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Low-dose intravenous immunoglobulin for children with newly diagnosed immune thrombocytopenia: protocol of a systematic review and meta-analysis

Xiangge Ren,1 Miaomiao Zhang,1 Xiaohan Zhang,1 Peidong Zhao,1 Wensheng Zhai2

ABSTRACT

Introduction Intravenous immunoglobulin (IVig) is a first-line treatment for children with newly diagnosed immune thrombocytopenia (ITP). However, the cost of IVig is high. Higher doses of IVig are associated with a more insupportable financial burden to paediatric patients’ families and may produce more adverse reactions. Whether low-dose IVig can quickly stop bleeding and induce a durable response in treating children with newly diagnosed ITP is not yet established.

Methods and analysis We will extensively search five English databases (PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health Literature) and three Chinese databases (CNKI, Wanfang and VIP). International Clinical Trials Registry Platform and ClinicalTrials.gov will also be searched as supplementary. Randomised controlled trials and prospective observational studies compared the efficacy of low-dose IVig and high-dose or moderate-dose IVig will be included. The primary outcome is the proportion of patients achieving durable response. Estimates of effect will be pooled with either a random-effect model or a fixed-effect model according to the heterogeneity of studies. If significant heterogeneity exists, we will conduct subgroup analysis and sensitivity analysis to explore the source of heterogeneity and evaluate the robustness of the results. Publication bias will also be assessed, if possible. The risk of bias will be assessed using the Risk of Bias 2 tool and the Risk Of Bias In Non-Randomised Studies of Interventions tools. The certainty of evidence will be evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.

Ethics and dissemination No ethical approval is required since this systematic review is based on previously published studies. The findings of this study will be presented at international conferences or published in a peer-reviewed journal.

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INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune haemorrhagic disease characterised by a low platelet count (<100×10^9/L) due to immune-mediated platelet destruction and impaired platelet production.1 It is the most common cause of thrombocytopenia in children,2 with an estimated incidence of approximately 1.9–6.4 per 100,000 children per year.3

Paediatric patients frequently present with a new onset of epistaxis, petechiae and bruising at the time of diagnosis.4 Many of them will experience spontaneous resolution and need no medical treatment.5 Nevertheless, severe bleeding such as gastrointestinal, rectal and other intra-abdominal haemorrhages may occur in 20.2% of children,6 adversely affecting the health-related quality of life, and requires pharmacological treatment.7 8 The current treatment of ITP is not strictly regimented. First-line therapy for children with newly diagnosed ITP usually consists of corticosteroids, intravenous immunoglobulin (IVig) or a combination of both for certain patients.19
IVIg is a blood product prepared from the serum of many healthy donors, containing microbial antigens, autoantigens and anti-unique type antibodies, which has been proven to be beneficial for children with ITP. Several studies have shown that IVIg can increase platelet counts (PC) more quickly than corticosteroids, with the initial response usually occurring in 1–2 days, and might also reduce the risk of progression to chronic ITP. However, the costs of IVIg are high, with the reported mean medical costs of US$6275.15 Since the administration of IVIg requires an inpatient admission, the cost increase is most pronounced for children who require high doses of IVIg. Furthermore, Kato et al enrolled 748 patients treated with IVIg for different diseases and found adverse events were recorded in 8.5% of patients received higher doses of IVIg while only 0.8% of patients received lower doses experienced adverse events. High-dose use was reported to be one of the main risk factors for undesirable IVIg-associated adverse events such as influenza-like symptoms, dermatological adverse effects, thrombotic events, aseptic meningitis, haemolysis and renal failure.

In order to alleviate patients’ financial pressure and improve the safety of treatment, the dosage regimen of IVIg has been explored over the last few decades, and how to rationally reduce the dose is always an essential problem of clinical concern. Usually, IVIg is administered at a total dose of 2 g/kg body weight distributed over 2–5 days, but in the 2019 American Society of Hematology guideline, a single dose of 0.8–1 g/kg body weight is recommended, even if lower doses of 0.6 g/kg body weight are also reported to be effective.

A 2010 systematic review compared the efficacy of different doses of IVIg for acute ITP, which considered the total dose of 2 g/kg body weight as ‘high-dose IVIg’ and less than 2 g/kg body weight as ‘low-dose IVIg’. This study found that low-dose IVIg was as effective as high-dose (OR=1.00, 95% CI: 0.61 to 1.63; p=1.00) but some apparent flaws threatened the veracity of their conclusions. First, only two databases were searched, and the reported search terms and strategies were neither sufficient nor complete. Second, the methodological quality of the included randomised controlled trials (RCTs) was poor, and all were with small sample sizes. Last but most important, although the systematic review claimed to compare different doses, most of the included 13 RCTs used 1 g/kg body weight in the low-dose group. The efficacy of the total dose of less than 1 g/kg body weight has not been adequately assessed.

Overall, there is still a lack of supportive evidence on the efficacy and safety of low-dose IVIg for children with newly diagnosed ITP. To our knowledge, there have been several recently published studies, so it is necessary to review currently available articles, providing enough information to help doctors and stakeholders choose the most appropriate dosage regimen.

**OBJECTIVE**
We primarily aim to assess the effect of low-dose IVIg on inducing durable and initial response when treating children with newly diagnosed ITP. We also attempt to assess the effect of low-dose IVIg on controlling bleeding and reducing the possibility of progressing to chronic ITP and its safety.

**METHODS AND ANALYSIS**
This protocol was performed and reported following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) 2015 (see PRISMA-P checklist on online supplemental appendix 1). If we modify the protocol in the future, the latest version will be updated on PROSPERO in due course. This systematic review and meta-analysis will be reported following PRISMA.

**Patient and public involvement**
Patients and/or individuals were not involved in the design, conduct, reporting or dissemination plans of this research.

**Inclusion criteria**

- **Type of studies**
  RCTs, quasi-randomised RCTs, and prospective observational studies compared different doses of IVIg for children with newly diagnosed ITP will be included. No restrictions will be applied to the language and status of publications.

- **Type of participants**
  Paediatric patients (<18 years old) with newly diagnosed ITP will be included. Newly diagnosed ITP is defined as the duration of ITP less than 3 months. Adult patients, patients with secondary ITP, and previously treated patients will not be part of our consideration. No further restrictions will be set for participants’ sex, nationality and ethnicity.

- **Type of interventions**
  All studies involving the administration of IVIg and comparing different doses will be considered for meta-analysis. We will define the total dose of <1 g/kg body weight as ‘low-dose IVIg’. RCTs will be included in which the experimental intervention is low-dose IVIg when the total dose of IVIg in the comparator intervention is higher than 1 g/kg body weight. If combined with corticosteroids, the course and type of corticosteroids should be the same, otherwise will be excluded.

- **Types of outcomes**
  
  - **Primary outcome**
    The proportion of patients achieving durable response. Durable response is defined as the achievement of PC returning to more than 100×10⁹/L (complete response) or more than 30×10⁹/L (partial response) at 6 months or longer without the necessity of medical treatment.
Secondary outcome

Secondary outcomes include the proportion of patients achieving initial response, the time to achieve haemostasis, the proportion of patients progressing to chronic ITP, PC, the level of platelet-related parameters and adverse events. The initial response is based on the earliest PC measurement. Chronic ITP is defined as a PC of <100×10^9/L at 12 months. We will contrast PC and the level of platelet-related parameters before and after IVIg treatment. Platelet-related parameters include mean platelet volume, platelet distribution width and plateletcrit. We will also summarise all reported adverse events and compare the incidence rate.

Search strategy

We will conduct an extensive search strategy to retrieve all eligible articles published from the establishment of the database to the formal search date by searching Pub, Embase, Web of Science, Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health Literature, and three Chinese databases including CNKI, Wanfang and VIP. International Clinical Trials Registry Platform and ClinicalTrials.gov will also be searched to identify relevant RCTs. In case of omissiveness, we will extend the search of reference lists of identified articles for potential studies. We identified all search terms from the previously published systematic review. The search strategy was established by two reviewers (MZ and PZ) and revised by an experienced librarian. The detailed search strategy that will be used for PubMed and CNKI can be found in online supplemental appendix 2.

Study selection

Two reviewers (XR and MZ) will independently conduct study screening and selection. All retrieved literatures will be imported into EndNote V.X9.2 software, and duplicates will be removed. The remaining literatures will be screened based on the titles and abstracts. We will further assess the full texts of potential literatures to identify eligible studies based on prespecified inclusion criteria. If multiple publications from the same study group occur, the one with the largest sample size or the most complete one will be included. Agreement between reviewers on initial study selection will be measured with the κ statistic. Any disagreements will be resolved through discussion and consensus of the third reviewer (WZ).

Data extraction and management

Two reviewers (XR and XZ) will independently extract data from each eligible study using a prespecified data extraction form and then cross-check the results. Disagreements between reviewers will be resolved through discussion and consensus of the third reviewer (WZ). The following information will be extracted: name of the first author, country of origin, year of publication, sample size, participant baseline characteristics (gender, age, PC, severity of bleeding), details of experimental and comparator interventions (the dose and course of IVIg, the type of corticosteroids if combined with corticosteroids), outcomes, follow-up period, and adverse events. Authors of the original studies will be contacted for further information if there are inadequate details or clarification.

Quality appraisal

The Risk of Bias 2 (RoB 2) tool and the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias of included RCTs and non-randomised studies, respectively, by two independent reviewers (XZ and PZ). The RoB 2 tool covers five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result. The ROBINS-I tool covers seven domains: bias due to confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes and bias in the selection of the reported results. The summary of the quality assessment results will be presented in tabular form with a brief justification for each judgement. If disagreements exist, they will be resolved through discussion or consultation with a third reviewer (WZ).

Measure of treatment effect

We will use a risk ratio with 95% CI to measure the estimated effect of dichotomous variables. For continuous variables, the estimated effect will be measured using mean difference with 95% CI. If data are measured or presented in different ways, we will use the standardised mean difference with 95% CI.

Dealing with missing data

If there are studies with missing data, we will contact the corresponding author by phone or via email to obtain complete results. If the missing data is not available, we will follow Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines for assessing the Risk of Bias Associated with Missing Participant Outcome Data in a body of evidence and choose to conduct a primary meta-analysis using a complete case analysis followed by sensitivity meta-analysis imputing data for those with missing data. For dichotomous outcomes, we will use ‘plausible worst case’ in which we assume that those with missing data in treatment arms have proportionally higher event rates than those followed successfully. For continuous outcomes, imputed mean values come from other studies within the systematic review, and the SD from the median SDs of the control arms of all studies. In addition, we will compare the complete case analysis to a series of sensitivity analyses to explore the impact of missing outcome data on results.
Data synthesis and statistical analysis

Data synthesis
We will perform a meta-analysis using Review Manager V.5.4 software only if the data are sufficient and treatment results are comparable. The Mantel-Haenszel method will be used for pooling dichotomous data, while the inverse variance method will be used for pooling continuous data. If the following conditions exist: the data are limited, the intervention or outcomes are not comparable, or the heterogeneity of the study population is high, we will consider reporting results qualitatively. For adverse outcomes, we will use narrative synthesis to summarise all reported adverse events in tabular format and calculate the percentages of different reactions in the experimental and comparator groups. We will also report the methods of dealing with adverse events and compare the percentage of severe adverse events between the two groups.

Assessment of heterogeneity
$X^2$ test and $I^2$ statistic will be used to estimate the statistical heterogeneity among the pooled studies. If $p<0.1$ and $I^2 <50\%$, the heterogeneity will be considered acceptable and the fixed-effect model will be adopted for meta-analysis. If $p<0.1$ and $I^2 \geq 50\%$, the heterogeneity will be considered significant and the random-effect model will be adopted. Furthermore, we will actively explore the sources of heterogeneity from aspects of study design and quality through subgroup analysis and sensitivity analysis.

Subgroup analysis and sensitivity analysis
We will perform a subgroup analysis based on different total doses of IVIg. We will define the total dose of 2 g/kg body weight as ‘high-dose IVIg’ and the total dose of 1–2 g/kg body weight as ‘moderate-dose IVIg’, dividing the comparator group into high-dose and moderate-dose subgroups. Besides, we assume that whether combined with corticosteroids, the type of corticosteroids if combined with corticosteroids and the severity of bleeding might have an impact on the results. If sufficient data are available, we will perform subgroup analyses based on the above factors. We will also conduct sensitivity analyses to evaluate the robustness of the pooled results by excluding low-quality studies or using different statistical models.

Assessment of reporting bias
The Risk of Bias due to Missing Evidence (ROB-ME) tool will be used to assess the ROB-ME in a synthesis by two independent reviewers (MZ and PZ). The summary of the assessment results will be presented in tabular form along with a brief justification for each judgement, and studies with missing results will be displayed and noted in forest plots. If disagreements exist, they will be resolved through discussion or consultation with a third reviewer (WZ). In addition, as a part of reporting bias assessment, we will use Begg’s rank correlation and Egger’s weighted regression tests to assess the publication bias, and funnel plot will be used when a meta-analysis includes 10 or more studies. If publication bias exists, the trim and fill method will be used to evaluate its effect on the results.

Assessment of the quality and certainty of the evidence
We will use the GRADE system to evaluate the certainty of evidence. We will determine whether to downgrade the quality of evidence from five aspects: the risk of bias, inconsistency, indirectness, imprecision and publication bias. The certainty of evidence will be categorised as ‘high’, ‘moderate’, ‘low’ or ‘very low’. The evaluation results of evidence will be presented by using the GRADE profiler Guideline Development Tool.

DISCUSSION
In 1981, Paul Imbach started the first IVIg administration in a boy with severe long-term bleeding caused by ITP and found his PC dramatically increased. Since then, IVIg has been applied to treating ITP. Studies on the pharmacological mechanism of IVIg have indicated that IVIg inhibits Fc-mediated phagocytosis of antibody-coated platelets by the reticuloendothelial system to protect platelets, promotes the development or activation of regulatory T cells, and regulates B-cell function and survival.

Regarding corticosteroids’ growth inhibition, IVIg is typically selected for the treatment of children. Alexandra Schifferli et al observed the most notable difference between children and adults was the choice of first-line treatment option, with IVIg used more frequently in children and corticosteroids used more frequently in adults. However, the shortcoming of IVIg is its expensiveness, which limits its clinical application. If the reduced dose can be as effective as the high dose, the medical costs and financial burden will be significantly reduced, especially for patients in some developing countries. Since the findings of the 2010 systematic review and meta-analysis is not sufficient for current clinical settings, whether low-dose IVIg can replace higher doses in treating children with ITP remains to be explored.

Based on the current clinical practice, we will conduct a comprehensive analysis with recently available RCTs to compare different dosage regimens, providing the strongest evidence of the efficacy and safety of low-dose IVIg for children with newly diagnosed ITP. The findings from this study may help healthcare providers and policymakers to select an appropriate dosage regimen which may ultimately lead to a reduction in medical costs.

ETHICS AND DISSEMINATION
Ethical approval is not required because this systematic review is based on previously published studies. The findings of this systematic review and meta-analysis may provide suggestions on selecting an appropriate IVIg regimen. We will present the findings at international conferences and publish the results in peer-reviewed journals.
conferences or publish the findings in a peer-reviewed journal.

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Contributors WZ and XR conceived and designed the study. XR registered the protocol on the PROSPERO database and drafted the protocol. WZ, MZ and XZ critically revised the protocol. MZ and PZ developed the search strategy. XR and XZ will extract data from included studies. XR, MZ and XZ will perform the study selection and data analysis. XZ and PZ will assess the quality of the included studies and the certainty of the evidence independently. WZ will be involved in consulting and settling disagreements. All authors reviewed and approved the final version before submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

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ORCID iD
Xiangge Ren http://orcid.org/0000-0002-5073-1528

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