recurrence for Ta tumors is up to 50%, while for T1 tumors it is over 70%. As for grade, low grade tumors (G1-G2) have recurrence rates of close to 50-60%. Up to 80% of G3 or high-grade tumors will recur and nearly 50% will suffer disease progression.

Bladder cancer is a disease of older individuals with greater than 90% of diagnosis in patients more than 55 years of age; although uncommon, bladder cancer can occur in young adults and even in children. In this study the median age of diagnosis was 61±13.69 (SD) years in Group A (MMC immediate single dose group) and was 62±13.70 (SD) years in Group B (MMC multi-dose group). This difference of age among groups was insignificant statistically.

Gender incidence has been reported 3:1 in between male and female¹². In this study (Table –II) the ratio between male and female in group A was 4:1 and in group B 5:1. The difference of male female ratio in between the groups was not statistically significant.

After dividing the respondents into two groups by random sampling intervention was done. Table I showed no recurrence in all patients of both groups at third month of follow-up. In current literature negative cystoscopy at third month of follow-up, following TURBT was considered as a good predictor of prognosis¹³

Solitary recurrences were seen at 6th month of follow-up cystoscopy. Table II showed that the number of

recurrences was 4 in Group A and was 3 in Group B. The difference of recurrences in both groups is not significant ($p > .05$). Overall tumor free rate was 86.67% in Group A and 90% in Group B. The result of study is similar to other studies¹⁴.

In this study the number of recurrences were related to the grade of the tumor and we observed that no recurrence was seen in case of grade I but 4 cases of recurrence were seen in case of grade II in Group A. In Group B no recurrence was seen in case of grade I but 3 cases of recurrence were seen in case of grade II at 6th month of follow-up. The difference in recurrence among the groups was insignificant ($p > .05$). The result of study is similar to other studies (Liu B et al, 2006). In case of number of tumors and their relation to recurrence at 6th month of follow up cystoscopies, we found 2 recurrences (7.40%) in Group A and 1 recurrence (3.85%) in Group B where the numbers of primary tumors were up to 2. Two (66.67%) recurrences were seen in Group A and Group B (66.67% versus 50%) where the number of primary tumor was 3.

These patients having recurrences at 6th month were scheduled to follow at 9th month showed no recurrences of tumor in above group of patients at 9th month of follow-up.

In the 12th month of follow-up, it was seen that 5 cases in Group A and 4 cases in Group B were recurred, with recurrence free rate of 83.33% and 86.67% respectively. The result of the present study was similar with the study¹⁴. The difference of recurrence among the groups is not significant ($p > .05$).

During evaluation of recurrences in relation to tumor size at 12th month present study showed no recurrence of tumor in both Groups where size of the primary tumor was <2cm. When the primary tumor was ≥2cm, 5 recurrences were seen in Group A and 4 recurrences in Group B.

The relationship between the grade of the tumor and tumor recurrences were observed in this study and we found 1 recurrence in case of grade I but 4 cases of recurrence in case of grade II in Group A. In Group B 1 recurrence was seen in case of grade I but 3 cases of

recurrence were seen in case of grade II at 12th month of follow-up.

In case of number of tumors and their relation to recurrence at 12th month of follow up cystoscopies, we found 3 (11.11%) recurrences in Group A, 2 (7.7%) in Group B and in each group number of primary tumor were $d \cdot 2$. Two recurrences were seen where the number of primary tumor was 3 in both groups. This study is compatible with the study¹⁵. He observed and compared the efficacy of post TURBT between immediate single instillation of Mitomycin C plus additional maintenance (I-MMC group) and only periodic instillation of Mitomycin C (MMC group) therapy

The side effect of intravesical Mitomycin c was absent in Group A. But only two patients (6.67%) complained mild dysuria and frequency in Group B. These symptoms were controlled and no alteration of patient compliance was seen. The side effect of Mitomycin c following prolonged treatment was reported 2% to 24%³ compatible with present study.

Conclusions:

In patients with superficial transitional cell carcinoma of urinary bladder (low & intermediate risk group), intravesical adjuvant chemotherapy with Mitomycin C after TURBT significantly increased the disease free state, and significantly decreased recurrence. The efficacy of MMC single dose was similar to MMC multi-dose regimen with insignificant difference of side effect among the two groups (0% versus 6.25%).

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