INPLASY PROTOCOL

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None declared.

Efficacy and safety of low doses of intravenous immunoglobulin in the treatment of pediatric immune thrombocytopenic purpura: a systematic review and meta-analysis

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Review question / Objective: **P: Patients diagnosed with Idiopathic thrombocytopenic purpura (ITP), and under 18 years old. I: High dose regimen-standard dose of intravenous immunoglobulin (IVIG). C: Low dose regimen-lower dose than the standard dose of IVIG. O:Is there any difference between high dose and low dose regimen of IVIG in treatment for ITP children? Can low-dose regimen replace high-dose regimen ? S: Randomized Controlled Trial.**
Information sources: **We systematically searched electronic databases including CNKI, WanFang, VIP, PubMed, Web of Science, and The Cochrane Library. ClinicalTrials.gov also was searched for supplement.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 July 2022 and was last updated on 26 September 2022 (registration number INPLASY202270126).

INTRODUCTION

Review question / Objective: **P: Patients diagnosed with Idiopathic thrombocytopenic purpura (ITP), and under 18 years old. I: High dose regimen-standard dose of intravenous immunoglobulin (IVIG). C: Low dose regimen-lower dose than the standard dose of IVIG. O:Is there any difference between high dose and low dose regimen of IVIG in treatment for ITP children? Can low-dose regimen replace high-dose regimen ? S: Randomized Controlled Trial.**

Rationale: **In 1981, Paul Imbach et al. applied IVIG to 7 children with chronic ITP**

and 6 children with acute ITP, and observed a significant increase in PLT counts in all cases. Since then, IVIG has been applied to the treatment of ITP in children, and has gradually become the first-line treatment of the disease. Although IVIG has significant therapeutic effect, there is still an important problem, that is, the medical cost is too high.

Condition being studied: Idiopathic thrombocytopenic purpura (ITP), also known as immune thrombocytopenia, is a very common hemorrhagic disease in children. The main mechanism of the disease is that excessive destruction and blocked production of platelets lead to decreased platelet count and reduced coagulation function, resulting in spontaneous bleeding of skin, mucosa or viscera. If intracranial hemorrhage is caused, it may be life-threatening. According to the degree of bleeding, glucocorticoids, intravenous immunoglobulin (IVIG) or platelet infusion can be chosen. Immunoglobulin is the first-line treatment for this disease, especially for children with acute ITP, severe bleeding. IVIG is not only effective, but also has a positive impact on the prognosis of early application. However, the price of immunoglobulin is too high, which is difficult for many families to bear. Therefore, how to reduce the treatment cost and improve the medical treatment rate of children while ensuring the clinical effect is one of the urgent problems to be solved.

METHODS

Search strategy: An extensive search strategy was designed to retrieve all relevant articles published from the establishment of the database to July 1, 2022 by using six databases: PubMed, Web of Science, The Cochrane Library, CNKI, WanFang and VIP. We apply no restrictions for language of publications. "Idiopathic thrombocytopenic purpura", "immune thrombocytopenia", "gamma globulin", "child", and "intravenous immunoglobulin" etc. were used as search words.

Participant or population: Patients diagnosed with ITP, and under 18 years old. Literatures included adult patients will be excluded.

Intervention: High dose regimen: IVIG 400mg/ (kg· d) for continuous use.

Comparator: Low dose regimen: IVIG 200mg/ (kg· d). The course of two groups should be same, if combined with glucocorticoids, the drugs and usage should also be same, otherwise will be excluded.

Study designs to be included: All RCTs about different doses of IVIG for children with ITP will be included. We apply no restrictions for language of publications.

Eligibility criteria: Selected studies were excluded if: (1) they were repeat publication; (2) they were not RCT; (3) they reported incomplete or incorrect data; (4) they were of low quality (modified Jadad scale score ≤3); (5) the full text of the literature is not available.

Information sources: We systematically searched electronic databases including CNKI, WanFang, VIP, PubMed, Web of Science, and The Cochrane Library. ClinicalTrials.gov also was searched for supplement.

Main outcome(s): (1) Clinical effective rate (① significantly effective: bleeding symptoms disappear, PLT count returns to the normal range, the PLT counts >100 × 109L; ② effective: there is no or almost no bleeding symptoms, and the PLT count rises to 50 ×109/L or above, or higher than 30 × 109/L compared with that before treatment; ③ no effects: there is no change or aggravation of bleeding symptoms, no improvement or further reduction of PLT count. Clinical effective rate = (number of significantly effective cases + number of effective cases) / total number of cases × 100%); (2) The time of bleeding symptoms to stop (day/d); (3) The time of PLT count rising to normal (day/d).

Additional outcome(s): (1) The time of PLT count starting to rise; (2) The time of PLT count rising to peak (day/d); (3) The PLT count after treatment (× 109L); (4) PLT related parameters such as MPV (fL), PDW (%) and PCT (%) mean level; (5) Hospitalized duration (day/d); (6) Hospitalization expenses (yuan); (7) Adverse reactions like fever, rash, nausea and vomiting etc.

Data management: Use NoteExpress software for literature management and use RevMan5.4.1 statistical software for Meta analysis.

Quality assessment / Risk of bias analysis: Included articles will be independently assessed for quality by two reviewers using the Cochrane collaboration's tool for assessing risk of bias.

Strategy of data synthesis: In this study, revman5.4.1 statistical software will be used for meta-analysis. Risk ratio will be chosen for the dichotomous data, and mean difference will be chosen for the continuous data as the effect analysis statistics. The interval estimation will select 95% confidence interval (CI). If the heterogeneity tests $p>0.1$ and $I^2<50\%$, use the fixed effect model for meta-analysis, while when there is obvious heterogeneity ($I^2\geq50\%$), the random effect model will be used. Subgroup analysis or sensitivity analysis will be performed when necessary. The level of meta-analysis is set as $\alpha= 0.05$. Funnel plot will be used to evaluate whether there was publication bias, and the Egger and Begg tests will be performed with Stata16.0 software. If there was publication bias, the shear and complement method was used to evaluate the robustness of the results.

Subgroup analysis: We assumed that whether combined with glucocorticoids, disease severity might have an impact on the results. If there is obvious heterogeneity among the literatures, the subgroup analyses will be performed by these factors.

Sensitivity analysis: If there is obvious heterogeneity among the literatures, we will actively explore the sources of heterogeneity, such as taking sensitivity analysis by eliminating each study one by one.

Language restriction: We apply no restrictions for language of publications.

Country(ies) involved: China.

Keywords: idiopathic thrombocytopenic purpura; intravenous immunoglobulin; gamma-Globulins; child; dose.

Contributions of each author:
Author 1 - Xiangge Ren - The author developed retrieval strategy and selection criteria, screened retrieved articles, reviewed each article, extracted data from each eligible study and then proceeded to data analysis, and drafted the manuscript.
Author 2 - Mengmeng Zhang - The author screened retrieved articles, extracted data from each eligible study, and assessed for quality of included studies.
Author 3 - Jinyu Ni - The author developed retrieval strategy and selection criteria, and assessed for quality of included studies.
Author 4 - Wensheng Zhai - The author designed this study, resolved the disagreement and approved the final manuscript.