INPLASY PROTOCOL

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Corresponding author:
Juan Li

lijuan20700057@163.com

Author Affiliation:
Liaocheng People's Hospital

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The authors declare that they have no competing interests.

Effect of sodium cantharidinate/vitamin B6 injection on survival, liver function, immune function, and quality of life in patients with hepatocellular carcinoma: protocol for a meta-analysis

Zhu, M[1]; Liu, XJ[2]; Zhou, CH[3]; Li, J[4].

Review question / Objective: **Is sodium cantharidinate/vitamin B6 (SC/VB6) injection effective on survival, liver function, immune function, and quality of life (QoL) in patients with HCC?**
Condition being studied: **Sodium cantharidinate/vitamin B6 injection, liver function, immune function, quality of life and hepatocellular carcinoma.**
Information sources: **Electronic databases including PubMed, Google Scholar, Cochrane Library, Excerpt Medica Database (Embase), Medline, Web of Science (WOS), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJ) and Wanfang Database will be systematically searched for eligible clinical trials from January 2000 to July 2020. Language is limited with English and Chinese.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2020 and was last updated on 28 July 2020 (registration number INPLASY202070121).

INTRODUCTION

Review question / Objective: **Is sodium cantharidinate/vitamin B6 (SC/VB6) injection effective on survival, liver function, immune function, and quality of life (QoL) in patients with HCC?**

Rationale: **SC/VB6 injection, a famous insect-derived traditional Chinese medicine**

preparation, has been widely applied as a promising adjunctive drug for HCC. However, the exact effect of SC/VB6 remains controversial. Therefore, in this study, we aimed to summarize the efficacy of SC/VB6 injection on survival, liver function, immune function, and quality of life (QoL) in patients with HCC through the meta-analysis, in order to provide scientific reference for the design of future.

Condition being studied: Sodium cantharidinate/vitamin B6 injection, liver function, immune function, quality of life and hepatocellular carcinoma.

METHODS

Search strategy: To perform a comprehensive and focused search, experienced systematic review researchers will be invited to develop a search strategy. The plan searched terms are as follows: "sodium cantharidinate" or "disodium cantharidinate" or "vitamin B6" or "sodium cantharidinate/vitamin B6" or "disodium cantharidinate/vitamin B6" or "aiyishu" or "banmaosuanna weishengsuB6 zhusheye" or "SC/VB6" or "DC/VB6" combined with "liver cancer" or "liver carcinoma" or "hepatocellular cancer" or "hepatocellular carcinoma" or "LC" or "HC" or "HCC" et al. An example of search strategy for PubMed database shown in Table 1 will be modified and used for the other databases.

Participant or population: Patients must be cytologically or pathologically confirmed as having HCC at a clinically advanced stage. No restrictions regarding age, gender, racial, region, education and economic status in this analysis. Patients with other malignancies or non-primary HCC are not included.

Intervention: HCC patients in the experimental group must be treated with conventional treatment (including radiotherapy, chemotherapy, and targeted therapy) combined with SC/VB6 injection.

Comparator: In the control group, HCC patient treated with the same conventional treatment as experimental group.

Study designs to be included: All available comparative clinical trials that assessed the efficacy of SC/VB6 injection in the treatment of HCC patients will be included.

Eligibility criteria: This study will include randomized controlled trials (RCTs) or quasi-RCTs, and high-quality prospective cohort studies that investigated the efficacy of SC/VB6 injection on survival, liver function, immune function, and QoL in patients diagnosed with advanced HCC. Articles without sufficient available data, non-comparative studies, non-peer reviewed articles, literature reviews, meta-analysis, commentaries, case reports and series, meeting abstracts, letter to the editor, editorials, and other unrelated studies will be all excluded from analysis.

Information sources: Electronic databases including PubMed, Google Scholar, Cochrane Library, Excerpt Medica Database (Embase), Medline, Web of Science (WOS), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJ) and Wanfang Database will be systematically searched for eligible clinical trials from January 2000 to July 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes will include: a) Overall survival (OS, which is defined as the time from the date of randomization to death from any cause); b) Immune function indicators: CD3+, CD4+, CD8+, NK cells percentage, and CD4+/CD8+ cell ratios, and serum cytokines level (IL-2, IL-4, IFN-γ and TNF-α); c) Liver function assessment: Liver function of patients with HCC was assessed in terms of total bilirubin (TBIL), serum albumin (ALB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, prothrombin time (PT) and prothrombin activity (PTA); d) QoL as evaluated by Karnofsky score.

Additional outcome(s): The primary outcomes will include: a) Overall survival (OS, which is defined as the time from the date of randomization to death from any

cause); b) Immune function indicators: CD3+, CD4+, CD8+, NK cells percentage, and CD4+/CD8+ cell ratios, and serum cytokines level (IL-2, IL-4, IFN-γ and TNF-α); c) Liver function assessment: Liver function of patients with HCC was assessed in terms of total bilirubin (TBIL), serum albumin (ALB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, prothrombin time (PT) and prothrombin activity (PTA); d) QoL as evaluated by Karnofsky score.

Data management: Two investigators (Zhu M and Liu XJ) will be responsible for the data extraction independently according to the Cochrane Handbook for Systematic Reviews of Intervention. The following data will be extracted from eligible literatures: a) Study characteristics and methodology: country of study, the first author, year of publication, study design, sample size, periods of data collection, total duration of study and follow-up duration, et al. b) Participant characteristics: tumor stage (staging of the tumor according to the AJCC TNM classification for esophageal cancer), age, gender, ethnicity, pathology diagnosis, pathologic tumor size, inclusion and exclusion criteria, et al. c) Interventions: therapeutic means, manufacturer of the drugs, dosage of SC/VB6, administration route and cycles, duration of treatment and follow-up time, et al. d) Outcome and other data: ORR, OS, QoL, immune indexes [(CD3+, CD4+, CD8+, NK cells percentage, and CD4+/CD8+ cell ratios, and serum cytokines level (IL-2, IL-4, IFN-γ and TNF-α)], Liver function indicators (TBIL, ALB, ALT, AST, PT and PTA), AFP and adverse effects, et al. Dealing with missing data: we will attempt to contact the authors to request the missing or incomplete data. If those relevant data are not acquired, they will be excluded from the analysis.

Quality assessment / Risk of bias analysis: At least two review investigators (Zhu M and Liu XJ) independently assessed risk of bias of the included RCTs by using the following criteria described in the Cochrane Handbook for Systematic Reviews of Interventions: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Evidence quality will be classified as low risk, high risk, or unclear risk of bias. EPOC guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Zhou CH).

Strategy of data synthesis: We will utilize Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp., College Station, TX, USA) statistical software to pool the data and carry out the data analysis. Heterogeneity between studies will be assessed using the Cochran's Q and Higgins I2 statistic. $P < 0.1$ for the Chi2 statistic or an $I2 > 50\%$ will be considered as showing considerable heterogeneity. A fixed effect model will be used to calculate the outcomes when statistical heterogeneity is absent; otherwise, the random effects model was considered according to the DerSimonian and Laird method. Continuous data will be presented as standardized mean difference (SMD) with their confidence intervals (CIs). Dichotomous data will be recorded as risk ratio (RR) with 95% CIs. For survival outcomes, Hazard ratios (HRs) with corresponding 95% CIs will be extracted from trials or be estimated from Kaplan–Meier survival curves by established methods. A two-tailed $P < 0.05$ was considered statistically significant.

Subgroup analysis: Subgroup and meta-regression analysis will be conducted to explore the source of heterogeneity with respect to tumor stage, region, course of treatment and therapeutic regimens, et al.

Sensibility analysis: Sensitivity analysis will be carried out to assess the reliability and robustness of the pooled results via eliminating trials with low quality. A summary table will report the results of the sensitivity analyses.

Language: Language is limited with English and Chinese.

Country(ies) involved: China.

Other relevant information: a) Publication bias analysis: Funnel plot, Begg's and Egger regression test will be performed to analyze the existence of publication bias if 10 or more studies are included in the meta-analysis. If reporting bias is suspected, we will consult the study author to get more information. If publication bias existed, a trim-and-fill method should be applied to coordinate the estimates from unpublished studies, and the adjusted results were compared with the original pooled RR. b) Evidence evaluation: The evidence grade will be determined by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The quality of all evidence will be evaluated as 4 levels (high, moderate, low, and very low).

Keywords: sodium cantharidinate/vitamin B6, hepatocellular carcinoma, liver function, immune function, quality of life, efficacy.

Dissemination plans: We will disseminate the results of this systematic review by publishing the manuscript in a peer-reviewed journal.

Contributions of each author:
Author 1 - Min Zhu - Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing-original draft.
Author 2 - Xiujing Liu - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 3 - Changhui Zhou - Funding acquisition, Investigation, Methodology, Validation, Writing-original draft, Writing-review & editing.
Author 4 - Juan Li - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.