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Comparison Between Intravesical Chemotherapy Epirubicin and Mitomycin-C after TURB vs TURB Alone With Recurrence Rate of Non-Muscle Invasive Bladder Cancer: Meta-Analysis

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ABSTRACT

Background: Bladder cancer is still a burden on the world of oncology medicine, which every year affects about 3.4 million people globally with 430,000 new cases per year. It is the fourth most common cancer in men and eighth most common women malignancy in the world. This makes bladder cancer a “silent killer” and it needs appropriate treatment planning. Single immediate instillation of chemotherapy after transurethral resection of the bladder (TURB) is recommended by EAU guideline, but its use remains a controversy. **Objective:** Study aimed to analyze benefit of intravesical chemotherapy following TURB in terms of recurrency of non-muscle invasive bladder cancer (NMIBC). **Methods:** Systematic review and meta-analysis of randomized controlled trials comparing the efficacy of a single instillation after TURB with TURB alone in NMIBC (pTa-pT1) patients was conducted. Studies searched throughout Medline, PubMed, Embase, and Cochrane in December 2018. Keywords were intravesical chemotherapy, combination, transurethral resection, bladder cancer. Inclusion criteria were RCT studies, subjects in study were treated single immediate chemotherapy instillation after TURB compared to TURB alone in patient with pTa-pT1 urothelial carcinoma of the bladder. Trials with additional treatment prior to first recurrence were not eligible. Studies using recurrence rate as dependent variable. From 361 studies, in total 11 studies were eligible for this meta-analysis. **Results:** From those 11 studies, it is shown that intravesical chemotherapy using Epirubicin and Mitomycin-C following TURB showed significant decrease of recurrence rate of bladder cancer even to progression of the disease compared to TURB alone ($p < 0.05$) with pooled Risk Ratio were 0.69 and pooled heterogeneity (I^2) were 26.6%. **Conclusion:** This meta-analysis study showed that combination therapy of intravesical chemotherapy after TURB is superior to TURB alone in showing the recurrence rate of NMIBC.

Keywords: Intravesical Chemotherapy, TURB, Non-muscle Invasive Bladder Cancer.

1. BACKGROUND

Bladder cancer is still a burden on the world of oncology medicine, which every year affects about 3.4 million people globally with 430,000 new cases per year. It is the fourth most common cancer in men and eighth most common women malignancy in the world (1).

This makes bladder cancer a “silent killer” and it needs appropriate treatment planning. Single immediate instillation of chemotherapy after transurethral resection of the bladder (TURB) is recommended by EAU guideline, but its use remains a controversy (2, 3). In low and intermediate risk patient with non-muscle invasive bladder cancer (NMIBC) EAU Guidelines panel recommends a single immediate instillation of chemotherapy after a single immediate instillation of chemotherapy after a complete trans-urethral resection of bladder (TURB) (2). American Urological Association (AUA) support the chemotherapy instillation as well to lower the risk of recurrence after TURB in patients with small volume, low grade tumor (3). Even though there are

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Patient	Patients diagnosed with Non-Muscle Invasive Bladder Cancer and treated with primary TURB and survived.
Intervention	Given single immediate chemotherapy (Epirubicin and Mitomycin C) instillation after TURB.
Comparison/ Control	Not given instillation after TURB
Outcome	Recurrence Rate

Table 1. PICO of the study.

some recommendations, the instillation is still not universally used in daily clinical practice.

Epirubicin and Mitomycin-C is well-known chemotherapy used for oncology medicine that prior to be recommendation from guideline for single immediate instillation from some RCTs (1, 2).

2. OBJECTIVE

Study aimed to analyze benefit of intravesical chemotherapy following TURB in terms of recurrency of non-muscle invasive bladder cancer (NMIBC).

3. MATERIAL AND METHODS

Information Sources and Search Strategy

This systematic review and meta-analysis was conducted based on PRISMA guidelines (9). Studies were obtained by searching electronic databases, Medline, PubMed, Embase, and Cochrane in December 2018. Only articles in English were included. Authors used the following search keywords to search all trials registers and databases: “intravesical chemotherapy”, “combination”, “transurethral resection”, and “bladder cancer”. No ethical clearance is needed for this study.

Eligibility Criteria

Inclusion criteria were RCT studies, subjects in study were treated single immediate chemotherapy instillation after TURB compared to TURB alone in patient with pTa-pT1 urothelial carcinoma of the bladder. Trials with additional treatment prior to first recurrence were not eligible. Unpublished articles, abstracts, study not written in English were excluded from the study. Study characteristics were presented as PICO in Table 1.

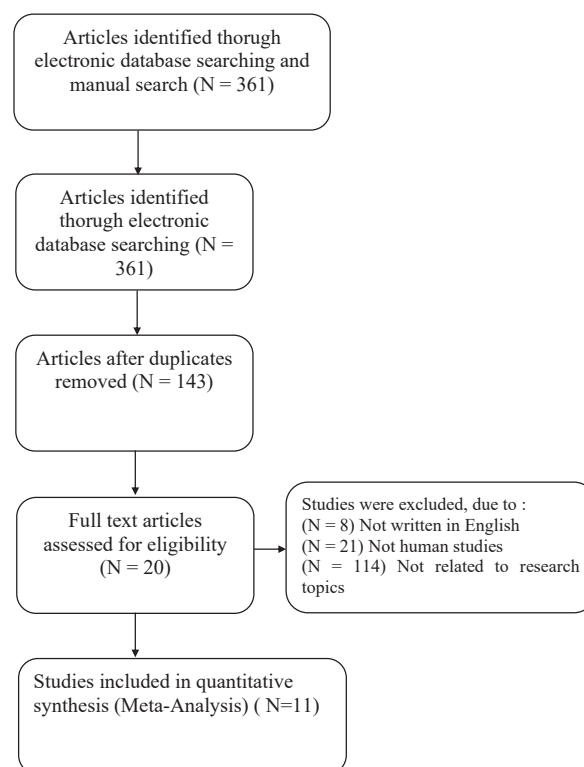
Quality Assessment

The methodological quality in each of these studies was assessed using the risk-of-bias assessment tool based on the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) by 2 reviewers (A.F.P. and B.D.).

Study selection and data collection

Study selection and data collection were performed independently in an unblinded standardized manner by 4 reviewers (A.F.P., B.D., K.P.S and T.N.B) with the same portion. Discrepancies between the two authors were resolved by discussion. All studies were screened for duplicate together after being collected in a single folder. After that, the selected articles will be judged on their title and abstract using the inclusion and exclusion criteria described earlier. Selected studies will be reviewed based on their full-text version. Statistical analysis was

Study, Publication Year	Country	Chemotherapy after TURB
Ali-El-Dein, 1997	Egypt	Epirubicin 50 mg / 50 mL
Berrum-Svennung, 2008	Sweden	Epirubicin 50 mg / 50 mL
Gudjonsson, 2009	Sweden	Epirubicin 80 mg / 50 mL
Oosterlinck, 1993	Multination	Epirubicin 80 mg / 50 mL
Rajala, 2002	Finland	Epirubicin 100 mg / 100 mL
Barghi, 2006	Iran	Mitomycin C 30 mg / 30 mL
De Nunzio, 2011	Italy	Mitomycin C 40 mg / 50 mL
El-Ghobashy, 2007	Egypt	Mitomycin C 30 mg / 50 mL
Solsona, 1999	Spain	Mitomycin C 30 mg / 50 mL
Tatar, 2011	Turkey	Mitomycin C 40mg / 50 mL
Tolley, 1996	United Kingdom	Mitomycin C 40 mg / 40 mL

Table 2. Characteristics of the included studies.**Figure 1. Study flow chart.**

done by Review Manager 5. From 361 studies, total 11 studies were eligible for this study.

Outcomes

The primary outcome was recurrence rate of those NMIBC patient who got Intravesical Chemotherapy and those not. This outcome was evaluated for all studies for which an Risk Ratio (RR) could be calculated.

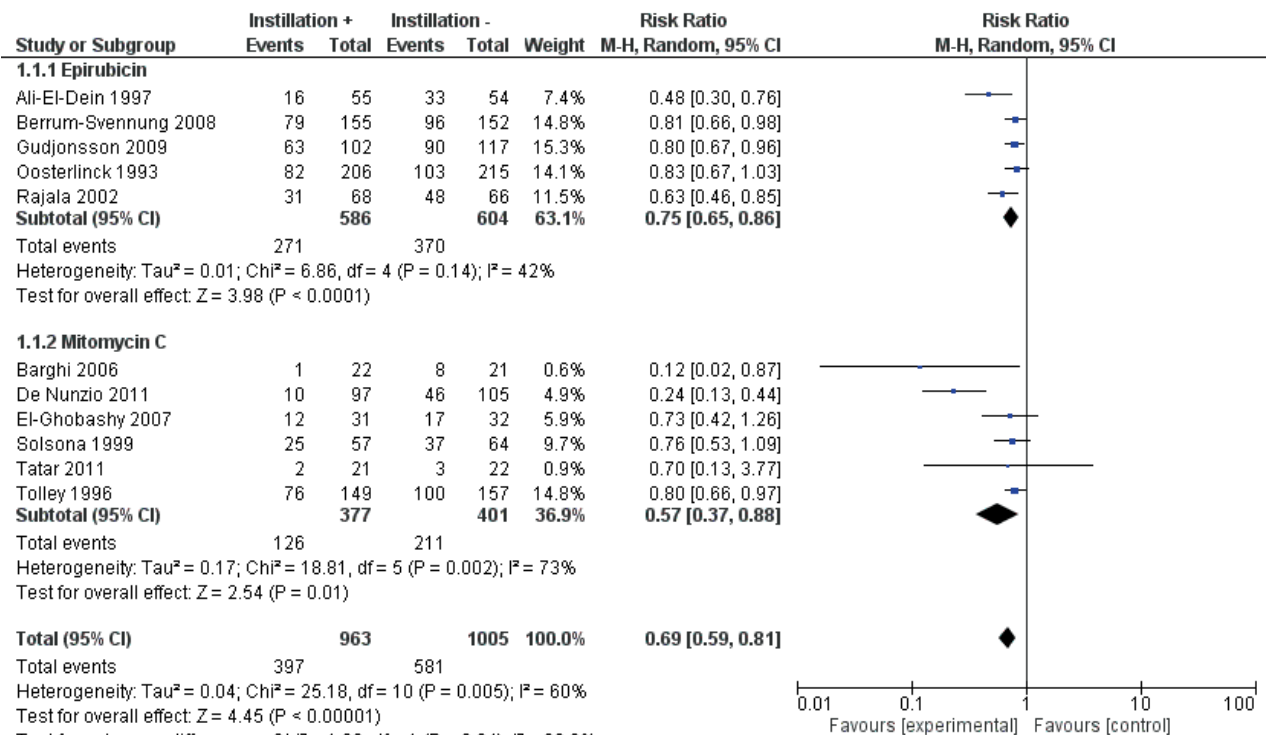


Figure 2. Forest plot comparing AKI incidence.

Assessment of bias and statistical methods

The quality of this study was assessed by B.D. and A.F.P with the same portion by using Cochrane-risk-of-bias tool (10). Bias assessed include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias.

Effect size using Risk Ratio (RR) and 95% confidence interval (CI) for Recurrence rate of patients treated with intravesical chemotherapy, compared to who were not given treatment. Homogeneity of study results is determined using Cochran Q test. Random Effect Model (REM) was used because statistical heterogeneity was found in the study ($I^2 > 75\%$). Otherwise, Fixed Effect Model (FEM) was used. $P \leq .05$ (2-sided) was considered statistically significant.

4. RESULTS

Literature Search

A flow diagram of study selection is shown in Figure 1. After initially identifying 361 articles, 218 were excluded and the full texts of 143 were reviewed. Subsequently, 132 studies were excluded, and 11 studies were included in the systematic review and meta-analysis (Table 2).

From those 11 studies, it is shown that intravesical chemotherapy using Epirubicin and Mitomycin-C following TURB showed significant decrease of recurrence rate of bladder cancer even to progression of the disease compared to TURB alone ($p < 0.05$) with pooled Risk Ratio were 0.69 and had narrow heterogeneity (I^2) were 26.6%.

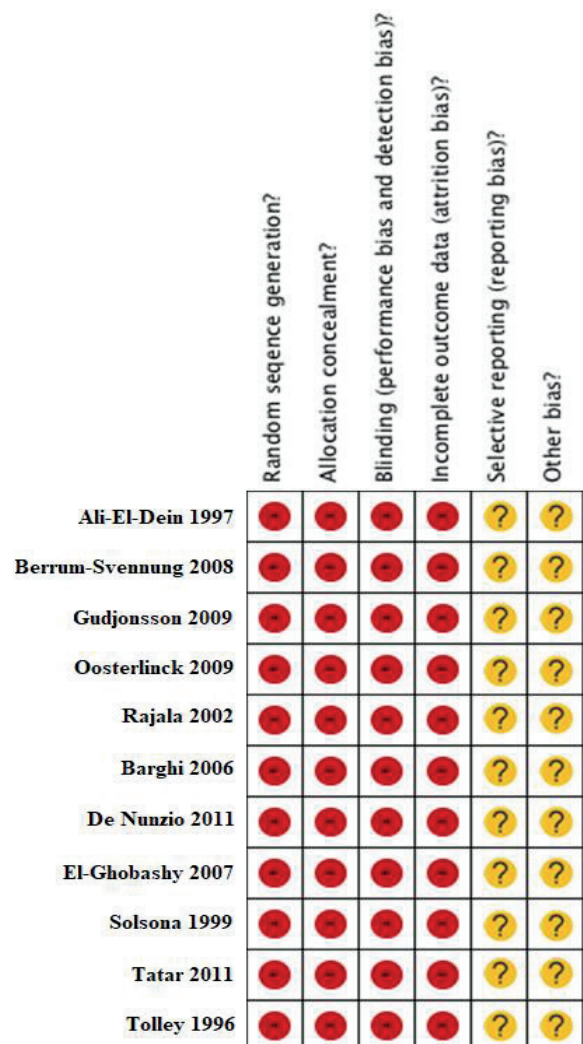


Figure 3: Risk of bias

Quality Assessment of the Included Studies

The quality assessment assessed included selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias (Figure 3). In 11 studies, reporting bias weren't adequately generated. But all studies had good quality in attrition bias, performance bias, and reporting bias.

5. DISCUSSION

In this meta-analysis study, there are 11 studies included in terms of inclusion criteria. Studies used Epirubicin as intravesical chemotherapy were 5 studies, and using Mitomycin C were 6 studies. Whether the study used Epirubicin or Mitomycin C, we calculated to pooled risk ratio to overlook the recurrence rate after being treated by respective chemotherapy agents. Five studies were using Epirubicin ranged from 1993-2009 was overall weighted to be less recurrent in groups were using instillation of Epirubicin (5-9). Total effect of the studies used Epirubicin were 3.98 with significant different between the group treated with Epirubicin instillation and not given treatment ($p < 0.0001$) with heterogeneity 42%. Studies elaborated into the other resources of chemotherapy, were using Mitomycin C, 6 studies were conducted and we got the pooled total effect was 2.54 with significantly better for the instilled groups of patient ($p = 0.01$) with broader heterogeneity 73%. It showed Mitomycin C instillation were also better than the group not being treated (10-15). The pooled risk ratio was 0.69 with total effect was quite high 4.45 ($p < 0.00001$), the data showed there were significant different between the groups used instillation were better in recurrence rate rather than groups not being treated.

6. CONCLUSION

Our current study has identified that intravesical chemotherapy using epirubicin and mitomycin-C after TURB significantly lower recurrence rate of NMIBC and it could serve as potential progressivity suppressor.

- **Author's contribution:** The investigation was arranged by BD, AFP, KPS, and TNB who also performed research, provided research materials, and collated and processed data. BD and AFP were responsible for data analysis and interpretation. BD, AFP, KPS, and TNB contributed with the initial and final versions of the article as well as practical assistance. All authors were in control of the manuscript's substance after critically reviewing and approving the final text.
- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** None.

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