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Hereditary thrombocytopenia, perioperative management in cardiac surgery patients

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ABSTRACT
Hereditary thrombocytopenia (HT) poses a significant challenge in the perioperative management of patients undergoing cardiac surgery due to the increased risk of bleeding complications. The aim of this study was to analyze current perioperative management strategies for HT in cardiac surgery patients.
An exhaustive literature review in several databases was used, selecting 43 high quality studies. The results emphasize the importance of a thorough preoperative evaluation, including detailed clinical history, physical examination, specific platelet function tests and strict follow-up by hematology. It is therefore important to emphasize that optimal perioperative management requires a multidisciplinary approach, with individualized strategies for each patient.
Key measures include optimizing platelet counts through transfusion support, the use of hemostatic agents and drugs that improve platelet function, and the use of meticulous surgical techniques. In addition, close monitoring of hemostasis is essential throughout the procedure and in the immediate postoperative period.
In conclusion, perioperative management of HT in cardiac surgery requires a comprehensive approach, coordinated according to individual needs. Only through methodical planning, multidisciplinary teamwork and continuous monitoring can the results be optimized and the risks associated with this complex hematological condition be minimized.

Keywords: cardiac surgery, blood coagulation, hemostasis, platelets, hereditary thrombocytopenia

INTRODUCTION

Hereditary thrombocytopenia, a hematological disorder that presents challenges in the context of perioperative management of patients undergoing cardiac surgery (1), on the one hand a relevant condition such as thrombocytopenia, which is defined as an abnormally low platelet count in the blood. These cells, known as thrombocytes, are fundamental in primary hemostasis and bleeding arrest (2). Thrombocytopenia, linked to various causes such as genetic disorders or autoimmune diseases, increases the risk of bleeding (3).
In the process of megakaryopoiesis, which is the formation of megakaryocytes which are precursor cells of platelets, there may be genetic alterations as it is with the MYH-9 gene, considered as one of the cases with low frequency, in the same way the myosin-IIA protein, which is a component of the cytoskeleton of thrombocytes plays an important role. At this stage, megakaryocytes move from their initial location near the osteoblastic cells to the sinusoidal regions of the bone marrow, then, after maturing, they release proplatelets into the sinusoidal lumen, signifying that there would be a possible mutation in the next generation (4).
In relation to prevalence, it varies according to population and diagnostic criteria, affecting approximately 1 in 10,000 people (5).
This review stands out for its unique relevance in specialized medical practice, as it addresses the urgent need to understand and optimize hereditary thrombocytopenia in cardiac surgery, where bleeding complications can

have serious consequences. This being a rare platelet disorder with genetic basis, it can trigger bleeding or in turn thrombotic events (6).
Preoperative evaluation is essential in the operating room, where primary hemostasis is fundamental to minimize risks. Despite its rarity, underestimating its incidence raises questions about its true burden, highlighting the importance of a comprehensive approach (1).
specific incidence in cardiac surgery is not yet fully defined, which highlights the need for special attention due to its implications in perioperative management.
Perioperative management of patients with hereditary thrombocytopenia is crucial, especially in cardiac surgery. This condition is complex and can present with a variety of manifestations, from mild to severe, highlighting the need for specialized medical care. Common genetic variants such as familial thrombocytopenia type 1 and type 2, Wiskott-Aldrich syndrome, and MYH9 gene-associated thrombocytopenia pose unique challenges during this period due to their clinical variability and potential associated complications (4).
Preoperative evaluation is essential in the operating room, where primary hemostasis is fundamental to minimize risks. Despite its rarity, underestimating its incidence raises questions about its true burden, highlighting the importance of a comprehensive approach (1). The specific incidence in cardiac surgery is not yet fully defined, highlighting the need for special attention due to its implications in perioperative management.
Perioperative management of patients with hereditary thrombocytopenia is crucial, especially in cardiac surgery. This condition is complex and can present with a variety of manifestations, from mild to severe, highlighting the need for specialized medical care. Common genetic variants such as familial thrombocytopenia type 1 and type 2, Wiskott-Aldrich syndrome, and MYH9 gene-associated thrombocytopenia pose unique challenges during this period due to their clinical variability and potential associated complications (4).
Preoperative evaluation of patients with hereditary thrombocytopenia requires a detailed medical history, including platelet function tests.
Studies have indicated that about 0.33% of the population may carry a genetic variant linked to platelet disorders, highlighting the importance of detecting this condition early and managing it appropriately (5). During cardiac surgery, careful management of hemostasis is crucial, involving specific surgical techniques and procedural modifications. Hereditary thrombocytopenia requires a comprehensive approach in the operating room to ensure successful outcomes. After surgery, meticulous follow-up is essential to detect and treat possible complications, ensuring optimal recovery (5).
The aim of the review is to explore and critically analyze current perioperative management strategies for hereditary thrombocytopenia in patients undergoing cardiac surgery in a comprehensive manner.

METHODOLOGY

The purpose of the narrative literature review was to collect updated information on hereditary thrombocytopenia and perioperative application in patients undergoing cardiac surgery in the following databases: Web of Science Scopus, UpToDate, DynaMed, Pubmed and Scielo. The health sciences descriptors MeSH terms: cardiac surgery, surgical procedure, hereditary thrombocytopenia. In addition, the Boolean operators AND and OR were used to construct the following search algorithms: "Thrombocytopenia AND Cardiac Surgery OR, Vascular Surgical Procedures", "Hereditary thrombocytopenia AND Cardiac Surgery OR Vascular Surgical Procedures". "Hereditary thrombocytopenia AND Perioperative management".
Obtaining a total of 2405 articles, the eligibility criteria were applied:

Inclusion criteria

- Titled papers on post-surgical complications in valve surgery.
- Scientific articles published between 2018 and 2024.
- Systematic reviews without language restriction published in scientific impact databases.
- Clinical trials and meta-analyses on post-surgical complications in surgery, performed in the last 5 years, without language restriction.

Exclusion criteria

- Clinical cases.
- Undergraduate and postgraduate theses.
- Publications not found in recognized scientific databases or with unreliable content.
- Book chapters
- Conferences
- Letters

A total of 157 articles were obtained. We proceeded with the analysis of the titles and summary of each one of the studies, excluding 106 because they were not related to the subject of the research, leaving 51 studies, of which after a complete reading, 8 articles were excluded: 4 not related to surgical procedures, 2 referring to pediatric studies and 2 not related to thrombocytopenia, leaving 43 quality studies for the bibliographic review.

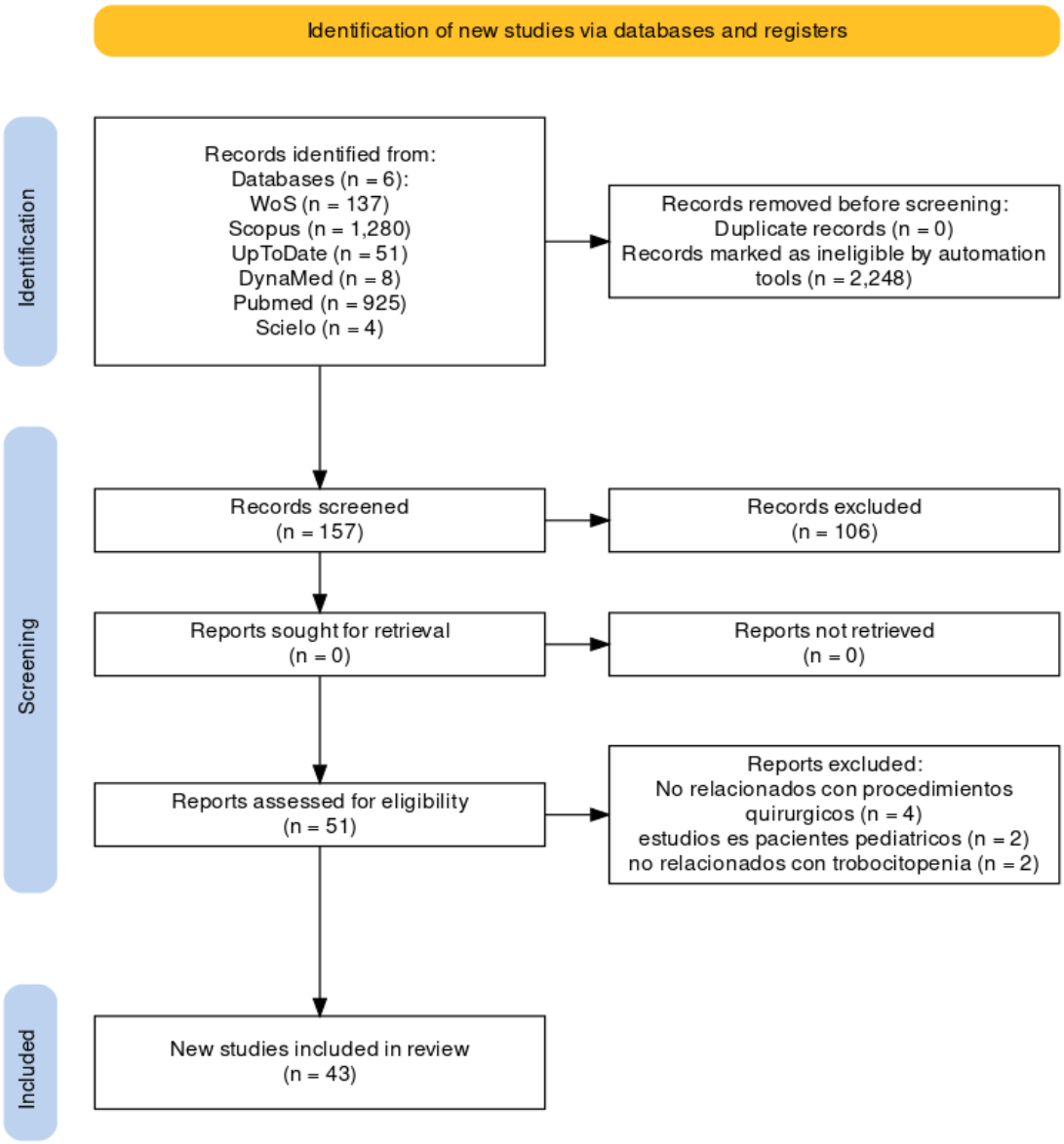

Figure 1. Data selection

Hereditary thrombocytopenia

Hereditary thrombocytopenia, a rare genetic disease, is defined by a marked decrease in the number of circulating platelets in the bloodstream, which leads to an increased predisposition to bleeding and clotting dysfunction. This condition can present in a variety of forms and levels of severity, from mild cases that may go unnoticed to more severe forms that require immediate medical intervention (4). Decreased circulating platelets increase susceptibility to bleeding, which may arise spontaneously or as a result of minor injuries. In addition, disturbances in adequate coagulation may cause wounds to take longer to heal and increase the risk of prolonged bleeding during surgical procedures or trauma (5). Perioperative management of patients with this condition undergoing cardiac surgery requires meticulous and specialized care throughout the surgical process (4).

Advances in pharmacological medicine have been significant in recent decades, with the development of new therapies and drugs that have revolutionized the treatment of various diseases. These advances have improved treatment, giving new hope to patients and helping to improve the quality of life of individuals around the world (7).

Epidemiology

Being a medical condition characterized by a reduction in blood platelet count, it presents a significant challenge in cardiac surgery (3). This rare condition has an estimated prevalence of approximately 2.7 per 100 000 individuals (8).

A study by Oved, et al. (9), who examined the frequency of naturally occurring loss-of-function variants in genes related to platelet disorders, 52% were related to hereditary thrombocytopenia's of the TUBB1 pLoF

gene, revealed that approximately 0.33% of individuals in the general population have a clinically significant loss-of-function variant in a platelet-associated gene (9).
Giving this hereditary characteristic to the group of platelet pathologies as hereditary thrombocytopenia. This group of uncommon pathologies encompasses about 45 disorders with different degrees of clinical complexity and with wide variability in their prognosis (5). Nair, et al. (6) for the United Kingdom Congenital Hemorrhagic Disorders Organization (UKHCDO) demonstrated that the incidence of hereditary thrombocytopenia is approximately 1 case per 10,000 persons (10). In Latin America, cases of hereditary thrombocytopenia have been reported in countries such as Mexico, Brazil, Argentina, Colombia, and Chile. In Ecuador, a study by Cevallos and Ruiz, et al (11), recorded that the prevalence of hereditary thrombocytopenia is approximately 1 case per 20,000 persons (12). In many countries of the region, thrombocytopenia has been reported to be a frequent complication during pregnancy, due to autoimmune mechanisms, which makes this problem particularly important (8).

Etiology
Hereditary thrombocytopenia can have multiple causes, which vary depending on the specific disorder present in the patient. Some of the most common inherited disorders associated with thrombocytopenia include:

Table 1. Hereditary thrombocytopenia with common inheritance type, associated gene and characteristics.

Disease	Inheritance Type	Gene	Characteristics
Large platelets			
TH related to MYH-9 gene	Autosomal dominant	MYH-9 (22q12-13)	Giant platelets, inclusions in neutrophils, Döhle's body type, nephropathy, deafness
Bernard Soulier bi andmonoallelic	Autosomal recessive	GP1BA (17p13), GPIBB (22q11), GP9 (3q21)	Large platelets, macroplatelets
Thrombocytopenia Paris-Trousseau	Autosomal dominant	LARGE DELETIONS (11Q23-TER)	Facial alterations, cardiac problems, delayed psychomotor development and others
Gray platelet syndrome	Autosomal recessive	NBEAL2 (3p21.1)	Hypo- and agranular large platelets, splenomegaly, myelofibrosis
Disease related to GATA1 mutations	X-linked	GATA1 (Xp11)	Hemolytic anemia, possibly congenital erythropoietic porphyria
Normal platelet size			
Congenital Amegakaryocytic thrombocytopenia	Autosomal recessive	c-MPL (1p34)	Thrombocytopenia and progressive bone marrow failure
Thrombocytopenia with absence of radium	Autosomal recessive	RBM8A (1q21.1)	Number of platelets, bilateral radial aplasia
Familial thrombocytopenia with a tendency towards acute myeloid leukemia	Autosomal dominant	CBFA2T2 (21Q22)	40% of patients develop acute myeloid
Thrombocytopenia related to ANKRD26 mutation	Autosomal dominant	ANKRD26 (10p2)	Predisposition to acute leukemia
Thrombocytopenia Amegakaryocytic synostosis radio-ulnar synostosis	Autosomal dominant	HOXA11 (7p15-14)	Decreased megakaryocytes, medullary failure, radial-ulnar synostosis and other defects.
Small platelets			

Wiscott-Aldrich syndrome	X-linked	WAS (Xp11)	Severe immunodeficiency
X-linked thrombocytopenia	X-linked	WAS (Xp11)	Without immunodeficiency

Source: Prepared by the authors based on data provided by Heller (16).

Pathophysiology

Hereditary thrombocytopenia results from various mechanisms that affect platelet production, function or survival, resulting in a low platelet count (14). This condition may be caused by genetic mutations that disrupt the normal creation of platelets in the bone marrow, accelerate the clearance of platelets into the bloodstream, or affect their ability to play their role in clotting. These genetic abnormalities can lead to thrombocytopenia and increase the risk of bleeding in affected individuals. In the perioperative management of patients with hereditary thrombocytopenia undergoing cardiac surgery, it is essential to consider the underlying pathophysiology of the disorder to tailor the therapeutic approach, as it represents a challenge that requires a thorough and specialized understanding (14).

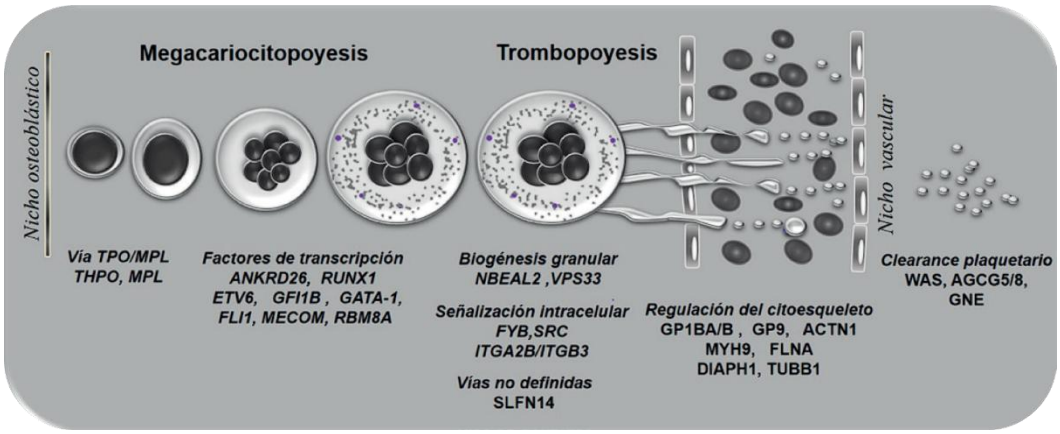

Figure 2. Familial thrombocytopenia with tendency to acute myeloid leukemia CBFA2 (21q22)
Source: Prepared by the authors based on data provided by Heller et al.

Cardiac surgery and bleeding risks in patients with hereditary thrombocytopenia

Cardiac surgery in patients with hereditary thrombocytopenia presents unique challenges due to increased predisposition to bleeding and bleeding complications. Hereditary thrombocytopenia, characterized by low blood platelet counts, can be caused by a variety of mutations at the genetic level that affect platelet production, function, or survival (14).

In the field of cardiac surgery, bleeding risks are also evident, with a percentage of 26.5% in interventional patients, as indicated by Klingele et al (15). These findings highlight the importance of implementing proactive strategies to prevent bleeding events in patients with hereditary thrombocytopenia undergoing surgical procedures (16).

In patients with hereditary thrombocytopenia, it is key to point out that platelets play an essential role in the formation of blood clots to stop bleeding (17).

On the other hand, thrombocytopenia after cardiac surgery is common and often normalizes spontaneously; however, when it persists after platelet transfusion, attention must be paid to avoid potentially serious morbidity (18).

A clinical case worth mentioning is described by Rey et al. (18), where, five patients after a coronary artery bypass grafting (CABG) procedure were diagnosed with persistent thrombocytopenia along with symptoms of fever, renal failure, thromboembolic events or altered mental status, in conjunction with microangiopathic hemolytic anemia (MAHA) (20).

Preoperative Evaluation

In the management of patients with hereditary thrombocytopenia, preoperative evaluation is crucial because these bleeding disorders represent major hemostatic obstacles to surgical intervention. Optimization of perioperative hemostasis in these patients requires meticulous attention, including careful preoperative planning, thorough surgical technique, timely identification of complications, and use of hemostatic agents and blood components as needed (21).

During this process, information about the patient's health, including medical history, allergies, current medications, and relevant underlying medical conditions, is thoroughly collected (22). In addition to this detailed data collection, the preoperative evaluation may include additional tests, such as blood count, blood smear, electrocardiograms or X-rays, tailored to the specific needs of each patient and the type of surgery scheduled (23,24).

These additional tests are aimed at detecting possible risks or potential complications during the surgical procedure (25). With the collaboration of a multidisciplinary team, composed of surgeons, anesthesiologists, nurses and other health professionals, all the information obtained during the preoperative evaluation is reviewed in a comprehensive manner, thus allowing the development of an individualized and meticulous care plan for each patient (26).

In the management of patients with preoperative thrombocytopenia

Performing a thorough preoperative evaluation in patients with hereditary thrombocytopenia is an essential step in order to ensure safe surgery and mitigate the risk of bleeding complications. Comprising a variety of genetic disorders that impact both platelet production and function, which can result in reduced blood platelet counts and consequently increase the propensity for bleeding (27,28).

Table 2. Preoperative Evaluation in Patients with Hereditary Thrombocytopenia

Preoperative Evaluation in Patients with Hereditary Thrombocytopenia	
Complete medical history	Obtaining detailed information on the patient's medical history, including family history of bleeding disorders and previous bleeding episodes, is essential as it is essential to collect comprehensive and developed information, and family history provides valuable insight into the presence of inherited bleeding disorders.
Physical examination	A complete physical examination is essential, paying special attention to signs of bleeding, such as ecchymosis, petechiae or mucosal bleeding.
Laboratory tests	Performance of laboratory tests to evaluate platelet function and blood coagulation. This may include platelet count, bleeding time, (PT), (aPTT), among others.
Evaluation of the severity of thrombocytopenia	It is important to know the thrombocytopenia of the person to predict the risk of bleeding during and after surgery, this helps to have a clear idea of how to carry out the proper preparation or management for the patient.
Consultation with a hematologist	In cases of hereditary thrombocytopenia, it is recommended that the patient be evaluated by a hematologist for a more specialized evaluation and management of the disorder. Hematologists are specialized in coagulation disorder diseases along with related disorders, so they are the most qualified to manage this situation.
Perioperative management planning	Based on the preoperative evaluation, an individualized perioperative management plan should be developed for each patient. This may include the administration of platelet transfusions before or during surgery, the use of hemostatic medications such as tranexamic acid, and careful monitoring during the surgical procedure.

Source: Prepared by the authors based on data provided by Makris (19) and Nieto (23).

Perioperative Management in Patients with Hereditary Thrombocytopenia

Perioperative management of patients with hereditary thrombocytopenia demands planning and close coordination between various medical specialties. This is crucial to ensure patient safety both during the surgical procedure and in the post-surgical period (28,29).

The management of anticoagulation after cardiac surgery presents considerable challenges. The timing of initiation, dose, and type of anticoagulant depend on what was performed, the determining presence of risk for both clot formation and bleeding, and rigorous clinical surveillance to achieve an appropriate balance between antithrombotic protection and prevention of complications during hospitalization. We will discuss three distinct postoperative scenarios: patients with valvular prostheses, those with atrial fibrillation requiring anticoagulation, and those at risk for venous thromboembolic disease, in addition to addressing how bleeding complications should be managed, tailoring treatment according to INR levels and the presence of bleeding (30). The interdisciplinary approach and standardization of procedures facilitate the care of these patients and reduce the incidence of complications, many of which are entirely preventable.

Table 3. Clinical follow-up in the perioperative management of anticoagulation in cardiac surgery.

Description	**Concept Of Use**
Pharmacological dosage	It allows adjusting the dose of anticoagulants according to the INR (International Normalized Ratio) values, ensuring that it remains within the desired therapeutic range.

Possible complications	Adequate clinical follow-up helps to prevent and detect hemorrhagic complications, allowing timely treatment should they occur.
Treatment	Each patient is unique and requires a personalized approach to anticoagulation, so clinical monitoring allows treatment to be tailored to the specific needs of each individual.
Reduction of avoidable complications:	The work of the multidisciplinary team and the protocols of patient management, reducing stumbling blocks, some of which are avoidable with proper follow-up.

Source: prepared by the authors based on data from Kubo (21) and Nieto (23).

Monoclonal Antibodies

Monoclonal antibodies, such as rituximab and alemtuzumab, can reduce platelet destruction by the immune system and improve blood platelet counts. These drugs, administered intravenously, may be effective in the perioperative management of patients with hereditary thrombocytopenia. Gutierrez et al. (24) investigated the safety and efficacy of rituximab in the perioperative management of patients with hereditary thrombocytopenia. In the study, ten patients with hereditary thrombocytopenia received rituximab before surgery. The platelet counts of all patients increased, and none had bleeding after surgery. Rituximab was administered intravenously at concentrations of 375 to 1000 mg/m2 (32). Regarding alemtuzumab, Yogendrakumar et al. (33) conducted an evaluation of the safety and efficacy of perioperative management in patients with hereditary thrombocytopenia where the platelet counts of all patients after administration of the antibody increased, and none of them presented hemorrhages during surgery. The amount of alemtuzumab administered was 10 to 30 mg intravenously (33). Caplacizumab is a new monoclonal antibody used for a type of hereditary thrombocytopenia, acquired thrombotic thrombocytopenia purpura (ATP); an antibody that was approved in 2019 in Europe and the U.S. Caplazizumab blocks the binding of von Willebrand factor to the platelet IB-IX-V receptor, and consequently decreases platelet adhesion and aggregation, avoiding the risk of microthrombus development. Although clinical studies have good results, there is an increased risk of bleeding, especially of the cutaneous-mucosal type. This antibody showed greater efficacy in the company of other treatments such as plasma exchange and immunosuppressive therapy; in the latter, the antibody made it possible to reduce the number of therapeutic plasma exchange sessions (34).

Thrombopoietin Analogs

Romiplostim and eltrombopag may be effective in reducing the risk of bleeding during surgical procedures in patients with hereditary thrombocytopenia. These drugs can increase the number of platelets in the blood and improve platelet function. However, side effects include headache, fatigue and nausea in a clinical study by Puavilai, et al. (35), they examined the safety and efficacy of an AMG-531 mimetic (romiplostin) in the perioperative management of patients with thrombocytopenia caused by an inherited in a clinical study conducted by Puavilai, et al. (35), they examined the safety and efficacy of an AMG-531 mimetic (romiplostin) in the perioperative management of patients with thrombocytopenia caused by an inheritance. Twenty-one patients with inherited thrombocytopenia who underwent major surgical procedures, including cardiac surgeries, were included (36,37). Prior to surgery, patients received AMG-531 subcutaneously at doses of 0.3 mg/kg to 10 mg once weekly for 6 weeks. An increase in blood platelet count was observed in patients treated with AMG 53 (38). The platelet count increased to a mean of 50,000/mm3 at week 2 and to a mean of 150,000/mm3 at week 6. Además, se observó una tasa de respuesta del 86% en los pacientes tratados con AMG-531. In addition, an 86% response rate was observed in patients treated with AMG-531. AMG-531 was well tolerated in patients with hereditary thrombocytopenia and no bleeding occurred during surgery. The most common side effects were headache, fatigue and nausea. No serious side effects were observed in patients treated with AMG-531 (14). On the other hand, the clinical study by Martinez, et al. (31), found that patients who received eltrombopag had a higher platelet count. The dose of eltrombopag was adjusted according to the patient's platelet count and ranged from 25 to 75 mg once daily. In addition, patients receiving eltrombopag were found to have a lower risk of bleeding (39,40).

However, side effects were mild to moderate, such as headache, nausea and diarrhea. Postoperatively, patients receiving eltrombopag had an increased risk of developing arterial and venous thrombosis, although these events were uncommon. rFVIIa is recombinant activated factor VII, a drug used as a bypass agent in patients with hemophilia A and, however, has also been used as an option in the perioperative management of patients with hereditary thrombocytopenia to reduce the risk of bleeding during cardiac surgeries (40,41). The rFVIIa is administered intravenously in doses of 20 to 90 μg/kg and may increase blood clot formation and reduce the risk of bleeding. However, rare side effects, such as arterial and venous thrombosis, myocardial infarction, and stroke, have been reported (40).

Hemostatic-topical agents

Perioperative management of patients with hereditary thrombocytopenia includes the use of topical hemostatic agents such as thrombin and collagen. These agents are applied directly to the bleeding site and have the ability to control the amount of blood produced during the surgical procedure. However, in recent years these strategies have been innovated, and the results have improved; a particular case is that performed by Sultan, et al. (41) where the efficacy and safety of a new topical hemostatic agent, oxidized cellulose powder (Fibrin Sealant with topical thrombin), was evaluated in the perioperative management of patients with hereditary thrombocytopenia. In the study, ten patients with hereditary thrombocytopenia were treated with oxidized cellulose powder at the bleeding site during bypass surgery. All patients had effective bleeding control and no perioperative bleeding. The amount of oxidized cellulose powder administered directly to the bleeding site varied according to bleeding intensity. In addition, patients who received oxidized cellulose powder did not experience significant side effects (42,43).

CONCLUSION

Perioperative management in patients with hereditary thrombocytopenia depends on the type of gene associated as a predisposing factor. These strategies focus on a thorough evaluation of the clinical history including family history, drugs, allergies and comorbidities.

Advances in pharmacological treatment, including the use of hemostatic agents, such as tranexamic acid or desmopressin, or the use of innovative topical hemostatic agents have proven to be effective in controlling intraoperative bleeding. On the other hand, effective monoclonal antibodies for this pathology are rituximab, alemtuzumab and caplacizumab. Thrombopoiesis agonists such as romiplostim and eltrombopag have proven to be effective in reducing bleeding and improving surgical results; however, in complex cases, it may be necessary to resort to adjuvant therapies, such as transfusion of platelet concentrates, platelet apheresis or administration of hematopoietic growth factors to stimulate endogenous platelet production.

REFERENCES

1. Nurden A, Nurden P. Trombocitopenias hereditarias: historia, avances y perspectivas. Haematologica. 2020;105(8):2004-15 Ferrata Storti Foundation Q1
2. Bury L, Falcinelli E, Gresele P. Learning the Ropes of Platelet Count Regulation: Inherited Thrombocytopenias. J Clin Med. 2021;10(3):533.
3. Rancati V, Scala E, Ltaief Z, Gunga M, Kirsch M, Rosner L, et al. Challenges in patient blood management for cardiac surgery: A narrative review. J Clin Med. 2021;10(11).
4. Thurlapati A, Guntupalli S, Mansour R. Myosin Heavy Chain 9 (MYH9)-Related Congenital Macrothrombocytopenia. Cureus. 2021;13(8):16964
5. Pecci A, Balduini C. Inherited thrombocytopenias: an updated guide for clinicians. Blood Rev. 2021;48(1):100784.
6. Nair D, Sreejith N, Bhambra A, Bruce J, Mellor S, Brown LJ, Harky A. Cardiac Surgery in Patients With Blood Disorders. Heart Lung Circ. 2022 ;31(2):167-9
7. Nugent D, Acharya S, Baumann K, Bedrosian C, Bialas R, Brown K, et al. Construyendo las bases para un plan de investigación nacional generado por la comunidad para los trastornos hemorrágicos hereditarios: prioridades de investigación para trastornos hemorrágicos hereditarios ultrararos. Experto Rev Hematol. 2023;16(1):55-15.
8. Balduini C. Treatment of inherited thrombocytopenias. Haematologica. 2022;107(6):1278-14
9. Oved J, Lambert M, Kowalska M, Poncz M, Karczewski K. Population based frequency of naturally occurring loss-of-function variants in genes associated with platelet disorders. J ThrombHaemost. 2021;19(1):248-6
10. Abad Zurita TA, Cermelj M, Scoles G. Trombocitopenia como factor de riesgo de morbi-mortalidad en los pacientes hospitalizados en una Unidad de Terapia Intensiva. RH.2021; 25(1):9-1
11. Cevallos A, Ruiz A. Prevalencia de trombocitopenia hereditaria en la ciudad de Cuenca, Ecuador. Facultad de Medicina, Universidad de Cuenca. 2019; 43(1):5-10
12. Klompas A, Boswell M, Plack D, Smith M. Thrombocytopenia: Perioperative Considerations for Patients Undergoing Cardiac Surgery. J CardiothoracVascAnesth. 2022;36(3):893-12.
13. Almazni I, Stapley R, Morgan N. Inherited Thrombocytopenia: Update on Genes and Genetic Variants Which may be Associated With Bleeding.2021;1(2):1-2
14. Palma V, Revilla N, Sánchez A, Zamora A, Rodriguez A, Marín A, González J, Vicente V, Lozano M, Bastida J, Rivera J. Inherited Platelet Disorders: An Updated Overview. Int J Mol Sci. 2021;22(9):4521
15. Warren J, Di J. Genetics of inherited thrombocytopenias. Blood. 2022;139(22):3264-13
16. Heller P, Goette N, Oyarzún C, Baroni Pietto M, Ayala D, Altuna D, Arrieta M, Arbesú G, Basquiera A, Bazack N, et al. Feno-genotipificación de trombocitopenias hereditarias: nuestra experiencia en 50 familias. Hematología. 2020;24(2):9-19.

17. Vinholt P. The role of platelets in bleeding in patients with thrombocytopenia and hematological disease. Clin Chem Lab Med. 2019;57(12):1808–17.
18. Rey J, Merino J, Iniesta Á, Caro J; investigadores CARD-COVID. Complicaciones arteriales trombóticas en pacientes hospitalizados con COVID-19. Respuesta a cartas relacionadas [Arterial thrombotic complications in hospitalized patients with COVID-19. Response to related letters]. Rev Esp Cardiol. 2021;74(1):116
19. Makris M. Thrombopoietin receptor agonists for the treatment of inherited thrombocytopenia. Haematologica. 2020;105(3):536-2
20. Bury L Learning the ropes of platelet count regulation: Inherited thrombocytopenias. J Clin Med. 2021; 10(3):1–24.
21. Kubo M, Matsumoto M. Frontiers in pathophysiology and management of thrombotic thrombocytopenic purpura. Int J Hematol. 2023;117(3):331-9
22. Tuñón J, Lázaro A, López M, Aceña Á. Anticuerpos monoclonales inhibidores de la proproteína convertasa subtilisina/kexina tipo 9: nuevas evidencias. Revista Española de Cardiología Suplementos. 2020;20(1):15-5.
23. Nieto C, Cruz O, Nieto G, Álvarez L, Cruz Y, Hernández M, et al. Evaluación preoperatoria de la hemostasia en cirugía mayor electiva. Revista mexicana de anestesiología.2023;46(2):98-5.
24. Gutiérrez G, Contreras J, Campa D, Sánchez E, Martínez R. Evolución clínica de 31 pacientes adultos con trombocitopenia inmune tratados con rituximab [Clinical evolution of 31 adult patients with immune thrombocytopenia treated with rituximab]. Rev Med Inst Mex Seguro Soc. 2023;2;61(1):21-11.
25. Nusrat S, Beg K, Khan O, Sinha A, George J. Hereditary Thrombotic Thrombocytopenic Purpura. Genes (Basel). 2023;8;14(10):1956.
26. Esteve M. Púrpura trombótica trombocitopénica hereditaria. MPG Journal. 2019;2(2):9-19
27. Bussel J, Soff G, Balduzzi A, Cooper N, Lawrence T, Semple J. Una revisión del mecanismo de acción y la aplicabilidad clínica de Romiplostim.2021;15(1):2243-25.
28. Skeith L, Baumann L, Crowther M, Warkentin T. A practical approach to evaluating postoperative thrombocytopenia. Blood Adv. 2020 ;4(4):776-7.
29. Palma V, Bury L, Kunishima S, Lozano M, Rodríguez A,et al. Expanding the genetic spectrum of TUBB1-related thrombocytopenia. Blood Adv. 2021 28;5(24):5453-14
30. Matejic M, Hassan K, Thielmann M, Geidel S, Storey RF, Schmoeckel M, Adamson H, Deliargyris EN, Wendt D. Management of perioperative bleeding risk in patients on antithrombotic medications undergoing cardiac surgery-a systematic review. J Thorac Dis. 2022;14(8):3030-14
31. Martínez L, Hernández A, Arango A. Trastornos plaquetarios hereditarios poco frecuentes: patología molecular y aspectos diagnósticos. Revista Cubana de Hematología, Inmunología y Hemoterapia.2021;37(1)
32. Secchim L, Migliari L, Franklin B. Regulation of Innate Immune Responses by Platelets. Frontiers in Immunology. 2019;10(1)1-9.
33. Engelman D, Ben Ali W, Williams J, Perrault L, Reddy V, Arora R, Roselli E, Khoynezhad A, Gerdisch M, Levy J et al. Guidelines for Perioperative Care in Cardiac Surgery: Enhanced Recovery After Surgery Society Recommendations. JAMA Surg. 2019;154(8):755-11.
34. Yogendrakumar V, Mayer S, Steiner T, Broderick J, Dowlatshahi D. Exploring Hematoma Expansion Shift With Recombinant Factor VIIa: A Pooled Analysis of 4 Randomized Controlled Trials. Stroke. 2023.;54(12):2990-8
35. Jiménez Rivera JJ, Llanos Jorge C, López Gude MJ, Pérez Vela JL. Manejo perioperatorio en cirugía cardiovascular. Med Intensiva.2021;45(3):175–83.
36. Bidika E, Fayyaz H, Salib M, Memon A, Gowda A, Rallabhandi B, Cancarevic I. Romiplostim and Eltrombopag in Immune Thrombocytopenia as a Second-Line Treatment. Cureus. 2020;12(8):9920.
37. Li T, Liu Q, Pu T, Liu J, Zhang A. Efficacy and safety of thrombopoietin receptor agonists in children and adults with persistent and chronic immune thrombocytopenia: a meta-analysis. Expert OpinPharmacother. 2023;24(6):763-11
38. Puavilai T, Thadanipon K, Rattanasiri S, Ingsathit A, McEvoy M, Attia J, Thakkinstian A. Treatment efficacy for adult persistent immune thrombocytopenia: a systematic review and network meta-analysis. Br J Haematol. 2020;188(3):450-9.
39. Ostadi Z, Shadvar K, Sanaie S, et al. Thrombocytopenia in the intensive care unit. Pakistan Journal of Medical Sciences. 2019;35(1):282-5.
40. Secchim L, Migliari L, Franklin B. Regulation of Innate Immune Responses by Platelets. Frontiers in Immunology. 2019;10(Art. 1320):1-9.
41. Sultan MT, Hong H, Lee O, Ajiteru O, Lee Y, Lee J, Lee H, Kim S, Park C. Biomateriales a base de fibroína de seda para aplicaciones hemostáticas. Biomoléculas. 2022 30;12(5):660.

42. Al N, Jonge E, Kocharian R, Ilie B, Barnett E, Berrevoet F. Seguridad y eficacia hemostática del polvo SURGICEL® en sangrado intraoperatorio leve y moderado. Clin Appl Thromb Hemost. 2023;29(1):10
43. Zhang S, Li J, Chen S, Zhang X, Ma J, He J. Oxidized cellulose-based hemostatic materials. Carbohydr Polym.2020;230(1):11558