Efficacy of intrathecal baclofen bolus on neuropathic pain in patients with spinal cord injury
A protocol for systematic review and meta-analysis
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Abstract
Background: This study will explore the efficacy and safety of intrathecal baclofen bolus (IBB) on neuropathic pain (NPP) in patients with spinal cord injury (SCI).

Methods: All potential literatures of IBB on NPP in patients with SCI will be searched from the following electronic databases from inauguration to the January 31, 2020: PUBMED, EMBASE, Cochrane Library, Web of Science, Chinese Scientific Journal Database Information, WANGFANG, and China National Knowledge Infrastructure. In addition, we will search other sources, such as dissertations and reference lists of included trials. There are no restrictions of language and publication status in searching all literature sources. The quality of each eligible trial will be assessed using Cochrane risk of bias tool, and publication bias will be checked using a funnel plot and Egger test. Statistical analysis will be conducted using RevMan 5.3 software.

Results: This study will scrutinize the efficacy and safety of IBB on NPP through pain intensity of NPP, spasticity, walking ability, health-related quality of life, duration of stay at hospital (days), incidence of adverse event, and mortality rate.

Conclusions: The findings of this study will present helpful evidence to judge whether IBB is effective on NPP in patients with SCI or not.

Study registration number: INPLASY202040192.

Abbreviations: CIs = confidence intervals, IBB = intrathecal baclofen bolus, NPP = neuropathic pain, RCTs = randomized controlled trials, SCI = spinal cord injury.

Keywords: efficacy, intrathecal baclofen bolus, neuropathic pain, spinal cord injury

1. Introduction

Spinal cord injury (SCI) is a common neurological disorder in adult population, with the ratio of male-to-female is around 2:1.[1–4] It is estimated that its incidence is about 40 to 80 new cases per million people annually from all causes.[5–7] Patients with SCI often experience paralyzed muscles, atrophy, walking disability, spasticity, and neuropathic pain (NPP).[8–10] A variety of studies have explored the efficacy and safety of intrathecal baclofen bolus (IBB) on NPP in patients with SCI.[11–21] However, it is plausible to hypothesize that IBB can reduce NPP in patients with SCI. In addition, its reports on NPP relief are rare at literature levels. Thus, the purpose of this study is to compare the efficacy and safety of IBB on NPP after SCI with those of other treatments.

2. Methods

2.1. Study registration

This protocol was registered on INPLASY202040192. We report this study based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol statement.[22,23]
2.3. Criteria for including studies
2.3.1. Types of studies. This study will only include randomized controlled trials (RCTs) of IBB on NPP in patients with SCI. Any other studies including quasi-RCTs will be excluded from this study.

2.3.2. Types of interventions. All patients in the experimental group underwent IBB alone as their management for NPP.

All participants in the control group received any treatments, such as alternative medicine, massage, or any other interventions. However, we will exclude patients who also taken IBB.

2.3.3. Types of patients. Any SCI patients who were diagnosed as NPP will be included in this study. No restrictions upon race, gender, age, severity, and duration of SCI and NPP will be applied to this study.

2.3.4. Types of outcome measurements. Primary outcome is pain intensity of NPP, as measured by Neuropathic Pain Symptom Inventory or any other relevant pain scales.

Secondary outcomes are spasticity (as assessed by Modified Ashworth Scale or other associated scales), walking ability (as checked by 10 m-Walk Test or other tools), health-related quality of life (as identified by 36-Item Short Form Survey or other questionnaires), duration of stay at hospital (days), incidence of adverse event, and mortality rate.

2.4. Data sources and search
A comprehensive search will be conducted in the following electronic databases from their onset to the January 31, 2020: PUBMED, EMBASE, Cochrane Library, Web of Science, Chinese Scientific Journal Database Information, WANGFANG, and China National Knowledge Infrastructure. We will not utilize any limitations of language and publication date to the literature search. The sample of search strategy for PUBMED is presented in Table 1. We will adapt similar search strategies with specific to other electronic databases.

In addition to the above electronic databases, we will also check other resources, including dissertations and reference lists of qualified studies.

2.5. Data collection and analysis
2.5.1. Study selection. All study records will be managed using Endnote X7 and all duplications will be removed. Titles and abstracts of all studies will be identified by 2 independent authors to investigate eligible studies in accordance with the eligibility criteria, and all unrelated records will be removed. Then, we will obtain all remaining studies with full-texts and will cautiously examine all inclusion criteria to determine whether they fulfill and should be included in this study. Any disagreements will be settled down with the help of a third author via discussion. We will present the study selection process in the flow chart (Fig. 1). The excluded reasons for all removed studies will be recoded.

2.5.2. Data collection. Data will be collected from the included trials by 2 independent authors using an advance-designed data extraction sheet. Any inconsistencies will be resolved by discussion with another experienced author. We will collect data of title, first author, publication date, country, demographic characteristics of patients (such as age, sex, race, et al), trial setting, sample size, trial methods (such as randomization, blind, et al), interventions, comparators, outcome variables, results, findings, follow-up data, and conflict of interest.

2.5.3. Missing data dealing with. If there is unclear or missing data, we will contact original authors to request it. If such data is not obtained, we will only analyze available data using an intention-to-treat analysis. In addition, we will discuss its potential impact on the study findings.

2.5.4. Risk of bias assessment. Two authors will independently appraise the study quality of each eligible trial using the internationally recognized Cochrane risk of bias tool for assessing RCTs. It consists of 7 aspects, and each item is classified as low, unclear, or high risk of bias. Any discrepancies will be solved by a third author, and consensus is reached.

2.5.5. Subgroup analysis. We will carry out subgroup analysis to find out possible reasons of the substantial heterogeneity according to the different types of treatments, controls, and outcome measurements.

2.5.6. Sensitivity analysis. We will preside over sensitivity analysis to identify the robustness and stability of study findings by excluding low quality trials.

2.5.7. Reporting bias. We will test reporting bias using funnel plot and Egger regression test when more than 10 eligible trials are included in this study.²⁴,²⁵

2.5.8. Quality of evidence. Grading of Recommendations Assessment, Development, and Evaluation²⁴ will be used for assessing the quality of evidence for the primary outcome by 2 independent authors. Any inconsistencies will be solved by a third author via discussion.

2.6. Data synthesis
This study will use RevMan 5.3 software to conduct all statistical analysis. Continuous outcome values will be expressed as mean

| Table 1 | Search strategy of PUBMED. |
|---|---|
| Number | Search terms |
| 1 | spinal cord injury |
| 2 | spinal cord |
| 3 | trauma |
| 4 | neuropathic pain |
| 5 | chronic pain |
| 6 | neuropathic pain |
| 7 | pain intensity |
| 8 | Or 1–7 |
| 9 | intrathecal baclofen bolus |
| 10 | baclofen |
| 11 | bolus |
| 12 | intrathecal baclofen injection |
| 13 | Or 9–12 |
| 14 | randomized controlled trials |
| 15 | clinical trials |
| 16 | random |
| 17 | randomly |
| 18 | control |
| 19 | allocation |
| 20 | placebo |
| 21 | blind |
| 22 | clinical study |
| 23 | clinical trials |
| 24 | Or 14–23 |
| 25 | 8 and 13 and 24 |
difference or standardized mean difference and 95% confidence intervals (CIs), and dichotomous outcome values will be explicated as risk ratio and 95% CIs. Statistical heterogeneity among qualified trials will be performed by $I^2$ statistics. $I^2 \leq 50\%$ suggests low heterogeneity, and a fixed-effects model will be used for synthesizing outcome data. $I^2 > 50\%$ states considerable heterogeneity, and a random-effects model will be employed for pooling outcome data. If sufficient data is collected and low heterogeneity is identified, we will carry out meta-analysis based on the similar study characteristics, types of interventions and controls, and outcome measurements. If significant heterogeneity is checked, we will perform subgroup analysis to explore its possible reasons of the considerable heterogeneity.

3. Discussion

It is reported that IBB can be a promising therapy to relieve NPP in patients with SCI.\textsuperscript{[11–22]} However, no systematic study reported and summarized the available evidence in this population. The present study will examine and synthesize the evidence for the efficacy and safety of IBB on NPP after SCI with those of other treatments. The results of this study may help clinicians choose the best options for the treatment of NPP in patients with SCI, as well as provide evidence for decision-making of guidelines.

**Author contributions**

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