

EFFICACY OF SINGLE DOSE INSTILLATION OF MITOMYCIN FOLLOWING TRANSURETHRAL RESECTION OF NON-MUSCLE INVASIVE BLADDER CANCER

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ABSTRACT

Introduction: Bladder cancer is the fourth most commonly diagnosed cancer in men and eighth in women in the United States (U.S). There are many predisposing factors of bladder cancer such as tobacco smoking, Chemicals, dye, rubber, petroleum, leather and artificial sweeteners. Treatment includes Transurethral Resection of Bladder Tumor (TURBT), Intravesical chemotherapy, Intravesical immunotherapy, radical cystectomy, systemic chemotherapy and radiotherapy. There are different chemotherapeutic agents such as Mitomycin C, Thiotepa and Adriamycin for Intravesical use.

Objectives: To determine the efficacy of single dose instillation of Mitomycin C following transurethral resection of non-muscle invasive bladder cancer.

Methods: It was a descriptive case series study, conducted at the Institute of Kidney Disease, Peshawar on the patients admitted with bladder cancer and underwent TURBT. The duration of the study was one year in which a total of 128 patients were enrolled. After TURBT patients received single dose of Intravesical Mitomycin within 24 hours. All the patients were called back after 3 months for the check cystoscopy and the findings of the cystoscopy were recorded so as to detect recurrence of bladder tumor.

Results: In this study 128 patients with transurethral resection of non-muscle invasive bladder cancer were observed, with male to female ratio was 5:1. The age ranged from 18 to 75 years. The Bladder growth recurrence was found in 20 patients (15.62%) while 108 (84.38%) patients were free of recurrence.

Conclusion: Our study concluded that the immediate post TURBT single dose of Intravesical Mitomycin is effective in preventing the recurrence of Non Muscle Invasive Bladder Tumor.

Key Words: Efficacy of Mitomycin C, TURBT, Non Muscle Invasive Bladder Cancer

INTRODUCTION

Bladder cancer is the fourth most commonly diagnosed cancer in men and eighth in women in the United States (U.S.)¹. It is the commonest urological malignancy in Pakistan⁴. There are many predisposing factors of bladder cancer such as tobacco smoking, chemicals, dye, rubber, petroleum, leather and artificial sweeteners. The disease presents in two different forms: Superficial bladder tumors also known as Non Muscle Invasive Bladder Cancer (stage Ta, Tis and T1) and Muscle-Invasive Bladder cancer (stage T2-4)⁵. Bladder tumors form a heterogeneous group, spanning from completely benign, non-invasive papillary tumors that rarely progress, to invasive high-grade bladder tumors. Non-muscle invasive (NMI) bladder cancer constitutes 75% of newly diagnosed cases¹.

The treatment and management of NMIBC ultimately depends on the patient's risk of recurrence

and progression⁶. Superficial tumors have a high rate of recurrence (25-40%) in the first year following transurethral resection^{4,3}.

For the treatment of stage Ta-T1 (non-muscle-invasive) bladder cancer TURBT only is associated with high rate of recurrence. There are different chemotherapeutic agents such as Mitomycin C, Thiotepa and Adriamycin for Intravesical use. In the past transurethral resection of the bladder tumor (TURBT) following by watchful waiting was performed for superficial bladder cancer with low grade, but immediate Intravesical Mitomycin C has recently frequently been used⁷. Mitomycin C is an alkylating agent derived from Streptomyces that has a molecular weight of 334 kDa. The most effective dose is 40 mg in 20-40 ml distilled water, administered intravesically, once weekly for 6 consecutive weeks.

Mitomycin C is used intravesically because it is cheap, easily available and having least side effects. A number of studies agree with the fact that intravesical instillation of cytotoxic agents within the first 24 hours after TURBT reduces the risk of tumour recurrence. It is assumed that transurethral resections of bladder tumor evoke relevant intravesical tumour cell suspensions. Thus, Reimplantation of tumour cells and consequently cancer recurrence is promoted^{9,12}.

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The current study is designed to determine the efficacy of single dose Mitomycin C in preventing recurrence of non-muscle invasive bladder tumors in our local adult populations. Both the bladder tumors and their recurrence after TURBT is not uncommon and there is a need to identify a procedure which could at last prevent recurrence after TURBT. The idea behind doing this study developed while carefully looking at the literature in which we found most of the studies either have in adequate sample size^{4,8} or even retrospective⁸. Regarding our study is the first of its kind in local patient population with adequate sample size regarding efficacy of Mitomycin C in preventing recurrence of bladder tumors after TURBT and if found to be significantly high it will be also be shared with other local urologists so as to recommend future guidelines for its use and further research over it.

MATERIALS AND METHOD

This study was conducted at Institute of Kidney Diseases, Hayatabad Medical Complex, and Peshawar. Study design was descriptive case series and the duration of the study was one year in which a total of 128 patient were observed. Conserved non-probability sampling technique was used for sample collection.

Inclusion criteria

Included all the patient with superficial bladder growth, age ranging from 18 & above, undergoing TURBT for the first time with complete resection of the bladder growth.

Exclusion criteria

Excluded patient were with extensive bladder tumor, partially resected and muscles invasive tumor, patient with bladder perforation during TURBT or with gross hematuria not settling within 24 hours.

Data Collection Procedure

After approval from local ethical committee, all patients (diagnosed as having non muscle invasive bladder tumor), who fulfill the inclusion criteria admitted in urology ward, were included in the study. The written informed consent was taken for this study from the patients. The procedure was performed under general anesthesia or spinal anesthesia depending upon anesthetist choice. After TURBT patient were catheterized with 22FR 3 ways Foley catheter and urinary bladder irrigation was started with normal saline, Mitomycin 40 mg dissolved in 20 ml of normal saline were instilled once hematuria settled within 24 hours. This solution was kept in bladder for one hour with patient in supine, prone, right lateral and left lateral positions for 15 minutes each. Catheter was removed after 48 hours if hematuria was settled. All the patients were called back after 3 months for the check cystoscopy and the findings of the cystoscopy were recorded so as to detect

the recurrence of the bladder tumor. All the information were recorded in a pre-designed proforma.

Data Analysis

Patient were followed after every three months with check cystoscopy for one year.

RESULTS

In this study, 128 patients with transurethral resection of non-muscle invasive bladder cancer were observed, in which 21 (16.41%) were female and 107 (83.59%) were male patients. Male to female ratio was 5:1. Patient age ranged from 18 to 75 years. Patients age wise divided into four groups, out of which most presented in the upper age group i.e. 41 (32%) patients were of age range of more than 60 years of age, 18 (4.1%) patients were in the age group of less than or equal to 30 years, 36 (28.1%) patients were of age group of 31-45 years, 33 (25.8%) patients have age 46-60 years. Mean age was 50.25 years \pm 15SD.

Recurrence was found in 20 (15.62%) patients while the remaining 108 (84.38%) patients were free of recurrence. (Figure 1). Age wise distribution of efficacy shows that low efficacy was seen in old age group of 61-75 years of age i.e. 76.6% age less than or equal to 45 years have 81.6% patients, age 46-60 years shows high efficacy of 87.8% (Table 1). Gender wise distribution of efficacy shows that efficacy was high in male. There were 93 (86.9%) male patients shows efficacy while efficacy in female was observed in 15 (71.4%) patients (Table 2).

DISCUSSION

Non-muscle invasive bladder tumor accounts for about 75-85% of bladder tumor cases^{13,22}. The recurrence and progression rate after transurethral resection of bladder tumors (TURBT) is 50-70% and 10-15% respectively. Risk factors for tumor recurrence and/or progression are tumor localization, tumor size, prior recurrences, presence of tumor at first follow-up

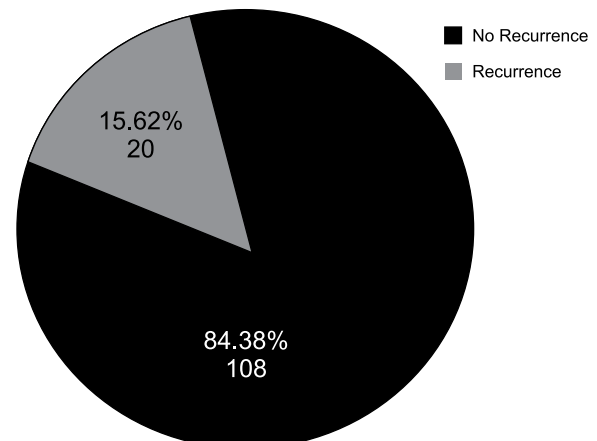


Figure No 1: Recurrence of bladder tumor

Table 1: Age wise Recurrence of Bladder tumor after single dose Mitomycin post TURBT.

			Total
	Non recurrences	Recurrences	
Age (in years) 18-45 years	40 81.6%	9 18.4%	49 100.0%
46-60 years	43 87.8%	6 12.2%	49 100.0%
61-75 years	23 76.6%	7 23.4%	30 100.0%
Total	108 84.4%	20 15.6%	128 100.0%

Table 2: Gender wise Recurrence of Bladder tumor after single dose Mitomycin post TURBT.

Gender	Recurrence	No Recurrence	Total
Male	14 13.1%	93 86.9%	107 100.0%
Female	6 28.%	15 71.4%	21 100.0%
Total	20 15.6%	108 84.4%	128 100.0%

cystoscopy, stage, grade and associated carcinoma in situ (CIS)^{9,13}.

Furthermore, in a study conducted using Mitomycin C and doxorubicin, it was reported that there was less benefit in the group in which the intravesical chemotherapy was performed between the 7th and 15th day than in the group in which the intravesical chemotherapy was performed on the day of the surgery¹⁰.

Recently, many clinical studies have been performed regarding the effect of single dose Mitomycin C instillation immediate post- TURB in the low-risk group of non-muscle-invasive bladder cancer patients. Solsona et al reported in a randomized study with 131 subjects by short-term follow up that the recurrence-free interval was longer and the recurrence rate was lower in the group in which post TURB immediate Mitomycin C instillation was performed than in the group in which only TURB was performed for non-muscle invasive bladder cancer¹¹.

Bladder cancer commonly affects the elderly, with the median age of 73 years at diagnosis^{12,13}. Bladder cancer incidence varies in terms of gender and ethnicity. The lifetime escalates with increasing age^{14,12}. Bladder cancer is the fourth-most-common cancer in men in terms of new cases, with an incidence 4 times higher than in women (37.9 versus 9.6 per 10,000)¹⁰. In our study the ratio of Bladder tumor in male to female was 5:1. In terms of ethnicity, the incidence of bladder cancer is approximately 2 times higher in white men than in African American men in the USA, although African Americans tend to present at a higher stage and with a lower median survival^{14,15}.

In a meta-analysis of several randomized trials. Sylvester et al. suggested that one immediate instillation of chemotherapy after TURBT decreases the percentage of patients with recurrence by 12% and the odds of recurrence by 39%^{16,17}. Although this meta-analysis

and the European Association of Urology Guidelines on Bladder Cancer recommend a single immediate postoperative intravesical instillation of chemotherapy in all cases of NMIBC and adjuvant intravesical immunotherapy with BCG in patients with high risk NMIBS¹⁷.

The chemotherapeutic agent Mitomycin C is considered a standard of care for bladder instillations after TURBT¹⁸. One study of patients with low-risk NMIBC (stage Ta and T1 disease) found that single-dose Mitomycin C resulted in a significantly lower early recurrence rate (11% versus 21% for placebo) within the first 24 months following initial TURBT¹⁹.

In our study, it was found that a single dose of intravesical Mitomycin C, the recurrence was noted in only 15.6% while no recurrence was noted in 74.4%. Therecurrence of bladder tumor was seen in all age groups with more in age more than 60 years.

Another study was performed with 502 patients (stage Ta or T1 disease) randomized after TURBT to either no further treatment, or one instillation of Mitomycin C immediately postoperatively, or one instillation of Mitomycin C immediately postoperatively plus intravesical instillation at 3-months intervals for one year²⁰. After a median follow-up of 7 years, a single instillation of Mitomycin C decreased tumor recurrence by 50% compared with those patients who did not receive any intravesical therapy²⁰. Thus, in patients with NMIBC at low risk of recurrence and progression, 1 immediate installation of chemotherapy is recommended after TURBT²¹.

Also, higher drug concentration and providing drug concentration optimization in the bladder has been suggested to provide better result²⁵. Thus, data examining duration of frequency of installation of intravesical chemotherapy for patient whose disease has recurred are generally inconsistent and do support use of any chemotherapy treatment longer than one year^{21,24}.

Mitomycin C has a high molecular weight, resulting in a low incidence of systemic side effects²² in particular, the most common adverse effect of Mitomycin C is chemical cystitis, which has been reported in up to 41% of patients²⁶.

The manifestations of cystitis include dysuria, urgency, suprapubic pain, and discomfort. In addition, the incidence of decreased bladder capacity has been as high as 2% in clinical trials. With the rare need for cystectomy due to severe bladder constrictures²⁷. Less common adverse effect include eczema-like reaction (4% to 12% and myelosuppression, which is rare²⁸. In our study we lack the control group for the comparison without post TURBT chemotherapy.

CONCLUSION

In patients with superficial bladder cancer a single Mitomycin C instillation significantly increase the disease free interval and significantly decreases recurrence, and tumor per year rates. The study suggests that cell implantation as a mechanism of early recurrence can be controlled with a single immediate Mitomycin C instillation.

This inexpensive and safe approach spares a significant number of transurethral resections in these patients. Consequently: this approach can be considered as an alternative to observation only in patients with low risk superficial bladder cancer. Our study confirmed the positive effect of a single dose Mitomycin C instillation in patients with non-muscle-invasive bladder tumour. This benefit was to control early recurrence and to maintain with long-term follow-up.

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