COMPARATIVE STUDY OF CLINICAL SAFETY OUTCOME OF NEOADJUVANT INTRAVESICAL MITOMYCIN-C THERAPY IMMEDIATELY BEFORE TRANSURETHRAL RESECTION OF BLADDER TUMOR VS PERIOPERATIVE INTRAVESICAL MITOMYCIN-C IN PATIENTS WITH NONMUSCLE-INVASIVE BLADDER CANCER

[1]Dhirendra Singh, [1]Umesh Sharma, [1]Hemant Kumar Goel, [1]Abhishek Saini.

[1] Urology and Renal Transplant, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohla Hospital, New Delhi, India

ABSTRACT

Objective: *This study aims to compare the outcome and complications of adjuvant vs neoadjuvant IMMC(intravesical mitomycin C) for non-muscle-invasive bladder cancer (NMIBC).* ***Material &Methods:*** *This prospective randomized observational study was conducted from June 2023 to December 2024. Sixty-two patients with clinico-radiological evidence of bladder growth were randomized into two arms: Neoadjuvant IMMC and Perioperative IMMC.* ***Results:*** *Immediate complications were more frequent in Group B, with significantly higher dysuria, suprapubic pain (74.2% vs 32.3%), and febrile UTIs (29% vs 3.2%). Haematuria was also more common in Group B (58.1%). Early complications showed similar trends: dysuria (51.6% vs 19.4%), haematuria (45.2% vs 19.4%), and bladder changes (23.3% vs 0%) were more prevalent in Group B. Allergic reactions were slightly lower in Group B (6.5%) than in Group A (9.7%).* ***Conclusion:*** *Pre-operative MMC instillation was more effective in reducing recurrence and improving resection ease, with fewer complications. Perioperative MMC was associated with increased inflammation and adverse events. Pre-TURBT MMC is recommended for improved clinical outcomes, while peri-operative MMC may be considered for select low-risk patients.*

Keywords: *Complication, IMMC, bladder cancer.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk membandingkan hasil dan komplikasi IMMC (mitomisin C intravesikal) adjuvan dan neoadjuvan untuk kanker kandung kemih non-invasif otot (NMIBC).* ***Bahan & Cara:*** *Studi observasional prospektif acak ini dilakukan mulai Juni 2023 hingga Desember 2024. Enam puluh dua pasien dengan bukti klinis-radiologis adanya pertumbuhan kandung kemih diacak kedalam dua kelompok: IMMC Neoadjuvan dan IMMC Perioperatif.* ***Hasil:*** *Komplikasi langsung lebih sering terjadi pada Kelompok B, dengan disuria, nyeri suprapubik (74,2% vs 32,3%), dan infeksi saluran kemih demam (29% vs 3,2%) yang secara signifikan lebih tinggi. Hematuria juga lebih umum terjadi pada Kelompok B (58,1%). Komplikasi dini menunjukkan trenserupa: disuria (51,6% vs 19,4%), hematuria (45,2% vs 19,4%), dan perubahan kandung kemih (23,3% vs 0%) lebih sering terjadi pada Kelompok B. Reaksi alergi sedikit lebih rendah pada Kelompok B (6,5%) dibandingkan pada Kelompok A (9,7%).* ***Simpulan:*** *Instilasi MMC pra-operasi lebih efektif dalam mengurangi kekambuhan dan meningkatkan kemudahan reseksi, dengan komplikasi yang lebih sedikit. Instilasi MMC perioperatif dikaitkan dengan peningkatan peradangan dan kejadian buruk. Instilasi MMC pra-TURBT direkomendasikan untuk hasil klinis yang lebih baik, sedangkan instilasi MMC perioperatif dapat dipertimbangkan untuk pasien berisiko rendah tertentu.*

Kata kunci: *Komplikasi, IMMC, kanker kandung kemih.*

Correspondence: Dhirendra Singh; c/o: Urology and Renal Transplant, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohla Hospital, New Delhi, India. Phone: +917620936062. Email: dhirendrabjmcpune@gmail.com.

INTRODUCTION

Bladder cancer is one of the most common malignancies worldwide, with significant variations in incidence, prevalence, and mortality across different regions. It ranks as the tenth most commonly diagnosed cancer worldwide, with around 573.000 new cases and 213.000 deaths reported each year.[1] The disease is more prevalent in developed countries, with higher rates observed in

North America, Europe, and parts of Western Asia, while lower rates are reported in Africa and Asia.[2] This disparity is attributed to differences in risk factors, healthcare infrastructure, and diagnostic capabilities.

The age-standardized incidence rate (ASIR) is approximately 9.5 per 100.000 in males and 2.4 per 100.000 in females globally.[3-4] Men are three to four times more likely to develop bladder cancer than women, primarily due to higher exposure to risk factors such as smoking and occupational hazards.[5] The prevalence of bladder cancer is influenced by its relatively high survival rates, particularly for non-muscle-invasive bladder cancer (NMIBC), which accounts for about 75% of cases.[6] However, muscle-invasive bladder cancer (MIBC) and metastatic disease have poorer prognoses, contributing significantly to mortality. The global age-standardized mortality rate (ASMR) is approximately 3.3 per 100.000 for males and 0.9 per 100.000 for females.[7]

The administration of a single intravesical dose of mitomycin-C (IMMC) immediately following transurethral resection of bladder tumors (TURBT) plays a crucial role in the early prevention of tumor recurrence in non-muscle-invasive bladder cancer (NMIBC). However, as a potent vesicant, mitomycin-C poses challenges in clinical practice, particularly in cases where TURBT involves deep resection or there is a risk of bladder perforation.8 The risk of extravesical leakage and associated severe complications has led to significant compliance issues globally.

Neoadjuvant IMMC offers a potential solution by exerting its anti-tumor effects at the onset of TURBT while minimizing toxicity. This approach may be suitable for all patients, regardless of the extent and depth of resection. Additionally, MMC has been found to induce immunogenic cell death (ICD), triggering the release of specific damage-associated molecular patterns, such as HMGB1, which enhance the phagocytosis of dying tumor cells. This process also stimulates innate immune responses and promotes tumor antigen presentation to T lymphocytes. Identifying ICD as a key immune-related mechanism of MMC provides an opportunity to refine bladder cancer treatment strategies, supporting the use of MMC in a neoadjuvant setting to optimize therapeutic outcomes. Very few studies have addressed this issue of adjuvant vs neoadjuvant IMMC.

OBJECTIVE

This study aims to compare the outcome and complications of adjuvant vs neoadjuvant IMMC (intravesical mitomycin C) for non-muscle-invasive bladder cancer (NMIBC).

MATERIAL & METHODS

It's a prospective randomized observational study, conducted at the Department of Urology &Renal Transplant, between June 2023 to December 2024. A total of 62 patients were recruited for the study. Patients presenting with clinico-radiological features of bladder growth were included in the study. Clinico-radiological features suggestive of MIBC or benign disease, variant histology including small cell carcinoma, micropapillary carcinoma, and plasmacytoid carcinoma, Prior intravesical MMC instillation or chemotherapy for NMIBC within 3 years, Prior hypersensitivity reaction history to MMC, Untreated urinary tract infection, Prior systemic chemotherapy for any malignancy within 6 months, Uncorrected coagulopathy and Prior Pelvic Irradiation were excluded from the study. Subjects who meet the inclusion criteria will be randomly divided into 2 arms, viz, Neoadjuvant IMMC and perioperative IMMC.

Patients included in this study according to the inclusion criteria are randomised by the envelope method into 2 groups. Group A undergoing Neoadjuvant Intravesical Inj. MMC (2 doses –Within 24 hrs and 4 hrs of TURBT). Group B undergoing Perioperative Intravesical Inj. MMC (1 dose within 6 hrs of TURBT).

Pre-procedure evaluation: Patient with bladder tumour will be evaluated based on CT/MRI KUB with Baseline blood investigations like CBC, KFT, Urine Cytology for Malignant Cells (D1-D3), Urine culture and sensitivity, and PT/INT.

Preoperative preparation: For patients randomized to the intervention group, at 1 day and 4 hours before TURBT, 40 mg MMC reconstituted in 50 mL of sterile water was infused intravesically via an 8Fr urethral catheter into an empty bladder and was retained for 1-2 hours.

Group A patients had undergone neoadjuvant intravesical MMC and TURBT. Group B patients will undergo TURBT and perioperative intravesical MMC. Both groups were assessed for the occurrence of postoperative complications. They were followed up.

RESULTS

The mean age in Group A is 55.29 ± 14.13 years, while the mean age in Group B is 60.23 ± 11.18 years. In Group A, 77.4% of the participants are male, while in Group B, 90.3% are male. The distribution of urine cytology results according to the Paris Classification showed that the majority of participants (87.1%) across both groups belong to categories 2 and 3, indicating the presence of urothelial carcinoma.

The distribution of study participants of both groups based on their intraoperative peri-tumour inflammation showed that Group B shows a higher percentage of peri-tumour inflammation (83.9%) compared to Group A (32.3%). This difference is statistically significant, as indicated by the p-value of <0.001. On comparison of intra-operative ease of resection, a statistically significant difference in the ease of resection was observed between the two groups. Group A has a higher percentage of cases with easy resection (61.3%) compared to Group B (19.4%).

On comparison of immediate complications, dysuria was significantly more common in Group B (77.4%) compared to Group A (41.9%). Group B had a slightly higher percentage of haematuria (58.1%) compared to Group A (41.9%), but this difference was not statistically significant (p = 0.204). Group B had a slightly higher percentage of allergic reactions (19.4%) compared to Group A (16.1%), but this difference was not statistically significant (p=0.739).

Suprapubic pain and tenderness were significantly more common in Group B (74.2%) compared to Group A (32.3%). Febrile urinary tract infections (UTIs) were significantly more common in Group B (29%) compared to Group A (3.2%).

On comparison of early complications, dysuria was significantly more common in Group B (51.6%) compared to Group A (19.4%). Group B had a higher percentage of haematuria (45.2%) compared to Group A (19.4%), but this difference was not statistically significant (p=0.056). Group B had a slightly lower percentage of allergic reactions (6.5%) compared to Group A (9.7%), but this difference was not statistically significant (p=0.640). Suprapubic pain and tenderness were significantly more common in Group B (48.4%) compared to Group A (16.1%). Group B had a slightly higher percentage of febrile UTIs (6.5%) compared to Group A (3.2%), but this difference was not statistically significant (p=0.550).

On comparison of late complications, the distribution of study participants based on pre- and post-operative Prevoid bladder volume is shown in Table 1.

Table 1. Distribution of preoperative prevoid bladder volume.

Variable	Group A (Mean ±SD)	Group B (Mean ±SD)	p value
Pre-operative Prevoid Bladder Volume (ml)	415.48 ± 92.29	356.45 ± 69.69	**0.006***
Post-operative Prevoid Bladder Volume (ml)	410.81 ± 99.50	340.32 ± 70.64	**0.002***
p value	0.387	**0.005***	

*p value statistically significant
** Independent t test/Mann-Whitney test- for intergroup comparison
***Paired t test- for intra-group comparison

Table 2. Distribution of study participants based on pre- and post-operative post-void residual (PVR) volume.

Variable	Group A (Mean ±SD)	Group B (Mean ±SD)	p valu
Pre-operative PVR Bladder Volume (ml)	24.52 ± 20.63	16.77 ± 10.77	0.217
Post-operative PVR Bladder Volume (ml)	25.06 ± 17.93	20.32 ± 16.63	0.266
p-value	0.848	0.215	

*p-value statistically significant
** Independent t-test/Mann-Whitney test- for intergroup comparison
***Paired t-test for intra-group comparison

Table 3. Distribution of study participants based on Cystopanendoscopic examination (CPE).

CPE FINDINGS	Group A	Group B	Total	p value
Restage	23 (74.2%)	30 (96.8%)	53 (85.5%)	
No Restage	8 (25.8%)	1 (3.2%)	9 (14.5%)	
Total	31 (100%)	31 (100%)	62 (100%)	**0.026***

*p-value statistically significant
**Chi-square test for comparison of CPE findings

Table 4. Distribution of study participants based on resection area changes (n=53).

Resection Area Changes	Group A	Group B	Total	p value
Inflammation	15 (65.2%)	25 (83.3%)	40 (75.5%)	
No Changes	8 (34.8%)	5 (16.7%)	13 (24.5%)	
Total	23 (100%)	30 (100%)	53 (100%)	0.129

*Chi-square test for comparison of resection area changes

The above table shows that on comparison of both the groups, pre- and post-operative prevoid bladder volumes were significantly higher in Group A compared to Group B.

Distribution of study participants based on pre- and post-operative post-void residual (PVR) volume is shown in Table 2.

The above table shows that comparison of the groups, pre- and post-operative PVR bladder volumes in both groups. Group A had slightly higher PVR bladder volumes than Group B, but these differences were not statistically significant ($p>0.05$). This suggests that both groups had similar PVR bladder volumes before and after the procedure.

We have compared the pre-installation IPSS scores in both groups. Group B had a higher percentage of patients with mild symptoms (51.6%) compared to Group A (32.3%), but this difference was not statistically significant ($p = 0.123$) when comparing post-instillation IPSS scores between the two groups. Both groups had similar percentages of patients with mild and moderate symptoms. The p-value of 1.000 indicates that there was no significant difference in symptom severity between the two groups after the procedure.

Comparison of pre- and post-instillation IPSS Score for group A indicates that there was no significant change in symptom severity in this group after the procedure. On comparison of IPSS scores in Group B. The p-value of 0.799 indicates that there was no significant change in symptom severity in this group after the procedure.Cystopanendoscopic examination (CPE) of the study participants is shown in Table 3.

The restaging was significantly more common in Group B (96.8%) compared to Group A (74.2%). The p-value of 0.026 indicates that this difference is statistically significant. This suggests that Group B had a higher rate of recurrence or persistence of bladder cancer than Group A. The comparison of resection area changes is shown in Table 4.

The aforementioned table displays the changes in the resection area in both groups. Group B had a higher percentage of inflammation (83.3%) compared to Group A (65.2%), but this difference was not statistically significant ($p=0.129$). This suggests that both groups had similar rates of inflammation in the resection.

The bladder changes were significantly more common in Group B (23.3%) compared to Group A (0%). The p-value of 0.015 indicates that this difference is statistically significant. This suggests that Group B had a higher rate of bladder changes, such as inflammation or scarring, than Group A.

DISCUSSION

This prospective randomized observational study was conducted on 62 patients. In our study, the mean age in Group A was 55.29 ± 14.13 years, while the mean age in Group B was 60.23 ± 11.18 years, with no statistically significant difference in the mean ages of the two groups ($p = 0.133$). Lee, et al. (2023) [9] also found a similar age group of patients with bladder cancer in their study, with a range of 56 - 76 years. Azab, et al. (2023) [10] also evidenced that

bladder cancer was found to be more common in the older age range of 47.7 –75.82 years.

On evaluating the urine cytology results according to the Paris Classification, the majority (87.1%) of participants in both groups fell into categories 2 and 3, indicating the presence of urothelial carcinoma without any significant difference (p = 0.330). Saarinen et al. (2024) [11] also observed category 2 (80.9%) and category 3 (9.5%) to be more frequent on evaluating 855 patients' urine cytology as per the Paris System of classification.

Group B showed a significantly higher percentage of peri-tumor inflammation (83.9%) compared to Group A (32.3%) (p - p-value < 0.001). Mostafid et al (2006)[12] had drawn a similar conclusion in their study that administering mitomycin C right before TURBT might result in a more concentrated inflammatory reaction in the immediate peri-tumor area due to the proximity of the drug to the tumor cells during surgical manipulation.

Group A had a significantly higher percentage of cases with easy resection (61.3%) compared to Group B (19.4%) (p = 0.001). This could be attributed to differences in tumor size, location, or other factors affecting the ease of resection. Chen et al. (2015), Kamat et al (2011),[13-14] observed that peri-operative MMC provided a sustained reduction in bleeding, which improved resection condition. However, pre-TURBT MMC led to more tumor fragility, making the procedure slightly faster but sometimes leading to incomplete resection due to fragmentation.

The early complications following intravesical Mitomycin-C (MMC) therapy in patients undergoing transurethral resection of bladder tumor (TURBT) provide critical insights into the safety profiles of neoadjuvant MMC (Group A) versus perioperative MMC (Group B). Our study demonstrates that patients in Group B experienced significantly higher rates of dysuria, suprapubic pain, haematuria, and bladder inflammation compared to Group A. Dysuria was a prominent early complication, with a significantly higher incidence in Group B (51.6%) compared to Group A (19.4%, p = 0.016). The increased dysuria in Group B is likely due to direct cytotoxic irritation of the exposed bladder mucosa post-TURBT, exacerbating local inflammation. Similar findings have been reported in previous studies, where perioperative MMC administration correlated with increased bladder irritation and a prolonged inflammatory response. In contrast, neoadjuvant MMC in Group A, administered before TURBT, may have led to a preconditioning effect, limiting direct MMC contact with a freshly resected bladder wall. While haematuria was more frequent in Group B (45.2%) than in Group A (19.4%), the difference was not statistically significant (p = 0.056). However, our findings align with prior research, which suggests that post-TURBT haematuria can be exacerbated by MMC exposure in the perioperative period, particularly due to impaired re-epithelialization and delayed mucosal healing. The early administration of MMC before TURBT may minimize post-resection bleeding by allowing a more controlled resection environment, reducing intraoperative vascular trauma.

Postoperative bladder inflammation and resection area changes were also more common in Group B. Our study found that intraoperative peri-tumor inflammation was significantly higher in Group B (83.9%) compared to Group A (32.3%, p < 0.001).

Suprapubic pain was another significantly more frequent early complication in Group B (48.4%) compared to Group A (16.1%, p = 0.013). This aligns with prior studies indicating that perioperative MMC exposure may exacerbate detrusor muscle inflammation, leading to more pronounced bladder spasms and persistent pain. Our findings support the hypothesis that neoadjuvant MMC, by reducing initial tumor burden and inducing an early immune response, leads to less post-TURBT inflammation, thereby minimizing bladder discomfort.

Overall, these findings highlight the potential advantages of neoadjuvant MMC over perioperative MMC in reducing early postoperative complications. The pre-resection administration of MMC may enhance urothelial integrity, minimize post-TURBT chemical irritation, and improve short-term recovery outcomes. Given the significant differences in dysuria, suprapubic pain, and inflammation, future multi-center trials should further investigate the optimal timing of MMC administration to balance oncologic efficacy with improved patient tolerance. The late complications following intravesical Mitomycin-C (MMC) therapy are critical in evaluating the long-term safety of neoadjuvant (Group A) and perioperative (Group B) MMC administration in patients with

non-muscle-invasive bladder cancer (NMIBC). Our findings suggest that bladder function preservation, symptom control, and cystoscopic outcomes were superior in Group A, indicating a possible advantage of neoadjuvant MMC in reducing long-term adverse effects.

Bladder capacity and post-void residual (PVR) volume are essential parameters for assessing bladder function and voiding efficiency. Our finding aligns with previous research, which indicates that perioperative MMC can cause chronic inflammatory changes, leading to bladder fibrosis and reduced capacity over time. The relatively preserved bladder volume in Group A suggests that pre-TURBT MMC administration may reduce long-term damage to the detrusor muscle by avoiding direct exposure to resection-induced tissue injury.

Cystopanendoscopic evaluation revealed significant differences between the two groups. Bladder structural changes, including inflammation, fibrosis, and scarring, were significantly higher in Group B (23.3%) compared to Group A (0%, $p = 0.015$). Additionally, a higher proportion of Group B patients required restaging cystoscopy (96.8% vs. 74.2%, $p = 0.026$). These findings suggest that perioperative MMC exposure might lead to prolonged urothelial damage, possibly through a mechanism of chronic submucosal fibrosis. Prior studies have shown that MMC exposure post-TURBT can delay mucosal regeneration, increasing the risk of chronic inflammation and scar formation.

The long-term safety concerns associated with perioperative MMC instillation underscore the potential benefits of neoadjuvant MMC administration in mitigating bladder dysfunction, structural changes, and persistent irritative symptoms. By administering MMC before TURBT, early tumor burden reduction can be achieved without compromising the urothelial recovery process, ultimately leading to better bladder function preservation and reduced long-term toxicity. Further studies with larger patient cohorts and extended follow-up periods are necessary to validate these findings and optimize MMC treatment strategies for NMIBC.

In the present study, both pre- and post-operative pre-void bladder volumes were significantly higher in Group A compared to Group B, with the p-values of 0.006 and 0.002, respectively. However, pre-and post-operative post-void residual bladder volumes in Group A were non-significantly slightly higher than Group B. In contrast to our study, other studies stated that pre-TURBT MMC instillation was associated with increased bladder irritability and potential reduced bladder volume due to spasm and increased contractility, and hence more bladder volume change after TURBT.[14-18]

The International Prostate Symptom Score (IPSS) serves as a valuable indicator of lower urinary tract symptoms (LUTS) following intravesical chemotherapy. In our study, both neoadjuvant MMC (Group A) and perioperative MMC (Group B) had no significant improvement in IPSS scores.

Our findings do not align with prior research, such as Manfredi et al. (2022)[18], which demonstrated that intravesical MMC significantly reduced median IPSS scores post-treatment in bladder cancer patients. The study emphasized that neoadjuvant MMC administration had a slightly better symptom recovery profile, possibly due to reduced immediate urothelial irritation compared to perioperative instillation.

Group B had a higher percentage of inflammation (83.3%) in the area of resection compared to Group A (65.2%), however without any significant difference. However, in contrast to our finding, Nieder et al. (2021)[19], Sharma et al. (2020)[20] and Cheng et al. (2019)[21] observed increased risk of inflammation postoperatively on immediate administration of MMC. We observed that bladder changes were significantly more common in Group B (23.3%) compared to Group A (0%) ($p = 0.015$). However, in contrast, other studies found more bladder changes in pre-TURBT MMC instillation.[14-19]

CONCLUSION

Pre-TURBT MMC instillation showed significantly lower immediate complications like dysuria, suprapubic pain, and tenderness as well as febrile UTI, as compared to peri-operative MMC instillation. Also, pre-TURBT MMC instillation showed insignificantly lower complications of hematuria and allergic reaction. Early complications like dysuria and suprapubic pain, and tenderness are significantly more common, and hematuria, allergic reactions, and febrile UTIs were insignificantly more common

in –peri-TURBT group. Pre- and post-operative pre-void bladder volumes were significantly higher, whereas pre-and post-operative post-void residual bladder volumes were slightly higher in the pre-TURBT MMC instillation group. Overall, pre-operative MMC instillation was more effective in reducing recurrence and improving resection ease, while peri-operative MMC instillation led to more inflammation and complications. Pre-TURBT MMC is recommended for better clinical outcomes, though peri-operative MMC may be suitable for lower-risk patients.

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