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Literature Reviews

Clinical Consideration of Thrombocytopenia in Children

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ABSTRACT

Background: *Pediatric patient with the history of bleeding disorder as thrombocytopenia is considered as a clinical case in dentistry. The patient with platelet count below normal has potential risk of bleeding disorders. The situation would be more dangerous if the dentist could not identify the problem.* ***Purpose:*** *The aim of this review is to describe how a dentist must understand the step and management that should be performed in pediatric patient with history of bleeding disorder due to thrombocytopenia.* ***Reviews:*** *Bleeding disorders might be the result of thrombocytopenia, a condition that alter the ability of blood vessels, platelet and coagulation factors in normal hemostatic system. Thrombocytopenia is defined as a platelet count of less than normal (150.000/mm^3–400.000/mm^3). Etiology, risk factor and preventive method of thrombocytophenia are still unknown.* ***Conclusion:*** *It is concluded that special attention is needed for pediatric patient with thrombocytopenia. A dentist should understand well about this disorder on how to take the history, to do clinical examination, to establish the diagnosis and to decide treatment plan as well as to consult to related collongues.*

Key words*: Bleeding disorder, thrombocytopenia, dentist*

ABSTRAK

Latar belakang: *Penderita anak-anak dengan riwayat gangguan perdarahan yang ditandai dengan adanya trombositopenia merupakan masalah klinis yang ditemukan dalam bidang kedokteran gigi. Beberapa perawatan di bidang kedokteran gigi beresiko menimbulkan terjadinya perdarahan. Keadaan akan berbahaya bila dokter gigi tidak dapat mengidentifikasi masalah.* ***Tujuan:*** *Artikel ini menunjukkan pentingnya seorang dokter gigi memahami dan mengetahui langkah dan tindakan apa yang harus dilakukan, bila suatu saat menghadapi penderita anak-anak dengan riwayat gangguan perdarahan akibat trombositopenia.* ***Review:*** *Gangguan perdarahan adalah suatu kondisi terjadinya penurunan kemampuan dari pembuluh darah, platelet, dan faktor pembekuan pada fungsi normal hemostasis. Trombositopenia adalah jumlah trombosit/platelet dalam darah berada pada jumlah di bawah normal (150.000/mm^3–400.000/mm^3), yang dapat mengakibatkan terjadinya gangguan perdarahan. Penyebab, faktor risiko dan cara pencegahan kasus trombositopenia belum diketahui dengan pasti.* ***Kesimpulan:*** *Diperlukan perhatian khusus pada penderita anak yang mengalami gangguan perdarahan. Seorang dokter gigi harus mengetahui dengan baik bagaimana menggali informasi tentang riwayat penyakit, melakukan pemeriksaan klinis yang tepat, menegakkan diagnosis, menentukan rencana perawatan serta melakukan rujukan bila diperlukan.*

Kata kunci: *Gangguan perdarahan, trombositopenia, dokter gigi*

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INTRODUCTION

The sign and symptom of thrombocytopenia that connected to hematologic disease, commonly caused by the decreasing or increasing of erythrocyte (anemia or erythrocytosis); leukocyte (leucopenia or leucocytosis); thrombocyte (thrombocytopenia or thrombocytosis), hemostatic disturbance (bleeding or coagulation) or

neoplasia in lymphoreticular system (lymphoma or dyscrasia of plasma cell).[1,2]

Thrombocytopenia defined as platelet count of less than normal, is the most common cause of defective primary hemostasis that can lead to significant bleeding in children.[3] This condition is sometimes associated with abnormal bleeding. Bleeding disorders are conditions that alters the ability of blood vessel, platelet and coagulation factor in normal hemostatic function. Genetic factor also plays an important role in bleeding disorders but without genetic factor, it should be due to disease related to the integrity of blood vessel wall, platelet and coagulation factor and can also be contributed by the use of medicine, radiation or chemotherapy in cancer case. Most of bleeding disorders are iatrogenic.[4]

Pediatric patient with the history of bleeding disorder indicated to have thrombocytopenia is considered clinical case in dentistry. Bleeding is also a potential risk in dental treatment. In normal patient, the risk of bleeding can be minimized. In patient with the decrease of bleeding control ability due to medication or a certain disorder, this condition would endanger the patient if the dentist could not identify the problem.

Correct diagnosis and management are really necessary. A dentist is highly requested to understand the step and the management that should be performed in pediatric patient with history of bleeding disorder due to thrombocytopenia. The management include medical history, review all medications, proper clinical examination, laboratory screening, establishing diagnosis and correct treatment plan. In addition it is also important to know family history of the patient and with consult to related colleagues.

Definition and etiology of thrombocytopenia

Thrombocytopenia is one of bleeding disorders indicated by decreasing number of thrombocyte/platelet in blood circulating (<150.000/mm^3). Platelet/thrombocyte is an important cell in the process of blood coagulation. The lower number of thrombocytes the higher the risk of bleeding will occur. The normal number of platelet is 150.000/mm^3–400.000/mm^3.[1,2] Etiology, risk factor and method of prevention are still unknown. Many conditions can cause thrombocytopenia.[1] Platelet disorders may devided into two catagories by etiology, congenital and acquired and into two additional categories by type, thrombocytopenias (quantity platelet disorders) and thrombocytopathies (qualitative platelets disorders).[5] The decrease number of platelet/thrombocyte is caused by the failure or decreasing of platelet production, disturbance of platelet distribution and increasing of platelet destruction. Decreasing or failure of thrombocyte production is due to cytotoxic drug (eg: chemotherapy, radiation in malignancy). Radiation therapy or chemotherapy destroys megakaryocytic, the precursor cells that produce platelets in the bone marrow. Aplastic anemia can impair platelet production, spinal cord transplantation, nutrition deficiency (eg: B12, folat, cobalamin) and short-term low platelets is also associated with some viral infection (eg: rubela, varicela, mumps, HIV, Epstein Barr Virus). Disturbance of thrombocyte distribution is caused by abnormal circulating thrombocyte in the spleen or splenomegaly. Meanwhile, increasing of thrombocyte destruction is contributed by immune system disturbance that is: shortening survival time of platelet from 10 days into at the longest 1 day.[2,6–8] Genetic abnormalities, may impair production of normal platelets. A cancer, such as lymphoma, in the bone marrow can inhibit production of platelets. Certain drugs, especially thiazide diuretics or alcohol, depresses production of precursor cells that produce platelets in the bone marrow.[2] Idiophatic thrombocytopenic purpura (ITP) is the most common cause of acute onset thrombocytopenia in otherwise healthy children. It characterized thrombocytopenia due to autoantobody binding platelet antigen, and causing premature destruction of platelet. This condition is frequently associated with history of in viral illness in 50–60% of cases.[9] Other autoimmune diseases, such as HIV infection, systemic lupus erythematosus (SLE), lymphoproliferative disorders, myelodysplasia, hypogammaglobulinemia, drug induced, can cause thrombocytopenia.[10]

Classification of bleeding disorders

Bleeding disorders are devided into non-thrombocytopenic purpuras, thrombocytophenic purpuras, and disorders of coagulant. The first, non-thrombocytopenic purpuras consist of vascular wall alteration (eg: scurvy, infection, chemicals, allergy) and disorders of platelet function (eg: genetic defects/Bernard-Soulier disease; drugs like aspirin, NSAID, alcohol, beta-lactam antibiotics, penicillin, cephalotins; allergy; autoimmune disease, Von Willebrand's disease/secondary factor VIII deficiency, uremia). The second, thrombocytopenic purpuras consist of primary-idiophatic and secondary (eg: chemicals, physical agents like radiation, systemic disease like leukemia, metatastic cancer to bone, splenomegaly, drugs (like alcohol, thiazide diuretics, estrogens, and gold salts), vasculitis, mechanical prosthetic heart valves, and viral or bacterial infections). The third, disorders of coagulant is catagorized into inherited and acquired. The inherited group consist of hemophillia A (deficiency of factor VIII), hemophillia B (deficiency of factor IX) and others. The acquired group consist of liver disease, vitamin deficiency (eg: biliary tract obstruction, mal-absorption, excesscive use of broad-spectrum antibiotics), anticoagulation drugs (eg: heparin, coumarin, aspirin and NSAID), disseminated intravascular coagulation and primary fibrinogenolysis.[4]

Pathophysiology of thrombocytopenia

Pathophysiology of thrombocytopenia frequently cannot be understood clearly (idiophatic).[1] Sixty percent of thrombocytopenic patients caused by autoimmune disorder, as a result the antibody would be against membrane of glycoprotein platelet as IgG. Platelet which has been covered by IgG susceptible to phagocytic macrophage of the spleen. IgG autoantibodies might also contribute destruction of megakaryocyte as precursor platelet. consequently in bone marrow the number of platelet would decrease.[11–13]

Clinical symptoms and oral manifestation of thrombocytopenia

Thrombocytopenia is bleeding disorders with the sign of bleeding in epidermal or mucosa, resulting in petechiae (small red patches) or ecchymosis (small hemorraghic spot) in oral mucosa, membrane mucosa and gingiva. Another sign of thrombocytopenia is bruises in epidermal layer or membrane mucosa with unknown cause and if the size of bruises is wider, it is called hematoma.[2,7]

When the platelet drastically decreases until below 40.000/mm^3, in general, the patient will have petechiae, ecchymosis, spontaneous bleeding in gingival, urinary and gastrointestinal tract. The most common character and symptom of thrombocytopenia is manifested in oral cavity, spontaneous bleeding after tooth brushing or small trauma. Gingival bleeding occur easily and repeatedly, followed by blood clot in gingival margin and the color will change gradually into dark color and finally cover the teeth.[2,4] The classical features in children from high income countries such as sudden on set of excessive bruising, petechiae, and or mucous membrane bleeding 1–4 weeks following viral infection.[10]

Laboratory examination

A dentist can recommend the patients suspected with bleeding disorder due to thrombocytopenia to undergo laboratory examination. Items which should be observed are complete blood count which show the size, number and maturity of blood cells. Platelet count is also important to understand the possibility of bleeding disorder due to thrombocytopenia through the number of thrombocyte/platelet: normally between 150.000/mm^3–400.000/mm^3 or 140.00/mm^3–400.000/mm^3. The patient with platelet number 500.000/mm^3–100.000/mm^3 has potential risk of bleeding more serious than normal if he has major trauma, while the patient with platelet number less than 50.000/mm^3 he will have symptom of pupura on the skin and mucosa if he has minor trauma. The patient will have spontaneous bleeding if the number of platelet is less than 20.000/mm^3. Bleeding time must also be examined to understand the bleeding duration and this examination is performed to find congenital disorder of platelet function. The normal bleeding duration is 1–6 minutes.[7] Platelet function analyzer 100 should be observed, to detect platelet dysfunction. The normal value is < 175 seconds. Finally the urine test is used to detect the possibility of infection.[2,4]

Dental management of thrombocytopenia

Patient's identification is very essential to be done by a dentist before performing the treatment. Four methods applied to indentify a patient: to understand the history of illness, to perform physical examination, laboratory examination and to observe postoperative bleeding.[2] To understand the history of illness, some questions are necessary to be given to the patient such as: whether there is bleeding problem in the family (spontaneous bleeding), serious bleeding after trauma, surgery or tooth extraction; what kind of past and present disease suffered by the patient. Patient with thrombocytopenia is not recommended to have regular dental treatment until good general condition is obtained. Emergency treatment should be done palliatively and the patient should be referred and consulted to related colleagues to establish the diagnosis and to decide proper treatment plan. Advice to increase oral hygiene, regular and periodical check up and treatment are really necessary. A dentist can recommend laboratory examinations to detect suspected patient with bleeding disorder by screening the complete blood count, platelet count, bleeding time, platelet function analyzer 100, urine test.[2,4]

The essential treatment in dentistry for thrombocytopenic patient is to reduce the inflammatory by elemination of local irritating factor. Periodontal treatment are scaling and root planning, usually safe for platelet count < 60.000/mm^3. Operation will be done if the platelet count is > 80.000/mm^3, platelet transfusion is possible to be done before surgery if it is necessary. Tooth extraction is the last choice of treatment but it should be performed at the hospital equipped with platelet transfusion.[7] Spontaneous gingival bleeding can be managed with oxidizing mouthwashes. Good oral hygiene and conservative periodontal therapy help to remove the plaque and the calculus that trigger the bleeding. Platelets level of 50.000/mm^3 are desirable before dental treatment and further transfusion should be given as needed to maintain hemostasis.[14]

Mandibular block anesthetic should be avoided to prevent complication such as: hematoma and obstruction of air way. Anti fibrinolytic administration such as: tranexamic acid 15–20 mg/kg body weight is recommended.[15]

The history of illness, the history of medication and the type of anticoagulant are essential to know, therefore, consulting to releated colleagues is needed. Trauma of the operation should be as minimal as possible and local hemostatic agent should be applied. In general, patient with thrombocytopenia is treated using corticosteroid and tends to stress during dental treatment, consequently stress control is necessary to be done. Interaction between barbiturate and anticoagulant must be observed. In thrombocytopenia patient with adequate hemoglobin, nitrous oxide-oxygen is well accepted anxiolytic. Analgesic selection should be well, acetaminophen and/or codein, aspirin and NSAID, should be avoided due to antiprostaglandin effect which will increase the possibility of bleeding. There are some medicines that are potential to contribute thrombocytopenia such: quinine and quinidine.[2,4,7] Penicillin per oral is the main choice to prevent and to treat infection with the main choice to prevent and to treat infection with condition that the patient has no hypersensitivity. Tetracycline is effective to increase coumarin anticoagulant. Prolonged antibiotic administration might disturb the balance of intestinal flora which has important in vitamin K absorption, therefore it might increase the risk of bleeding.[16]

DISCUSSION

Some dental treatments are risky to the occurrance of bleeding. In normal patient, the risk of bleeding can be minimized but in patient with decreasing ability to control bleeding due to medication or a certain disease, this condition would be dangerous if the dentist could not identify the problem.[4] Prolonged bleeding can occur when haemostasis is disturbed. Primary haemostasis is initiated after injury to a blood vessel with the formation of a primary platelet plug. The process is mediated by interactions between platelets, plasma coagulation factors and vessel wall. Defect of primary haemostasis generally result in bleeding from the skin or mucosal surfaces. In patient with thrombocytopenia, the number of platelet is less than normal due to decreasing ability to control bleeding. Decreasing thrombocyte or thrombocyte function will cause initial clot formation failure. Children with thrombocytopenia will have instant bleeding after trauma or surgery. This case is very different from children with hemophilia who suffer from bleeding 4 hours after the onset of trauma.[15]

Acquired thrombocytopenia is classified into immune and non-immune. The example of immune classification is ITP currently, it is known as idiopathic thrombocytopenic purpura is acquired bleeding disorder which most commonly happens in children.[17] The incidence of ITP is 50–100 in 1.000.000 individual/year, and the percentage of children is 50%. This condition is not malignancy and the prognosis is good. According to a research, 15–30% children suffer from acute ITP and alter into chronic ITP.[18] As noted, acute ITP is the most common bleeding disorder of childhood. It occurs most frequently in children aged 2–5 years and often follows infection with viruses such as rubella, varicella, measles, or Epstein-Barr. Most patients recover spontaneously within a few months.[19] Childhood ITP is acute and generally seasonal in nature, suggesting that infectious or environmental agents may trigger the immune response to produce platelet-reactive autoantibodies 4 to 8 weeks following an infection. In general, the patient is well apart from the diffuse bruising and petechiae indicative of a profound thrombocytopenia. The peak age of acute ITP is 2 to 5 years of age, a period when children experience the greatest frequency of viral infections.[20] In infection condition, inbalance of thrombocyte number frequently happens consequently abnormal bleeding can occur such as spontaneous epistaxis in children when having an infection.[21]

The cause, risk factor and preventive method of thrombocytopenic are still unknown. Mostly due to IgG auto body, which bind the platelet by itself.[13] Misdiagnosis of thrombocytopenia sometimes happen. In a research by Bader-Meunier *et al.*, was found that children the suspected diagnosis on referral was autoimmune thrombocytophenic purpura and the final diagnosis was inherited thrombocytopenia. The suggestive of inherited thrombocytopenia included a history of familial thrombocytopenia, failure of steroid and or intravenous Ig to raise the platelet count to normal level.[22]

Thrombocytopenia and splenomegaly was also found as unusual presentation in children with congenital hepatic fibrosis. A 10-year-old girl of Caucasian was reported that the bood count showed thrombocytopenia, platelet count ($68\times10^3/mm^3$). Congenital hepatic fibrosis is a rare autosomal recessive desease that affects hepatobiliarry and renal systems.[23]

Children with severe iron deficiency has been reported have less platelet count. But the validity of the association and the mechanism of thrombocytopenia are not well established.[24]

Thrombocytopenia also had a link with vaccination in childhood. The Immunization Monitoring Program Active data on vaccine-associated thrombocytopenia, conducted by the Canadian Paediatric Society, reports 103 cases vaccine-associated thrombocytopenia since 1992. The median age was 13 months, and 61% of those affected were boys. Petechiae and bruising were the typical presenting sign. Thrombocytopenia is a rare, but important adeverse event following vaccination. The clinical sign and management are similiar to ITP.[25] ITP in children is usually self-limiting disorder presenting most commonly with short history of bruising and purpura. It may follow a firal infection or immunization and caused by an appropriate response of the immune system.[26]

Ryugo Sato and Massimo Franchini found the correlation between Heliobacter pylori infection and ITP. The patient is given antibiotic to eliminate bacterial infection causing drastically decrease of platelet number.[16,27] Oral care providers like dentist and dental hygienist, must be aware of the impact of bleeding disorders on the management of dental patients. Initial recognition of a bleeding disorder, which may indicate the presence of a systemic pathologic process, may occur in dental practice.[28] Thrombocytopenia is a common hematologic finding in patients infected with the human immunodeficiency virus. Multiple mechanisms may contribute to the development of chronic thrombocytopenia as immune-mediated platelet destruction, enhanced platelet splenic sequestration and impaired platelet production.[29] Congenital abnormalities, of platelet function or production for example Glanzmann's thromboasthenia and Wiskott-Aldrich syndrome are rare. Clinical symptoms are bruising, epistaxis, gingival hemorrhage or bleeding, palatal petechiae and menorrhagia.[5] Acute malaria is often associated with mild or moderate thrombocytopenia in non immune adult and children from malaria-endemic areas. It is not specific indicator of infection with malaria parasites.[30]

Promoting oral hygiene motivation and plaque control are crucial problem to prevent gingival bleeding, inflammation and severe periodontal disease in patient with thrombocytopenia. Understanding clinical finding in oral cavity, good cooperation among dentist, patients and related colleagues are essentially needed in patient's management. Good dental management can support to increase general

health.[18] Medicines causing thrombocytopenia can be classified into 3 group: medicine related with decreasing thrombocyte production (chemoteraphy, diuretic, thiazide, alcohol, estrogen, cloramphenicol, ionization radiation), medicine related with trombocyte destruction (sulfonamide, quinidine, kinine, carbamazepine, valproic acid, heparin, digoxin), and medicine related with the alteration of thrombocyte function (aspirin, dipiridamol).[32]

It is concluded that special attention is needed for pediatric patient with thrombocytopenia, therefore a dentist should understand well about this disorder on how to take the history, to do clinical examination, to establish the diagnosis and to decide treatment plan as well as to consult to related colleagues.

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