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Experimental Models of Thrombocytopenia in Laboratory Animals and their Application in Identifying the Complications of Chemotherapy Drugs

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ABSTRACT

BACKGROUND AND OBJECTIVE: Thrombocytopenia is one of the complications of chemotherapy drugs that may cause death. Different animal models of thrombocytopenia are used for clinical research and identification of its causes, each with advantages and disadvantages. The aim of this review article is to investigate the methods of thrombocytopenia induction in laboratory animals and their advantages and disadvantages.

METHODS: This systematic review was conducted using the keywords "thrombocytopenia platelet", "chemotherapy", "animal model", in PubMed, Science Direct and Scopus databases from 1990 until October 2017. The title and abstract of several articles were reviewed, and after excluding the unrelated items, final articles were selected and reviewed.

FINDINGS: Animal models of thrombocytopenia are of two types of immune and non-immune. Non-immune models reduce platelet production through bone marrow suppression. Antiplatelet antibodies are used in immune models. The immune and non-immune thrombocytopenic models have some advantages and limitations and are selected according to the current therapeutic goals. Mice and rats are commonly used as laboratory animals, and cyclophosphamide and carboplatin are the most commonly used drugs.

CONCLUSION: According to the results of this study, due to the limitations of human subject research in diseases that lead to thrombocytopenia, there is a need to develop appropriate animal models for studying and identifying the factors affecting thrombocytopenia.

KEY WORDS: *Thrombocytopenia, Platelet, Chemotherapy, Animal Models.*

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Introduction

Thrombocytopenia is a blood disorder that reduces platelet count to less than 100,000 per microliter and is classified into three types of mild, moderate and severe, and is observed in both acute and chronic forms (1, 2). Its clinical manifestations are purpura, bleeding from the nose, gum and digestive system and hematuria (3). The mechanism of thrombocytopenia is to reduce platelet production (with bone marrow suppression) or to increase platelet degradation due to immune system disorders (4). The primary treatment of this disease is corticosteroid, which often relapses and is reversible. The use of intravenous IGs also causes a transient increase in the number of platelets, but requires repeated administration (5).

Study and research on human thrombocytopenia is associated with ethical constraints and several issues. In addition, the in vitro models of cell culture are few and lack efficiency. For this reason, there is a special interest in the animal model of thrombocytopenia, which is generally divided into two types, namely immune and non-immune. In immune models, antiplatelet antibodies can degrade and reduce platelets. Non-immune models are produced by bone marrow suppression agents (6 – 7) (Fig. 1). There are several empirical models for the development of thrombocytopenia and identification of its effective factors, each with some advantages and disadvantages, but so far no comprehensive study has been conducted on them. Therefore, this review article was conducted to investigate the methods of inducing of thrombocytopenia in laboratory animals and to introduce the advantages and disadvantages as well as applications of these models.

Methods

This review article was conducted using the keywords “thrombocytopenia”, “platelet”, “chemotherapy”, and “animal model”, in PubMed, Science Direct and Scopus databases from 1990 until October 2017. The title and abstract of several articles were reviewed, and after excluding the unrelated items, final articles were selected and evaluated..

Results

Non-immune thrombocytopenia models: These include the use of drugs that suppress bone marrow to reduce platelet production (Fig. 1). The use of chemotherapy drugs is associated with reduced production of blood cells. Bone marrow is the tissue that restricts the dose of these drugs, and the suppression of hematopoiesis reduces leukocytes and platelets. However, severity, period and cellular pattern of bone marrow suppression differ in different types of alkylating agents (8). In this study, the main drugs used in animal models of thrombocytopenia are examined. All of these drugs are widely used in chemotherapy for cancer patients, and their side effects include thrombocytopenia (Table 1) (9 – 39).

Cyclophosphamide: Cyclophosphamide was introduced as an antitumor agent in the treatment of cancer. Subcutaneous (SC) injection of the three doses of 100, 120 and 140 mg/kg of this drug to mice reduced the platelet count by 7% on day seven by 30%, 18% and 21%, respectively. In addition, in two other models in one group (A), tail vein injection of 200 mg/kg as the initial dose and 30 mg/kg as the maintenance dose were administered intraperitoneally (IP) in the next six days. The other group (B) received a dose of 150 mg/kg (SC) for three consecutive days. The mice in group A started to die from day 6, but no death was observed in group B. The platelet count in group A on days 7 and 15 was 59% and 74%, respectively, while in group B, they fell to 33% and 75%, respectively, on days 7 and 11. This model is suitable for pharmacodynamic testing of drugs that are designed to increase platelet count (9).

The lowest dose of cyclophosphamide was 15 mg/kg, which was administered intraperitoneally for 10 days (10). In other studies, 50 mg/kg and 100 cyclophosphamide were used (SC) in rats (11, 12) for three days and 30 mg/kg (IP) for three days (13). In addition, 200 mg/kg dose was administered to mice through tail vein injection to induce thrombocytopenia through intravenous injection and seven days later, 30 mg/kg was injected as maintenance dose (IP). The thrombocytopenia was very intense in this model, and the mice started to die from day 6 and on day 15, death rate reached 60% (14).

Comparing doses of 25, 50, 100 and 150 mg/kg (SC) and once daily for three consecutive days, platelet count decreased significantly in all groups receiving cyclophosphamide on day 7. However, all rats receiving doses of 150 and 100 mg/kg died on days 7 and 8. Therefore, all doses caused thrombocytopenia, but 25 mg/kg was more effective and less toxic (15). Different methods for the induction of thrombocytopenia

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with cyclophosphamide are presented in Table 1. In our experimental study, administration of 100 mg/kg cyclophosphamide (IP) into rats within three consecutive days resulted in the death of animals from the seventh day. Doses of 50, 70 and 80 mg/kg were also injected (IP) for three consecutive days, indicating insignificant thrombocytopenia in tested animals. Therefore, after examining different doses, 100 mg/kg dose was injected to induce thrombocytopenia, and then in the next two days, a maintenance dose of 50 mg/kg was injected. In addition to observing successful thrombocytopenia from the seventh day, animal deaths were also prevented.

Carboplatin: Carboplatin is a chemotherapy drug used to induce thrombocytopenia in animal models. Doses of 200 mg/kg (close to the dose of patients) (16) and 125 mg/kg (17, 18) were administered through tail vein injection in the studies. A study investigated the effects of carboplatin along with radiotherapy on the induction of thrombocytopenia compared with cisplatin was studied and 8 mg/kg cisplatin was administered as single dose (IP) in the first group and the other group was exposed to radiotherapy (at 3 Gy/fraction). Another group was exposed to radiotherapy (at 5 Gy/fraction) after IP injection of single dose carboplatin (1.2 mg/kg) (19). In another study on dogs, carboplatin (175 mg/m^2) and doxorubicin (15 mg/m^2) were used, and grade one thrombocytopenia was induced. The pharmacokinetics of carboplatin is similar to humans in dogs and is therefore a suitable model for determining dosages and therapeutic programs (20).

In another model, carboplatin was injected into mice (IP) for two consecutive days at a dose of 50 mg/kg, which reduced platelets, RBC and WBC (21). In addition, after intravenous injection (IVI) of this drug (60 mg/kg) into rats on days 9 – 11, platelet count decreased to 90% (22). McElroy et al. examined the effects of Romiplostim on mice undergoing two or three CRT (chemoradiotherapy) cycles. In the first cycle, IP injection of carboplatin (62.5 mg/kg) was done and radiotherapy (at 5 Gy/fraction) was performed four hours later. In the 2nd and 3rd cycles, 56.25 mg/kg carboplatin and radiotherapy (at 4.5 Gy/fraction) were used (23). In another model, significant thrombocytopenia was induced in cat after intravenous injection of 150, 200 and 250 mg/m^2 carboplatin (24) (Table 1).

Cisplatin: Cisplatin IP injection (5 and 7.5 mg/kg) was done to induce thrombocytopenia and anemia in mice (25). In a study, 5 mg/kg of this drug (IP) was injected for five consecutive days, which significantly reduced platelet count (26). Intravenous injection of cisplatin (20 mg/m^2) was administered once a week for five weeks in dogs and then, radiotherapy (at 4 Gy/fraction) was done. The dogs also underwent radiotherapy (at 2 Gy/fraction) four days a week, which eventually led to a significant reduction in leukocyte, neutrophil and platelets (27). In a study on dogs, cisplatin (60 mg/m^2) (IVI), and oral administration of Firocoxib (5 mg/kg) alone or with cisplatin resulted in bone marrow suppression in 60% of dogs receiving cisplatin and 40% of the dogs receiving both medications (28).

Busulfan: Injection (SC) of busulfan (25 mg/kg) did not produce a clear thrombocytopenia in rabbits on days 0 and 3 until the 6th day. However, platelet count dropped rapidly from the second week (29). The dose of 15 mg/kg of this drug was administered to rabbits (SC) on days 0, 2, 4 and 6 (30). Busulfan was also injected (IP) to rats on days 0 and 3 at a dose of 20 mg/kg. The platelet count decreased ten days after the injection of Busulfan. The RBC and WBC count also began to decrease one day after injection (31). In another model, mice received 15 mg/kg (SC) on days 0 and 3 and thrombocytopenia was observed in mice in days 15 to 18 (32). Busulfan was used in mice (IP) at a dose of 15 mg/kg in days 0 and 3 and 20 mg/kg in days 1, 2 and 4 (33).

Bortezomib: Bortezomib is an anti-cancer drug. Tail vein injection of 2.5 mg/kg Bortezomib into mice reduced platelet count significantly on days 2 to 4 and started to improve on day 6 (34). In another model, Bortezomib (1 mg/kg) and Romidepsin (2 mg/kg) were used alone or in combined form. The mice receiving Romidepsin or a combination of the two drugs showed a decrease in WBC (50%) on day 2 and started to improve on day 4, but the group receiving the combination of Bortezomib and Romidepsin showed a more obvious thrombocytopenic effect (35).

Hydroxyurea: Gammulle et al. used Hydroxyurea in inducing thrombocytopenia in rats for the first time. Thrombocytopenia was observed 24 hours after oral administration (15 mg/kg). This drug has a high toxicity, and a low dose and one-tenth of the dose used in patients was used in this study (36).

Anagrelide: Anagrelide is used to treat chronic myeloid leukemia and thrombocytosis, and it leads to thrombocytopenia by inhibiting the puberty of megakaryocytes. The IP injection of this drug (100

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µg/day) after 24 to 48 hours leads to significant thrombocytopenia (40% normal count) (37). In another model, oral administration of this drug (0.083 mg/kg) for 15 days induced thrombocytopenia (38).

Oxaliplatin: Oxaliplatin is an anticancer drug that was injected intraperitoneally in rats at a dose of 0.8 mg/kg twice a week for 8 weeks, and induced significant thrombocytopenia eight days after the last injection. The weight of the spleen was significantly higher, indicating that the mechanism of platelet reduction in this model was associated with platelet aggregation in the spleen (39).

Immune thrombocytopenia

Passive antibody transfer model of immune thrombocytopenia: Almost all animal models of immune thrombocytopenia are passive, in which serum injections or antiplatelet monoclonal antibodies induce thrombocytopenia. Various animals including mice, rats, rabbits and dogs have been used in these models (40, 41) (Fig. 1). Corash et al. induced thrombocytopenia by transferring the antiplatelet serum to the C57BL/6 and CH3 mice (42). Cox et al. also observed that the injection of rabbit IgG of anti-platelet serum led to the induction of severe thrombocytopenia in Balb/c and C57BL/6 mice (43). Lecut et al. also reduced platelet in Balb/c mice by injecting antiplatelet antibodies prepared from guinea pig serum (44).

Over the past three decades, monoclonal antibodies were used against platelets of different animals. One of the first cases was the monoclonal antibody (4A5) of rats that was used to induce thrombocytopenia in mice (45). Hamster's 1C2 antibody was also used against mice and rat platelets (46). RPM.9 antibody was also used to induce thrombocytopenia in rats (47). Advantage of 1C2 and 4A5 monoclonal antibodies is the reaction with platelet and megakaryocyte.

Adoptive cell transfer of immune thrombocytopenia: Adaptive immune thrombocytopenia is a kind of passive immunity that is caused by the transfer of immunological agents, such as splenocyte (from the white blood cells of the spleen) to the host's body and creating an immune response. In the primary models, splenocyte was transmitted from patients with chronic thrombocytopenia to BALB/c mice exposed to lethal radiation. Antiplatelet antibodies were observed in mice after 2 – 8 weeks, but did not result in thrombocytopenia (48). BALB/c CD61 knockout mice were immunized through wild-type platelets and their splenocytes were transferred to the mice with SCID (severe combined immunodeficiency) for induction of antibody-dependent thrombocytopenia. In a study, splenocytes of mice after developing thrombocytopenia through wild-type platelets were transferred to SCID mice, and the antibody-induced thrombocytopenia was resistant to platelet injection (49). Apart from SCID mice, which received splenocyte without cell depletion, depletion of T cells (CD4 +) from splenocytes reduced their ability to produce thrombocytopenia or the production of antiplatelet antibodies, but the release of splenocytes from T cells (CD8 +) does not influence their ability to produce thrombocytopenia (50).

Secondary immune thrombocytopenia: Platelet reduction may be primary or may occur due to antibodies that lead to platelet destruction. Secondary immune thrombocytopenia occurs is conditions such as chronic and acute infections and certain medications, leading to the production of antibody against platelet.

Drug – induced immune thrombocytopenia (DITP): This immune thrombocytopenia model examines the role of certain drugs in the production of this type of thrombocytopenia. In a study, the effect of phenobarbital on thrombocytopenia in dogs was investigated (51). In another study, thrombocytopenia, leukopenia, and anemia were induced using phenobarbital in dogs (52). Another drug that leads to immune thrombocytopenia is heparin. In the study of Reilly et al., spleen tyrosine kinase (Syk) prevented heparin–induced thrombocytopenia in transgenic mice (53). The induction of an animal model of heparin – induced thrombocytopenia is difficult due to the lack of FcγRIIA receptors in mice platelets. In addition, the platelets of the mice do not express the human PF4 platelet factor (54). Thus, transgenic mice that express both human FcγRIIA and PF4 were used here. In this case, the monoclonal antibody of knockout mice (KKO) reacted against the PF4/heparin complex and reduced the platelet count by 80% (55). This model can be used as a systematic study to identify important factors in the development of HIT and to explore possible therapies to improve patients' health.

Infectious thrombocytopenia: Viral infections have led to antibody-dependent autoimmune diseases such as anemia and thrombocytopenia in both animal and human models. One of them is the Lactate dehydrogenase elevating virus (LDV), which was used to induce thrombocytopenia in mice (56). This thrombocytopenic model is related to the activation of phagocytic cells by interferon gamma (57). In the

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study of Aslam et al., the expression of Toll-like receptors on mice platelets modified the thrombocytopenia induced by lipopolysaccharide (58). Moreover, Endotoxin and Thioflavin were used to induce infection and thrombocytopenia in rats and mice (59, 60). In an in vitro study, lipopolysaccharide significantly increased the enzyme-linked phagocytosis of antibody-coated platelets by human monocytes (61).

Thrombocytopenia in NZW x BXSB: One of the first animal models of immune thrombocytopenia was caused by systemic lupus erythematosus (SLE), which was induced in male NZW x BXSB (W/BF1) mice (62). The mating between female NZW mouse and male BXSB mouse resulted in the birth of male mice (F1) with systematic autoimmune conditions with progressive thrombocytopenia (63).

The parent mice (NZW and BXSB) and the three-month-old female mouse (W/BF1) have normal platelet count (62). Bone marrow transplantation or stem cell transplantation from W/BF1 mouse to the mouse with resistance to autoimmune disease induces thrombocytopenia and lupus nephritis in the recipient animal (63).

Thrombocytopenia caused by platelet injections

Fetal and neonatal immune thrombocytopenia: Chen et al. developed the fetal and neonatal immune thrombocytopenia model (FNIT) in which the platelets of the mice with integrin β3+ (β3 $^{+/+}$ FcRn $^{-/-}$ and β3 $^{+/+}$ FcRn $^{+/+}$) were transmitted to mice lacking this protein (β3 $^{-/-}$ FcRn $^{-/-}$ and β3 $^{-/-}$ FcRn $^{+/+}$) and immunized them. Antibodies produced against β3 resulted in the formation of thrombocytopenia in adult mice β3 $^{+/+}$ FcRn $^{-/-}$. FNIT was observed when β3 $^{-/-}$ FcRn $^{+/+}$ female immunized mice were fertilized by β3 $^{+/+}$ FcRn $^{+/+}$ male mice. However, it was not observed when β3 $^{-/-}$ FcRn $^{-/-}$ female immunized mice were fertilized by β3 $^{+/+}$ FcRn $^{-/-}$ male mice (64).

CBA/Ht model: This is a model for inducing thrombocytopenia in mice that results in transient thrombocytopenia in mice through the transfer of rat platelets to CBA/Ht mice (65). Three weeks after transfer of platelet from rats, significant thrombocytopenia was observed in the mice. BALB/C, DBA/2 and C57BL/6 mice were also examined, but no thrombocytopenia is induced after transfer of platelet from rats (45).

Table 1. Summary of non–immune thrombocytopenia animal models and their results

Author	Platelet count	Injection method	Frequency of injection	Dose mg/kg	Animal model	Drug
Hong et al. 2009 (9)	On day 7, 30% decrease	SC	Three consecutive days	100	Mouce Balb/c	Cyclophosphamide
	On day 7, 18% decrease	SC	Three consecutive days	120		
	On day 7, 21% decrease	SC	Three consecutive days	140		
	On day 15, 60% mortality	Tail vein injection	Day 1	200		
	On day 7, 59% decrease On day 15, 74%	IP	Day 2 – 7	30		
Merwid-Ląd et al. 2011 (10)	On day 7, 33% decrease On day 11, 75% decrease Platelet count decreased to 396 × 10^9/L	SC Intragastric	Three consecutive days 10 Days	150 15	 Rat	
Patil et al. 2013 (11)	Thrombocytopenia on day 7 (167 and 555 cell/mm^3)	SC	Three consecutive days	50	Rat	
Akhter et al. 2014 (12)	Thrombocytopenia on day 7 (2.68 × 10^5 /µL)	SC	Three consecutive days	100	Rat	
Chang et al. 2009 (13)	--	IP	Three consecutive days	30	Rat	
Zhang et al. 2003 (14)	49% decrease	Tail vein injection IP	Day 1 Day 2 – 8	200 30	Mouse Balb/c	
Kristiana et al. 2013 (15)	Thrombocytopenia on day 7 (176.6 × 10^3 /µL)	SC	Three consecutive days	25	Rat	
	Thrombocytopenia on day 7	SC	Three	50		

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	(111.2× 10^3 /µL)		consecutive days			
	Thrombocytopenia on day 7 (34×10^3 /µL)	SC	Three consecutive days	100		
	Thrombocytopenia on day 7 (46×10^3 /µL)	SC	Three consecutive days	150		
Rinehar et al. 1995 (16)	Thrombocytopenia on days 3 – 10 (Highest decrease on day 10)	Tail vein injection	Single dose	200	Mouse C3H/HeJ	Carboplatin
Tahir et al. 2014 (17)	Thrombocytopenia on day 7 (46×10^9 /µL)	IP	Single dose	125	Syrian Mouse	
Ulich et al. 1995 (18)	Thrombocytopenia on days 5 – 8 Recovery on days 15 – 17	IP	Single dose	125	Mouse Balb/c	
Konishi et al. 1995 (19)	60% decrease	IP	Single dose Single dose	1.2 5 Gy/fraction	Mouse ICR	
Bailey et al. 2003 (20)	75 to 180 thousand in most of the studied dogs	IV	Single dose	175	Dog	
Saitoh et al. 2001 (21)	On day 8, the highest decrease	IP	Two consecutive days	50	Syrian Mouse	
Woo et al. 2007 (22)	On days 9 to 11, 90% decrease	IV	Single dose	60	Rat	
McElroy et al. 2013 (23)	Thrombocytopenia on days 7 – 14	IP	Single dose Single dose	62.5 5 Gy/fraction	Mouse B6D2F1 (BDF1)	
McElroy et al. 2013 (23)	Thrombocytopenia on days 35 – 42	IP	Single dose Single dose	56.25 4.5 Gy/fraction	Mouse B6D2F1 (BDF1)	
Hahn et al. 1997 (24)	Significant platelet loss at doses of 200 and 250 (On day 14, 96.500/Lµ).	IV	Single dose Single dose Single dose	150 200 250 mg/m^2	Cat	
Bartucci et al. 2011 (25)	Thrombocytopenia on day 7	IP	Days 0 and 4	5	Mouse C57/BL6	Cisplatin
Asna et al. 2005 (26)	75% decrease	IP	Five consecutive days	5	Mouse ICR	
Hahn et al. 1997 (27)	Platelet count after 5 weeks (308×10^3/µL)	IV	One day a week for 5 weeks 4 days a week	20 mg/m^2 2 Gy/fraction	Dog	
Knapp et al. 2013 (28)	Bone marrow suppression in 60% of dogs	IV Oral	21 days One day a week	60 mg/m^2 5	Dog	Cisplatin Firocoxib
	Bone marrow suppression in 40% of dogs	IV	21 days	60 mg/m^2	Dog	Cisplatin
Kuter et al. 1995 (29)	Thrombocytopenia on day 14 (11696/µL)	SC	Days 0 and 3	25	Rabbit	Busulfan
Nasiri et al. 2012 (30)	Thrombocytopenia on day 7 ($50 – 70 \times 10^3$/µL)	SC	Days 0, 2, 4, 6	15	Rabbit	
Taguchi et al. 2015 (31)	Thrombocytopenia on day 10 (27.7×10^4/µL)	IP	Days 0 and 3	20	Rat	
Inagaki et al. 2004 (32)	Platelet count on days 15 – 18 (less than 200000/µL)	IP	Days 0 and 3	15	Mouse Balb/c	
Pitchford et al. 2005 (33)	83% decrease	IP	Days 0, 2, 4	20	Mouse C57BL/6	
Murai et al. 2014 (34)	Thrombocytopenia on day 4	Tail vein injection	Single dose	2.5	Mouse ddY	Bortezomib
Giver et al.	Thrombocytopenia on day 4	—	Single dose	1	Syrian Mouse	Bortezomib

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2012 (35)	(Plate count, 250 × 10^3/µL)			2		Romidepsin
Gammulle et al. 2012 (36)	Thrombocytopenia, 24 hours after injection	Oral	Single dose	15	Rat	Hydroxyurea
Lane et al. 2001 (37)	Platelet count on day 7, declining to 40% normal	IP	Single dose	100 µg/day	Mouse BALB/c	Anagrelide
Arollado et al. 2013 (38)	Thrombocytopenia on day 15	Oral	15 days	0.083	Rat	
Bano et al. 2013 (39)	Thrombocytopenia, 8 days after the last injection (287 × 10^9/µL)	IP	Two days a week (8 weeks)	0.8	Rat	Oxaliplatin

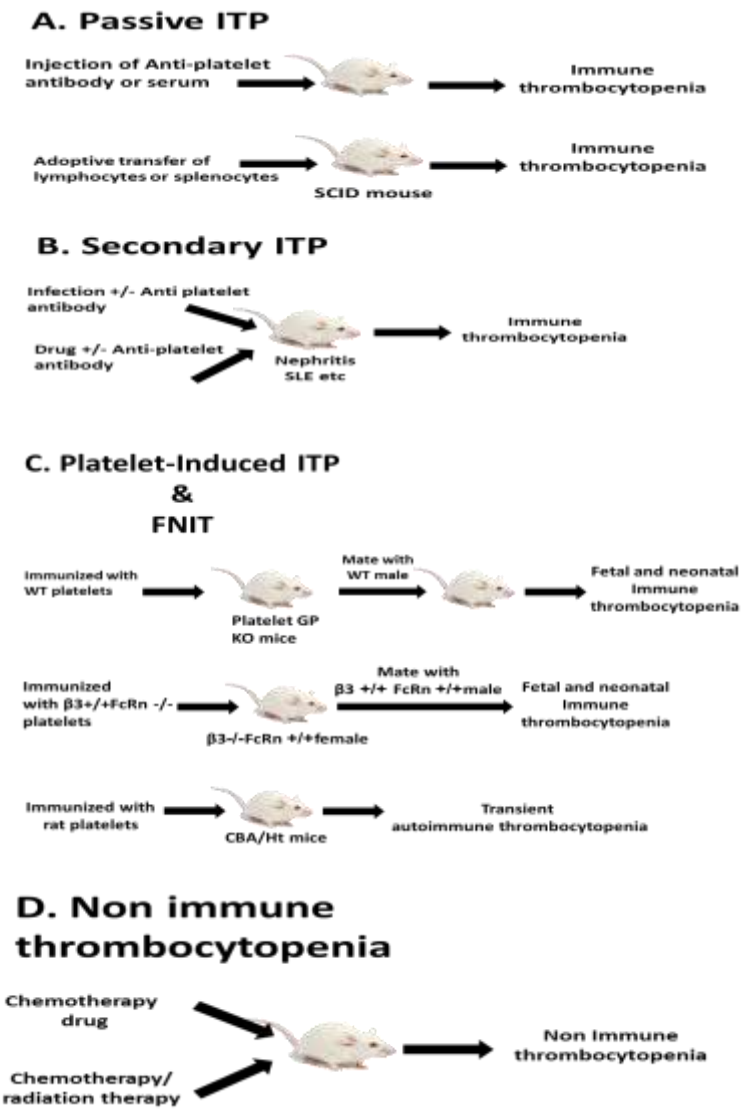

Figure 1. Summary of various animal models of thrombocytopenia. A. Passive immune thrombocytopenia is caused by the transfer of monoclonal antibodies or serum or transient cell transduction. B. Secondary immune thrombocytopenia is associated with certain diseases and some drugs and infections. C. In the platelet-induced thrombocytopenia model, the GPIIIa female knockout mice were immunized by wild-type platelets plus GPIIIa. Then, they mated with wild-type male mice, and as a result, fetuses with GPIIIa showed significant thrombocytopenia. The transfer of platelets from rats to CBA/Ht mice resulted in transient thrombocytopenia in these mice. Another variant of this model is observed in the fatal and embryonic immune thrombocytopenia in which β3 $^{-/-}$ FcRn $^{+/+}$ mice are immunized by β3 $^{+/+}$ FcRn $^{-/-}$ mouse platelets and after being fertilized by β3 $^{+/+}$ FcRn $^{+/+}$ mice, fetal and neonatal immune thrombocytopenia (FNIT) is observed. D. Non – immune thrombocytopenia is caused by the injection of chemotherapy drugs or simultaneous use of radiation and chemotherapy drugs.

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Discussion

The study of human thrombocytopenia is associated with ethical constraints and numerous problems. In addition, in vitro models of cell culture are few and inefficient. For this reason, particular attention has been paid to animal models. There are several empirical models for the development of thrombocytopenia and the identification of the effect of its causative factors, each of which has advantages and disadvantages. The proposed immune and non-immune thrombocytopenia models have advantages and limitations and are selected for therapeutic purposes. In non-immune models, chemotherapy drugs are often used to suppress bone marrow and reduce platelet production, and experimental animals used are often rats and mice.

Cyclophosphamide and carboplatin drugs are most commonly used and inducing thrombocytopenia using these drugs is more efficient. Most animal models of immune thrombocytopenia have been performed on mice. Among the immune models, passive thrombocytopenia and the transfer of antiplatelet antibodies have been used more frequently. Fewer capabilities of antiserums (serum containing antiplatelet antibodies) with polyclonal antibodies against monoclonal antibodies to produce thrombocytopenia is due to their lower specificity in binding to platelet antigens. Although there are numerous empirical models for animal thrombocytopenia, because of the importance of the subject, the development of research in this field and the identification of more effective models are necessary.

Conflict of Interest: No conflicts of interest.

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