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Chapter 6

Thrombocytopenia in Liver Transplant

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Abstract

Thrombocytopenia is a common complication of both chronic liver disease and liver transplantation (LT). The mechanism of thrombocytopenia is multifactorial implicating not only sequestration in the spleen, or in the graft, reduction in the mean platelet survival but also decreased platelet production due to low synthesis of thrombopoietin (TPO) or direct toxicity to the bone marrow. Platelets play a dualistic role in liver transplant, both beneficial and detrimental. The beneficial role of platelets is due to platelet-derived serotonin that is involved in liver regeneration. During surgery for liver transplant, in addition to the preoperative causes for thrombocytopenia, we have other mechanisms that will contribute to further deterioration of the platelets count and function: hemodilution, immunological reactions, and sequestration in the newly transplanted graft. This might result in a life-threatening level of thrombocytes. The concern is when we should treat thrombocytopenia because despite life-saving benefits, transfusion has also been related to complications and platelet transfusion has been identified as an independent risk factor for postoperative complications. Risks related to platelet concentrate administration are allergic reactions, alloimmunization, bacterial sepsis, and transfusion-related acute lung injury (TRALI). Administration of platelets is not indicated if there is no bleeding or immediate bleeding risk. New emerging therapies like thrombopoietin-receptor agonist will furthermore limit the administration of blood products.

Keywords: thrombocytopenia, liver transplant, thrombopoietin, splenectomy, cirrhosis

1. Introduction

Thrombocytopenia is a common complication of both chronic liver disease and liver transplantation (LT) contributing to the complex hemostasis disturbances of those patients. Liver disease induces a complicated imbalance between pro- and antihemostatic elements, thrombocytopenia just being one of them. The mechanism of thrombocytopenia is multifactorial

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implicating not only sequestration in the spleen, reduction in the mean platelet survival but also decreased platelet production due to low synthesis of thrombopoietin (TPO) [1].

In chronic liver disease, a low platelet count is a marker of severity and is associated with poorer prognosis [2].

Liver transplantation (LT), the main treatment of end-stage liver disease, can also induce decrease of thrombocytes starting intraoperative with the reperfusion syndrome and going on after the procedure due to several mechanisms among which sequestration in the graft plays an important role [1]. Platelets have a dualistic role in LT, both beneficial and detrimental [3].

Thrombocytopenia is defined by platelet count <150,000/mm^3; it is mild if platelets are between 75,000 and 150,000/mm^3, moderate for values between 50,000 and 75,000/mm^3, and severe if the count is <50,000/mm^3. Definitions may vary and the limits of platelet count might be different in different studies [4].

The incidence of decreased platelets in chronic liver disease is as high as 76% but moderate in only 13% and severe in 1% of cirrhotic patients [5]. The degree of thrombocytopenia is dependent on the stage of cirrhosis. However, spontaneous bleeding does not occur unless the values reaches 10,000–20,000/mm^3. There is a difference if an invasive procedure such as liver biopsy, variceal ligation, paracentesis, or major surgery is intended; platelet threshold levels are higher and differ depending on the invasiveness of the maneuver. However, bleeding is not the only concern with thrombocytopenia as platelets have other roles in inflammation, angiogenesis, antimicrobial defense and, of specific importance, in ischemia/reperfusion injury and a beneficial role in liver regeneration [6].

2. Causes/mechanisms for thrombocytopenia in liver transplant

2.1. Thrombocytopenia and platelet dysfunction in liver disease

Platelet count, as well as their function, is altered in patients with cirrhosis in the waiting list for transplantation. The pathogenesis of this phenomenon is not well understood. There are several mechanisms implicated in this process: on one hand, depletion of platelets due to destruction and on the other, an altered production. The main cause seems to be platelet sequestration in the enlarged, congestive spleen due to portal hypertension.

Apart from **hypersplenism,** other causes are reduced production of platelets, low TPO levels, existence of antiplatelet antibodies, alcohol toxicity, folate deficiency, chronic low-grade disseminated intravascular coagulation, and direct viral suppression of platelet production as provided in **Table 1** [7, 8].

There is a strong correlation between spleen volume and thrombocytopenia, thus measures that aim to diminish hypersplenism will probably have a good impact on platelet count. Splenectomy prior to transplantation has been proposed as a therapeutic option to increase platelet count but this approach remains controversial because splenic pooling is not so significant as it was first described and the removal of the spleen does not always lead to

Mechanisms	
Altered production	Low TPO levels
	Bone marrow suppression (HCV, alcohol)
	Medication
Sequestration	Congestive spleen due to portal hypertension
Enhanced destruction/loss	Platelet antibodies
	Chronic low-grade disseminated intravascular coagulation
	Bleeding

Table 1. Causes for thrombocytopenia in chronic liver disease.

substantial and persistent increase in thrombocytes. On the other hand, elimination of the spleen increases the risk of septic complications and portal thrombosis [4].

Shunt procedures done either surgically or percutaneously [transjugular intrahepatic portosystemic shunt (TIPS)] are intended at decreasing portal hypertension and hypersplenism might also have a beneficial effect on platelet count. Massoud, following 92 patients that had a TIPS placement, reported a significant increase in platelet number after the procedure, this increase being more important in patients with more severe thrombocytopenia. But TIPS would not have any effect on TPO, this being a possible reason why in some cases there was no effect on platelet number [7].

Cirrhotic patients waiting for transplantation are sometimes in need for invasive procedures like liver biopsies, endoscopic variceal ligation, paracentesis, and transjugular intrahepatic portosystemic shunt. There is no absolute threshold of platelet count for performing any of those procedures but if platelets are <75,000/mm^3, the risk of bleeding seems to be higher [4].

Thrombocytopenia was also a concern in patients with hepatitis C virus (HCV), who needed antiviral therapy with interferon and had to reduce doses or even stop treatment. Nowadays with the new antiviral therapies, this should not be a problem anymore.

TPO is a thrombopoietic hormone produced in the liver by both parenchymal cells and sinusoidal endothelial cells at a constant rate. The blood level of TPO is dependent on the uptake by platelets and megakaryocytes, where it is destroyed so if platelet count decreases, less TPO will be uptake and destroyed and its level will rise. Production of TPO is dependent on liver cell integrity; if that is impaired, production will decrease as in cirrhosis. This explains why with a reduction in platelet number TPO level in liver disease would not be elevated, as production is lower. TPO level is inappropriate to platelet level and as a consequence the bone marrow stimulation to produce thrombocytes would not be adequate [2, 4].

Antiplatelet antibodies contribute to the premature destruction of the thrombocytes. It was shown among patients with liver disease that up to 64% irrespective of the etiology have platelet-associated anti-glycoprotein (anti-GP) antibodies that are directed against the GP IIb-IX complex. The serum of those patients also has higher levels of platelet-associated immunoglobulin G also implicated in the immune-mediated destruction of platelets [2].

Decreased platelet production by the bone marrow is also one of the mechanisms implicated in thrombocytopenia of chronic liver disease. HCV directly inhibits the growth and differentiation of bone marrow stem cells and alcohol leads to ineffective megakaryopoiesis. Production of platelets is also inhibited by some of the medication those patients might need, for example, interferon [2].

Bleeding is not as frequent in cirrhotic patients as one can imagine and that can be explained by some compensatory mechanisms. Part of the complex problem of platelet function in cirrhosis is the demonstrated capacity of platelets to sustain thrombin generation at an equal level with control if adjusted to normal levels. This concludes that their function might not be as altered as primary thought [9]. And there are compensatory mechanisms to bleeding disorders of the cirrhotic patient, one of them being the elevated level of von Willebrand factor reaching 10-fold the plasma level of control and supporting platelet adhesion better than in healthy volunteers [3, 10].

2.2. Intraoperative challenges

Liver transplantation is a huge challenge with any anesthesiologist for two main problems such as hemodynamic changes during surgery and coagulation status of the patient. Surgery consists of three phases: removal of the cirrhotic liver during which, due to portal hypertension, there is a high bleeding risk aggravated by the patients' coagulopathy; the anhepatic phase with hemodynamic disturbances; and the neohepatic phase that starts with the reperfusion of the graft inducing hypotension, cardiac rhythm disturbances, and impacts on coagulation.

During surgery, in addition to the preoperative causes for thrombocytopenia, we have other mechanisms that will contribute to further deterioration of the platelets count and function such as bleeding, hemodilution, immunological reactions, and sequestration in the newly transplanted graft [3].

Several authors present the hypothesis that removal of the spleen during LT procedure will ameliorate platelet count. Ohira et al. [11] reported an analysis of the relationship between preoperative spleen volume and thrombocytopenia and suggested that splenectomy might be considered simultaneously with LT in chronic hepatitis C virus (HCV) patients with a preoperative platelet count of <60,000/mm^3. The intent is to facilitate an interferon therapy immediately after LT. Almost all recipients will have a reinfection of the graft with HCV; they need antiviral therapy during the postoperative period but this might be impossible to apply due to thrombocytopenia. However, there are risks related to splenectomy; patients are prone to develop portal vein thrombosis and have a higher risk for infection and sepsis.

Morimoto et al. [12] analyzed their results for 36 patients undergoing LT and reported similar conclusions. Their criteria for performing splenectomy were a platelet count <50,000/mm^3 and a spleen volume reported to the body surface area of >400 ml/m^2 and so it was done in six patients, all of them completing their interferon therapy after LT. They registered only one systemic infection possibly related to splenectomy.

In the publication by Chu et al. addressing 40 patients selected for splenectomy during LT because they had HCV infection associated with hypersplenism or they were expected to develop small-for-size syndrome or they had huge spleens that affected surgical maneuvers during transplant. In this selected group of patients, the authors indicated that simultaneous splenectomy did not increase the rate of perioperative complications or risk of mortality [13].

All the authors do not have the same opinion. In a recently published study recording 169 patients who underwent living-related LT with splenectomy [14], the authors found that concomitant splenectomy with LT surgery did not increase platelet count in the early postoperative period but they had more reinterventions due to hemorrhage, the operative time was longer, intraoperative blood loss was higher, and the incidence of lethal infectious disease was higher when compared to patients not having splenectomy during living donor LT.

Reperfusion of the graft is one of the most delicate moments during transplant surgery resulting not only in hemodynamic changes but also in alterations of the circulating platelets. Decreased aggregation of thrombocytes has been observed after reperfusion of the liver with a peak value within 1 hour and postoperative reduction in platelet surface markers glycoprotein (GP) IIb/IIa and P selectin [15]. Secondary to ischemia/reperfusion, platelets will suffer in number and function. They undergo a decrease by 30–55% due to entrapment in the graft. Platelets will adhere to the sinusoidal endothelium that has been activated during the cold and warm ischemia and will induce direct injury to the liver cell [3].

There is also a rare condition that might lead to severe thrombocytopenia after transplantation such as de novo development of idiopathic thrombocytopenic purpura [3].

2.3. Postoperative outcome

After transplantation, thrombocytopenia occurs during the first days and is a common disorder. The lowest values are observed on days 3–5 and if no complication happens, the resolution of the process will start after the first week. The main mechanism implicated in this thrombocytopenia is the sequestration of the platelets in the graft (**Table 2**). However, the lowest the platelets count in this period, the most severe and complicated the course of the posttransplant period [16].

Mechanisms	
Altered production	Bone marrow suppression (medication)
Sequestration	Liver graft
Enhanced destruction/loss	Bleeding
	Infectious complications
	Platelet antibodies
	Heparin-induced

Table 2. Causes for thrombocytopenia post liver transplant.

Lesurtel et al. proposed a new criterion in evaluating the extent and impact of thrombocytopenia they called the 60-5 criterion. In their study, they demonstrated a strong correlation between a platelet count of <60,000/mm^3 on postoperative day 5 and the incidence of severe complications and a twofold increase in mortality at 90 days [17].

A rare cause of low platelet count in this stage is heparin-induced thrombocytopenia, heparin therapy being the standard of care in many centers post LT. Bachmann et al. in a single center study looking at 205 LT found in 1.95% of patients, a suspicious clinical platelet course with elevated antibody levels [18].

Chang et al. looked at the role platelets have in antimicrobial host defense. They analyzed 50 LT recipients and looked at the impact of thrombocytopenia as a related variable to infectious complications in the posttransplant period. They found a significant correlation between low platelet count (<30,000/mm^3) and infections in the first month following transplantation. The correlation was very strong for fungal and bacterial infections but not for viral ones. Infection can determine thrombocytopenia but the authors stated that the lowest platelet count preceded the infection with a median time of 7 days [19].

Generally, platelet transfusion is not needed during the postoperative period and one can wait for the spontaneous resolution. Resolution starts after the first week due to increasing levels of thrombopoietin. It will reach normal values on time due to the regression of splenomegaly once portal hypertension has been resolved [20].

After liver transplantation, the blood level of TPO increases but it will take several days for the rise of platelet number to happen [21].

The **beneficial role** of platelets is due to platelet-derived serotonin that is involved in liver regeneration. This phenomenon is of great importance in living-related LT, small-for-size syndrome, and also plays a role in hepatic repair after ischemia/reperfusion injury. Serotonin accumulates in thrombocytes and is released in areas of tissue injury stimulating mitogenesis [3]. All the mechanisms promoting liver regeneration and involving platelets are not yet very well understood but they certainly play an important role through the release of various mediators like serotonin, hepatocyte growth factor, insulin growth factor, and vascular endothelial growth factor. The last one supports liver regeneration by stimulating neoangiogenesis [22].

3. Treating thrombocytopenia

Blood loss is a major concern during liver transplantation due to the precarious hemostatic condition of these patients combined to a surgical procedure at high risk for bleeding. Since the beginnings of LT, surgical techniques and anesthetic patient management have improved and the blood loss and transfusion needs have decreased. Despite life-saving benefits, transfusion has also related complications and platelet transfusion has been identified as an independent risk factor for postoperative complications. Risks related to platelet concentrate administration are allergic reactions, alloimmunization, bacterial sepsis, and transfusion-related acute lung injury (TRALI), and nowadays to a lesser extent viral transmission [23]. Therapeutic

rather than prophylactic administration of platelets concentrate is recommended with a possible threshold of 50,000/mm^3 during surgery associated with diffuse bleeding [24].

In a study analyzing possible complications related to platelet administration during LT, Pereboom [25] has shown that patients who received platelet concentrates had lower patient and graft survival than patients who had only blood loss or low level of thrombocytes but were not transfused with platelets. Their main complication was related to platelet transfusion and at the same time the specific cause of death was TRALI. TRALI is more frequently associated with plasma-rich blood products such as platelet concentrates and fresh frozen plasma and this might be related to the growth of inflammatory mediators in the stored platelets. It has been shown that cytokine levels are 1000-fold greater in stored platelets when compared to healthy volunteers and this might be related to the fact that platelets need to be kept at room temperature that also makes them prone to bacterial contamination. One could argue that transfusion needs are related to sicker patients but the author has shown that survival rates for those patients with severe blood loss and a low platelet count are similar to reference population if they were not transfused with platelet concentrates [25].

Despite the general consensus that platelet transfusions are related to worse outcome, there is a type of LT, the living-related LT where recipients might benefit from exogenous thrombocytes. Kim et al. on a series of 227 living-related LT conducted a study to define the effects of platelet transfusion on the liver regeneration and reached the conclusion that it has a beneficial effect [26].

The use of blood products and fibrinogen concentrate following a thrombelastometry-guided protocol (TEG/ROTEM) has led to a decrease in overall transfusion requirements, platelet concentrates as well, by offering a picture of the complete coagulation process with information on the dynamics of clot formation [27, 28].

Eltrombopag is an oral thrombopoietin-receptor agonist still looking for its place in the treatment of thrombocytopenia in chronic liver disease. It has got an indication for patients with chronic HCV infection for the initiation or maintenance of interferon therapy. Afdhal et al. published in the name of the ELEVATE study group a paper showing that eltrombopag reduced the need for platelet transfusion in liver disease patients undergoing invasive procedures [29].

4. Conclusion

In conclusion, thrombocytopenia is a common figure of chronic liver disease and liver transplant with multifactorial etiologies. Platelet count exclusively is not a good marker to anticipate risk for bleeding in cirrhotic patients because compensatory mechanisms increasing production of von Willebrand factor will interfere. Splenectomy is not indicated anymore as a therapeutic measure for regulating thrombocytopenia in the pretransplant period. It still may have some indications if done concomitantly with the transplant procedure especially in living-related LT or when small-for-size complication is anticipated.

Thrombocytopenia will be aggravated during the surgical procedure due to bleeding and entrapment in the graft secondary to reperfusion. The decrease in platelet number will continue in the initial postoperative phase but a spontaneous resolution will take place if no complication.

Administration of platelets is not indicated if there is no bleeding or immediate bleeding risk. New emerging therapies like thrombopoietin-receptor agonist will furthermore limit the administration of blood products.

Conflict of interest

No potential conflict of interest.

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