


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 in patients with SCI 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

S-FW and Z-MW contributed equally to this study.

The authors report no conflicts of interest

This study was supported by Scientific Research Project of Heilongjiang Health and Family Planning Commission (2017–387). The supporters had no role in this study.

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

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How to cite this article: Wang Sf, Wang Zm, Song Wd, Tang Zc, Chai Y. Efficacy of intrathecal baclofen bolus on neuropathic pain in patients with spinal cord injury: a protocol for systematic review and meta-analysis. *Medicine* 2020;99:25 (e20484).

Received: 27 April 2020 / Accepted: 30 April 2020

<http://dx.doi.org/10.1097/MD.00000000000020484>

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]

2.2. Ethics and dissemination

It is not necessary to provide ethical approval, because this study only extracts data from included study. It will be submitted and published in a scientific peer-reviewed journal or a conference meeting.

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 specifics 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 recorded.

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.

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	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

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 Evaluation^[26] 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

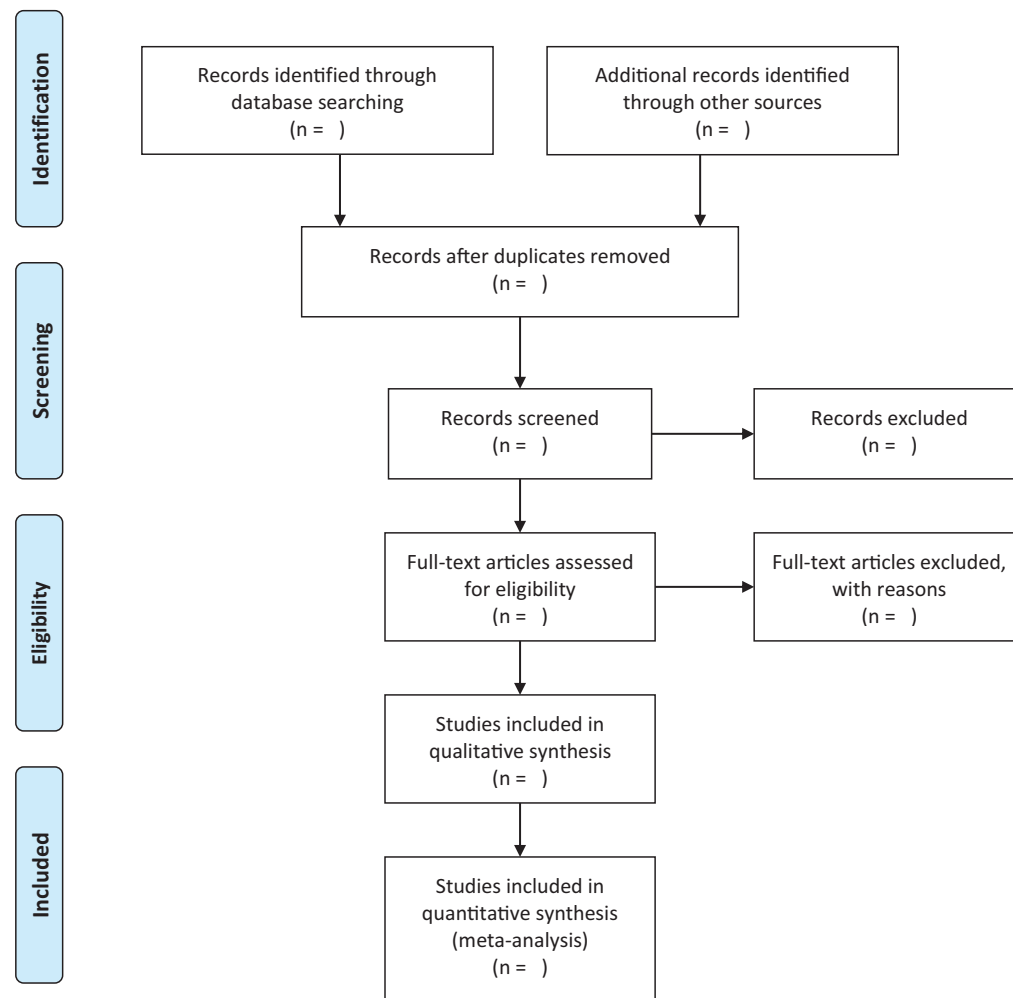


Figure 1. Flow chart of study selection process.

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.^[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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References

- [1] Shiao R, Lee-Kubli CA. Neuropathic pain after spinal cord injury: challenges and research perspectives. *Neurotherapeutics* 2018;15:635–53.
- [2] Rabinstein AA. Traumatic spinal cord injury. *Continuum (Minneapolis)* 2018;24:551–66.
- [3] Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. *Nat Rev Dis Primers* 2017;3:17018.
- [4] Rogers WK, Todd M. Acute spinal cord injury. *Best Pract Res Clin Anaesthesiol* 2016;30:27–39.
- [5] Burke D, Fullen BM, Stokes D, et al. Neuropathic pain prevalence following spinal cord injury: a systematic review and meta-analysis. *Eur J Pain* 2017;21:29–44.
- [6] Singh A, Tetreault L, Kalsi-Ryan S, et al. Global prevalence and incidence of traumatic spinal cord injury. *Clin Epidemiol* 2014;6:309–31.
- [7] Furlan JC, Sakakibara BM, Miller WC, et al. Global incidence and prevalence of traumatic spinal cord injury. *Can J Neurol Sci* 2013;40:456–64.
- [8] Karatas G, Metli N, Yalcin E, et al. The effects of the level of spinal cord injury on life satisfaction and disability. *Idegyogy Sz* 2020;73:27–34.
- [9] Argetsinger LC, Singh G, Bickel SG, et al. Spinal cord injury in infancy: activity-based therapy impact on health, function, and quality of life in chronic injury. *Spinal Cord Ser Cases* 2020;6:13.
- [10] Massa LM, Hoffman JM, Cardenas DD. Validity, accuracy, and predictive value of urinary tract infection signs and symptoms in individuals with spinal cord injury on intermittent catheterization. *J Spinal Cord Med* 2009;32:568–73.
- [11] Kumru H, Benito-Penalva J, Kofler M, et al. Analgesic effect of intrathecal baclofen bolus on neuropathic pain in spinal cord injury patients. *Brain Res Bull* 2018;140:205–11.
- [12] Vaidyanathan S, Oo T, Soni BM, et al. Severe, protracted spasm of urinary bladder and autonomic dysreflexia caused by changing the suprapubic catheter in a cervical spinal cord injury patient: treatment by a bolus dose and increased total daily dose of intrathecal baclofen. *Clin Med Insights Case Rep* 2016;9:119–21.
- [13] Kumru H, Kofler M. Effect of spinal cord injury and of intrathecal baclofen on brainstem reflexes. *Clin Neurophysiol* 2012;123:45–53.
- [14] D'Aleo G, Rifici C, Kofler M, et al. Favorable response to intrathecal, but not oral, baclofen of priapism in a patient with spinal cord injury. *Spine (Phila Pa 1976)* 2009;34:E127–9.
- [15] Elovic E, Kirshblum SC. Managing spasticity in spinal cord injury: safe administration of bridge boluses during intrathecal baclofen pump refills. *J Spinal Cord Med* 2003;26:2–4.
- [16] Yu JG. Observation of the therapeutic effect of baclofen on myospasm after spinal cord injury. *Chin Foreign Med Sci* 2013;32:120–1.
- [17] Li D, Liu W, Wang JC. Observation of the therapeutic effect of baclofen on myal spasm after spinal cord injury. *Modern J Integr Trad Chin West Med* 2011;20:39–40.
- [18] Lin SD, Qian SQ, Zhang YC, et al. Evaluation and clinical progress of spasticity after spinal cord injury. *Chin J Orthop Surg* 2008;6:435–7.
- [19] Liu GL, Li JJ, Zhou HJ, et al. Observation of the therapeutic effect of Baclofen on spasticity after spinal cord injury. *Chin Rehab Theory Pract* 2008;1:77–8.
- [20] Du DP, Xu YM, Jiang W. Effect of intrathecal injection of baclofen on the content of excitatory amino acids in spinal cord of rats with acute incisional pain. *Shanghai Med* 2007;7:500–3.
- [21] Hu AL, Liang XY, Zhang BY, et al. Baclofen relieves muscle spasm after spinal cord injury. *Chin J Clin Rehab* 2003;22:3145.
- [22] Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- [23] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- [24] Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000;320:1574–7.
- [25] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [26] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.