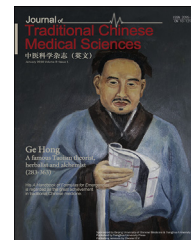


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# New mechanisms of the TCM spleen-based treatment of immune thrombocytopenia purpura from the perspective of blood neurotransmitters

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## KEYWORDS

Immune thrombocytopenic purpura;  
Vasoactive intestinal peptide;  
Beta endorphin;  
5-hydroxytryptamine

**Abstract Objective:** To explore new mechanisms of the traditional Chinese medicine (TCM) spleen-based treatment of immune thrombocytopenic purpura (ITP) from the perspective of blood neurotransmitters.

**Methods:** In this randomized controlled multi-center clinical study, 271 ITP patients who met the diagnostic criteria of "syndrome of spleen failing to manage blood" were randomized into three groups: group A administered *Jianpi Yiqi Shexue* (JYS) granules, 1 bag per treatment, bid; group C administered prednisone as a draught at an initial dose of 1.0–1.5 mg/kg/day at 8:00 am; and group B administered a combination of the interventions in groups A and C. Each treatment cycle lasted 21 days.

**Results:** After treatment, scores of platelet distribution width (PDW) were significantly decreased in groups B and C, and there were significant differences among the three groups ( $P = .0131$ ). Pairwise comparisons showed that PDW was significantly different between group A and group B ( $P = .005$ ) and between group A and group C ( $P = .041$ ) but not between group B and group C. Hemorrhage grading scores were significantly different between day 1 and day 7 in group A and group B ( $P < .001$ ) but not in group C. The hemorrhage grading scores on day 14 and day 21 were significantly different from that on day 1 in all three groups ( $P < .001$ ). Serum 5-hydroxytryptamine levels did not change significantly before and after treatment in the three groups ( $P > .05$ ). Serum  $\beta$ -endorphin and vasoactive intestinal peptide levels were significantly different between group A and group B (both  $P < .001$ ).

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**Conclusions:** The JYS prescription may regulate the expression levels of blood neurotransmitters via the brain-gut axis in patients with "spleen deficiency" ITP and thus activate hemostatic mechanisms to promote hemostasis.  $\beta$ -EP and VIP are key neurotransmitters of the JYS-induced functional regulation.

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Immune thrombocytopenic purpura (ITP) is a common autoimmune disease of the circulatory system. Clinically it mainly manifests as skin and mucosa bleeding, and it can also be associated with a risk of visceral bleeding in severe cases. However, clinical observations have showed that some ITP patients have thrombocytopenia without significant bleeding symptoms.<sup>1–3</sup> It is therefore speculated that peripheral thrombocytopenia is not the only cause of bleeding in ITP patients, and that an imbalance of active substances released from the brain-gut axis might also be involved. Based on the idea the brain-gut axis is involved in bleeding, we measured 5-hydroxytryptamine (5-HT),  $\beta$ -endorphin ( $\beta$ -EP), and vasoactive intestinal peptide (VIP) levels in ITP patients, with an attempt to explore new mechanisms of treatment of ITP with *Jianpi Yiqi Shexue* (JYS) prescription (TCM medicine for tonifying the spleen, benefiting qi, and controlling blood) from the perspective of blood neurotransmitters.

## Study design and patients

### Diagnostic criteria

#### Diagnostic criteria of ITP

The diagnosis of ITP was based on the diagnostic criteria for ITP described in the *Diagnostic Criteria and Response Evaluation Criteria of Blood Diseases* (3rd Edition)<sup>4</sup>: (1) reduced platelet count in multiple laboratory tests; (2) the spleen is not enlarged or only slightly enlarged; (3) bone marrow examination reveals normal or increased numbers of megakaryocytes, with the presence of megakaryocyte maturation disorders; (4) with at least one of the following five conditions: a) responsive to prednisone treatment; b) splenectomy is effective; c) increased platelet-associated IgG (PAIgG); d) increased platelet-associated C3 (PAC3); e) shortened platelet life span; or (5) secondary thrombocytopenia is excluded.

#### Diagnostic criteria of TCM syndrome

The TCM-based "syndrome of spleen failing to manage blood" was diagnosed according to the Guiding Principles for Clinical Research on the Treatment of Spleen Deficiency Syndromes by Using Novel TCM Drugs and the Guiding Principles for the Clinical Research on the Treatment of Qi Deficiency Syndromes by Using Novel TCM Drugs in the Guiding Principles for the Clinical Research on Novel TCM Drugs<sup>5</sup> and based on the following clinical manifestations:

(1) primary symptoms: chronic bleeding (recurrent subcutaneous petechiae or ecchymoses that are light in color; menorrhagia or menostaxis), along with fatigue and lack of spirit; (2) secondary symptoms: loss of appetite or abdominal distention after meals; and (3) tongue and pulse: the tongue body is fat and pale-colored, with tooth-marks on its edge; the pulse is thin and weak. A syndrome of spleen failing to manage blood can be diagnosed with the presence of two main symptoms (item 1 is required) and one secondary symptom in addition to tongue and pulse examination findings.

### Enrollment criteria

#### Inclusion criteria

Patients meeting all of the following three criteria were included in this study: (1) meeting the diagnostic criteria for ITP; (2) meeting the TCM diagnostic criteria for the syndrome of spleen failing to manage blood; or (3) voluntarily attended the trial and signed the informed consent.

#### Exclusion criteria

Patients with any of the following conditions were excluded: (1) accompanied with severe heart, brain, liver, and/or kidney diseases; (2) with mental disease; (3) pregnant or lactating women; (4) with severe complications of diabetes and hypertension; or (5) allergic to the tested drug (or any TCM ingredient in the formula).

#### Criteria for dropout cases

The criteria included: (1) poor treatment compliance (medication compliance was <80% or >120%) or use of any TCM drug or modern drug forbidden in the study protocol; (2) natural dropout during the observation; or (3) severe adverse events and complications that made the clinical trial unfeasible for the patients.

## Methods

### Determination of the study size

Based on previous findings, the overall sample size was determined as 240 cases. The subjects were divided into groups A (treated with JYS prescription,  $n = 90$ ), group B (treated with JYS + prednisone,  $n = 90$ ), and group C (treated with prednisone,  $n = 90$ ). Considering the low follow-up duration and a potential dropout rate of 10%, 273

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