

THE EFFECTIVENESS OF SINGLE SHOT INTRAVESICAL CHEMOTHERAPY WITH MITOMYCIN-C IN PREVENTING RECURRENCE OF NON-MUSCLE INVASIVE BLADDER CANCER

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ABSTRACT

OBJECTIVES:

To determine the efficacy of single dose intravesical chemotherapy with Mitomycin-C following transurethral resection of non-muscle invasive bladder cancer

METHODS:

It was a Descriptive case series study conducted in the admitted patients of bladder cancer in the institute of kidney disease, Peshawar within one year duration. Total of 128 patients were enrolled in the study. After TURBT patient were catheterized with 22 FR 3 ways foley's catheter and urinary bladder irrigation was started with normal saline. Mitomycin 40 mg dissolved in 20 ml of normal saline was instilled once hematuria settles within 24 hours. All the patients were called back after 3 months for check cystoscopy and the findings 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 have been observed; male to female ratio was 5:1. The age ranges of patients were from 18 to 75 years. Average age was 51.13 years \pm 14.33SD. Recurrence was found in 20(15.62%) of cases while the remaining 108(84.38%) were free of recurrence.

CONCLUSION:

Our study confirmed the effectiveness of a single shot immediate Mitomycin-C instillation in patients with non-muscle-invasive bladder tumors.

KEY WORDS:

Mitomycin-C, transurethral resection, bladder cancer, muscle invasive, Efficacy

INTRODUCTION

Bladder cancer is one of the commonest urological cancer diagnosed world wide.¹ In the United States in 2011, there were an estimated number of new cases approximately 69,000 with high mortality.² Urological malignancy is common in Pakistan as well as the developed regions of the world.³ Tobacco smoking, chemicals, dye, rubber, petroleum, leather and artificial sweeteners are predisposing factors causing bladder cancer. Most common presentation of bladder cancer is painless haematuria with lower urinary tract symptoms. Depending on the bladder muscle invasion, bladder cancer can be divided into non muscle invasive bladder cancer (stage Ta, Tis and T1) which constitutes 75% of newly diagnosed cases and muscle invasive bladder cancer (stage T2-4).^{1,4} Treatment modalities include Trans-Urethral Resection Bladder Tumor (TURBT) with intravesical chemotherapy or intravesical immunotherapy, radical cystectomy, systemic chemotherapy and radiotherapy. The treatment and management of NMIBC ultimately depends on the patient's risk of recurrence and progression.⁵ Following transurethral resection non-muscle invasive bladder cancer have a high rate of recurrence (25-40%) in the first year.³

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High rate of recurrence is associated with TURBT, as this is the only treatment of superficial bladder tumors (stage Ta, Tis and T1). Different chemotherapeutic agents such as mitomycin -C, thiotepa and adriamycin are available for intravesical use. Previously TURBT followed by regular check cystoscopies was routine for low grade superficial bladder cancers but now immediate intravesical mitomycin-C treatment is gaining popularity.⁶ In Jung SJ study recurrence of superficial bladder tumour after single instillation of Mitomycin-C in first year was 15%³ while in another study it was 11.3%.⁷ Mitomycin-C is preferred for intravesical use 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 operation reduces the risk of tumor recurrence. It is assumed that transurethral resections of bladder tumors promote relevant intravesical tumor cell suspension that re-implants and causes cancer recurrence.⁸

The current study is designed to determine the efficacy of 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 least 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 inadequate sample size or they have done a comparative study^{3,7} or even retrospective.⁷ So our study will be first of its kind in our local adult population over adequate sample size to draw conclusive results regarding efficacy of mitomycin -C in preventing recurrence of bladder tumors after TURBT and if found to be significantly high it will also be shared with other local urologists so as to recommend future guidelines for its use or further research over it.

MATERIALS AND METHOD

This study was a descriptive case series conducted at the Institute of kidney diseases, Hayatabad Medical Complex, Peshawar from 1st January 2013 to 31st December 2014. Sample size was 128, using 11.3%⁷ proportion of recurrence of bladder tumor after TURBT with Mitomycin -C, 95% confidence interval and 5.5% margin of error under WHO sample size calculations. Sampling technique was consecutive non-probability sampling and all the patients undergoing TURBT for the first time of either gender from 18 -75 years of age were included and exclusion criterion was all those patients who were having muscle invasive bladder tumors, patients with perforation of the bladder, gross haematuria not settling within 24 hours, incompletely resected tumor, those having recurrent bladder tumor and bladder fistula. The above mentioned conditions act as confounders and if included, introduce bias in the study results. After approval from hospital 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 procedure was performed under general anesthesia or spinal anesthesia depending upon anesthetist choice. After TURBT patients were catheterized with 22 FR 3 ways foley's catheter and urinary bladder irrigation was started with normal saline. Mitomycin-C 40 mg dissolved in 20 ml of normal saline was instilled once haematuria settles within 24 hours. This solution was left 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 haematuria is settled. All the patients were called back after 3 months for the check cystoscopy and the finding of the cystoscopy was recorded so as to detect recurrence of bladder tumor. All the above mentioned information was recorded on pre-designed Proforma. Strict exclusion criteria were followed to control confounders and bias in the study results. Data was analyzed using SPSS version 16. Results were described in terms of mean and standard deviation for age. Frequency and percentages were calculated for the categorical variables like gender and age. All the results were

shown in figures and tables. Efficacies (prevention of recurrence on check cystoscopy) were also stratified among age and gender to see the effect modifications.

RESULTS

In this study, 128 patients with transurethral resection of non -muscle invasive bladder cancer had been observed, in which 21(16.41%) were female and 107(83.59%) were male patients. Male to female ratio was 5:1.

Patients age was divided in four categories, out of which most presented in upper age i.e.41(32%) patients were of more than 60 years and 18(14.1%) patients were in the age range of less than or equal to 30 years. Average age was 50.25 years + 15.83SD. (Table I)

Recurrence was found on first check cystoscopy at three months in 20(15.62%) of cases while the remaining were free of recurrence (Figure I).

Gender wise distribution of efficacy shows that efficacy was high in male. There were 93(86.9%) male patients showing efficacy while efficacy in female was observed in 15(71.4%) patients (Table II).

Table: 1 Age Wise Distribution Of The Patients

AGE IN YEARS	EFFICACY		TOTAL	
	YES	NO		
Age	<= 30.	17	1	18
		94.4%	5.6%	100.0%
	31 – 45	28	8	36
		77.8%	22.2%	100.0%
46 – 60	30	3	33	
	90.9%	9.1%	100.0%	
61+	33	8	41	
	80.5%	19.5%	100.0%	
Total	108	20	128	
	84.4%	15.6%	100.0%	

Figure # 1: RECURRENCE

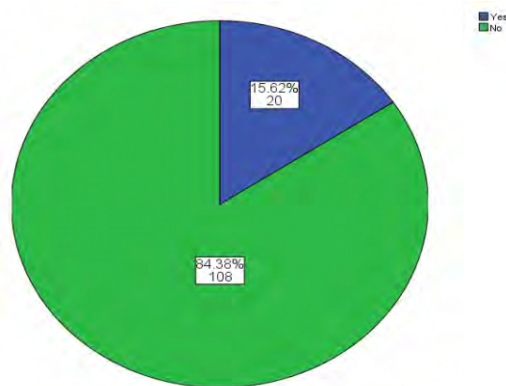


Table: 2 Gender Wise Distribution Of Efficacy

		EFFICACY		TOTAL
		YES	NO	
Gender	Male	93 86.9%	14 13.1%	107 100.0%
	Female	15 71.4%	6 28.6%	21 100.0%
Total		108 84.4%	20 15.6%	128 100.0%

DISCUSSION

Non-muscle invasive bladder tumor accounts for about 75 -85 % of bladder cases. ⁹ The recurrence and progression rate after transurethral resection of bladder tumors (TURBT) are 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 cystoscopy, stage, grade and associated carcinoma in situ (CIS).¹⁰ Bladder cancer commonly affects the elderly, with the median age of 73 years at diagnosis¹¹ which is confirmed in our study, having higher incidence 32.08% (41/128) in elderly. Bladder cancer incidence varies in terms of gender and ethnicity. The lifetime risk of developing bladder cancer is 3.81% for males and 1.18% for females, and the risk increases with advancing age. Bladder cancer is the fourth -most-common cancer in men in terms of new cases, with an incidence 4 times higher than women (37.9 versus 9.6 per 100,000) while in our study it came out to be 5 times higher in males as compared to females. In a meta-analysis of seven randomized trials, Sylvester et al. suggested that one immediate instillation of chemotherapy after TURBT decreased the percentage of patients with recurrence by 12% and the odds of recurrence by 39%.¹² Although this meta -analysis and the European Association of Urology Guidelines on Bladder Cancer recommend a single immediate postoperative installation of chemotherapy in all cases of NMIBC and adjuvant intravesical immunotherapy with BCG in patients with high risk NMIBC.¹³

Our study shows that the recurrence is 15.62% after single dose mitomycin -C installation which is comparable with a national study done by Ather MH and colleagues in 2007, in which recurrence was 15% after one year follow-up with single dose mitomycin -C installation³, while comparing our study with international study conducted by Jung SJ and colleagues in 2011, which showed recurrence of 11.3% after single dose installation of mitomycin-C.⁷ Mitomycin-C has a high molecular weight, resulting in a low incidence of systemic side effects with most common adverse effect being chemical cystitis reported in up to 41% of patients. The manifestations of cystitis include dysuria, frequency, urgency, supra -pubic pain, and discomfort. In addition, the incidence of decreased bladder capacity has been as high as 22% in clinical trials, with the rare need for cystectomy due to severe bladder contractures.¹⁴ Less common adverse effects include eczema -like reactions (4% to 12%) and myelo-suppression, which is rare.

This inexpensive and safe approach spares a significant number of transurethral resections in these patients. Consequently; this approach can be considered an alternative for observation only in patients with low risk superficial bladder cancer. Our study confirmed the

positive effect of a single mitomycin -C instillation in patients with non -muscle-invasive bladder tumors. This benefit was to control early recurrence and was not maintained with long-term follow-up.

CONCLUSION

In patients with superficial bladder cancer a single shot of mitomycin -C within 24 hrs of resection of tumor decreases recurrence and improves disease free interval by preventing early cell implantation. The results were more promising in male patients

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