

Comparison of Recurrence of Low Risk Superficial Bladder Cancer in Patients with And Without Single Dose Intravesical Doxorubicin Instillation

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ABSTRACT

Introduction: Urinary bladder Cancer (UC) is second most common cancer among patients with genitourinary malignancies. Because of high recurrence rate the patients with Non-muscle-invasive bladder cancer (NMIBC) requires a lifelong surveillance. Doxorubicin has been shown to decrease recurrence rate on long term follow up. However, evidence on its efficacy on short term follow-up is limited. The purpose of the current study was to find out early recurrence rate after Doxorubicin treatment. If found low, this study will reduce the costs and hospital burden for patients needing Re-TURBT. **Objective:** The study objective was to compare the frequency of recurrence in patients with low risk superficial bladder cancer receiving a single dose intravesical Doxorubicin instillation with placebo. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Urology, Khawaja M Safdar Medical College, Sialkot. **Duration:** One year from 10-03-16 to 09-03-2017. **Methodology:** 70 patients with Non-muscle-invasive bladder cancer were randomly allocated into 2 groups. Group-A received Doxorubicin treatment while Group-B received Placebo. Patients were followed after 3 months on cystoscopy. All the patients were informed about the procedure. **Results:** The mean age of the patients was 56.84 ± 7.28 years and majority (n=58, 82.85%) of the patients were male and only 12 (17.14%) patients were female giving a male to female ratio of 4.38:1. The mean age of the patients in Group-A was 56.44 ± 7.10 years while in Group-B it was 57.23 ± 7.50 years. Among Group-A 80% patients were male and 20% were female while in Group-B 82.9% were male and 17.1% were female. However, the difference in term of age and gender was not significant statistically. On follow up at 3 months, 19 (27.14%) patients had recurrence while 51 (72.85%) patients were clear of disease. The rate of recurrence was similar across different age groups and gender. Doxorubicin treatment was associated with decreased frequency of recurrence (18.6% vs. 35.7%; $p=.023$) as compared to Placebo. **Conclusion:** This comparative randomized control trial showed that intravesical Doxorubicin instillation within 6 hours of TURBT is effective in reducing recurrence in patients with NMIBC. **Keywords:** Doxorubicin, Bladder Cancer, Recurrence.

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INTRODUCTION

Among genitourinary malignancies, Urothelial Cancer (UC) is second most common, while it is the 7th most common tumor with 4 times more common in males than in females.¹ The NMIBC is most common in males. It is 4th common cancer and accounts for 7% of all cancers. Among cancer mortality rate it is the eight most common cancer, and the eighth highest cancer-related mortality rate in American men.² High recurrence rate are seen in (NMIBC) requiring lifelong surveillance.³ The majority of patients of carcinoma of urinary bladder are (NMIBC) with an approximate percentage about 70%.⁴

NMIBC is initially treated by Transurethral resection of the bladder tumor (TURBT). For reduction of recurrence rates and prevention of disease

progression intravesical immunotherapeutic and chemotherapeutic agent are instilled post TURBT. Doxorubicin, Mitomycin C, Thiotepa, and BCG (Bacillus Calmette-Guerin) are commonly used intra-vesical chemotherapeutic & immunotherapeutic agents. BCG (an attenuated mycobacterium produces an inflammatory reaction in the bladder). It is also reducing the recurrence rate of NIMBC. gents. The above-mentioned agents reduce the incidence of recurrence, are in practice since long and have shown to reduce recurrence rates.⁵ Low risk superficial bladder cancer patients are treated by TURBT. Immediate instillation of Doxorubicin, BCG and Mitomycin-C are a relatively new recommendation for patients with bladder cancer but these are not a widely practiced entity.⁶

Instillation of epirubicin/Doxyrubicin as a single perioperative causes a decrease in recurrence in primary superficial bladder cancer recurrence significantly.⁷ Studies also suggests effectiveness of single dose MMC and Doxorubicin after TUR and advantage of excellent cost effectiveness.^{8,9} This study will find out early recurrence if this is appreciably low in Doxorubicin group then it will be helpful in reducing the costs and hospital burden for patients needing repeat re-TURBT (Transurethral resection of Bladder tumor).

METHODOLOGY

The study objective was to compare the frequency of recurrence of low risk superficial bladder cancer in patients receiving single dose intravesical doxorubicin instillation with placebo within 6 hours of TURBT.

This randomized controlled trial was conducted at Department of Urology, Khawaja M Safdar Medical College, Sialkot. The duration of this study was 1-year 10-03-2016 to 09/03/2017. Sample size of 70 with 35 in each group was estimated using 5% level of significance and power of 80% with an expected recurrence rate of 16.1%⁷ in group C and 34.3%⁷ in placebo. Patients were selected by probable simple randomization Sampling. All newly diagnosed patients of either sex and age range 45 to 70 years with low risk tumor (Single, solitary, less than three 3 cm size, papillary in nature confirmed on cystoscopy and later on histopathology proven as TaG1) were included in our study. Patient with history of surgery of urinary bladder/prostate, suspicion of urinary bladder perforation and patients with T1, G2 or G3 on biopsy were excluded.

All patients, attending Urology Department of KSMC and fulfilling the inclusion criteria were enrolled in this study. Patients were explained about research protocol and informed written consent was obtained. Patients were designated into two groups A and B according to random number table as single block (given in appendix). At enrollment in group A Doxorubicin instillation was carried out within six hours of the TUR as defined above whereas in group B normal saline 50 cc was instilled in the bladder for two hours. The two groups were followed after three months with cystoscopy and recurrence was recorded by getting histopathology report and all parameters were filled in the proforma.

SPSS version 19 was used for descriptive analysis. Two groups have been compared with respect to the recurrence of growth. Mean and standard deviation has been calculated for quantitative variables like age. Percentages and frequencies have been calculated for categorical variables like gender,

recurrence of tumor. For comparison between two groups chi-square test was applied. P-value less 0.05% was considered significant. Stratification done with respect to age and gender.

RESULTS

70 patients with superficial bladder cancer were included in this randomized controlled trial. The age of the patients ranged from 45 years to 70 years with a mean of 56.84±7.28 years as shown in table 1.

Table 1: Descriptive statistics for age

	N	Minimum	Maximum	Mean	Std. Deviation
Age	70	45	70	56.84	7.284
Valid N	70				

Majority (n=58, 82.85%) patients were male and only 12 (17.14%) patients were female giving a male to female ratio of 4.83:1 as shown in table 2.

Table 2: Frequency table for gender

		Frequency	Percent
Valid	Male	58	82.85
	Female	12	17.15
	Total	70	100.0

These patients were divided into two groups through simple randomization. Group-A containing 35 patients treated by Doxorubicin and Group-B containing 35 patients treated by placebo. The mean age of the patients in Group-A was 56.44±7.10 years while in Group-B it was 57.23±7.50 years. However, the difference was statistically insignificant (p=.525) as shown in table 3. Among Group-A 80% were male and 20% were female while in Group-B 82.9% were male and 17.1% were female. However again the difference was statistically insignificant (p=.664). Thus, randomization was adequate and both the groups were comparable in terms of age and gender. On follow up at 3 months, 19 (27.14%) patients had recurrence while 51 (72.85%) patients were clear of disease as shown in table 4. When compared among groups, Doxorubicin treatment was associated with decreased frequency of recurrence (18.6% vs. 35.7%; p=.023) as compared to Placebo and this difference was statistically significant.

Table 3: Independent samples test for comparison of age among groups

	Treatment Group	N	Mean	Std. Deviation	Std. Error Mean	P value
Age	A-Doxorubicin	35	56.44	7.095	.848	.525
	B-Placebo	35	57.23	7.499	.896	

Table 4: Frequency table for tumor recurrence

Tumor recurrence at 3 months		Frequency	Percent	Valid Percent
Valid	Yes	19	27.15	27.15
	No	51	72.85	72.85
	Total	70	100.0	100.0

DISCUSSION

Transurethral resection of bladder tumor (TURBT) is the treatment of choice in patients with NMIBC. It not only provides us stage but helps us in risk stratification. The tendency of recurrence in patients with NMIBC is high possibly due to tumor cell implantation and residual tumor not visible at that time.¹⁰ In 2004 Sylvester et al conducted a comprehensive meta-analysis. They analyze 1500 patients. According to their statistical analysis of patients receiving single dose intravesical chemotherapy a reduction in recurrence rate from 48.4% to 36.7% (11.7%) was noted. { $P < 0.001$ with odds ratio (OR) 0.61}.¹¹ In solitary, low-volume tumors, Doxorubicin and epirubicin showed documented benefit.¹² The use of intravesical chemotherapy immediately after TURBT has been recommended in the current guidelines.¹³ In case of urinary bladder perforation instillation of these agents is contraindicated as it can lead to fatal complication.¹⁴ These chemotherapeutic agents has also been used in transitional cell carcinoma of upper tract. A systematic review and meta-analysis by Fang et al. examine over 600 patients who received intravesical chemotherapy after nephroureterectomy. There was a 41% decrease in odds of recurrence ($P = 0.0001$), with no serious complication. Keeping in view these results, intravesical therapy should not only be used in patients with NMIBC but can also in patients with upper tract tumors. However, there is no substantial evidence available currently where intravesical chemotherapy can be used to prevent recurrence after ureteroscopy for upper-tract urothelial carcinoma.

Doxorubicin treatment has been shown effective in reducing recurrence after (TURBT). On long term follow up multiple studies are available internationally and nationally on the efficacy of Doxorubicin and Mitomycin. In one study done by Al Gallab et al (2009) showed a significant increase in recurrence-free interval and a significant decrease in recurrence rate per year in the doxorubicin group compared to the control group. Early recurrence has been documented to be 23% in the doxorubicin group.¹⁵ However another study showed recurrence rate as low as 30% with the same regimen.¹⁶ However, currently the evidence on efficacy of Doxorubicin on short term follow up is limited to only

1 study which showed Doxorubicin being highly effective in reducing recurrence after TURBT (recurrence rate, 0% versus 23.80%; $p=.02$) as compared to control group.⁹

We included 70 patients with NMIBC in this randomized control trial which were randomly divided into two groups. Group-A received Doxorubicin treatment while Group-B received Placebo. Majority ($n=58$, 82.85%) patients were male and only 12 (17.15%) patients were female giving a male to female ratio of 4.38:1. Our finding matches closely with that of Parkin et al.2002 who showed a male predominance among patients with bladder tumor in a ratio of 4:1.¹⁷ There was no significant difference between the two groups in terms of age ($p=.525$) and gender ($p=.664$) proving effective randomization. On follow up at 3 months, 38 (27.1%) patients had recurrence while 102 (72.9%) patients were clear of disease. When compared among groups, Doxorubicin treatment was associated with decreased frequency of recurrence (18.6% vs. 35.7%; $p=.023$) as compared to Placebo and this difference was statistically significant.

When stratified for age, there was statistically insignificant ($p=.657$) difference among various age groups as shown in table 9-8. Similarly, the rate of recurrence was similar across gender (27.2% Male vs. 26.9% Female; $p=.978$).

Thus, results of our study show that single dose intravesical Doxorubicin instillation within 6 hours of TURBT is highly effective in reducing recurrence (18.6% vs. 35.7%; $p=.023$) in patients with NMIBC as compared to placebo regardless of age and gender.

Our study however was restricted to the efficacy of Doxorubicin treatment and we didn't study the side effects and complications which is an imperative component of treatment however. Our study provides basis for future studies to evaluate these aspects of Doxorubicin treatment.

CONCLUSION

This comparative randomized control trial showed that intravesical Doxorubicin instillation within 6 hours of TURBT is effective in reducing recurrence in patients with NMIBC.

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