INPLASY PROTOCOL

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None declared.

The safety and efficacy of BCG combined with mitomycin C compared with BCG monotherapy in patients with Non-Muscle-Invasive bladder cancer: A Systematic Review and Meta-Analysis

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Review question / Objective: **We sought to determine the efficacy and safety of BCG combined with MMC compared with BCG monotherapy in intravesical therapies for non-muscle-invasive bladder cancer.**
Condition being studied: **Non-Muscle-Invasive bladder cancer.**
Information sources: **Systematic literatures were performed of PubMed, EMBASE, Cochrane Library, CNKI, CBM, VIP, Wan Fang and Clinical Trials.gov. Randomized controlled trials (RCTS) of comparing BCG combined with MMC and BCG monotherapy in intravesical therapies for non-muscle-invasive bladder cancer patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 February 2022 and was last updated on 22 February 2022 (registration number INPLASY202220095).

INTRODUCTION

Review question / Objective: **We sought to determine the efficacy and safety of BCG combined with MMC compared with BCG monotherapy in intravesical therapies for non-muscle-invasive bladder cancer.**

Condition being studied: **Non-Muscle-Invasive bladder cancer.**

METHODS

Search strategy: **Through a systematic literature search of PubMed, EMBASE, Cochrane Library, CNKI, CBM, VIP, Wan Fang and Clinical Trials.gov, we found the**

related randomized controlled trials (RCTs) of BCG combined with MMC intravesical instillation in the treatment of NMIBC patients compared with BCG alone.

Participant or population: All patients were pathologically diagnosed as NMIBC for the first time.

Intervention: Intravesical instillation of BCG combined with MMC.

Comparator: Intravesical instillation of BCG alone.

Study designs to be included: Only RCTs were included.

Eligibility criteria: ①participants: all patients were pathologically diagnosed as NMIBC for the first time; ②intervention: intravesical instillation of BCG combined with MMC; ③control: intravesical instillation of BCG alone; ④outcomes: at least one of the following, disease recurrence, disease progression, adverse reactions, disease-specific mortality, all-cause death; ⑤only RCTs were included.

Information sources: Systematic literatures were performed of PubMed, EMBASE, Cochrane Library, CNKI, CBM, VIP, Wan Fang and Clinical Trials.gov. Randomized controlled trials (RCTS) of comparing BCG combined with MMC and BCG monotherapy in intravesical therapies for non-muscle-invasive bladder cancer patients.

Main outcome(s): At least one of the following, disease recurrence, disease progression, adverse reactions, disease-specific mortality, all-cause death.

Quality assessment / Risk of bias analysis: Two researchers evaluated the quality of each original study with The Cochrane Collaboration Risk of Bias Tool, which included the following six items: ①the generation of random sequences; ②Allocation concealment; ③whether to implement blind method for participants and researchers; ④whether to implement blind method for outcome evaluation; ⑤whether to selectively report research results; ⑥other sources of bias.

Strategy of data synthesis: The meta-analysis of the original research data was carried out by using Revman5.4 software and Stata16.0 software. The data types extracted in this study are binary variables, using relative risk (relative risk, RR) and its 95% confidence interval (confidence interval, CI) to combine statistics. Forest Chi-square test and the size of I2 were used to evaluate the heterogeneity among the included results. The size of heterogeneity is determined according to the value of I2. When $P \geq 0.1$and $I2 < 50\%$, the heterogeneity among the studies is low, then the fixed effect model (fixed effect model, FEM) is used for combined statistical analysis. When $P < 0.1$, $I2 > 50\%$, it indicates that the heterogeneity among the studies is large, then sensitivity analysis and subgroup analysis are used to find the source of heterogeneity and eliminate heterogeneity as far as possible. After excluding the influence caused by obvious clinical heterogeneity, random effect (random effect model, REM) model is selected for combined statistical analysis. The test level set by Meta-analysis was $\alpha = 0.05$ ($P < 0.05$), which indicated that the difference of combined statistical effect was statistically significant. Publication bias was detected by funnel chart, Egger regression analysis and Begg rank correlation method.

Subgroup analysis: We divided into subgroups according to whether maintenance perfusion was performed, whether Tis was included, and different doses of BCG.

Sensitivity analysis: We will carry out sensitivity analysis to explore the effect of trial quality on important outcomes in the review. Where there is a high risk of bias in the allocation of participants to groups associated with a particular study or high levels of missing data, we will explore this by sensitivity analysis.

Country(ies) involved: China.

Keywords: urinary bladder neoplasms, intravesical therapies, Bacillus Calmette-Guérin, mitomycin C.

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