Study Protocol Systematic Review

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Efficacy and safety of Bacillus Calmette-Guerin for bladder cancer

A protocol of systematic review

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Abstract

Background: This study will systematically assess the efficacy and safety of Bacillus Calmette-Guerin (BCG) for patients with bladder cancer (BC).

Methods: Literature searches will be performed in multiple electronic databases from inception to present: MEDLINE, EMBASE, CINAHL, Science Direct, Cochrane Library, Web of Science, and China National Knowledge Infrastructure. We will also examine grey literature through identifying conference proceedings, thesis, dissertations, and website of clinical trials registry. Two investigators will independently scan all citation titles, abstracts, and full-text studies. The study quality will be assessed by Cochrane Risk of Bias Tool. If possible, we will perform meta-analysis. Additional analyses will be carried out to test the potential sources of heterogeneity among included trials.

Results: The present study will summarize high quality trials on investigating the efficacy and safety of BCG for patients with BC.

Conclusion: The results of this study will supply helpful evidence to determine whether BCG is effective or not for BC.

Study registration number: INPLASY202070042.

Abbreviations: BC = bladder cancer, BCG = Bacillus Calmette-Guerin, CIs = confidence intervals, RCTs = randomized controlled trials.

Keywords: Bacillus Calmette-Guerin, bladder cancer, efficacy, safety

1. Introduction

Bladder cancer (BC) is one of the most common and prevalent urological cancers globally.[1–5] It is reported that about 400,000 new cases diagnosed annually, and most of them were diagnosed as BC at an age of 65 to 70 years.[6,7] Its incidence is steadily rising worldwide, with incidence rates of 3 to 4 times more in men than in women.[6,7] The main risk factors include cigarette smoking, age, sex, race, family history, chemicals, chronic bladder problems, arsenic exposure, and cyclophosphamide, or pioglitazone, or schistosomiasis usage.[8–15] Understanding the risk factors for this disorder is paramount to help BC treatment and prevention.

Bacillus Calmette-Guerin (BCG) is widely utilized for the management of patients with BC.[16–18] Although a variety of clinical trials reported that BCG could treat BC,[19–23] there is still little literature evidence to specifically and systematically support BCG for BC. Therefore, this systematic review aims to particularly investigate the efficacy and safety of BCG for BC.

2. Methods

2.1. Study registration

This study was registered on INPLASY202070042. We have reported the present study protocol according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol statement.[24]

2.2. Eligibility criteria for included studies

This study only includes randomized controlled trials (RCTs) of BCG for patients with BC, regardless language and publication time.

This study will include participants who were diagnosed as BC, in spite of their educational background, economic status, and stages of BC.

Patients who were treated with BCG for BC will be included. Patients who received other treatments will be selected as a comparator, except BCG.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Table 1

Search strategy of Cochrane Library.

Number	Search terms
1	MeSH descriptor: (urinary bladder neoplasms) explode all trees
2	MeSH descriptor: (urine) explode all trees
3	((bladder*) or (urinary*) or (urine*) or (urination*) or (cancer*) or (tumor*) or (neoplasm*)):ti, ab, kw
4	Or 1–3
5	MeSH descriptor: (vaccines, combined) explode all trees
6	((vaccine*) or (Bacillus Calmette-Guerin*) or (immunotherapy*) or (BCG*)):ti, ab, kw
7	Or 5–6
8	MeSH descriptor: (randomized controlled trial) explode all trees
9	((controlled trial*) or (clinical trial*) or (placebo*) or (allocation*) or (concealment*) or (sham*) or (randomly*) or (random*) or (trial*) or (study*)):ti, ab, kw
10	Or 8–9
11	4 and 7 and 10

Outcomes consist of pathological complete response, overall survival, progression-free survival, time to progression, recurrence-free survival, disease-free survival, and adverse events.

2.3. Strategy of literature searches

The primary source of literatures will be searched from inception to present in MEDLINE, EMBASE, CINAHL, Science Direct, Cochrane Library, Web of Science, and China National Knowledge Infrastructure. The secondary source of potential records will be identified from grey literatures, such as conference proceedings, thesis/dissertations, and clinical trials registry. We build a preliminary search strategy of Cochrane Library (Table 1). We will adapt similar search strategy for other electronic databases to avoid missing potential studies.

2.4. Study selection

All searched records will be imported to EndNote X7, and all duplicates will be removed. Two authors will examine titles/abstracts of all citations to exclude unrelated studies. Full papers of remaining studies will be further identified and evaluated according to all inclusion criteria. Any different views will be solved with the help of another author through discussion. A detailed process of study selection is presented in a flow diagram.

2.5. Data extraction process

For all included studies, data will be extracted using a pilot tested data extraction form. It includes primary author, time of publication, trial setting, trial methods, country, trial population, age, eligibility criteria, treatments, controls, comodalities, study limitations, study quality, outcomes, study findings, and other important data. Two authors will independently extract data from each eligible trial, and all divisions will be solved by a third author through discussion.

2.6. Dealing with missing data

Whenever insufficient or missing data are found, we will contact primary trial authors to obtain it. If we cannot receive reply, only available data will be analyzed using an intention-to-treat analysis.

2.7. Study quality assessment

Study quality of all included trials will be appraised using Cochrane risk of bias tool. This tool will evaluate 7 domains, and each one is rated as low, unclear, or high risk of bias. We will clear up any confusion with the help of a third author through discussion.

2.8. Statistical analysis

This study will employ RevMan 5.3 software to perform statistical analysis. All continuous outcome indicators will be expressed as weighted mean difference or standardized mean difference and 95% confidence intervals (CIs). All dichotomous outcome indicators will be showed as risk ratio and 95% CIs. We will quantify statistical heterogeneity using I^2 test. If $I^2 \leq 50\%$, we will pool outcome data using a fixed-effects model, and we will carry out meta-analysis if sufficient data on the same outcome is extracted. If $I^2 > 50\%$, we will synthesize outcome data using a random-effects model. In addition, we will perform a subgroup analysis to examine its possible heterogeneity sources.

A subgroup analysis will be undertaken based on the differences in types of treatments, comparators, and study quality. A sensitivity analysis will be carried out to investigate the stability of study findings by taking away trials with low quality. If data permits, reporting bias will be evaluated by inspection of the funnel plot[25] and Egger regression test.[26]

2.9. Ethics and dissemination

This study will only extract data from published trials, thus, no ethic approval is needed. We will publish this study on a peer-reviewed journal.

3. Discussion

BC is a very common urological cancer around the worldwide.[1–4] Studies suggested that BCG has been widely utilized to treat patients with BC.[16–23] However, there is still insufficient evidence to support BCG for BC. Therefore, this study will specifically appraise the efficacy and safety of BCG for the treatment of BC systematically and comprehensively. It will synthesize current available data to provide evidence and inform beneficial information for both patients and clinicians.

Author contributions

Conceptualization: Lei Yin, Jing Song.
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