

## To Compare Frequency of Tumour Recurrence in Low Risk Transitional Cell Carcinoma of Bladder Between Single Dose Mitomycin C Instillation and Control Group

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### ABSTRACT

**Background:** Many regimes of intravesical therapy have been tried in attempt to reduce the recurrence rate of non muscle invasive bladder cancer, these generally require frequent attendance for instillation. Multiple non-comparative studies have demonstrated the favourable outcomes of the immediate treatment by instillation of mitomycin C after transurethral resection of bladder tumor (TURBT) in cases of non-muscle invasive Transitional Cell Carcinoma.

**Objective:** To compare frequency of tumour recurrence in low risk transitional cell carcinoma of bladder between single dose Mitomycin C instillation and control group.

**Material and Methods:** This study was conducted at urology departmentsaidu teaching hospital and Nawaz sharif kidney center swat. Study Design Quasi Experimental. Study Duration was (From: Feb 2018 to February 2019). Total 62 patients fulfilling the inclusion criteria were selected. Patient were divided between group A and B according to Non probability purposive sampling. TURBT was done in all patients. In those assigned to group A Mitomycin C 40mg was instilled through foleys catheter and clamped within 12 hrs of resection once haematuria has cleared. Mitomycin C was retained for 2 hrs and then foleys catheter was removed.

**Results:** Mean age of patients in Group-A and in Group-B was 54.90±11.48 and 60.03±13.58 years respectively. In Group-A 1(3.2%) and in Group-B 9(29%) patients had recurrence after 3 months follow up time period. Recurrence rate of Group-B was significantly higher. i.e. (p-value=0.006).

**Conclusion:** Results of this study showed the superiority of mitomycin C in patients with low risk non muscle invasive bladder cancer in terms of significantly lower recurrence rate as compared to that of control group. So, it can be said that single mitomycin C instillation significantly decrease recurrence in patients with low risk non muscle invasive bladder cancer.

**Key Words:** Tumour recurrence, Low risk, Transitional cell carcinoma, Bladder, single dose, Mitomycin C, Instillation

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### INTRODUCTION

Carcinoma of bladder is the 4th most common malignancy in men following prostate, lungs and colon cancers, but it has become the most prevalent tumour due to high recurrence rate<sup>1</sup>. About 90% of bladder tumours are transitional cell carcinomas (TCC)<sup>2</sup>.

Approximately 70% of recently diagnosed cases of bladder tumour are non-muscle invasive bladder cancers (NMIBC), in that these are confined to the urothelium and lamina propria of the bladder<sup>3, 4</sup>. About 30% of these initially non-muscle invasive tumours recur and 15% progress to muscle invasion<sup>5</sup>. Recurrence and progression necessitate repeat investigation and intervention to treat, thus incurring suffering to patient and costing finances to health system. Efforts have been made to reduce the recurrence/progression rate by employing various intra-vesical chemotherapeutic agents.

Intra-vesical BCG instillation has proven to be an effective agent which prevents recurrence as well

as progression. However, BCG is toxic to the patient and costly<sup>6</sup>, so other chemotherapeutic agents have been employed to overcome this problem.

Mitomycin C is a chemotherapeutic agent, relatively cheap and much less toxic to the patient as compared to BCG<sup>8</sup>. Various studies have demonstrated its effectiveness as a single agent which prevents recurrence of TCC, when employed only once immediately after resection<sup>7</sup>. A group of investigators have studied recurrence rate in low risk non-invasive (superficial) bladder cancer i.e. Ta and G1, G2. They have used 40mg Mitomycin C as a single dose. They reported 16.1% recurrence rate in the study arm and 34.3% in the control arm<sup>8</sup>.

In another group of study regarding low grade TCC recurrence of bladder, they observed 5.56% recurrence in patient receiving Mitomycin C single instillation as compared to control group having recurrence of about 38.92%<sup>9</sup>.

Single use of Mitomycin C has shown lower rate of recurrence but long-term recurrence in the two groups is similar<sup>10</sup>.

Since different studies have reported different results of recurrence, we want to study the

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recurrence rate in our patients with an appropriate sample size. Rationale of the study is to establish an evidence-based protocol about the superiority of Mitomycin C in lieu of single use and cost effectiveness. This will be helpful in reducing the cost of future TURBT in patients with superficial (non-invasive) TCC bladder i.e. Ta with grade of G1 and G2.

This study was conducted at urology department Saidu Teaching Hospital and Nawaz sharif Kidney Centre, Swat. The Study Design was Quasi Experimental. Study Duration was (From: Feb 2018 to February 2019). Total 62 patients fulfilling the inclusion criteria were selected. Patient were divided between group A and B. In those assigned to group A Mitomycin C 40mg was instilled through foleys catheter and clamped within 12 hrs of resection once haematuria has cleared. Mitomycin C was retained for 2 hrs and then foleys catheter was removed. To compare frequency of tumour recurrence in low risk transitional cell carcinoma of bladder between single dose Mitomycin C instillation and control group.

#### MATERIAL AND METHODS

This study was conducted at Department of Urology, Saidu teaching hospital and Nawaz Sharif Kidney Center Swat from February 2018 to February 2019. A total of 62 patients were randomized into two groups i.e. Group A and Group B. Sample size was calculated as per WHO calculator. Informed consent was taken from all patients. The patients remained unaware as to which group they were randomized to. The study was approved by hospital ethical review board.

Total 62 patients fulfilling the inclusion criteria were selected such as, newly diagnosed case, patient without any evidence of muscle invasion and/or hydro-nephrosis on ultrasound. Single tumour of size less than 3cm, Stage Ta. Patient having Patients with carcinoma in situ, Patients

with any evidence of muscle invasion or hydro-nephrosis on ultrasound, Patients in whom hematuria didn't settled down within 12 hrs of TURBT was excluded from Mitomycin C group and included in control group. Selected patients were explained objective, merits and demerits of study and their informed written consent was obtained. Patient were divided into group A and B according to Non probability purposive sampling. TURBT was done in all patients with the help of electrocautery device attached to a cystoscope. Growth was completely resected. Both superficial and deep biopsy were taken. Coagulation done and three-way foleys catheter were passed after the procedure. In those assigned to group A Mitomycin C 40mg was instilled within 12 hours of resection through foleys catheter and clamped once haematuria has cleared. Mitomycin C was retained for 2 hrs and then foleys catheter was removed. While in those patients in whom haematuria didn't settled down or having fever after TURBT were assigned group B and received simple saline irrigation. The variables given in Annexure No 6.12 (i) (proforma) was filled by the researcher himself.

Data was entered by using SPSS20. Quantitative variables like age was presented as mean  $\pm$  standard deviation. Qualitative variables like gender was presented as frequency and percentage. Comparison of two groups i.e with Mitomycin C instillation and without Mitomycin C apply chi-square. p-value = 0.05 was taken as significant.

#### RESULTS

In our study Mean age of patients in Group-A and in Group-B was  $54.90 \pm 11.48$  and  $60.03 \pm 13.58$  years. In Group-A minimum and maximum age of patients was 25 and 75 years and in Group-B minimum and maximum age of patients was 27 and 87 years as given in (table no 1)

**Table No 1. Age distribution of patient**

|      | GROUP A | GROUP B |
|------|---------|---------|
| N    | 31      | 31      |
| MEAN | 54.90   | 60.03   |
| SD   | 11.48   | 13.58   |
| MIN  | 25      | 27      |
| MAX  | 75      | 87      |

GROUP A; MITOMYCIN INSTILLATION  
GROUP B; SALINE IRRIGATION

**Table No 2. Gender distribution of patient**

|        | GROUP A     | GROUP B   |
|--------|-------------|-----------|
| MALE   | 28(90.3 % ) | 31(100 %) |
| FEMALE | 3(9.7 % )   | 0(0 %)    |
| TOTAL  | 31          | 31        |

GROUP A; MITOMYCIN INSTILLATION

GROUP B; SALINE IRRIGATION

**Table No 3. Descriptive statistic of tumor size**

|      | GROUP A | GROUP B |
|------|---------|---------|
| N    | 31      | 31      |
| MEAN | 1.58    | 1.53    |
| SD   | 0.53    | 0.54    |
| MIN  | 1       | 1       |
| MAX  | 3       | 3       |

**Table No 4. Recurrence of TCC in treatment group**

| RECURRANCE | GROUP A    | GROUP B  |
|------------|------------|----------|
| YES        | 1 (3.2%)   | 9 (29%)  |
| NO         | 30 (96.8%) | 22 (71%) |
| TOTAL      | 31         | 31       |

In Group-A there were 28(90.3%) male and 3(9.7%) females while in Group-B all 31(100%) patients were male as given in (table no 2). Regarding stage, each group having 31 patients with stage Ta.

Mean tumour size in Group-A and in Group-B was  $1.58 \pm 0.53$  and  $1.52 \pm 0.54$ . In both treatment groups minimum and maximum tumour size was 1 and 3 respectively given in (table No 3)

In Group-A, 1(3.2%) patients had recurrence while in Group-B 9(29%) patients had recurrence after 3 months follow up time period. Recurrence rate of Group-B was significantly higher. i.e. (p-value=0.006) given in (Fig. 01).

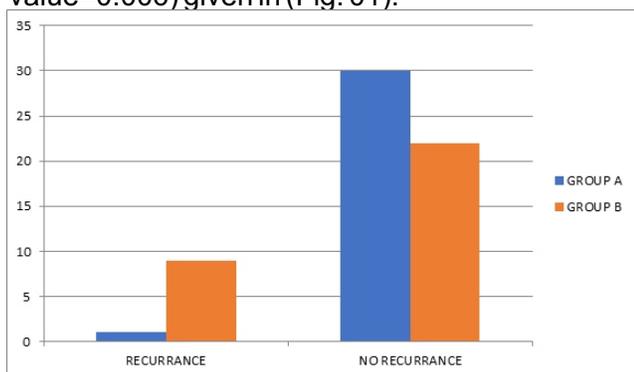


Figure 01

GROUP A; MITOMYCIN INSTILLATION

GROUP B; SALINE IRRIGATION

**DISCUSSION**

Intravesical chemotherapy has been shown to reduce the rate of Non-Muscle invasive bladder cancer (NMIBC) recurrence, and mitomycin C (MMC) has become the most commonly used intravesical cytotoxic agent.<sup>16,18,20</sup>

In addition, a single Mitomycin C instillation is an inexpensive approach with minimal and slight local and systemic side effects. The effect of one single instillation of Mitomycin C may be explained either by chemoresection of tumour left after incomplete transurethral resection (TUR) or by destroying circulating tumour cells that could implant at the site of resection.

Our study aimed to assess the efficacy of a single dose Mitomycin C instillation on recurrence of low risk non muscle invasive bladder cancer.

Total 62 patients fulfilling the inclusion criteria were selected. Patients were divided between two groups i.e Mitomycin C group (group A) and control group (Group B). In group A 90 %<sup>28</sup> patients were male and approximately 10 %<sup>3</sup> were female with mean age of patient in group A was 54.90 with minimum age of 25 years and maximum age of 75 years, while in group B i.e the control group we had 100 % male with mean age of patient was 60.03 years, with minimum age of 27 years and maximum age of 87 years. This mean age of patient is comparable with mean age of internationally published data i.e mean age of 62 years in group A and 60 years in group B i.e control group.

Regarding bladder tumour recurrence we had 3.2 %<sup>1</sup> recurrence in group A (i.e in Mitomycin C group) and 29 %<sup>9</sup> recurrence in group B (i.e in control group). This shows a significant difference between the two groups regarding recurrence.

Butt et al reported a study from Pakistan comprising of 36 patients. At three months, none of the patient in Mitomycin C group had recurrence. However approximately 28 % of control group had recurrence<sup>11</sup>. This recurrence rate is 3.2 % in Mitomycin C and 29 % in control group in our study. As there was recurrence in one patient in Mitomycin group in our study as compared to none in their study. This is probably due to the fact that we had almost double number of patients as compared to their study. Otherwise results are almost similar in both studies. This is not surprising as patients had similar demographic characteristics drawn from same ethnicity and environment. At 9 months their recurrence rate was 5 % in Mitomycin C group compared to almost 38 % in control group.<sup>12</sup> This is in accordance with the fact that as time passes beneficial effect of Mitomycin C wears off (as in some studies) at 24 months (REF). Whereas in other studies a significant protection remains (54.2% vs 84.7%)<sup>11</sup>

A study done by El-Ghobashy et al showing recurrence rate of 3.2 % in the Mitomycin C group and 18.7 % in the control group, while long term follow up recurrence rate was similar between the two groups, indicating that Mitomycin C delays recurrence and have no role in preventing recurrence<sup>12</sup>. Recurrence in this study (3.2%) is comparable to our study. However, recurrence is

almost 10% less in control group (18.7%) in this study as compared to our control group (29%).

Nasiri and Kareem reported 50 patients with low risk NMIBC. At three months, recurrence was 8.3 % in control group vs no recurrence in Mitomycin C group<sup>13</sup>. In our study, recurrence in control group (29%) is significantly greater than this study (8.3%). In our Mitomycin C group there was one recurrence (3.2%) as compared to none in this study. However, at 24 months, recurrence was 45.8% in control vs 15.3% in Mitomycin C group<sup>13</sup>. This is an important study which demonstrate that single Mitomycin C instillation effect is maintained in long term.

Thus, our results are comparable to internationally published data and support the idea that bladder tumour recurrence can be delayed by single immediate intravesical instillation of Mitomycin C.

Because of this positive effect of Mitomycin C on recurrence of Transitional cell carcinoma (TCC), we can spare the patients repeated follow up cystoscopies. Instead of every three months we may plan cystoscopy every six month or even yearly, or may be substituted with other non invasive procedures such as bladder ultrasonography and urine cytology in the Mitomycin C group which would have provided additional cost saving.

## CONCLUSION

Results of this study showed the superiority of mitomycin C in patients with low risk non muscle invasive bladder cancer a in terms of significantly lower recurrence rate as compared to that of in control group. So, it can be said that single mitomycin c instillation significantly decreased recurrence in patients with low risk non muscle invasive bladder cancer.

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