Effectiveness of shengxuexiaoban capsules combined with glucocorticoid therapy for immune thrombocytopenia: A meta-analysis

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Abstract

Objective
To evaluate the effectiveness of the Shengxuexiaoban Capsules combined with glucocorticoid therapy for immune thrombocytopenia (ITP).

Methods
We collected randomized controlled trials (RCTs) using shengxuexiaoban capsules in combination with glucocorticoid to treat ITP by searching major Chinese and English electronic databases. The outcome indicators were the effective rate, recurrence rate, the number of platelets in the blood, recovery time of platelets, and adverse reactions. We used STATA 16.0 and RevMan 5.3 for meta-analysis and GRADE pro. for evidence quality evaluation.

Results
A total of 27 RCTs were included in the meta-analysis, and the results showed a significant difference (all p<0.05) in the effective rate, recurrence rate, the number of platelets, and the recovery time of platelets (≥ 100×10^9) between ITP patients in the control group (who received glucocorticoid therapy alone) and test group (who received glucocorticoid therapy combined with the Shengxuexiaoban Capsules). And that Shengxuexiaoban capsules combined with glucocorticoid therapy were safe. The funnel plot and Egger’s test results indicated no obvious publication bias. The GRADE evidence rating showed an intermediate quality of evidence rating for recurrence rate and overall effectiveness.

Conclusion
Glucocorticoid therapy combined with the Shengxuexiaoban Capsules showed more effectiveness in the treatment of ITP. It can improve the effective rate, reduce the recurrence rate, increase the number of platelets and shorten the recovery time of platelets, and has a good safety profile.
1. Introduction

Immune thrombocytopenia (ITP) is a common bleeding disorder encountered in clinical practice. Patients with ITP usually have spontaneous skin and mucous membranes bleeding caused by a decrease in the number of platelets in the blood [1]. At present, glucocorticoid remain the first choice for treating of ITP [2, 3], which significantly increases the number of platelets. However, long-term use of glucocorticoid can lead to various adverse effects [4], such as central obesity and osteoporosis. Recent studies have discovered that the Shengxuexiaoban Capsules are effective for ITP. Because it contains Indigo Naturalis, Cortex Moutan, Forsythia, Agrimonia, and Licorice, which can clear away heat and toxic materials, cool blood, arrest bleeding, disperse blood stasis and reduce freckles. However, studies reporting on Shengxuexiaoban Capsules for patients with ITP were all sample sizes studies. Herein, we performed a meta-analysis of the included RCTs to present evidence for the clinical treatment.

2 Materials and methods

2.1 Inclusion criteria

2.1.1 Study design. All included studies were RCTs, and the language was not limited, whether blinding or allocation concealment.

2.1.2 Research objects. a. Patients diagnosed with ITP (meeting the clinical diagnostic criteria of primary immune thrombocytopenia).

b. It is not affected by the included patients’ age, sex, and region.

2.1.3 Intervention comparison. The patients in the control group received glucocorticoid therapy alone, while those in the test group received glucocorticoid therapy combined with the Shengxuexiaoban Capsules.

2.2 Exclusion criteria

Repeated studies, unrelated articles, animal tests, reviews, conference reports, and studies with unclear data were excluded from the analysis.

2.3 Outcome

The outcome indicators were the effective rate (the effective rate = (number of apparent cases + number of good cases + number of improved cases)/total number of cases in the case of consistent clinical efficacy criteria. The other is the effective rate = (number of complete responses + number of effective cases)/total number of cases in the case of consistent clinical efficacy criteria), the recurrence rate, the number of platelets in the blood, and the recovery time of platelets, adverse reactions.

2.4 Retrieval of RCT

A full-test search was performed in the databases to select the RCTs where the glucocorticoid therapy was combined with the Shengxuexiaoban Capsules to treat ITP, including China National Knowledge Infrastructure (CNKI), VIP database (VIP), China Biology Medicine disc (CBMdisc), Wanfang Data Knowledge Service Platform (Wanfang Da-ta), PubMed and Embase. The retrieval time was the time from the establishment of the database to April, 2022. The following key search terms and their potential combination were used: "升血小板胶囊 (Shengxuexiaoban Capsules)”, "免疫性血小板减少症 (Immune Thrombocytopenia)” and "激 素 (glucocorticoid)”, and the English keywords included "Immune Thrombocytopenia”, "Idio-pathic Thrombocytopenia”, "shengxuexiaoban Capsules” and "Glucocorticoid”. The search mode included combining keywords with free words. Take the China Biology Medicine disc.
2.5 RCT selection and data extraction

Two researchers followed the inclusion and exclusion criteria and independently selected the RCTs and collected data, including basic information about the selected RCTs (number, gender distribution, and average age of the patients in the control group and test group), specific intervention measures, outcome indicators, result data. In the event of any disagreement, a third researcher was invited.

2.6 Quality evaluation

The quality of the included RCTs was evaluated by the risk of bias assessment tool of the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0). The biases mainly covered six aspects: selection bias, performance bias, measurement bias, attrition bias, reporting bias, and other biases, and were categorized with "low risk", "unclear risk" and "high risk" one by one.

2.7 Statistical analysis

RevMan5.3 and Stata16.0 software were adopted for the Meta-analysis. The P and I² values were used to assess the heterogeneity. P-value < 0.1 or I² > 50% indicated the presence of heterogeneity, and a random-effect model was applied for heterogeneity and sensitivity analysis. For a P-value > 0.1 or I² < 50%, a fixed-model was applied.

2.8 Evidence quality evaluation

The results of the meta-analysis were evaluated using the GRADE method, and considered for degradation in terms of risk of bias, inconsistency, indirectness, accuracy, and publication bias. They were classified as "high quality", "moderate quality", "low quality" and "very low quality".

3 Results

3.1 RCT selection results

According to the search strategy, 172 Chinese pieces of literature were preliminarily selected, and no English literature was found. After excluding 75 pieces of literature with duplicate content, 27 RCTs were finally included in the meta-analysis. The selection process is shown in Fig 1.

3.2 Basic characteristics of included subjects

A total of 1,668 patients who were diagnosed with ITP were included in the 27 RCTs. 50.7% were treated by glucocorticoid therapy combined with the Shengxuexiaoban Capsules, and there maining eight hundred twenty-three by glucocorticoid therapy alone. In four RCTs [5–8], the observation time was not reported. In the remaining 23 RCTs, the course of the disease ranged from two weeks to two years. The baseline characteristics of ITP patients (n = 1668) were presented in Table 1.
3.3 Risk of bias assessment for included RCTs

Among the 27 RCTs that were randomly grouped, 6 [5, 8–10, 16, 27] were grouped by random number table, 4 [7, 11–13] by medication regimen or therapeutic regimen, 2 [14, 15] by order of admission, and 2 [17, 21] by random odd or even number of the hospital beds (Fig 2).
3.4 Meta-analysis results

3.4.1 Effective rate. All 27 RCTs [5–31], including 845 patients in the test group (glucocorticoid therapy combined with the Shengxuexiaoban Capsules) and 823 in the control group (glucocorticoid therapy alone), analyzed the effective rate. The heterogeneity test results were $P = 0.94$ and $I^2 = 0\%$. Therefore, the Meta-analysis used a fixed model. The results showed that the effective rate of the test group (glucocorticoid therapy combined with the Shengxuexiao-ban Capsules) was higher than that of the control group (glucocorticoid therapy alone) (95\% CI [2.67, 4.87], $P < 0.00001$) (Fig 3).

3.4.2 Changes in number of platelets. The changes in the number of platelets were measured in 12 RCTs [5, 6, 10–13, 20, 22, 25, 27–29], including 332 patients in the test group and 316 in the control group. Heterogeneity existed as the test results were $P = 0.005$ and $I^2 = 59\%$. In this case, we chose a random-effect model calculation. The results showed that the number of platelets in the test group was significantly higher than that in the control group (95\% CI [20.26, 32.17], $P < 0.00001$) (Fig 4).

3.4.3 Recurrence rate. The recurrence rate was analyzed in seven RCTs [12, 15, 17, 21, 26–28], including 228 patients in the test group and 195 in the control group. No heterogeneity
Fig 2. Assessment of risk of bias.

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Fig 3. Forest plot of the effective rate.

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existed (the test results were P = 0.99 and I² = 0%). In this case, the Meta-analysis used a fixed model. The results showed that the recurrence rate was lower when the glucocorticoid therapy was combined with the Shengxuexiaoban Capsules (95% CI [0.34, 0.59], P<0.00001) (Fig 5).

### 3.4.4 Recovery time of platelets (≥100×10⁹).

Five RCTs [16, 18, 24, 30, 31], including 153 patients in the test group and 145 in the control group, reported the time required for platelets ≥100×10⁹. No heterogeneity existed (test results were P = 0.99 and I² = 0%). Therefore, we chose a random-effect model calculation. The results showed that the recovery time of platelets was shorter when the glucocorticoid therapy was combined with the Shengxuexiaoban Capsules (95% CI [-13.26, -11.04], P<0.0000) (Fig 6).

### 3.4.5 Adverse reactions.

There were no adverse cardiac, hepatic, renal, or gastrointestinal reactions after the administration of shengxuexiaoban Capsules in any of the 16 studies [6, 7, 9, 12–16, 18, 23, 24, 26, 27, 29–31]. Four studies [6, 16, 18, 24] reported no adverse reactions in either group. Five studies [9, 14, 23, 27, 29] reported varying degrees of adverse reactions to glucocorticoid in both groups, but none affected treatment. Seven studies [7, 12, 13, 15, 26, 30, 31] did not provide specific data on the incidence of adverse reactions in the treatment and control groups. Therefore, studies [14, 23] with clearly reported adverse reactions and valid and differing data were analyzed. Heterogeneity test results: p = 0.53, I² = 0%, suggesting no heterogeneity. Meta-analysis using a fixed-effects model showed that shengxuexiaoban Capsules combined with glucocorticoid therapy for ITP had fewer adverse effects than...
glucocorticoid therapy alone. The difference between the two groups was statistically significant (95% CI [0.11, 0.50], P = 0.0002) (Fig 7).

### 3.5 Publication bias

Meta-analysis was performed on the above outcome indicators to evaluate the publication bias. For example, the funnel plot that represented recurrence rates was basically symmetrical (Fig 8), and Egger’s test also showed that no publication bias existed (p > 0.681), suggesting that the results were reliable.

### 3.6 Evidence quality evaluation

We used the GRADE pro system to evaluate the quality of evidence for the primary outcomes: recurrence rate and effective rate. The RCT was pre-set to the highest level of evidence in the GRADE evidence quality assessment and was processed according to five degradation factors. The results suggested that the quality of the evidence in recurrence rate and effective rate were intermediate (see S3 Table in S1 File). The analysis of the included studies revealed that the main reasons for this result were poor study design and insufficient sample size.

### 4 Discussion

ITP is an autoimmune-mediated acquired disease in which immune dysfunction is the leading cause of thrombocytopenia. Humoral and cellular immunity disorders can lead to increased platelet destruction or decreased platelet production [32]. It belongs to the category of “purpura” in Chinese medicine, and blood heat is one of the primary pathogenesis of ITP [27]. Shengxuexiaoban Capsules can clear heat and detoxify the blood, cool the blood, and stop bleeding. Modern pharmacological studies have found that shengxuexiaoban capsules can significantly increase the number of platelets, significantly enhance platelet aggregation function,
and significantly shorten the clotting time [10]. The results of Li Linfeng’s study [33] showed that shengxuexiaoban capsules could achieve the effect of treating ITP by suppressing the body’s immune function and reducing platelet antibody production. He Muqing [8] found that shengxuexiaoban capsules can regulate Treg cells and increase the immunosuppressive properties of Treg cells to influence the development of ITP. In addition, the glucocorticoid is a medicine that helps Yang to generate heat in Chinese medicine. Patients who take glucocorticoid for a long time may show signs of Yin deficiency and fire [34], and the effectiveness of shengxuexiaoban capsules in clearing heat and detoxifying toxins can reduce such signs.

The META analysis results showed that in treating patients with ITP, shengxuexiaoban capsules combined with glucocorticoid therapy improved the efficiency and reduced the relapse rate compared with glucocorticoids therapy alone. It can also improve platelet count, shorten platelet recovery time, and have a low incidence of adverse events. The above indicates that shengxuexiaoban capsules have an excellent therapeutic effect on ITP patients. Thus, we concluded that the effect of shengxuexiaoban capsules combined with glucocorticoid therapy for ITP is better than that of glucocorticoid therapy alone. The results of this study are consistent with the findings of previous studies by Huami Ye [35]. The number of RCTs included in this study and the sample size was significant, and the results were more accurate compared to the study by Huami Ye [35]. This study further evaluated the quality of evidence based on GRADE criteria, which provided a reference for clinical decision-making. However, the quality of evidence for this conclusion is not high, and we do not rule out the inclusion of future large-sample, multicenter, high-quality clinical studies to further validate this conclusion.
Our study has some strengths and limitations. Firstly the quality of the included RCTs was not high. Only 6 out of 27 RCTs were grouped with prednisone by a random number table, which may affect the reliability of the conclusions. Therefore more high-quality clinical studies are needed to validate the effectiveness of glucocorticoid therapy combined with Shengxuexiaoban capsules in ITP. Secondly, all RCTs used glucocorticoid therapy combined with Shengxuexiaoban capsules. However, the dose and age of Shengxuexiaoban capsules and glucocorticoid were not uniform, which may also affect the accuracy of the conclusions. However, we included a more significant number of studies than before, increased data than before, and obtained more accurate results.

In conclusion, based on the current evidence, shengxuexiaoban capsules combined with glucocorticoid are effective in treating ITP without serious adverse effects. However, due to the low quality of the included literature and the generally low quality of the evidence, more and higher quality studies are needed to validate the results and better guide the clinical practice.

Supporting information
S1 Checklist. PRISMA 2020 checklist.
(DOCX)
S1 File. Search strategy, table—Risk of bias (quality) assessment table, GRADE (certainty) assessment table.
(DOCX)
S1 Table. Detailed data.
(XLSX)
S1 Fig. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
(DOCX)

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References
1. Lu Zhou, Yingjian Zeng. Progress in the Treatment of Primary Immune Thrombocytopenia Based on Qi and Blood [J]. Chinese Journal of Ethnomedicine and Ethnopharmacy. 2021, 30(11): 58–61.
2. Zhenjian Zhang, Donglian Pan, Wenjue Tang, et al. Clinical Efficacy of Different First-line Treatment Regimens for Primary Immune Thrombocytopenia in Children [J]. Chinese Journal of Clinical Rational Drug Use. 2021, 14(15): 115–117.
3. Xiaolin Zhang, Ming Hou. Progress in the Diagnosis and Treatment of Primary Immune Thrombocytopenia [J]. Journal of Clinical Internal Medicine. 2020, 37(01): 5–7.
4. Xuxu Pan, Ruowen Sun, Hong Wang. Progress of Pathogenesis and Treatment of Primary Immune Thrombocytopenia [J]. Practical Pharmacy and Clinical Remedies. 2020, 23(02): 181–185.
5. Haiming Li, Chunyan Wang, Runhui Zheng, et al. Clinical Observation on the Treatment of Primary Immune Thrombocytopenia with Shengxue-xiaoban Capsules and Glucocorticoid [J]. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine, 2016, 26(11): 51–52.
6. Xiaoyue Han, Yi Cheng, Fang Wang. Observation on the Effect of Shengxue-xiaoban Capsules in Treating Children’s Idiopathic Thrombocytopenic Purpura [J]. Central China Medical Journal. 2008(04): 273–274.
7. Yi Wang, Zhenghua Ji. Clinical Observation of Traditional Chinese Drug Treatment on Idiopathic Thrombocytopenic Purpura in Children [J]. Chinese Journal of Hemorheology. 2006, 16: 563–564.
8. Muqing He, Muqiu He, Wenjian Guo. Effect of Sheng Platelet Capsule on CD4^+CD25^+ Treg cells in immune thrombocytopenic purpura [J]. Chinese Journal of Traditional Chinese Medicine, 2015, 33 (2): 422–425.
9. Fang Yuan. Observations of Shengxue-xiaoban Capsules Combined with Conventional Therapy on Treatment of Idiopathic Thrombocytopenic Purpura [J]. Chinese Journal of Pharmacoepidemiology. 2015, 24(08): 457–459.
10. Hui Du. Clinical Observation of Shengxue-xiaoban Capsules Combined with Hormone in Treating Idiopathic Thrombocytopenic Purpura [J]. The Medical Forum. 2014, 18(07): 867–868.
11. Tianlian Hu. Clinical Observation of Hormone Combined with Shengxue-xiaoban Capsules in Treating Idiopathic Thrombocytopenic Purpura [J]. The Medical Forum, 2016, 20(29): 4067–4068.
12. Wei Wang. Curative Effect Observation on Opathic Thrombocytopenic Purpura Treated by Sheng Xuexiaoban Capsules Combined with Prednison [J]. Zhejiang Journal of Traditional Chinese Medicine. 2008(11): 641–642.
13. Lijie Liang, Xiaoying You. Sheng Platelet Capsule combined with hormone treatment of idiopathic thrombocytopenic purpura curative effect observation [J]. Medical Forum Journal, 2011, 32 (05) : 116–117.
14. Ling Xu. Clinical Observation of Maintenance Therapy by Shen Xue-xiao-ban Capsules Combined with Low-dose Prednisone in Chronic ITP Patients [J]. Chinese Journal of Trauma and Disability Medicine. 2014: 27–28.
15. Jiru Wang. Observation on the Therapeutic Effect of Shengxue-xiaoban Capsules Combined with Prednisone in the Treatment of Adult Chronic Idiopathic Thrombocytopenic Purpura [J]. Herald of Medicine. 2012, 31(04): 440–441.
16. Xiaowen Zhang. Observation on the Therapeutic Effect of Shengxue-xiaoban Capsules and Prednisone in the Treatment of Idiopathic Thrombocytopenic Purpura [J]. The Medical Forum, 2015, 19(30): 4218–4219.
17. Jianlan Chen. Study on the Effect of Shengxue-xiaoban Capsules Combined with Prednisone in the Treatment of Chronic Immune Thrombocytopenic Purpura [J]. Contemporary Medical Symposium. 2019, 17(20): 106–107.
18. Wenlei Li. Observation on the Effect of Shengxue-xiaoban Capsules on Idiopathic Thrombocytopenic Purpura [J]. Health Must-Read Magazine, 2018: 192.
19. Gangli Cai, Lvyuan He, Ying Zhu, et al. Clinical Observation of Ascending Platelets Capsule Combined with Prednisone in Treatment of Primary Immune Thrombocytopenia and Its Effect on Treg and Th17 Cells [J]. Chinese Archives of Traditional Chinese Medicine. 2019, 37(05): 1205–1207.
20. Bin Yu. Clinical Observation of the Clinical Effect of Shengxue-xiaoban Capsules Combined with Prednisone Acetate in the Treatment of Primary Immune Thrombocytopenia [J]. Chinese Remedies & Clinics. 2019, 19: 1319–1320.
21. Ming Jiang, Xiaotong Yang. Study on the effect of Shengban Capsule combined with prednisone in the treatment of chronic immune thrombocytopenic purpura [J]. Health Vision, 2021(23): 42.
22. Qi Xiang, Fangfang Yang, Shunqing Wang, et al. Effect of L Platelet Capsule Combined with Prednison on Treg Cells and Th17 Cells of Primary Immune Thrombocytopenia [J]. Chinese Journal of Thrombosis and Hemostasis. 2015: 360–363.
23. Wei Wang, Jiamin Wang, Haipeng Cui. Observation on the Treatment of 62 Patients with Chronic ITP by Shengxue-xiaoban Capsules Combined with Prednisone [J]. China Modern Doctor. 2009, 47(02): 75–79.
24. Shaoyuan Sun. Observation on the Efficacy of Shengxue-xiaoban Capsules Combined with Prednisone in the Treatment of 20 Patients with Idiopathic Thrombocytopenic Purpura [J]. Chinese Journal of Clinical Rational Drug Use. 2014, 7(26): 96–97.
25. Jiawei Chen, Bin Liao, Zhenping Huangfu. Observation of Therapeutic Effect of Shengxuexiaoban Capsules Combined with Glucocorticoid on Idiopathic Thrombocytopenic Purpura [J]. Journal of North Pharmacy. 2012, 9(10): 23–24.
26. Jixiang Yang. Clinical Observation on Treatment of Adult Primary Immune Thrombocytopenia with Shengxuexiaoban Capsules and Low-dose Hormone [J]. Shanxi Medical Journal. 2016, 45(14): 1683–1684.
27. Weidong Zhang. Clinical Observation on the Treatment of 32 Patients of Idiopathic Thrombocytopenic Purpura with Shengxuexiaoban Capsules and Hormone [J]. Medical Information. 2011, 24: 77, 79.
28. Jinqiu Liang, Wei Yin. Clinical Observation on the Treatment of 40 Patients of Idiopathic Thrombocytopenic Purpura with Shengxuexiaoban Capsules and Hormone [J]. China Medical Herald. 2007(19): 54–55.
29. Chunge Song, Jin Zhang, Jingyu Chen. Observation on the Efficacy of Sheng Xuexiaoban Capsules Combined with Prednisone on the Treatment of Idiopathic Thrombocytopenic Purpura [J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine. 2010, 16(10): 917–918.
30. Ling Liu, Ying Feng, Ying Pang, et al. Observation of the Efficacy of Sheng Xuexiaoban Capsules on the Treatment of Idiopathic Thrombocytopenic Purpura (ITP) [J]. Evaluation and Analysis of Drug-Use in Hospitals of China. 2004(04): 233–235.
31. Liangming Ma, Yanping Ma, Zhenhua Qiao, et al. Observation on curative effect of Sheng Platelet Capsule combined with prednisone in the treatment of idiopathic thrombocytopenic purpura [J]. Chinese Journal of Clinical Medicine, 2004, 5 (7) : 97–98.
32. Semple JW, Rebetz J, Maouia A, Kapur R. An update on the pathophysiology of immune thrombocytopenia. Curr Opin Hematol. 2020 Nov; 27(6):423–429. https://doi.org/10.1097/MOH.0000000000000612 PMID: 32868673
33. Linfeng Li, Chonghua Chen, Shengnan Li, et al. Study on the Material Basis and Mechanism of Shengxuexiaoban Capsules Based on Network Pharmacology [J]. Chinese Traditional Patent Medicine. 2020, 42(12): 3330–3335.
34. Chengpin Wen, Zhijun Xie. Guidelines for diagnosis and treatment of Chinese medicine evidence of different stages of hormone use [J]. Chinese Journal of Traditional Chinese Medicine. 2020. 35(09): 4536–4540.
35. Huami Ye, Jianping Hao, Fang Zhao, et al. Effectiveness of Shengxuexiaoban Capsules Combined with Hormone in Treating Idiopathic Thrombocytopenic Purpura: A Systematic Review [J]. Chinese Journal of Evidence-Based Medicine. 2013, 13(07): 852–857.