EFFECT OF INTRAVESICAL MITOMYCIN–C IN THE TREATMENT OF SUPERFICIAL BLADDER CANCER AFTER COMPLETE TRANSURETHRAL RESECTION OF TUMOUR MASS

MIA ZI[1], RAHMAN MM[2], CHOWDHURY MSA[2], RAHMAN MM[2], AMIN ATMN[3], BARUA U[4], KARMAKAR U[5], KIBRIA SGMG[6]

Abstract:

Purpose *: To evaluate the eftectiveness of installation of mitomycin C after Complete transurethral resectin in superficial bladder Cancer.*

Materials & Method *: Study take place in the department of urology in Dhaka medical college hospital and Faridpur Diabetic hospital from January 2000 to December 2009. About 240 cases of superficial bladder Cancer were selected. Of them 120 cases received 40mg mitomycin–C included study group and 120 Cases did not received Mitomycin–C included Control group. The patients admitted with superficial bladder tumour within the study period were initially randomized prospectively into two group. One group is the odd numbers of the patients have taken mitomycin – C and another group even numbers of the patients is a control group.Each and every patient followed up for one year.*

Result*: Following intervention there was no recurrence in 3rd month of mitomycin – C group and 7.5% of recurrence rate was observed in control group. In 6th month of follow up 5% recurrence rate was observed in mitomycin C group and 20% recurrence rate was observed in control group. In 9th month 7.5% recurrence was observed in Mitomycin C group and 32.5% recurrence observed in control group. In 12th month of follow up 12.5% recurrence was observed in Mitomycin C group and 47.5% recurrence was observed in control group. When compared the result of the study in between two groups, the difference was highly significant (P < .001). the result of the present study is compatible with other international studies.*

Conclusion *: The present randomized comparative interventional study was done to observe the efficacy of intravesical instillation of Mitomycin – C in preventing the recurrence of superficial bladder Cancer (Ta, Ti) . It was randomly included in two groups. The sample size was 240 in number. 120 were in each group. When compared the result of the study in between two groups, the difference was highly significant (p < .001).*

Key Words: *Bladder cancer, Intravesical Mitomycin C, Transurethral Resection, Prevention of deseiase, Recurrence.*

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Introduction

Bladder Cancer is the second most common Cancer of genitourinary tract. In men it is fourth common cancer after prostate, lung , colorectral cancer, accounting for 5.5% of all cancer Cases. Including genitial Cancer it is the eight most common Cancer, accounting for 2.3% of all Cancer.

Bladder Cancer can occur at any age even in children. It is generally disease of middle aged and elderly, 98% of all bladder Cancer are epithelial malgnancy and approximatey 90% of all bladder Cancer are transitional cell carcinomas. This tumour most commonly appear as papillary, exophytic lesions,less commonly they may be sessile or ulcerated.

1. Dr. Md. Zohirul Islam Mia, Principal, Diabetic Research Medical College, Faridpur
2. Dr. Md. Mizanur Rahman, Dr. Md. Shafiqul Alam Chowdhury, Dr. Md. Mostafizur Rahman, Assistant Professor, Department of Urology, DMCH, Dhaka
3. Dr. ATM Nurul Amin, Registrar, Department of Urology, DMCH, Dhaka
4. Dr. Ujjal Barua, Assistant, Registrar, Department of Urology, DMCH, Dhaka
5. Dr. Uttam Karmakar, Resident, Department of Urology, DMCH, Dhaka
6. Dr. SGMG Kibria, Professor of Urology, BSMMU, Dhaka

Correspondence : Dr. Md. Zohirul Islam Mia, Principal, Diabetic Research Medical College, Faridpur

The former group are usually superficial in nature , sessile and solid growths are often invasive (carrol PR- 2000)

Superficial bladder cancer accounts for approximately 70% to 80% of all newly diagnosed bladder tumour of various histological grade (I & III). Superficial tumour include carcinoma in situ (CIS), tumour confined to the epithelium (Ta) and superficial tumours that involve the lamina propria (T1) but do not involve superficial muscle layers (duqne JL; Loughim KR 2000).

Transurethral resection (TURBT) is the initial approach for this disease. Unfortunately, superficial bladder cancer commonly recurs in a large proportion of cases usually within 12 months of surgery even with complete resection, although most recurrent tumour are the same grade and stages as the primary, 5-30% progress to more advanced disease (Hall RR, et al 1994). These characteristic of superficial bladder cancer prompted the development of intravasical chemotherapy in an attempt to eradicate residual disease and possibly reduce the likelihood of recurrence (Lamm DL, et al,1995).

The anti tumour antibiotic Mitomycin – C (MMC) is one of the drug of choice in the treatment of superficial blader cancer today. Intravesical Instillations with MMC even resulted in approxinmatily 80% response rate, regardless of the number of tumours, provided individual tumour diameter were below 1cm (Somerville etal, 1985) . Mitomycin – C is efficetive both for prophylaxis and ablative treatment of superficial bladder cancer (Huland H etal , 1984. Flanigan RC etal, 1986, solowar Ms, 1985).

The first step in management of superficial bladder tumours is to attempt transurethral resection of all visible and suspicious lesions. Surgical excision effectively control primary tumours, confirm the superficial nature of the disease, provides cytological and histological tumour charactersties as of prognostic significance, and give the idea about the superficial involvement of the tumour. A complete transurethral resection may require several sessions and it is not an uncommon that all recognized papillary tumour can not be recorded (Herr, Hw etal 1987).

Materials and Method :

Between January 2000 to December 2009 about 240 patients of superficial bladder cancer were selected. All patients underwent complete transurethral resection of the bladder mass. Patient records were prospectively maintained database to identify post operative complications and associated riskfactors. Study population include the patients who were admitted in the department of urology for the treatment of low risk superficial bladder cancer stage Ta and T1 with grade I and II by transurethral resection. Total 240 cases of superficial bladder cancer were selected. 120 received 6 dose of 40 mg Mitomycin – C included study group and 120 cases did not received Mitomycin – C included in the control group. The patients admitted with superficial bladder toumour within study period were initially randomized prospectively into two groups. One group is the odd numbers and the patients have taken Mitomycin – C and another group even number of the patients is a control group. In this way 120 were selected as a group of instillation of Mitomycin-C and 120 patients were selected as a control group who were not received Mitomycin-C.

Evaluation of the patient is based on history, physical examination, investigation, cystoscopic findings, Histopathological report of resected tumors and tumor base. Patients included at any age, irrespective of sex, Ta. T1 cancer, grade I and II cancer. Number of tumor not more than 4 and size not more than 4 cm and complete transurethral resection of tumor mass. Patient excluded were non co- operative, carcinoma in situ and Tcc upper tract, Higher than grade II and anaplastic , greater than stage T1 tumour, thimble bladder, VUR and evidence of bladder outflow obstruction . USG of kidney, ureter and urinary bladder, intravenous urography and cystoscopy was done in all cases.

Study design :

The study included 240 patients with superficial bladder cancer (stage Ta &T1) who had underwent transurethral resection in whom prospective follow up was12 months.

After initial screening patient and his relatives were counseled natural history of bladder cancer and its initial management with TUR alone, possibility of further recurrence with or without instillation of Mitomycin-C. Need for intravesical instillation of Mitomycin – C to control the recurrence was discussed and thoroughly examined. The aim of the study was also discussed. Patients then randomly selected in to Mitomycin – C group and control group. Urethrocystosopy was done in all cases for proper inspection of the interior of the bladder to confirm the site and number of the tumour. Then complete transurethral resection of the bladder tumour was performed. Specimen of resected tumour and tissue from the base of the tumour were sent seperately for histopathological examination. After 3rd post operative day patients were instructed abstain from solid food and liquid food for 6 hour prior to drug instillation. 40 mg of mitomycin – C were dissolved in 40ml of distilled water for a final concentration of lmg/ml instilled through catheter into the urinary bladder, catheter was then clamped for 2 hours. Patient were encouraged to rotate in different position every 15 minuets namely supine, left lateral, prone, rt lateral position. After 2 hours bladder was emptied and then catheter was removed, patient was discharged with advice to attend weekly for 5 weeks in the department of urology to receive another 5 doses of Mitomycin – C therapy. In subsequent visit the patients were catheterized with 14fr Nelaton catheter,their bladder drained and drug instilled in the urinary bladder as the same dose and procedure, bladder was emptied through the catheter, perineum and external genitalia washed with soap water.

After the primary treatment they were advised to attend follow up at 3rd , 6th , 9th , 12th month. During the follow up all patients were evaluated clinically with history and physical examination, urinalysis, urine for cytology, ultrasonogram of kidney and urinary bladder region and cystoscopic examination in each and every patient. CT-scan, X-ray chest and isotope bone scan were carried out in suspected cases. During check cystoscopy, primary site of tumour was inspected first then systematically interior of bladder was surveyed. TURBT and biopsy of the tumour base was done in those who were found to have recurrence during follow up. Also biopsy from suspected areas was taken. The resected specimen and tissue from the base of the tumour and suspected area were sent separately for histopathology.

Data analysis:

After collecting of data, these were edited by meticulous checking and rechecking. SPSS – WIN 10.01 version, a statistical analysis package program was used. Measures of dispersion (Mean, Standard Deviation) and the test of significance (Unpair T- test, X^2 test) were performed to detect statistically significance of the study.

Results and observations :

The main objective of this study is to compare the result of intravesical instillation of 40mg of Mitomycin –c weekly for 6 weeks after complete transurethral resection of the tumour with that of transurethral resection of bladder tumour alone.

Table – I

Distribution of sex among the study subjects.

Group		Sex		Total	M/Fratio	X^2/P
		Male	Female			
Control(n= 120)	Count	102	18	120	5.7:1	.092/1.00
	% within group	255	45	300		
Case(n=120)	Count	99	21	120	4.7:1	
	% within group	247.5	52.5	300		
GrandTotal	Count	201	39	240		
	% within group	251.91	48.09	300		

The number of male was 102 (85%) and female was 18 (15%) in control group and the number of male was 99 (82.5%) and the female was 21 (17.5%) in Mitomycin-C group. The sex difference between the group was not significant (p> 0.05)

Table – II

Distribution of age among the study subjects.

Group	Mean age in yrs ±SD	Minimum age in yrs.	Maximum age in yrs.
Control (n= 120)	64.28 ±11.89	40	85
Case (n=120)	63.38 ± 12.08	38	82
Analysis Control VS Case	t/p 0.34/0.738		

In this study mean age group was 64.28±11.89 years, minimum age was 40 years and maximum age was 85 years in control group. Mean age was 63.38±12.08 years, minimum age was 38 years maximum age was 82 years in Mitomycin C group. There was no significant difference between the age of two groups (p> 0.05).

In the present study mean number of tumor in control group was 1.38±67 and in Mitomycin C group was 1.48±68. There was no significant difference in the groups of patients in relation to the number of tumors (p>0.05).

Table-III

Distribution of number of tumors among the study subjects.

Group	Mean No. of tumor±SD	Minimum No. of tumor	Maximum No. of tumor
Control (n= 120)	1.38 ±67	1	4
Case (n=120)	1.4868	1	4
Analysis Control VS Case	t/p 0.660/.508		

Table-IV

Distribution of size of tumors among the study subjects

Group	Mean size of tumor±SD	Minimum No. of tumor	Maximum No. of tumor
Control (n= 120)	2.21±0.85 cm	1	4
Case (n=120)	2.23±0.85 cm	1	4
Analysis Control VS Case	t/p 0.150/0.885		

In this study the mean size of the tumor in control group was 2.21**±.**85cm and in Mitomycin C group was 2.23**±.**85 cm. The difference in between two group was statistically insignificant (p>0.05).

Table-V

Distribution of Stage of tumors among the study subjects.

Group		Stage		Total	X2/P	df
		Stage Ta	Stage T1			
Control	Count	72	48	120	.00/1.00	1
	% Within group	180	120	300		
Case	Count	72	48	120		
	% Within group	180	120	300		
Grand Total	Count	144	96	240		
	% Within group	180	120	300		

In the present study the mean of Ta & T1 stage of tumor between the groups is same. There was no significant difference statistically between the groups, (p> 0.05).

Table – VI

Distribution of grade of tumors among the study subjects.

Group		Stage		Total	X2/P	df
		I	II			
Control	Count	78	42	120	.054/1.00	1
	%Within group	65.0	35.0	300		
Case	Count	75	45	120		
	% Within group	62.5	37.5	100		
Grand Total	Count	153	87	240		
	% Within group	63.8	36.3	300		

In the present study the grade of the tumor in control group was compared to that of Mitomycin C group and was statistically insignificant, (p> 0.05).

Table – VII

Distribution of recurrence status at 3rd , 6th , 9th and 12th month follow up among the study subjects.

Group	3rd month		6th month		9th month		12th month	
	No.	%	No.	%	No.	%	No.	%
Control (n=120)	9	7.5	24	20	39	32.5	57	47.5
Case (n=120)	0	0	6	15	9	7.5	15	12.5
X^2 p Value	4.28/0.241		9.37/.087		8.3/.01		2.25/.001	

In this study the table showed in 3rd month follow up the number of recurrence of superficial bladder cancer following complete transurethral resection in control group was9 and there was no recurrence in Mitomycin C group. It was significantly different but as the number was small it is statistically insignificant (p>0.05).

In 6th month follow up the number of recurrence of superficial bladder cancer after complete transurethral resection in control group was 24 and in Mitomycin C group was 6, It was statistically insignificant due to small number of recurrence (p>0.05).

In 9th month follow up the number of recurrence of superficial bladder cancer after complete transurethral resection was 39 in control and 9 in Mitomycin C group. There was statistically significant difference between groups (p<0.01).

In 12th month follow up the number of recurrence of superficial bladder cancer after complete transurethral resection was 57 in control group and 15 in Mitomycin C group. There was statistically highly significant difference between the study groups (p<0.001).

Table-VIII

Distribution of number of tumors and their relation to recurrence seen in 12th month follow up.

Group	Stage		X^2/P	df
	Stage Ta	Stage T1	Value	
Control (n=57)	24	33		
Case (n=15)	0	15		
Control VS Case			3.03/0.82	1

In the study the table showed in stage Ta tumor there was no recurrence in Mitomycin C group and 24 recurrence in control group and in stage T1 tumor there was 15 recurrence in Mitomycin C group and was 33 recurrence in control group.

Table-IX

12th month recurrence in relation to grade of the primary tumor

Group	Stage		X^2/P	df
	I	II	Value	1
Control (n=57)	24	33		
Case (n=15)	0	15		
Control VS Case			3.03/0.82	

In the study the table showed in stage I tumor, there was no recurrence in Mitomycin C group and 24 recurrence in control group and in stage II tumor there was 15 recurrence in Mitomycin C group and 33 recurrence in control group.

Discussion :

Various protocols of intravesical adjuvant chemotherapy with Mitomycin C were practiced worldwide in preventing the recurrence of superficial bladder tumor. The dose of Mitomycin C therapy was used in different strength in different studies. In an experimental study it was seen that Mitomycin C when administered at a concentration of 1 mg/ml, it induces apoptosis and necrosis of tumor cells (Kelly JD, et al .2000). Ogawa (1969) observed " Normal bladder epithelium is resistant to Mitomycin C" (cited by Mishina T et al . 1975). There is a lot of debate regarding the duration of Mitomycin C therapy. The response of intravesical chemotherapy with various drugs including Mitomycin C has been shown to be dose dependent (De Furia et al , 1980; Soloway et al . 1981).

The use of intravesical chemotherapy with Mitomycin C either for treatment of superficial bladder cancer or for prophylaxis following transurethral resection has been gaining popularity in the last decade, after favourable reports from Mishina et al (1975, 1982) Misina and watahabe (1982), Soloway (1980), Soloway et al (1981), Prout GR, Jr., et al (1982), Harrison et al. (1983) and Somerville et al ,(1985).

Systemic toxic side effects from intravesical Mitomycin C is generally low, and life threatening side effects were not observed (Bracken & Johnson 1980).

A large randomized trial demonstrate a clear benefit in terms of lowering the recurrence rate and increasing recurrence free interval in patients receiving Mitomycin C. The 7 year follow up shows that there also is a long-term benefit from the prophylactic use of Mitomycin – C. The estimated 5 years decrease in risk of recurrence is 15% with 1 instillation and 23% with 5 instillations (Tolley DA et al. 1996)

Intravesical chemotherapy for the treatment of superficial bladder cancer was initially reported in 1990 when Herring described the use of intravesical chemotherapy for superficial bladder cancer has become more generally accepted. The main goals of intravesical therapy are to prevent tumor recurrence or tumor progression after TUR of primary tumor and to treat possible residual tumor after endoscope surgery (Jose Luis F et al .2000).

Prophylactic use after complete resection of a primary tumor in patient with identifiable risk factor for tumor recurrence is usually the most common indication for intravesical chemotherapy (Batts CN 1992).

Several studies have examined the effect of the time interval between TUR and the start of intravesical chemotherapy. Boffioux and Co-worker reported that patients who began treatment early (less than 2 weeks after TUR) had a long time to recurrence when compared with patients who began intravesical therapy 2 weeks or longer after resection of primary tumor (Bouffioux et al 1995).

Devonce et al treated 26 patients with superficial bladder tumors in a nonrandomized study. After complete TUR, Mitomycin C was administered in a dose of 40mg for ten consecutive days, starting twenty four to forty eight hours after TUR. After a mean follow up of 12.2 months recurrence was observed in 22 of the patients a (85%) keeping in this view the present study was conducted to observe the effect of Mitomycin C and compare the recurrence rate of post TURBT Mitomycin C group with the TURBT alone.

In standard text the male female ratio for bladder carcinoma is 2.7:1. But in this study (Table -1) the incidence of bladder cancer is very low in female. Male female ratio in control group is 5.7:1 and in Mitomycin C group is 4.7:1. This discrepancy may be due to low incidence of disease or under reporting of cases as a result of poor socio- economical , cultural and religious background. Multi- centric prospective study is to be carried out to rule out the actual causes of low incidence in this study.

In USA it has been reported that bladder cancer occurs in middle age and elderly . The median age of diagnosis for male is 69 years and female is 71 years , though it can occur even in children (Messing EM et al. 1998). In this study the median age of diagnosis was 64.28±11.89 years in control group and was 63.38±12.08 years in Mitomycin C group (Table-II). This difference of age was statistically insignificant.

The side effect of intravesical Mitomycin C was minimum only 5 (12.5%) patient developed dysuria and frequency of micturition which was subsided after completion of doses, no alteration of patient compliance was seen. The side effect of Mitomycin C following prolonged treatment was reported 6% to 41% (Thrasher, J. Brantley et al. 1992) compatible with the present study. One patient excluded from the study due to bladder intolerance, cystitis & hematuria.

In this study there was no recurrence found in 3rd month follow up in Mitomycin C group and in 12th month follow up there was total 47.5% recurrence found in control (TUR alone) group and 12.5% recurrence in Mitomycin C group.

The result of present study is compatible and consistent with international studies. In this study follow up of each patient was done for 1 year after initial TURBT. However at the end of the study follow up have been continuing as per protocol in the department of urology, Dhaka Medical College Hospital and Diabetic Association Medical College Hospital Faridpur.

Summary :

The present randomized comparative interventional study was done to observe the efficacy of intravesical instillation of Mitomycin C, in preventing the recurrence of superficial bladder cancer (Ta, T1). It was randomly included in two groups. The sample size was 241.120 were in each group. One patient was excluded from the study due to adverse effect of the drug.

History, clinical examination and investigation were recorded in a similar protocol. Pre-operative diagnosis was done by urine cytology and ultrasound scan of kidney and urinary bladder region in all cases. An informed written consent was taken, informing them regarding the nature of intervention and probable benefit. Following cystoscopy and Transurethral Resection of Bladder Tumor, Mitomycin C 40mg / 40ml distilled water was instilled after 3rd post- operative day then weekly for another 5 weeks. Follow up was done on 3rd , 6th , 9th & 12th month after TURBT.

Following intervention there was no recurrence in 3rd month of Mitomycin C group and 7.5% of recurrence rate was observed in control group. In 6th month of follow up 5% recurrence rate was observed in Mitomycin C group and 20% recurrence rate was observed in control group. In 9th month 7.5% recurrence rate was observed in Mitomycin C group and 32.5% recurrence observed in control group. In 12th month of follow up 12.5% recurrence rate was observed in Mitomycin C group and 47.5% recurrence was observed in control group. When compared the result of the study in between two groups, the difference was highly significant (p<.001). The result of the present study is compatible with other international studies (Krege S et al. 1996; Tolley et al. 1996).

Conclusion:

From the findings of the present study it can be concluded that intravesical adjuvant chemotherapy with Mitomycin C after complete TURBT is effective in preventing the recurrence of superficial transitional cell carcinoma of the urinary bladder with insignificant side effect.

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