



Disorders of Platelet Function

An Information Booklet for Patients,
Families and Health Care Providers

Third Edition

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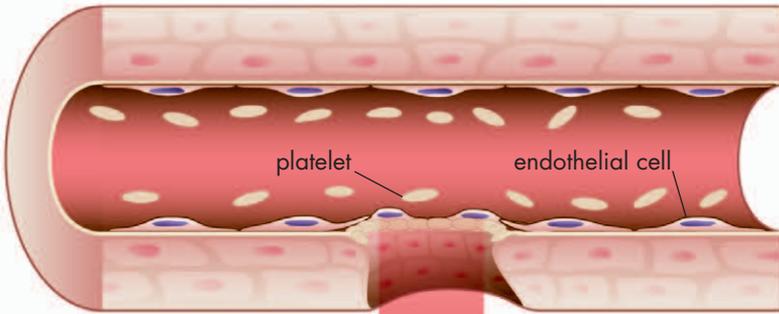
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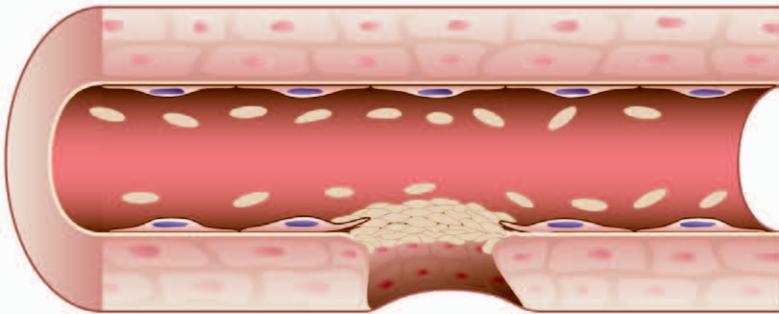
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Introduction

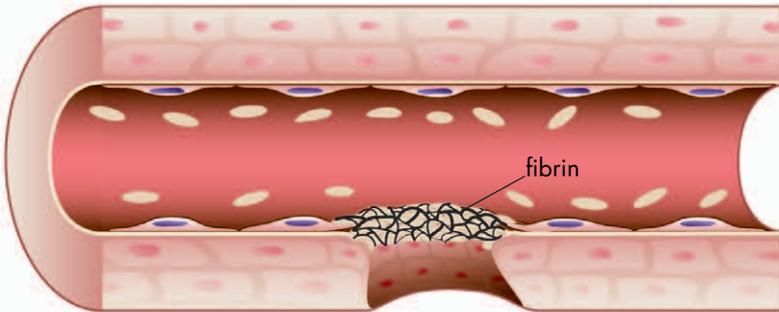
Blood is carried throughout the body in a network of blood vessels. When tissues are injured, damage to a blood vessel may result in leakage of blood through breaks in the vessel wall. Normally, bleeding stops through two processes that work together to form a blood clot: the formation of a platelet plug that is then made stable by a protein called fibrin. Platelets are small cells (about 1/5000th of a centimeter in diameter) that circulate in blood, and that play a primary role in stopping the bleeding and beginning the repair of injured blood vessels. Platelets stick to, and spread on, areas of the damaged blood vessel wall (this is called platelet adhesion). These spreading platelets release substances that activate other nearby platelets, which clump at the site of injury to form a platelet plug (this is called platelet aggregation). The activated platelets then provide a surface on which clotting proteins are activated to form a mesh-like fibrin clot (**Figure 1**). A normal blood clot will not form when platelet numbers are low, platelet function is abnormal or clotting protein levels are low or absent. Individuals with these conditions have a bleeding disorder. This booklet will focus specifically on disorders of platelet function.



When a blood vessel is injured, platelets stick to the area of damaged vessel



Platelet plug forms at site of injury



Fibrin clot formation

Figure 1 Platelet adhesion and aggregation. Platelets adhere to the damaged vessel wall, spread, and release substances from their granules that recruit other platelets to the plug. The platelet plug is stabilized by a meshwork of fibrin.

What is a platelet?

Platelets are small disc-shaped cells that circulate in the blood in large numbers. A teaspoon of blood contains approximately one billion platelets. A normal platelet count is usually reported as $150\text{-}400 \times 10^9/\text{L}$. Platelets have a number of important components responsible for their normal function (**Figure 2**).

Receptors

Receptors are proteins on the surface of the platelet that allow the platelet to interact with the blood vessel wall or with other blood cells, or to respond to substances in the circulation or

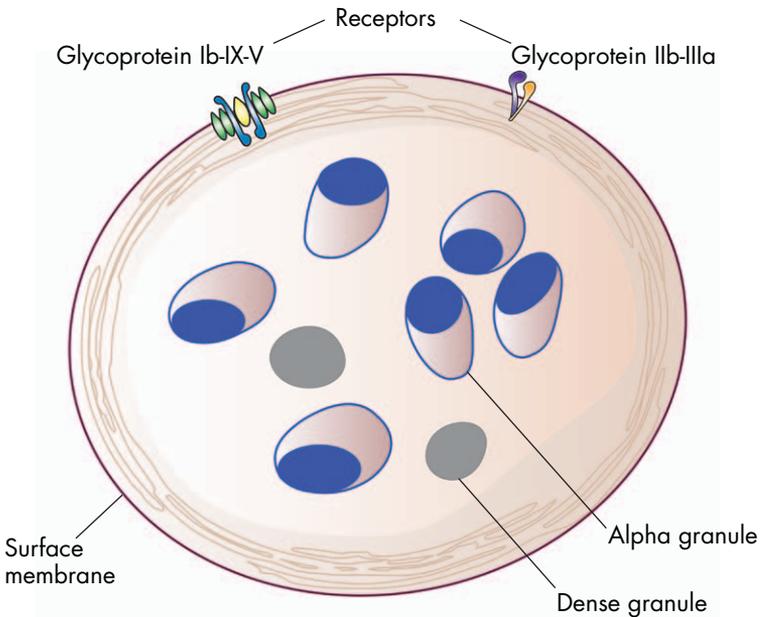


Figure 2 Platelet structure.

released by other platelets. Two receptors that are important for platelet adhesion and aggregation are Glycoprotein Ib-IX-V and Glycoprotein IIb-IIIa. Glycoprotein Ib-IX-V is a receptor for a large protein called von Willebrand factor (VWF) that promotes the adhesion and spreading of platelets on an injured blood vessel wall. Glycoprotein IIb-IIIa, also called the fibrinogen receptor, is necessary for platelet clumping or aggregation to form the platelet plug.

Granules

Granules are small sacks inside platelets where proteins and chemicals are stored. When platelets are activated, the granule contents are released into the blood (**Figure 3**). There are two types of granules: (1) Alpha granules contain proteins that bring other cells to the platelet plug and promote healing of injured blood vessels. (2) Dense (or delta) granules contain substances that promote platelet activation and cause the blood vessel wall to contract, constricting blood flow, and decreasing blood loss.

Surface membrane

The surface membrane is made up of fatty molecules called phospholipids. These phospholipids promote the binding and activation of blood clotting proteins and ultimately the formation of the fibrin mesh clot that strengthens the platelet plug.

Abnormalities or deficiencies of any of these important components can lead to disorders of platelet function. When the platelet plug does not form properly, increased or prolonged bleeding can occur.

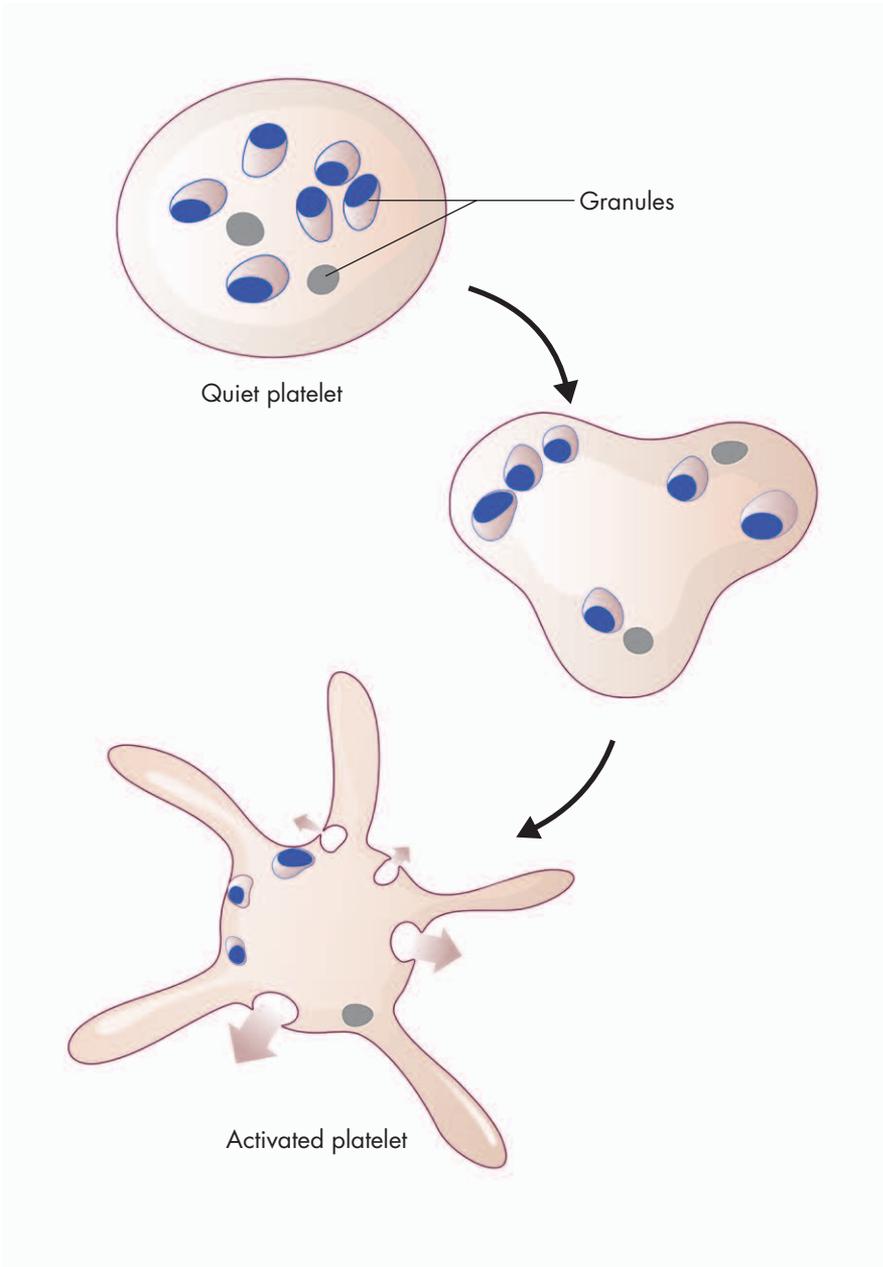


Figure 3 Release of platelet granule contents.

What type of bleeding difficulties do people with platelet function disorders have?

The diagnosis of a platelet function disorder can be made at any age. Usually, people with more severe bleeding problems will be diagnosed earlier than those with mild problems.

Typical problems include:

- frequent nosebleeds
- easy bruising
- bleeding from the gums
- heavy or prolonged menstrual periods or bleeding with childbirth
- prolonged or excessive bleeding at the time of surgery or dental work.



The bleeding symptoms can be highly variable, even among members of the same family. The majority of people will have mild symptoms and many individuals have no symptoms at all unless they have a serious injury or an operation. In some individuals, however, platelet function disorders can cause severe bleeding. Information about your platelet function disorder or that of a family member should always be given to a dentist or surgeon planning an operation so that steps can be taken to prevent bleeding.

How can platelet function disorders be diagnosed?

Information about your bleeding problems will help the doctor decide whether you need to be tested for a platelet function disorder. No single test can diagnose all platelet disorders. Useful tests include:

Platelet counts

Counting the platelets present in the blood can show whether the number of platelets is normal or decreased. A decreased number of platelets is called thrombocytopenia. There are many causes of decreased platelet numbers, but some platelet function disorders also have decreased numbers of platelets.

Examining platelets with a microscope

Looking at a drop of blood under the microscope can show whether platelets are larger or smaller than normal, and whether they contain granules. Looking at the other types of blood cells (red blood cells and white blood cells) can also provide clues to certain platelet disorders.

Bleeding time

The bleeding time is measured by inflating a blood pressure cuff on the upper arm and making a small cut on the forearm. The time it takes for this cut to stop bleeding is called the bleeding time. The bleeding time is longer than normal in patients with decreased numbers of platelets or abnormal platelet function. The bleeding time is rarely used if more specific tests are available.

Closure time

The closure time is a test that measures the time it takes to form a platelet plug using a laboratory instrument called the PFA-100®. This test mimics some of the conditions of a bleeding time. The closure time is often prolonged in patients with decreased numbers of platelets or abnormal platelet function.

Platelet aggregation studies

Platelets are separated from a blood sample and stirred in tubes in an instrument called an aggregometer that monitors for platelet clumping (aggregation). Substances (examples: collagen, epinephrine, ADP, ristocetin) are added to stimulate the platelets to aggregate and the effects are recorded (**Figure 4**). Decreased or absent platelet clumping will give an indication of the type of platelet function disorder.

von Willebrand factor (VWF) studies

VWF is a large blood protein that promotes platelet adhesion to blood vessels. In von Willebrand disease (VWD), VWF is deficient or abnormal and platelet adhesion to injured vessel walls is decreased. Because the bleeding symptoms can be similar in VWD and platelet disorders, tests to measure VWF may be done.

If the bleeding time, closure time, or platelet aggregation studies are abnormal, a platelet function disorder may be present. To determine the exact nature of the disorder it may be necessary to do further specialized tests that examine the surface membrane receptors, granules or the platelet's ability to promote clotting.

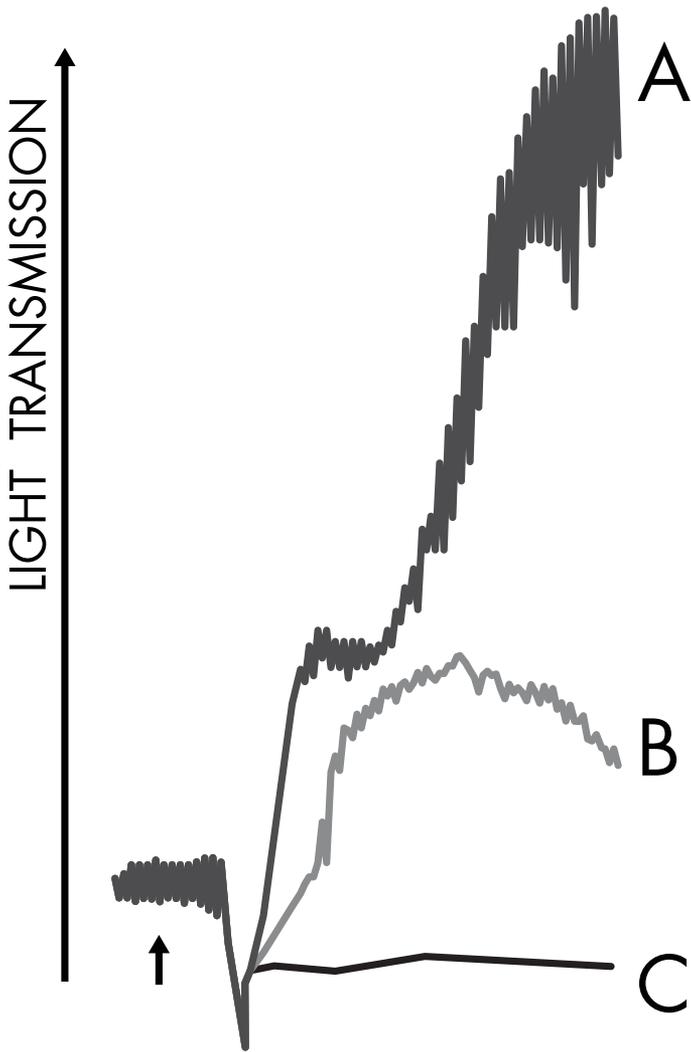


Figure 4 Platelet aggregation response as measured by an aggregometer. After the addition of an activator (arrow) normal platelets change shape and then clump, increasing light transmission (A). Platelets from a person with a platelet function disorder may show a partial response (B) or no response (C).

Types of platelet function disorders

Platelet function disorders may be hereditary (meaning that they are passed down from parent to child), or acquired (meaning that they are caused by other diseases or medications).

Hereditary platelet disorders can be divided into subgroups depending on the type of abnormality:

Disorders of platelet adhesion

Bernard-Soulier syndrome is a rare hereditary deficiency in the platelet receptor Glycoprotein Ib-IX-V. Glycoprotein Ib-IX-V is the receptor for von Willebrand factor and when it is absent, platelets cannot stick or spread at sites of blood vessel injury. Bleeding problems often begin in childhood with bruises, nosebleeds or mouth bleeds. There may also be bleeding from the gastrointestinal tract or, in women, heavy menstrual periods. The bleeding time and closure time are usually markedly prolonged, the platelet count is low, and the platelets are larger than normal. Platelet aggregation tests with a substance called ristocetin are also abnormal.

Disorders of platelet aggregation

Glanzmann thrombasthenia, a rare hereditary deficiency of Glycoprotein IIb-IIIa, results in an inability of platelets to aggregate. Patients with thrombasthenia usually have bleeding problems that start during childhood with bruising, nosebleeds or mouth bleeding. Women may experience heavy menstrual periods

or bleeding at the time of childbirth. Bleeding times and closure times are markedly prolonged and platelet aggregation to all stimuli except ristocetin is absent.

There are other rare disorders of platelet aggregation in which receptors to activating substances such as ADP are absent.

Disorders of platelet secretion

Abnormalities in the release of platelet granule contents may be due to abnormalities of the platelet granules themselves, or due to an abnormality of the secretion mechanism.

Alpha granule deficiency (gray platelet syndrome) results in the absence of important proteins contained inside the alpha granule that promote platelet adhesion, aggregation and repair of the injured blood vessel wall. The bleeding time and closure time are often prolonged and the platelet count is usually low. Platelet aggregation studies may show some abnormalities and an examination of platelets with a microscope shows the absence of granules; the absence of these granules make the platelets appear gray.

Dense granule deficiency (delta storage pool deficiency) results in decreased numbers of these granules and the chemicals stored inside them that promote clot formation. This can cause mild to moderate bleeding problems, usually bruising and nosebleeds. Bleeding times and closure times are often long, and platelet aggregation studies can have an abnormal pattern. Special studies can show whether the dense granules or their contents are missing. Some patients have additional conditions including

light hair and eye colour, poor vision, or an increased susceptibility to infection (Hermansky-Pudlak syndrome and Chediak-Higashi syndrome).

Secretion defects occur when the granule secretion mechanism is abnormal. The platelets have normal numbers of granules but they do not empty their contents when platelets are activated. These individuals have a platelet disorder that resembles the effect of aspirin on platelets (discussed on page 17).

Disorders of platelet procoagulant activity

Rare patients have a deficiency of the platelet surface membrane to promote the activation of blood clotting proteins. In this condition (Scott syndrome), bleeding time, closure time and platelet aggregation are all normal. Specialized testing is required to examine the platelet surface membrane to determine whether it can support the binding of blood clotting factors.

Combined abnormalities of number and function

Some inherited disorders of platelets have a combination of decreased numbers of platelets, platelets of abnormal size (either larger or smaller than normal) and function abnormalities. The most common example is the MYH9-related disorders, named for the gene that is defective in all of the related disorders (these disorders are: May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome, and Sebastian syndrome). These individuals have low platelet counts, and larger than normal platelets. Specialized testing can show abnormalities of a protein called myosin. Some individuals will have additional health problems including poor kidney function, hearing loss or cataracts.

Non-specific abnormalities

Platelet function abnormalities that do not fit neatly into one of the five categories listed above are quite common. Patients often have mild to moderate bleeding problems, prolonged bleeding times or closure times and variable abnormalities on platelet aggregation tests. Although it is not possible to give these abnormalities a specific name, they usually respond well to the treatments described in the next section.

Acquired disorders of platelet function are far more common than hereditary disorders. Information about medications or illness is very important in determining the cause of a platelet abnormality. The most frequent causes of acquired disorders of platelet function are:

- Commonly used drugs that block platelet function including aspirin (ASA) and other non-steroidal anti-inflammatory drugs (such as indomethacin, ibuprofen, naproxen). Antiplatelet medications (such as clopidogrel) block platelet activation or aggregation. Many other types of medication including blood thinners, seizure medications, heart drugs, antidepressants, anesthetics, and antihistamines, can affect platelet function. Platelet function returns to normal when these medications are stopped.
- Medical conditions associated with the development of abnormal platelet function including chronic kidney disease, cardiac bypass surgery, infections, some forms of leukemia or other bone marrow problems (such as myeloproliferative disorders).

How can bleeding difficulties in patients with platelet function disorders be treated?

The treatment of platelet function disorders will depend on the particular type of disorder, as well as the severity of the bleeding. Most patients require no therapy on a regular basis, but may need treatment at the time of surgical procedures (including tooth extraction and dental surgery) or following an injury. Dentists and surgeons should be told that a patient or family member has a platelet function disorder so that they can plan appropriate treatment. Treatment options may include the following:

1. **Desmopressin (DDAVP® and Octostim®).** Desmopressin is a drug that can be used to shorten the bleeding time and decrease blood loss in many patients with platelet function disorders. It can be injected intravenously (into a vein) or subcutaneously (under the skin), before surgery or following an accident, to prevent or decrease excessive bleeding. Desmopressin may also be given as a nasal spray (Octostim®).
- The response to desmopressin varies among individuals – giving a trial dose of desmopressin to determine whether it is effective can be done before deciding whether it will be useful.
 - Side effects of desmopressin include headache, flushing and a fall in blood pressure. Serious side effects of desmopressin are very rare but may occur under certain circumstances. Because desmopressin promotes blood clot formation there is a small risk of heart attack in older patients with coronary artery disease. Because it causes water retention, careful control of fluid intake is important in children and the elderly. Water retention can cause changes in the blood salt content, increasing the risk of seizures.

2. **Recombinant Factor VIIa (rFVIIa; Niasase®).** Recombinant Factor VIIa has been reported to be effective in some patients with Glanzmann thrombasthenia and Bernard-Soulier syndrome for treatment of bleeding and for operations. This agent can be useful in patients who no longer respond to platelet transfusions because they have developed antibodies to platelets from previous transfusions. It is also useful in place of platelet transfusions to avoid the development of platelet antibodies. For treatment of bleeding and in preparation for operations, rFVIIa appears to work well when it is given by short repeated injections than by a continuous slow injection.
3. **Antifibrinolytics.** Aminocaproic acid (Amicar®) and tranexamic acid (Cyklokapron®) are antifibrinolytic drugs that stabilize the blood clot and help prevent bleeding from starting again. These drugs can be taken by mouth. They can also be made into a solution and put directly on the lining of the nose or mouth using a piece of gauze or gently swished in the mouth.
4. **Hormonal therapy.** Birth control pills can be used to decrease heavy menstrual bleeding. An intrauterine device that releases a synthetic progesterone hormone (Mirena IUS®) has also been shown to decrease menstrual bleeding in women with bleeding disorders.
5. **Platelet transfusion.** Some types of platelet function disorders, including Bernard-Soulier syndrome and Glanzmann thrombasthenia, usually do not respond to desmopressin therapy and may require treatment with platelet transfusions for bleeding or in preparation for surgery.



Recommendations for some common types of bleeding are discussed on the next two pages.

Nosebleeds

Repeated nosebleeds can be a serious problem for some people with platelet function disorders. Start treating a nosebleed with local measures: sit quietly with the head tilted forward pinching the soft parts of the nose firmly for at least ten minutes. Apply cold compresses on the bridge of the nose or face. Treatment for a prolonged nosebleed may require the use of desmopressin or platelet transfusion. Antifibrinolytic medications are often useful once the nosebleed has stopped to prevent recurrence. In addition, other treatments may be useful:



- Ointments and creams can be applied to the inside of the nose once bleeding has stopped to prevent drying of the nasal membrane and promote healing. These can be simple lubricants such as petroleum jelly or propylene glycol (Secaris®), or for more severe problems, estrogen cream can be used for short periods of time.
- In places where the weather is dry, increasing the humidity of the room or using saline nose sprays several times a day may help to decrease the frequency of nosebleeds.

Bleeding associated with menstruation and childbirth

Some women with platelet function disorders have heavier or longer menstrual periods. Girls can experience heavy bleeding from the time that they begin menstruation. Desmopressin, antifibrinolytic drugs, or rFVIIa may help decrease bleeding if used at the beginning or during each period. Long-term control of heavy periods may require the use of hormonal therapy (birth control medications) or the Mirena IUS® to control excessive menstrual bleeding.

During pregnancy, women with platelet function disorders should discuss a plan for delivery with their doctors. The management plan will depend on the specific platelet function disorder, the individual's experience with previous bleeding episodes, and the type of delivery (vaginal delivery or caesarean section). There is an increased risk of bleeding immediately following delivery and the risk continues for a few weeks. If heavy bleeding occurs during that time, you should contact your doctor immediately.



Dental extraction surgery

Appropriate preparation for dental work should include desmopressin (or other effective alternative) if teeth will be pulled or local anesthetic (freezing) will be given. Mandibular blocks should not be used unless the platelet function abnormality is completely corrected by desmopressin (or other effective alternative). Antifibrinolytic medication can decrease bleeding following tooth extraction or surgery. These drugs are often started immediately before the surgery and continued for several days. Application of fibrin glue (sealant) to the surgical/extraction wound is also useful.



Depending on the specific platelet disorder, other types of treatments may be recommended by your doctor.

Can bleeding associated with platelet function disorders be prevented?

Most individuals with mild to moderate platelet function disorders lead normal lives without having serious bleeding but do require treatment before or after major surgery. A number of precautionary measures can be taken to decrease the likelihood of bleeding:

- Aspirin, medications that contain aspirin, and other nonsteroidal anti-inflammatory medications (ibuprofen, naproxen, indomethacin and many others) cause a further defect in the function of platelets and therefore should be avoided. Many over-the-counter medications and remedies contain aspirin or other nonsteroidal anti-inflammatory medications and you must read the labels carefully. For fever or pain, acetaminophen (Tylenol® or Tempra®) should be used.



- Blood thinners, such as warfarin or heparin, may cause increased bleeding in patients with platelet abnormalities.



- Some foods, food additives and herbal remedies can interfere with platelet function. Examples are: alcohol, diets rich in fish oils, Chinese black tree fungus, ajoene (a component of garlic), feverfew, willow bark, and saw palmetto.

- Preventive dental care can decrease the need for dental surgery. Care includes regular tooth brushing, flossing, supplemental fluoride, and regular dental check-ups. Babies should not be put to bed with bottles once their first teeth appear. Older children should avoid snacks high in sugar.



- Individuals with a platelet function disorder should carry information about their disorder, the treatment required, and the name and telephone number of their physician or treatment centre. The wallet-sized TreatFirst card can be used for this purpose (available at: www.hemophilia.ca/emergency). A medical bracelet or card can alert medical personnel to the platelet abnormality in case of an emergency.

- All children should wear a helmet while riding a bicycle, skating, rollerblading or skateboarding, and this recommendation should certainly be followed for children – and adults – with a platelet function disorder.



Conclusion

Please discuss your platelet disorder with your doctor. Depending on the type of disorder and its severity, your doctor will make specific recommendations regarding diagnosis and treatment. Your doctor will also recommend whether other family members should be tested for this platelet function disorder.



Further information

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