



## **Thrombocytopenia in liver cirrhosis: efficacy of eltrombopag and partial splenic artery embolization in determining optimal treatment indications**

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### **Abstract**

**Relevance.** *Thrombocytopenia is a frequent complication of liver cirrhosis that significantly increases the risk of hemorrhagic complications and limits the possibilities of invasive diagnostic and therapeutic procedures. Currently, two fundamentally different approaches are used to correct this condition: pharmacological therapy with thrombopoietin receptor agonists and invasive methods such as*

*partial splenic artery embolization (PSAE). This study presents a comparative analysis of the efficacy and safety of these methods in patients with liver cirrhosis and severe thrombocytopenia.*

**Objective.** *A comparison of the efficacy and safety, and optimal indications for eltrombopag versus partial splenic artery embolization in the management of thrombocytopenia in patients with liver cirrhosis and hepatic failure.*

**Material and methods.** *A single-center prospective study was conducted at Moscow Multidisciplinary Scientific and Clinical Center n.a. S.P. Botkin involving 59 patients with liver cirrhosis and thrombocytopenia ( $<50 \times 10^9/L$ ). Non-inclusion criteria included oncological diseases, severe renal failure (GFR  $<45$  mL/min), and active infectious processes. Patients were divided into two groups: Group 1 (n=28) received eltrombopag therapy at a dose of 50 mg/day for 14 days; Group 2 (n=31) underwent PSAE. Efficacy was assessed by platelet count dynamics, compensation duration, and complication rates. The literature search was conducted in the following databases: PubMed/MedLine, ResearchGate, and the Russian Scientific Electronic Library (eLIBRARY.RU), covering publications from 2010 to 2024.*

**Results.** *Eltrombopag therapy achieved target platelet levels ( $>50 \times 10^9/L$ ) in 78.6% of patients, but the effect lasted only 6 weeks on average. In the PSAE group, platelet count normalization was observed in 100% of patients 1 month after the procedure, with subsequent increase to  $110 \pm 17.37 \times 10^9/L$  by week 12. The median compensation duration in this group was  $50.35 \pm 9.12$  weeks. Complications after PSAE were recorded in 41.9% of patients, though mortality remained low (3.2%).*

**Conclusions.** *The study results demonstrate that PSAE provides a more sustained thrombocytopenia correction compared to the drug therapy and may be considered the method of choice for patients with hypersplenism.*

*Eltrombopag remains preferable for short-term preparation for planned invasive procedures. While PSAE complications require careful patient selection, they do not outweigh the method's long-term benefits.*

**Keywords:** thrombocytopenia, liver cirrhosis, eltrombopag, splenic artery embolization, hypersplenism

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MGDF, Megakaryocyte Growth and Development Factor

PSAE, partial splenic artery embolization

TIPS, Transjugular intrahepatic portosystemic shunt

TPO, thrombopoietin

## **Introduction**

Thrombocytopenia is a common pathological condition that significantly limits the possibility of invasive manipulations and is determined as any decrease in the platelet count below the minimum normal level ( $<150\ 000/\mu\text{L}$ , with subdetermined figures of 50–100 000/ $\mu\text{L}$  classified as moderate and  $<50\ 000/\mu\text{L}$  classified as severe) [1]. Severe cytopenia is detected in one third of patients undergoing examination for liver transplantation [2]. Clinical manifestations of thrombocytopenia in 56% of cases are cutaneous hemorrhagic syndrome [1]; in 44% of cases, thrombocytopenia may be asymptomatic, but is accompanied by risks of hemorrhagic complications. Most researchers have indicated that a decrease in platelet levels below 60 000–75 000 / $\mu\text{L}$

correlates with the development of bleeding in patients who have undergone invasive interventions, whereas with moderate thrombocytopenia 75 000–150 000 / $\mu$ L no such relationship was found [3].

In a healthy adult, average of  $10^{11}$  platelets are produced daily, proportional to the consumption [4]. The cells remain in the bloodstream for 8–10 days and are then eliminated by monocytes and macrophages of the reticuloendothelial system [5]. The development of thrombocytopenia in liver cirrhosis is due to four main pathogenetic mechanisms: a decreased platelet production, increased destruction/consumption of platelets, hemodilution, and increased sequestration of platelets by the spleen [1, 5, 6]. The liver plays a minor role in platelet removal: Ashwell-Morell receptors recognize changes in the glycan structure on the platelet surface and remove desialylated platelets [6]. However, the main role in platelet elimination belongs to the spleen, which at any given time contains a third of the total platelet mass [5]. Congestive splenomegaly associated with portal hypertension may lead to thrombocytopenia, anemia and/or leukopenia (either alone or in combination) [8, 9].

A significant role in the development of thrombocytopenia is played by a decrease in the synthesis of thrombopoietin (TPO, Megakaryocyte Growth and Development Factor (MGDF)), which is a glycoprotein hormone produced primarily by the liver and kidneys. TPO has an affinity for megakaryocytes, the precursor cells of platelets in the bone marrow [10], and, by binding to the c-Mpl receptors of megakaryocytes, it induces phosphorylation of this receptor and stimulates multiple signal transduction pathways responsible for thrombopoiesis [11]. Thus, the main pathogenetic approaches to the correction of thrombocytopenia are currently aimed at reducing the size of the spleen and activating the synthesis of thrombopoietin.

Thrombopoietin receptor agonists are currently used in chronic liver diseases. [12]. This group of drugs, including eltrombopag, romiplostim, avatrombopag, and lusutrombopag, increases platelet production by interacting with the thrombopoietin receptor. The use of TPO agonists to treat thrombocytopenia before invasive procedures in patients with liver cirrhosis has proven effective [13]. Current guidelines suggest administering thrombopoietin agonists for 10–14 days before and 5–8 days after the intervention, with the expected effect of increasing platelet levels for 30–36 days [3]. Long-term use of eltrombopag is limited by its high cost.

Splenic embolization is a minimally invasive alternative to splenectomy in the treatment of hypersplenism, it has fewer complications, and the immune system is not significantly altered due to the preservation of splenic tissue [14]. With embolization of >50% of the spleen, a statistically significant regression of thrombocytopenia and leukopenia is observed with good medium-term and long-term results [15]. In case the partial splenic artery embolization (PSAE) is ineffective, is possible to perform embolization repeatedly and even several times [6, 16–18].

At the same time, it is reported that the PSAE implementation can be accompanied by such positive effects as an increase in the levels of albumin, total cholesterol and an increase in liver volume in patients with liver cirrhosis of various etiologies [19], which is probably associated with an increased the blood flow via the hepatic and superior mesenteric arteries due to the redistribution of blood flow from the celiac trunk after embolization of the splenic artery [20]. A significant limitation of the use of splenic artery embolization may be the risk of complications such as post-embolization syndrome, splenic abscess and rupture, gastrointestinal bleeding, but their incidence is not high [21]. The most common complication is post-embolization syndrome, which usually resolves

completely within 1-2 days with conservative treatment [19]. Postoperative abdominal pain usually correlates with the volume of splenic infarction and also resolves within 1-4 days with therapy with non-steroidal anti-inflammatory drugs [21].

Thus, it is advisable to conduct a comparative study to determine the indications for the use of various methods of thrombocytopenia correction.

**The aim of the study was** to compare the efficacy and safety and determine the optimal indications for the use of eltrombopag or partial splenic artery embolization to treat thrombocytopenia in patients with liver cirrhosis and liver failure.

### **Material and methods**

To compare the effectiveness of various methods to treat thrombocytopenia in patients with liver cirrhosis, we conducted a single-center study that included 59 patients admitted to the Moscow Multidisciplinary Scientific and Clinical Center n.a. S.P. Botkin from 2020 to 2023, the study conduct having been approved at the Meeting of the Ethics Committee of the Moscow Multidisciplinary Scientific and Clinical Center n.a. S.P. Botkin No. 1 of January 27, 2025. The inclusion criteria for the study were the presence of liver cirrhosis, splenomegaly (spleen area more than 60 cm<sup>2</sup>) with signs of hypersplenism, thrombocytopenia below 50x10<sup>9</sup>/L with hemorrhagic syndrome and(or) a critical decrease in the platelet level below 20x10<sup>9</sup>/L. Exclusion criteria were cancer, glomerular filtration rate below 45 mL/min, portal vein thrombosis without signs of recanalization, an active infectious disease, sepsis, West Haven stage 4 hepatic encephalopathy (coma), uncorrectable coagulopathy, disseminated intravascular coagulation syndrome, intolerance to iodinated contrast agents, patient refusal to participate in

the clinical trial, unavailability to follow-up, and decompensation of systemic pathology. Patients were assigned to groups completely at random, using a simple randomization method.

Group 1 received eltrombopag therapy, while group 2 received PSAE. The study included 59 patients, 32 men and 27 women of a mean age of  $48.35 \pm 10.47$  years. The severity of liver failure was assessed as moderate with a mean MELD-Na score of  $12.32 \pm 3.46$ , Child-Pugh-Turcotte score of  $10.1 \pm 1.991$ . The mean platelet level made  $27.9 \pm 6.25 \times 10^9/L$ , manifestations of hemorrhagic syndrome were identified in 48 patients (81.3%). The characteristics of the patients are presented in Table 1.

**Table. Characteristics of patients included in the study**

Characteristics of groups	Group 1	Group 2
Number of patients, n	28	31
Gender, m/f, n	15/13	17/14
MELD-Na, score	$11.45 \pm 2.22$	$12.45 \pm 3.46$
Child–Pugh–Turcotte, score	$9.6 \pm 1.72$	$10.3 \pm 1.99$
Platelet level, $n \times 10^9/L$	$27.9 \pm 2.2$	$27.9 \pm 3.45$
Intraportal administration of mononuclear cells	–	1
Simultaneous transjugular intrahepatic portosystemic shunt (TIPS), n	–	5
Duration of the compensation period after in-hospital treatment according to MELD-Na and bleeding recurrence, $M \pm SD$ , weeks	$6 \pm 1.2$	$50.35 \pm 9.1$
Mortality in the group within 1 year, n (%)	0	1 (3.22%)

All patients included in the prospective study, as well as those in the comparison group, received treatment according to clinical guidelines published at the Clinical Guidelines Index Website (<https://cr.minzdrav.gov.ru/>, link active as of July 28, 2025). The conservative therapy during the inpatient phase included infusion-corrective, transfusion, antibacterial, antisecretory, and symptomatic

therapy. Symptomatic therapy, including platelet concentrate transfusion, was administered at all stages of follow-up, if indicated. However, in the cases of persistent thrombocytopenia, this did not affect the prognosis.

Evaluation of efficacy and safety was performed based on the dynamics of platelet levels, the compensation length, and the incidence of complications (after 2, 4, 12, 24, 48, 52 weeks).

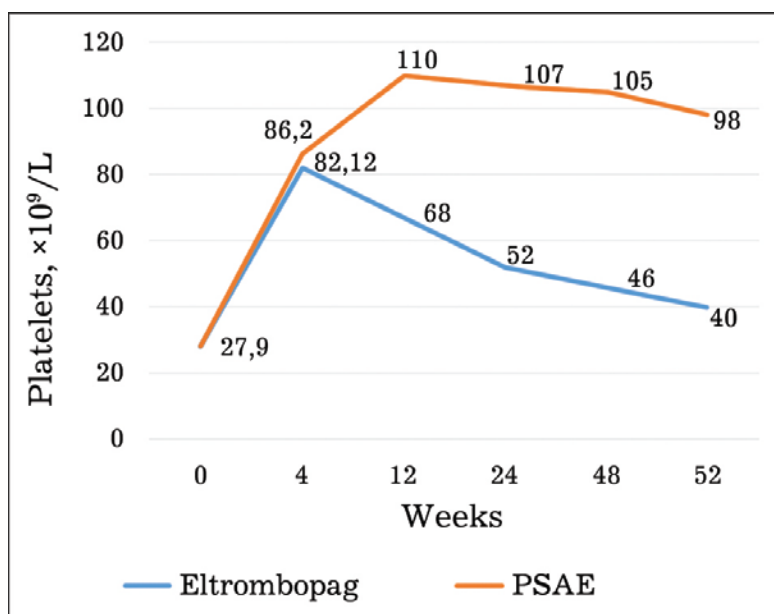
Statistical analysis was performed using SPSS Statistics 26 software (IBM, USA). To compare groups, the quantitative data were tested for normal distribution, and depending on the result, either the Mann–Whitney test or the Student's t-test was used; nonparametric statistical methods (Pearson's method) were used to compare small groups. Relapse-free survival analysis was performed using the Kaplan–Meier method with the Breslow and Tarron–Ware tests.

## **Results**

Twenty eight patients were treated with eltrombopag olamine, crushed, 50 mg per day for 14 days (group 1). The clinical effect of the drug administration was achieved in 22 patients (78.57%), the mean platelet level in the group was  $82 \pm 11.8 \times 10^9/L$ , the compensation period (platelet level over  $50 \times 10^9/L$ ) averaged 6 weeks, no mortality or complications associated with drug administration were seen.

In 31 patients (52.3%), group 2, PSAE was performed; in 5 (16.1%) cases, the embolization of the splenic arteries was performed simultaneously with transjugular intrahepatic portosystemic shunt (TIPS); in 1 case (3.22%), TIPS and the intraportal administration of autologous bone marrow mononuclear cells were used. One month after the intervention, an increase in the platelet level of more than  $50 \times 10^9/L$  was detected in 100% of patients; subsequently an increase in the platelet

level to  $110 \pm 17.37 \times 10^9/L$  was noted over 12 weeks, the compensation period (platelet level over  $50 \times 10^9/L$ ) averaged  $50.35 \pm 9.12$  weeks (Fig. 1).



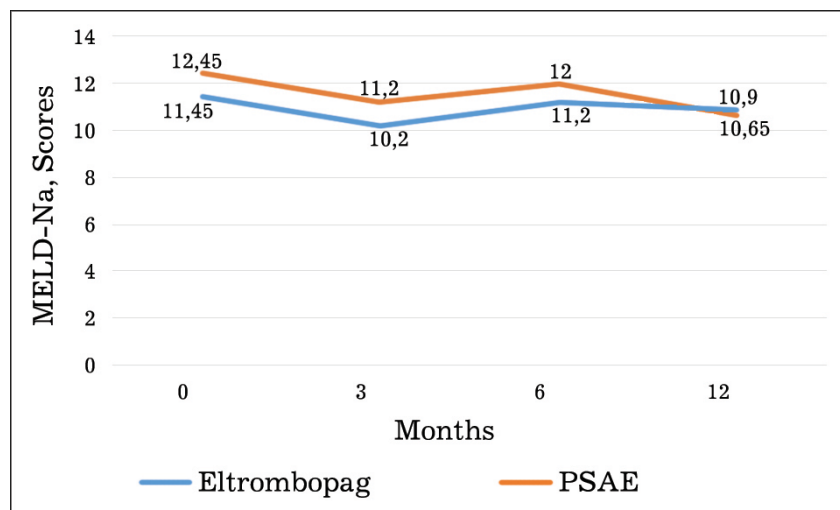
**Fig. 1. Dynamics of platelet level during 52 weeks of follow-up in patients after after eltrombopag administration and partial splenic artery embolization**

The PSAE effectiveness in patients with liver cirrhosis and thrombocytopenia due to splenomegaly, associated with portal hypertension, is undeniable. However, when determining indications for this procedure, it is advisable to consider the risk of complications.

Immediate complications of PSAE were identified in 13 patients (41.9%). In 11 patients (35.5% of all PSAE cases), a severe abdominal pain syndrome developed, requiring an increase in hospitalization to 10 days. In 2 cases (6.45%), cystic changes in the spleen developed 24 weeks after the intervention, in one case with signs of infection. In this case, drainage of the fluid formation was performed. In 1 patient (3.22%), after infected ascites, portal vein thrombosis was diagnosed according to abdominal CT scan data, without decompensation of liver failure. In all

cases of simultaneous PSAE, worsening hepatic encephalopathy was noted in 5 cases (16.21% of all PSAE cases), which completely resolved with conservative therapy.

Simultaneously performed TIPS, the intraportal administration of autologous bone marrow cells, and the splenic artery embolization were not associated with worsening of the clinical condition. In the case of simultaneous administration of autologous bone marrow cells, a significant positive change in MELD-Na was observed (the score decrease from 14 to 9–10 with a persistent effect over 8 months of follow-up), which, however, did not affect the statistical parameters of the group. Despite the previously described positive effect of PSAE on the liver function due to the redistribution of hepatic blood flow, this study did not reveal statistically significant changes in MELD- Na over 1 year of follow-up (Fig. 2).



**Fig. 2. Dynamics of the MELD-Na level in patients with thrombocytopenia after eltrombopag therapy and partial splenic artery embolization**

Mortality among patients who underwent PSAE was 3.22% (1 patient) and was associated with increasing hepatocellular failure with the progression of liver cirrhosis.

When comparing methods for correcting thrombocytopenia in patients with hypersplenism, we found that the use of TPO agonists was not associated with a risk of complications, but with the recommended period of its use for 14 days until the clinical effect had been achieved, it did not lead to a persistent increase in platelet levels. Therefore, it is advisable to consider its use in preparation for planned single invasive interventions.

### **Discussion**

Thrombocytopenia is a common complication in patients with liver cirrhosis, significantly limiting the possibility of invasive interventions and increasing the risk of hemorrhagic complications [2, 7]. This study compared two methods to treat thrombocytopenia: the use of TPO receptor agonists (eltrombopag) and PSAE. Both methods have demonstrated efficacy [1, 10–12], but the choice of their use should be differentiated depending on the clinical situation.

Eltrombopag therapy demonstrated a good short-term effect, achieving target platelet levels ( $>50 \times 10^9/L$ ) in 78.57% of patients, which is consistent with data from other studies confirming the efficacy of TPO agonists in preparation for elective interventions [7, 10–12]. However, the compensation period was limited (6 weeks on average), making this method less suitable for patients requiring a long-term correction of thrombocytopenia. Furthermore, a high cost of the drug and the need for long-term administration may limit its widespread use in clinical practice.

In contrast to drug therapy, PSAE provided a more lasting effect, with an increase in platelet levels to  $110 \pm 17.37 \times 10^9/L$  and a mean

compensation length of  $50.35 \pm 9.12$  weeks. This method is particularly relevant for patients with severe splenomegaly and portal hypertension, since it poses an effect on one of the key pathogenetic mechanisms of thrombocytopenia, i.e. the platelet sequestration in the spleen [14]. However, the use of PSAE is associated with a risk of complications, the infected ascites being the most common (11 people (35.5%)), which is probably related to the initial severity of liver failure in the patients included in the study. Nevertheless, despite the development of complications, mortality in the PSAE group remained low (3.22%), and the long-term effect in the form of a long-lasting increase in platelet levels makes this method preferable in patients with critical thrombocytopenia.

Our study did not confirm the previously described positive effect of PSAE on liver function tests (MELD-Na) [7, 18, 20], which may be explained by the limited sample size and the initial severity of cirrhosis in the patients included in the study. Nevertheless, the method remains promising, given its effect not only on platelet levels but also on the potential improvement of portal hemodynamics [18].

Therefore, the choice of the methods to treat thrombocytopenia should be based on the individual patient's characteristics. TPO agonists are appropriate for use in preparation for elective interventions, while PSAE may be considered the method of choice in patients with severe thrombocytopenia requiring long-term correction, despite the potential risk of complications. Further studies with larger sample sizes and longer follow-up periods will help clarify the optimal indications for each method.

## **Conclusion**

The partial splenic artery embolization is the treatment of choice in the patients with critically low platelet counts and results in long-lasting

platelet count increase for up to a year. Even with the risk of complications, which developed in 13 patients (41.9%) after the partial embolization of the splenic arteries, there was no statistically increase in mortality or decrease in the compensation length.

**Based on the study results we may conclude the following:**

1. The use of thrombopoietin agonists ensured the target platelet level ( $>50 \times 10^9/L$ ) achieved in 78.57% of patients. However, the mean compensation length was only 6 weeks, which makes this method less effective for a long-term correction of thrombocytopenia in patients with liver cirrhosis and liver failure.

2. Partial splenic artery embolization ensured the achievement of normal platelet levels in 100% of patients after just 1 month, with its further growth to  $110 \pm 17.37 \times 10^9/L$  by the 12<sup>th</sup> week. The mean compensation length was  $50.35 \pm 9.12$  weeks. Complications were observed in 41.9% of patients, but the mortality rate was only 3.22%, which did not indicate a significant increase in the patient mortality risk.

3. Thrombopoietin receptor agonists are indicated primarily for short-term preparation for planned invasive interventions, while partial splenic artery embolization should be considered as a method of sustained correction of thrombocytopenia, especially in patients with hypersplenism and severe portal hypertension.

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