Original Article

Effect of Single Instillation of Intravesical Mitomycin-C following Transurethral Resection of the superficial Transitional cell Carcinoma of the Urinary Bladder

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Abstract

Introduction: *We analyzed the impact of a single instillation of mitomycin-C in patients with low risk superficial urinary bladder cancer with short-term follow-up.*

Methods: *This comparative interventional study was conducted on 60 patients with low risk superficial urinary bladder transitional cell carcinoma (TCC), admitted to the Urology unit in Rajshahi Medical College Hospital, Rajshahi during the period from July, 2008 to June, 2010. Patients with muscular invasion, Grade-III tumour or bladder carcinoma in situ (CIS) on pathological examination were excluded from the study. After complete transurethral resection of the bladder tumour (TURBT), patients were divided into two arms : First group who had received no instillation of mitomycin-C (i.e. non-mitomycin-C or control group) and a second group with a single immediate intravesical instillation of 40 mg mitomycin-C (i.e. mitomycin-C or study group). Recurrences were considered early if they occurred within the first 12 months of follow up.*

Results: *Follow-ups were conducted on 3rd, 6th, 9th and 12th month (i.e. 3 monthly) following transurethral resection. Following intervention, there was no recurrence in 3rd and 9th month. Recurrence free rate was observed as 86.66% in mitomycin-C group and 80% in non-mitomycin-C group on 6th month (i.e. recurrence rate in mitomycin-C group 13.34 % and non-mitomycin-C group (20 %) of follow-up. On the 12th month, 90% and 83.33% of recurrence free rate was observed in mitomycin-C group and non-mitomycin-C group respectively (i.e. recurrence rate in mitomycin-C group (10 %) and non-mitomycin-C group (16.67 %). Overall, the recurrence rate in mitomycin-C group was 23.33 % and in non-mitomycin-C group was 36.67%.*

Conclusion: *These data confirm the positive effect of a single immediate mitomycin-C instillation in patients with low risk superficial transitional cell bladder carcinoma. This benefit is limited to early recurrence and is not maintained with long-term follow-up. This study also suggests that, cell implantation as a mechanism of early recurrence can be controlled or minimized with a single mitomycin-C instillation.*

Key words: *Bladder cancer, Mitomycin C, Recurrence*

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Introduction

Urinary bladder cancer continues to be a significant health problem for the mankind. Ninety percent of bladder cancers are transitional cell carcinoma (TCC) with the remainder being squamous cell carcinoma and adenocarcinoma.[1] Approximately 75-85% of new bladder TCC is superficial i.e. confined to the mucosa or lamina propria.[2] Recurrence, rather than progression of superficial bladder cancer after primary transurethral resection (TUR), is common. With no adjuvant treatment, there is a 70% chance of recurrence of superficial tumours within 5 years of resection.[3] This level of recurrence might seem alarmingly high and out of proportion to the acceptable recurrence rates of other tumours. Superficial bladder TCC can be fully resected via transurethral route in the first instance. Yet the question arises that why the recurrence rates are so high. Theories regarding the aetiology of tumour recurrence include - reimplantation of cells liberated at transurethral resection, inadequate resection of the residual tumour and diffuse field change giving rise to new tumours.[1] As recurrence of superficial bladder transitional cell carcinoma is such a common phenomenon, it necessitates repeated and often prolonged cystoscopic follow-up.

The administration of one instillation of intravesical mitomycin-C immediately after transurethral resection of superficial transitional cell carcinoma of urinary bladder has been demonstrated to decrease the risk of early recurrence.[4,5] The mechanism by which post TUR intravesical mitomycin-C reduces recurrence is thought to involve destruction of the liberated tumour cells in the bladder and a direct ablative effect on any viable residual tumour cells at the resection site. Instillation within 24 hours of transurethral tumour resection provides superior protection from tumour recurrence. Therefore, it appears that, tumour recurrence can be reduced simply by mitomycin-C instillation close to the time of surgery, possibly by preventing seeding or implantation of tumor cells at the time of resection.[6] On the other hand, various intravesical immunotherapies (such as BCG and Interferon Alfa 2b) and chemotherapies (such as Thiotepa, doxorubicin, epirubicin, mitomycin-C etc) have been used. BCG carries a greater risk of both the local and systemic effects. Interferon Alfa 2b is not specifically approved for superficial bladder cancer and it is costly also. Thiotepa is absorbed due to its low molecular weight and causes blood dyscrasias. doxorubicin, epirubicin and mitomycin-C are of equal efficacy. But a single mitomycin-C instillation is an inexpensive approach with minimal local and systemic side effects in comparison to doxorubicin and epirubicin. These are the rationalities for the use of mitomycin-C than the other intravesical agents.

It can be concluded that, transurethral resection of bladder tumours followed by optimal use of immediate post operative intravesical mitomycin-C is feasible way to reduce short-term recurrence of superficial bladder cancer than the transurethral resection alone. In this study, we reported single insertion of mitomycin-C following transurethral resection of bladder tumour.

Materials and Methods

This study was conducted on 60 patients with superficial transitional cell carcinoma of urinary bladder admitted into the urology unit in Rajshahi Medical College Hospital during the period from July, 2008 to June, 2010. A hospital based comparative interventional study was performed in patients with primary transitional cell carcinoma of urinary bladder. The patients were free of urinary infection and had a normal upper urinary tract on ultrasonography and /or excretory urography. Patients with muscle invasive or Grade III tumours or bladder carcinoma in situ (CIS) on pathological examination and abnormal upper urinary tract on ultrasonography and / or IVU were excluded from the study. After complete transurethral resection (TUR) of tumour, each patient was numbered serially. Of them, the odd number of patients were not instilled with intravesical mitomycin-C (i.e. non-MMC or control group) and the even number of patients were instilled with intravesical mitomycin-C (i.e. MMC group or study group). Thus all the selected patients were divided into two groups :

First group - had no post TUR instillation of intravesical mitomycin-C (i.e. non-mitomycin C or control group). Second group - had a single dose of 40 mg mitomycin-C (i.e. mitomycin-C group or study group) diluted in 40 ml distilled water which were instilled when haematuria ceased, usually within 6-24 hours of transurethral resection. The instillation was retained for 2 hours with catheter clamping and then the bladder was irrigated with saline if needed.

Patients were evaluated with bladder ultrasound and cystoscopy at 3, 6, 9 and 12th months (i.e. every three months for one year). At each cystoscopy, any tumour or abnormal looking urothelium were resected and the resected tissue was sent for histopathological examination to confirm the recurrence. Recurrences were considered early if they occur within the first 12 months of follow up. Ethical clearance from the ethical committee of Rajshahi Medical College was taken to carry out this study. After explanation of the study purpose, an informed consent was taken from the patient.

All clinical information including history, physical findings and investigation reports were collected and recorded in a pre-designed data collection sheet. Comparison between numerical data was performed using the unpaired students' 't' test while comparison between categorical data was done using the Chi square test. The Data was analyzed and compiled by SPSS II. Values less than or equal to 0.05 was considered as significant *p* value.

Results

The main objective of this study is to know and compare the effect of single intravesical instillation of mitomycin-C (MMC group) within 24 hours of transurethral resection with that of control group. Distribution of respondents in terms of different parameters is shown in tabulated form and statistical analysis is done to show the significance of intervention in both groups. The results obtained in follow up cystoscopies were compared in both groups and analyzed to see statistical significance.

Table I: Recurrence status at 3rd, 6th, 9th and 12th month of follow up cystoscopy (n-60, MMC Group-30 and non-MMC Group-30)

Modality of Treated Groups	3rd Month Recur-rence	6th Month Recurrence				9th Month Recur-rence	12th Month Recurrence			
		No no.(%)	Yes no.(%)	Total			No no.(%)	Yes no.(%)	Total	
MMC Group	0	26 (86.66)	4 (13.34)	30	χ^2-0.154 df-1 p-0.690	0	27 (90.00)	3 (10.00)	30	χ^2-0.108 df-1 p-0.742
Non MMC Group	0	24 (80.00)	6 (20.00)	30		0	25 (83.33)	5 (16.67)	30	
Grand Total	**0**	**50 (83.33)**	**10 (16.67)**	**60 (100)**		**0**	**52 (86.67)**	**8 (13.33)**	**60 (100)**	

At 3rd month: the study shows no recurrence in follow-up cystoscopy in both MMC immediate single dose group and non-MMC group. At 6th month: the table shows the number of recurrences of superficial bladder cancer following transurethral resection of bladder tumor (TURBT) and MMC chemotherapy seen in follow-up cystoscopy at 6th month. In MMC immediate single dose group it was 4 and in non-MMC group it was 6 (Table I). This result is statistically insignificant (p>0.05). At 9th month: the table also shows that, recurrence of superficial bladder tumor seen in 4 cases of MMC immediate single dose group and 6 cases of non-MMC group on follow-up cystoscopy at 6th month, when they were resected at 6th month, further recurrence at 9th month was not seen. At 12th month of follow-up cystoscopy: the Table II shows the number of recurrence in MMC immediate single dose group was 3 and in non-MMC group was 5. The difference is not significant in statistical analysis (p>0.05).

Table II: Distribution of recurrence number in relation to tumour size among the respondents in 6th and 12th month of follow up cystoscopy

Modality of treated Group	6th month				12th month			
	Primary tumor size (cm)	Patients no. (%)	Recurrence no. (%)	Overall recurrence no.(%)	Primary tumor size (cm)	Patients no. (%)	Recurrence no. (%)	Overall recurrence no.(%)
MMC group	<2	6 (20.0)	0	4 (13.33)	<2	26 (86.67)	0	3 (10.00)
	≥ 2	24 (80.0)	4 (13.33)		≥ 2	4 (13.33)	3 (10.00)	
Non-MMC group	<2	9 (30.0)	0	6 (20.0)	<2	23 (76.67)	1 (3.33)	5 (16.67)
	≥2	21 (70.0)	6 (20.0)		≥2	7 (23.33)	4 (13.33)	

At 6th month of follow up: it was seen that, there was no recurrence of tumor when the size of the primary tumor was < 2 cm in both groups of patients. Four cases (13.33%) of recurrences were seen out of 24 having primary tumor size ≥ 2 cm in MMC immediate single dose group. Six cases (20.0%) of recurrence out of 21 belonged to same size were seen in non-MMC group (Table II). The difference in recurrence among the groups was insignificant (p>0.05). At 12th month of follow up: the study shows no recurrence of tumor where size of the primary tumor was <2 cm. Three recurrences were seen when the primary tumor was > 2 cm in MMC immediate single dose group. In non-MMC group 1 recurrence was seen where the size of primary tumor was < 2 cm and 4 recurrences when the primary tumor size was ≥ 2 cm (Table II). Here the difference in recurrence among the groups was statistically significant (p<0.05).

Table III: Distribution of number of recurrence in relation to grade of the tumour among the respondents at 6th and 12th month

Modality of treated Group	6th month				12th month			
	Primary tumour Grade	Patients no. (%)	Recurrence no. (%)	Overall recurrence no.(%)	Primary tumour Grade	Patients no. (%)	Recurrence no. (%)	Overall recurrence no.(%)
MMC group	I	19 (63.33)	1 (3.33)	4 (13.33)	I	17 (56.67)	1 (3.33)	3 (10.00)
	II	11 (36.66)	3 (10.00)		II	13 (43.33)	2 (6.67)	
Non-MMC group	I	14 (46.66)	2 (6.67)	6 (20.00)	I	18 (60.00)	1 (3.33)	5 (16.66)
	II	16 (53.33)	4 (13.33)		II	12 (40.00)	4 (13.33)	

At 6th months of follow up: recurrence was seen in 1 case of Grade I and 3 cases of recurrence were seen in case of Grade II in MMC immediate single dose group. In Non-MMC group, 2 cases in Grade I and 4 cases in Grade II were found to recur (Table III). Histopathologically, there was no progression of the grade of recurrent tumors.

At 12^{th} months of follow up: 1 recurrence were found in case of Grade I and 2 recurrences in Grade II in MMC immediate single dose group. One recurrence was seen in Grade I and 4 recurrences were found in case of Grade II in non-MMC group (Table III).

Discussion

It is well known that, the multifocal field changes in the urothelium and the implantation of tumor cells following transurethral resection contribute to the high incidence of recurrence of bladder tumors. It seems futile to rely solely on transurethral resection alone. Intensive topical chemotherapy initiated shortly after surgical resection might reduce the likelihood of the recurrences by destroying viable tumor cells. Anti-neoplastic agents administered transurethrally, place a high concentration of drug in contact with the neoplastic cells and urothelium. It acts by exerting a cytotoxic action on microscopic foci of carcinoma, carcinoma in situ, floating malignant cells, thus diminishing the number and/or frequency of new recurrences, while minimizing systemic toxicity.[7] Regimens based on chemotherapeutic drugs have often been established on empirical basis, which compromises between potential toxic effect and aimed benefit.[4] In USA, the choice of drug is BCG, occasionally Thiotepa but in Japan and Europe the choice of' treatment is mitomycin C and Doxorubicin.[8] 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.[9] Keeping in this view, the present study was conducted to observe and compare the efficacy of post TURBT single immediate dose of mitomycin C to that of conventional non-MMC group treatment in preventing the recurrence of superficial bladder transitional cell carcinoma. Bivariate analysis of different factors having prognostic importance has been identified. These include previous recurrence rate (<1 per year or $\geq$ 1 per year), size of the tumor (up to 2 cm or more than 2 cm.), tumor grade (Grade I or II). Considering the above factors good prognostic group in relation to low rate of recurrence and progression was identified. These are the size of the tumor <3 cm, grade of the tumor I or II. In this study, mean size was 2.075 (± 0.567) cm and 2.231 (±.642) cm in MMC immediate single dose group and non MMC group respectively. The distribution of grade of the tumor in both groups (I & II) were statistically insignificant when compared in between groups. The important variables which influence the recurrence and outcome of treatment (tumor size and grade) were same in this study and both groups of patients included in this study were of low risk group. 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 prognosis.[10]

Solitary recurrences were seen at 6th month of follow-up cystoscopy. This study showed that the number of recurrence was 4 in MMC immediate single dose group and was 6 in non MMC group. The difference of recurrences in both groups are not significant (p>0.05). Overall tumor free rate

was 86.66% in MMC immediate single dose group and 80.0% in non MMC group. The result of the study is similar to other studies.[4,11] The recurrent tumors were resected. After taking biopsy, the base of the tumors were fulgurated. No intervention was made. There was no evidence of progression in the specimen, confirmed by histopathological report. These patients having recurrence at 6th month were scheduled to follow at 9th month. No recurrence of tumor in above group of patients at 9th month of follow-up.

In the 12th month follow-up, it was seen that 3 cases in MMC immediate single dose group and 5 cases in non MMC group were recurred, with recurrence free rate of 90% and 83.33% respectively. The result of the present study was similar with the other studies.[4,11,12] The recurrent tumors were resected. After taking biopsy, the base of the tumor was fulgurated. No intervention was made. There was no evidence of progression in recurrent tumors, confirmed by histopathological report. The difference of recurrence among the groups is not significant ($p>0.05$). It is established that the tumor size and grade are intimately related to the recurrence. These are considered as prognostic factors in study of Parmar MKB et al.[10]

In this study, follow-up of each patient was done for 1 year after initial TURBT. The analysis confirms the positive effect of a single immediate mitomycin-C instillation in patients with low risk superficial bladder cancer.

Conclusion

This study confirms the positive effect of a single immediate mitomycin-C instillation in patients with low risk superficial bladder cancer. This benefit is limited to early recurrence and is not maintained with long-term follow-up. Overall, mitomycin-C is perceived to be very well tolerated but some respondents need to reassess their usage of mitomycin-C for high-grade superficial tumours and CIS. Thus, this approach is an alternative to observation or intravesical chemotherapy, sparing patients a significant number of transurethral resections during the first 12 months postoperatively. This study also suggests that, cell implantation as a mechanism of early recurrence can be controlled or minimized with a single mitomycin-C instillation. In this way, single instillation of intravesical mitomycin-C immediately following transurethral resection of transitional cell carcinoma of urinary bladder reduces the risk of early recurrence.

Contribution of the Authors

First author was the principal researcher, second author was the guide of this research work, third and fourth authors did the statistical analysis and computer composing.

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