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ORIGINAL ARTICLE

Efficacy of High and Low Dose of BCG and Their Complications in Superficial Transtional Cell Carcinoma of Urinary Bladder

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ABSTRACT

Background: Bladder cancer patients mostly (75%) present with non-muscle invasive bladder tumors.
Aim: To compare tumor recurrence and side effects between high and low dose of BCG in NMIBC.
Study Design: Randomized controlled trial.
Methodology: Patients (n=30 each group) were enrolled with expected percentage of side effects with low dose (40 mg) as 2.5 % and high dose (80 mg) as 25.8%. Patients of all age groups with both genders having NMIBC (Ta, T1, Tis) and high grade tumors (G3) determined on histopathology of TURBT sample. Patients with history of renal transplant and chemotherapy were excluded. The difference between both groups was analyzed using Chi Square test with P- value of $\leq$ 0.05 was considered statistically significant.
Results: The mean age of patients in group A was 55.83 ± 9.17 and group B was 59.17 ± 8.13 years. There was no significant difference in the age of two groups (P= 0.142). There was no difference in gender distribution in two groups (P=0.688). Regarding the stage of tumor there were 13 cases of stage Ta and T1 in both groups.
Conclusion: It was concluded that 40 mg dose of intra-vesical BCG in patients with NMIBC had lower recurrence and side effects as compared to higher dose of intra-vesical BCG.
Key words: Recurrence, Side Effects, Low dose BCG and High Dose BCG.

INTRODUCTION

Urinary bladder carcinoma is the second most common urologic neoplasm that has high mortality globally especially USA 14,680 deaths/year[1]. It accounts for 7% and 2% malignancies among men and women respectively. Epithelial tumors are the most common bladder malignancies. Transitional cell carcinoma is the most common Histologically, transitional cell carcinoma (90%) is the commonest of all urological cancers while adenocarcinoma and squamous cell carcinoma account for 5% and 7% respectively[2].

Tumor staging is important and is broadly divided into muscle invasive (MIBC) and non muscle invasive (NMIBC). At the time of diagnosis 20-30 % is MIBC and remainders are NMIBC[2]. At the time of presentation 70-80% of tumors are NMIBC and 45% have carcinoma in situ[3].

Lamina propria is invaded by NMIBC but fails to invade detrusor muscle. NMIBC is of three types; Stage Ta (confined to mucosa), Stage T1 (invades lamina propria) and Carcinoma insitu (CIS). Approximately 70% of NMIBC at initial assessment is Ta, 20% T1 and 10% CIS. CIS is high grade, Ta or T1 is low or high grade tumors[4]. Intra-vesical BCG instillations is in use for 30 years for NMIBC[5]. It reduces the tumors recurrence and progression[6]. BCG works by local immune response mainly through T- helper cells and mediators like IL2,IL-8,INF-gamma and INF alpha[7]. It is now accepted that a functional host immune system is a necessary pre-requisite for successful BCG immunotherapy[8]. Literature review showed that BCG therapy has reduced the recurrence and progression of disease for carcinoma in situ in comparison to TURBT alone or Intra-vesical chemotherap[9]. Despite its efficacy, it causes frequent local and systemic adverse effects. Due to lack of research culture and data in our setups, this common health issue remained untouched so we planned current study in-order to evaluate adverse effects associated with different BCG dosages.

The objective of the study was to compare tumor recurrence and side effects between high and low dose of BCG in NMIBC.

METHODOLOGY

This randomized control trial was carried out in Department of Urology, Dialysis and Renal Transplantations Mayo Hospital Lahore. Patients (n=30 each group) were enrolled with expected percentage of side effects with low dose (40mg) as 2.5% and high dose (80mg) as 25.8%. Patients of all age groups with both genders having NMIBC (Ta, T1, Tis) and high grade tumors (G3) determined on histopathology of TURBT sample. Patients with history of renal transplant and chemotherapy were excluded. Methodology adopted in current study with few modification as done previously after permission from Ethical Review Board.

Group A: Patients were treated 40 mg BCG, diluted in 50ml of normal saline was instilled intravesical for one hour, once weekly induction for six week.

Group B: Patients were treated 80 mg BCG, diluted in 50ml of normal saline was instilled intravesical for one hour, once weekly induction for six week. Patients were followed after three months of BCG instillation. Any recurrence and side effect (Increase frequency of urine, Cystitis, Fever, Hematuria were noted on performa.

Statistical analysis: SPSS (v25.0) analyzed data. The quantitative variables were described as mean ±SD. The difference between both groups was analyzed using Chi Square test with P- value of ≤0.05 was considered statistically significant.

RESULTS

The mean age of patients in group A was 55.83 ± 9.17 and group B was 59.17 ± 8.13 years. There was no significant difference in the age of two groups (P= 0.142). There were four and three females in groups A and B respectively while there were 26 males in group A and 27 males in group B respectively. There was no difference in gender distribution in two groups (P=0.688). Regarding the stage of tumor there were 13 cases of stage Ta and T1 in both groups as summarized in table-1.

Table 1: Stage of Tumour in Groups (A&B)

Stage	Group-A (40mg)	Group-B (80mg)
Ta only	13	13
T1 only	17	17

There was no significant difference between two groups (P=0.382) with regard to complications like hematuria, cystitis, micturation frequency, fever and recurrence as shown in table-2. In 3 months follow up, no cancer-specific death occurred in either of the groups A or B respectively.

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Table-2: Side effects Distribution in Both Groups

Side Effects		Group-A (40mg)	Group-B (80mg)
Hematuria	No	24 (80%)	20 (66.7%)
	Yes	06 (20%)	10 (33.3%)
Cystitis	No	26 (86.7%)	26 (86.7%)
	Yes	04 (13.3%)	04 (13.3%)
Micturaition Frequency	No	27 (90%)	19 (63.3%)
	Yes	03 (10%)	11 (36.7%)
Fever	No	24 (80%)	17 (56.6%)
	Yes	06 (20%)	13 (43.4%)
Recurrence	No	25 (83.3%)	26 (86.7%)
	Yes	05 (16.7%)	04 (13.3%)

DISCUSSION

BCG is the most effective immunotherapy against Non Muscle Invasive Bladder Cancer. Patients of bladder tumor (non muscle invasive) were compared for recurrence of tumor at three months after treatment and side effects associated with BCG (Gross hematuria, cystitis, frequency of micturation and fever) between low dose (40mg) and high dose (80mg) BCG.

We have found that in terms of recurrence, there was no difference between two groups (P=0.72). Regarding the side effects in our study frequency of micturation was more common with high dose BCG. All other side effects i.e. gross hematuria, cystitis, and fever were almost similar and no significant difference was seen.

Current study demonstrated that low-dose BCG had a 48% lower risk of severe side effects (fever, hematuria and cystitis) than the high dose of BCG and withdrawal rate with low dose is less as compared to high dose. Similar results were shown by one previous meta analysis thus depicting BCG associated with reduced side effects at lower dose[9].

Another study showed that no significant improvement seen in efficacy of BCG therapy between 3 and 1-year maintenance therapy. This study demonstrated no significant differences in subgroup analysis for recurrence[11]. It was found that no difference in tumor progression and recurrence are seen in high and low dose of BCG (P=0.64) for the BCG maintenance and BCG induction subgroups, respectively [12,13].

One researcher reported that high dose of BCG reduced recurrences in high-risk patients when compared to low-dose BCG however, difference was insignificant[14]. Results showed that recurrence rates were 28% vs. 31% and progression was 11.5% vs. 13.3%. Hence, no difference was seen in the two groups.

One researcher reported on the use of BCG instillation in 45 patients. With median follow up of 14 months, 24 patients (53%) responded to six weekly induction of BCG without recurrence and 21 patients (47%) shows recurrence[15]. There was no disease specific mortality. Our results were in-line with above mentioned study. Similar results were shown by another study that showed insignificant difference in recurrence rate among two groups who received different doses of BCG[16].

There were significant differences between groups A (70%) who received 90mg dose of BCG as compared to group B (60%) who received 45mg dose of BCG. So they concluded that half of the dose of intra-vesical instillation of BCG can reduce the toxicity and side effects that are associated with treatment of NMIBC without affecting the efficacy of BCG immunotherapy[17-19].

The potential for BCG dose reduction has been evaluated by several investigators. When comparing low dose with high dose, different rates of recurrence, progression and toxicity were Found[11]. Dose reduction of BCG (about one half to one third) has been associated with a corresponding reduction in BCG-related toxicity[12].

Irie et, al, have reported that with low dose (40mg) adverse effects were seen in 2.5 % patients compared to that with high dose (80mg) adverse effects were seen in 25.8 % patients[13]. Currently different centers are using different dose schedule of BCG.

Limitations: Limitations included limited sample size, time frame, resources and financial constrains.

CONCLUSION

It was concluded that 40 mg dose of intra-vesical BCG in patients with NMIBC had lower recurrence and side effects as compared to higher dose of intra-vesical BCG. Hence, low dose BCG (40 mg) instillation significantly reduced side effects and recurrence in NMIBC.

Author's contribution: MU: Conceptualized the study, analyzed the data, and formulated the initial draft, **FS:** Contributed to the proof reading, **AAS:** Collected data.

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REFERENCES

1. Jmal A, Siegel R, Fuji E .Cancer statistics. CA Cancer Journal for Clinicians.2010;60(5):277- 300.
2. Williams SK,Hoenig DM, Ghavamian R, Soloway M.Intravesical therapy of bladdr cancer. Exprt opinion on Pharmacotherapy.2010;11(6):947-58.
3. Smaldone, MC, Casella, DP, Welchons, DR, and Gingrich, Investigational therapies for non- muscle invasive bladder cancer.cancer Journal Urology 2010; 19: 371–83.
4. Andrew J. Lightfoot, Henry M. Rosvear,and Micha A.O'Donnll.Recognition and treatment of BCG failure in bladder cancer Journal 2011 (11);602-13.
5. Kowalski, M., Jones, N., Jewett, M., and Cuthbert.Treatment with vicinium results in durable responses in patients with carcinoma in situ previously treated with bacille Calmette-Guerin (BCG). Urology 2011;11: 602-13.
6. Babjuk M, Oosterlinck W, Sylveste . EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder.EurpeaUrology.2011;59(6):997-1008.
7. Gontero P, Bohle A, Malmstrom. The role of bacillus Calmette-Guerin in the treatment of non– muscle-invasive bladder cancer.Eur. Urol 2010;57:410–29.
8. Rakesh Kapoor ,Vivek Vijian, and Pratipal Singh. BCG in the management of superficial carcinoma of bladder. Indian journal of urol. 2008;24(1):72-76.
9. Timothy P Krosowik and Thomas S Griffith.BCG Immunotherapy for urothelial carcinoma of bladder.2009;1(2):281-88.
10. Shelly MD,Kynaston H ,Court J.A systemic view of intravesical BCG plus transurethral resection vs transurthral resection alone in TA AND T1 bladder cancer BJU Int. 2011;88(3):209- 16.
11. Gakis G1, Todenhöfer T, Renninger M, Schilling D, Sievert KD, Schwentner Development of a new outcome prediction model in carcinoma invading the bladder based on preoperative serum C-reactive protein and standard pathological risk factors: the TNR-C score 1464- 410X.2011.10234.x. BJU Int. 2011;108(11):1800-5. doi: 10.1111/j.1464-410X.2011.10234.
12. Sylvester RJ, Van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer.A met-analysis of published results of randomized clinical trials. J Urol 2012;168:196470
13. Akira Irie, Toyoaki Uchida, Hideyuki Yamashita, Kazumasamatsumoto, Takefumi Satoh, Hideshige Koh, Satoru Shimura,Masatsugu Iwamura And Shiro Baba. Sufficient prophylactic efficacy with minor adverse effects by intravesical instillation of low-dose bacillus Calmette-Guérin for superficial bladder cancer recurrence 2003;10(4): 183– 189,.DOI: 10.1046/j.0919-8172.2003.00607.
14. Maurizio ,Brausi Jorg Oddens, Richard Sylvesterc, Aldo Bono, Cees van de Beek, George van Andel, Paolo Gontero, Levent Turkeri, Sandrine Marreaud, Sandra Collette and Willem Oosterlinck. Side Effects of Bacillus Calmette-Guérin (BCG) in the Treatment of Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Bladder: Results of the EORTC Genito-Urinary Cancers Group Randomised Phase 3 Study Comparing One-third Dose with Full Dose and 1 Year with 3 Years of Maintenance BCG . European Urology, 2014; 65(1):69-76.
15. Teruo Inamoto, Takanobu Ubai, Takeshi Nishida, Yutaka Fujisue, Yoji Katsuoka and Haruhito Azuma . Comparable effect with minimal morbidity of low-dose Tokyo 172 strain compared with regular dose Connaught strain as an intravesical bacillus Calmette–Guérin prophylaxis in nonmuscle invasive bladder cancer: Results of a randomized prospective comparison Urol Ann. 2013r; 5(1): 7–12 **doi**: 10.4103/0974-7796.106873.
16. Yokomizo A, Kanimoto Y, Okamura T, Ozono S, Koga H, Iwamura M, Tanaka H, Takahashi S, Tsushima T, Kanayama HO, Akaza H, Shinohara N, Mugiya S, Nomata K, Nakamura T, Naito S. Randomized Controlled Study of the Efficacy, Safety and Quality of Life with Low Dose Bacillus
17. Calmette-Guérin Instillation Therapy for Nonmuscle Invasive Bladder Cancer J.Urol. 2015.pii: S0022-5347(15)04674-1.doi:10.1016.
18. P.Andius, S.Holmang. BCG therapy in stage Ta /T1 bladder cancer prognostic factors for time to recurrence and progression.BJU international 2009,93:980-84.
19. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013 Feb;63(2):234-41.