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Original Article

THE USE OF TRANEXAMIC ACID MOUTHWASH IN THE GINGIVAL BLEEDING MANAGEMENT IN APLASTIC ANEMIA PATIENT

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ABSTRACT

Objective: The aim of this study was to describe the role of tranexamic acid mouthwash in the management of gingival bleeding in aplastic anemia patients.

Methods: Complete subjective, objective, and supporting examinations were carried out to confirm the diagnosis. Treatments were given in collaboration between the departments of internal and oral medicine. Anamnesis and history taking were done, and it was revealed that a 21-year-old male patient came with the chief complaint of active anterior mandible gum bleeding, starting two weeks ago and accompanied by fever. Extra-oral examination revealed a hematoma on the lip. Intra-oral examination found spontaneous bleeding from the anterior mandible gingiva and hematomas on the labial mucosa and lateral of the tongue. Laboratory examination results showed hemoglobin, hematocrit, erythrocytes, leukocytes, and platelets below the normal range, and the bone marrow morphology examination confirmed the diagnosis of aplastic anemia.

Results: Treatment included a blood transfusion of 39 flasks for 14 d for the systemic condition. Tranexamic acid and chlorine dioxide mouthwash were given for intra-oral problems, and petroleum jelly to treat lip lesions. Gingival bleeding and hematomas resolved within 8 d.

Conclusion: Tranexamic acid mouthwash, along with manual scaling of calculus, which is a predisposing factor for gingival bleeding, as well as blood transfusion, have an important role in the successful comprehensive management of gingival bleeding due to pancytopenia in patients with aplastic anemia.

Keywords: Antifibrinolytic agent, Chlorine dioxide, Gum bleeding, Pancytopenia

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INTRODUCTION

Aplastic anemia is a rare, non-contagious, and potentially life-threatening hematological disorder [1, 2]. The first patient was described by Paul Ehrlich in 1885. The mention of *"anemia aplastique"* came from Vaquez in 1904, but its clinical features were described by Cabot and other pathologists in the early 20th century [3]. The incidence of aplastic anemia is approximately 0.6-6.1 cases per million population; this fig. is largely based on data from a retrospective review of death records. The ratio of males to females is approximately 1:1, and there is an even distribution between races. Although aplastic anemia occurs in all age groups, the peak incidence occurs in childhood. The second peak occurred in the age group of 20-25 y [4].

Aplastic anemia is a syndrome of chronic primary hematopoietic failure that occurs due to reduced or absent hematopoietic precursor injury in the bone marrow and can be accompanied by pancytopenia [1, 4]. Aplastic anemia is classified as acquired or congenital [1]. The most common etiology of aplastic anemia is idiopathic (65% of cases). Other precipitating factors for this disease can include autoimmune, chemicals, drugs, infections, and radiation [2, 4]. The pathophysiology of aplastic anemia, namely the relationship between suppression of hematopoietic stem cells mediated by extrinsic immune disorders and intrinsic abnormality of marrow progenitor. Symptoms of aplastic anemia include anemia, progressive weakness, pallor and dyspnea, neutropenia, frequent and persistent mild infections, fever, thrombocytopenia, ecchymosis, mucosal bleeding, and petechiae. The most common complication of aplastic anemia is bleeding associated with pancytopenia, infection, or progression to a lymphoproliferative disorder [2, 4].

Oral manifestations are common in patients with aplastic anemia mainly due to pancytopenia [1, 5]. Pancytopenia is a hematological condition characterized by a decrease in all three peripheral blood cell lines. The condition is characterized by hemoglobin, platelet and leucocyte values or absolute neutrophil counts being well below normal threshold values. These thresholds mainly depend on age, gender, race, and various other clinical conditions [5, 6]. Pancytopenia can also occur due to an adverse side effect of cancer chemotherapy treatment. Cytotoxic chemotherapy is known to cause varying degrees of bone marrow suppression or failure. Many of these agents have the ability to reversibly suppress one or more cells [5]. Pancytopenia causes infectious symptoms such as fever and cough due to decreased white blood cells; palpitations, shortness of breath, and fatigue due to decreased red blood cells; and thrombocytopenic hemorrhagic, especially epistaxis and gingival bleeding. Gingival bleeding can make patients hesitant to brush their teeth, resulting in poor oral hygiene and subsequent periodontitis [1, 2, 7].

Management of systemic conditions is by monitoring and symptomatic treatment, including antibiotics, chemotherapy, and/or blood transfusions [4], while the management of gum bleeding can use tranexamic acid mouthwash [8]. Tranexamic acid is an antifibrinolytic agent used to treat bleeding by blocking the binding site of lysine to plasminogen, thereby reducing local degradation of fibrin by plasmin [2, 8-12]. 5% tranexamic acid mouthwash has been shown to be useful in treating episodes of oral bleeding in patients undergoing anticoagulant therapy or with bleeding disorders [8, 11, 13]. Tranexamic acid mouthwash 5% is traditionally made by diluting the preparation of tranexamic acid solution (medicine in vials for intravenous administration) with aquadest or using commercially available tablets, made into powder, then dissolved with aquadest to become a suspension preparation [11, 13]. This study aimed to describe the role of the use of tranexamic acid mouthwash in the management of gingival bleeding in patients with aplastic anemia. The uniqueness of this study is due to the use of tranexamic acid

mouthwash for the management of bleeding gums; although it has been known for a long time, it has not been widely published in the form of case report articles, so it is hoped that this writing can provide new insights for related medical personnel.

METHODS AND MATERIALS

This study has received approval and full consent from the patient's mother for the publication of data and images. This study complied with the Declaration of Helsinki. The institution has approved the publication of this study. Complete subjective, objective, and supporting examinations were carried out to confirm the diagnosis. This patient came to the oral medicine division because he was consulted by the inpatient division of Internal Medicine at Hasan Sadikin General Hospital, Bandung. A complete blood count and bone marrow examination were performed to determine the diagnosis of a malignant systemic disease that the patient was suffering from. Extra and intra-oral examinations were performed to determine the diagnosis of his oral condition. Treatments were given in collaboration between the departments of internal and oral medicine. Pharmacological therapy given consisted of paracetamol, folic acid, granulocyte colony-stimulating factor (G-CSF), ceftriaxone, calcium carbonate, and potassium chloride as chemotherapeutic agents for aplastic anemia, while tranexamic acid and chlorine dioxide mouthwash were given for intra-oral conditions and petroleum jelly to treat lip lesions. The blood transfusion given consists of a transfusion-packed red cell (PRC) of 2 flasks per day until hemoglobin>10 g/dl and a platelet transfusion of 6 flasks per day until platelets>20,000 thousand/µl or until the bleeding stops.

RESULTS

First visit

Subjective examination through anamnesis resulted in information that a 21 y old male with the chief complaint of spontaneous bleeding on the gingiva, especially on the front lower jaw since two weeks ago. This complaint was asymptomatic in the gingival area or other parts of the mouth but accompanied by fever. The patient tried to manage the bleeding by pressing the bleeding area using gauze or cloth and rinsing the mouth, but it could not stop well. The patient had seen a dentist a month ago and was given 1% povidone-iodine antiseptic mouthwash but there was no improvement. The patient had not brushed his teeth for the past two weeks for fear of bleeding in the gums. The patient cleaned the oral cavity by gargling with 1% povidone-iodine antiseptic mouthwash. There was no history of malignancy in the patient's family. The patient could only consume a soft diet during hospitalization. The patient had no history of food allergy and did not have bad habits of consuming alcohol and smoking.

The results of the health and morbidity history search found that the patient had a history of chronic myelogenous leukemia (CML) malignancy diagnosed by the Internal Medicine Department at another Hospital seven months ago. Previously, the patient routinely took drugs related to his CML disease, namely Glivec/Imatinib 200 mg twice a day orally, and the patient's condition has been quite stable since taking the drug. However, the patient's general condition worsened due to stopping taking the drug for 2 w about 1 mo ago.

The results of the physical examination found that the patient was moderately ill with compos mentis consciousness. The results of the vital signs examination showed that the patient had a fever with a temperature of 39 °C. Extra-oral examination showed anemic conjunctiva and non-icteric sclera, with no lymph node abnormalities. The lips were dry and exfoliated, and there was a hematoma but no pain. Intra-oral examination revealed spontaneous bleeding of the mandibular anterior gingiva in the region of teeth 41, 31, and 32, with no pain. A yellowish-white plaque that could be scraped off without leaving an erythema area was found on the posterior 2/3 of the dorsum surface of the tongue, with no pain. There were red petechiae, multiple, round, pinpoint, and painless on the mucosa of the soft palate. The oral mucosa was generally pale. Several teeth were found to be carious and oral hygiene was poor (fig. 1). The results of the blood laboratory examination showed a decrease in hemoglobin, hematocrit, erythrocytes, leucocytes, and platelets (table 1).

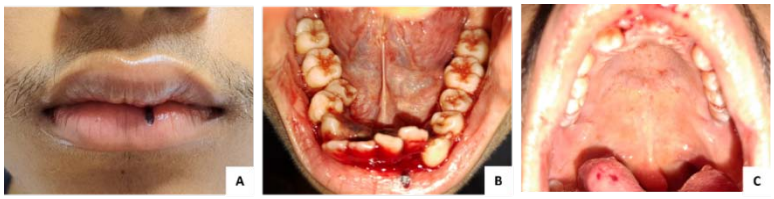

Fig. 1: Clinical features of the patient's lips and oral cavity at first visit, (A) hematoma on the lower lip, (B) bleeding gums on mandibular anterior gingiva, and (C) petechiae on the palate

Based on the comprehensive examination, the patient was diagnosed with oral manifestations of pancytopenia due to aplastic anemia, which included gingival bleeding, petechiae on the palate region, pale mucosa, and hematoma on the lower lip region. There were also other intra-oral findings, including exfoliative cheilitis, Miyazaki scale 2 coated tongue, reversible pulpitis of tooth 18, irreversible pulpitis of tooth 48, and chronic marginalized periodontitis localized to the anterior region of the mandible.

Chlorine dioxide mouthwash was given to the patient, used as a compressed liquid to wet the gauze and suppress the source of bleeding in both the gums and lip lesions, as well as to rinse the mouth in an effort to maintain oral hygiene. The use of sterile gauze soaked in chlorine dioxide mouthwash was carried out for one minute, then continued with the administration of tranexamic acid liquid to compress the gums with the aim of stopping gingival bleeding, and petroleum jelly was applied for the dry lips.

The tranexamic acid liquid was made from the preparation of 500 mg tranexamic acid tablets crushed into powder and then dissolved in 10 ml of distilled water. The use of chlorine dioxide compresses and tranexamic acid mouthwash was done alternately, each for 1 minute, with a frequency of 4 times a day. Petroleum jelly was applied to dry lips 3 times a day. The non-pharmacological therapy provided consisted of instructions to maintain dental and oral hygiene by cleaning the teeth, tongue, and oral cavity at least 2 times a day.

Second visit

The second visit was conducted D+1 after the first visit. The patient's general condition had not improved significantly and was still febrile with a temperature of 39.4 °C. The extraoral examination resulted in an anemic conjunctiva and icteric of the sclera. The patient already used the medicines given by the oral medicine division, but gingival bleeding still occurred spontaneously. The results of the intra-oral examination revealed new hematomas on the upper and lower labial mucosa, as well as the left and right lateral tongue. The calculus on the anterior region of the mandible, which was the predisposing factor of the gingival bleeding, was cleaned with manual equipment. The use of tranexamic acid and chlorine dioxide mouthwash, also petroleum jelly was continued as instructed at the first visit.

Third visit

The 3rd visit was conducted D+2 after the first visit. The patient's general condition had not improved much, with a body temperature of 39 °C. The extra-oral examination also showed no improvement, but the intra-oral examination showed no gingival bleeding. The patient had received a platelet transfusion 12 h prior to this examination and was still taking regular medications from the oral medicine division. Dry and exfoliative lips, hematoma on the lips, upper and lower labial mucosa, left and right lateral of the tongue, and petechiae on the palate have not improved. Management from the oral medicine division consisting of chlorine dioxide mouthwash and petroleum jelly was continued, but the use of tranexamic acid mouthwash was stopped because the bleeding in the gingiva had resolved. The patient was scheduled for a bone marrow examination from the internal medicine department to reconfirm the diagnosis.

Forth visit

The 4th visit was conducted D+3 after the first visit. The patient's general condition had not improved, the patient's body temperature was 39 °C, the conjunctiva was still anemic and the sclera was icteric. The results of the oral medicine division examination found that the extra-and intra-oral conditions showed a slight improvement in the lips which were previously dry and exfoliative, but there was no hematoma on the lips. Likewise, there was no gingival bleeding and petechiae on the palate, and hematomas on the upper labial mucosa, lower labial, left and right lateral tongue had improved. Management in the oral medicine division consisting of chlorine dioxide mouthwash and petroleum jelly was continued according to previous instructions. The results of bone marrow imaging showed the patient's diagnosis as aplastic anemia (fig. 2).

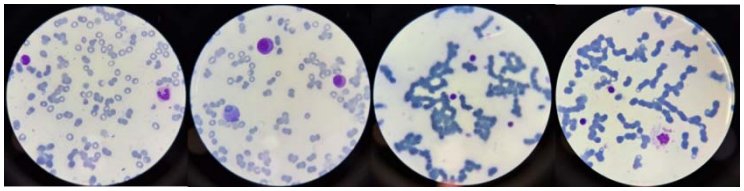

Fig. 2: Microscopic view of the patient's bone marrow examination at 1000x magnification. Bone marrow fragments (grey) and hematopoietic nests (purple) are visible (source: Clinical Pathology documentation of RSHS Bandung)

Fifth visit

The 5th visit was conducted D+8 after the first visit. The patient's general condition began to improve, although he was still feverish with a body temperature of 38.7 °C, anemic conjunctiva, and icteric sclera. Intra-oral examination showed no gingival bleeding, petechiae, or hematoma on the oral mucosa (fig. 3). The results of the blood laboratory examination showed that the levels of hemoglobin, hematocrit, erythrocytes, leucocytes, and platelets were still below the normal threshold (table 1). The use of petroleum jelly and chlorine dioxide mouthwash was continued according to previous instructions, until the lips were moist again, and the patient was able to independently maintain the health of his teeth and oral cavity. The patient received a total of 39 blood transfusions consisting of packed red cell (PRC) transfusions and platelet transfusions during her 14-day hospital stay. This study has obtained approval from the patient through informed consent given to be published in scientific journals, with respect to ethical principles and confidentiality.

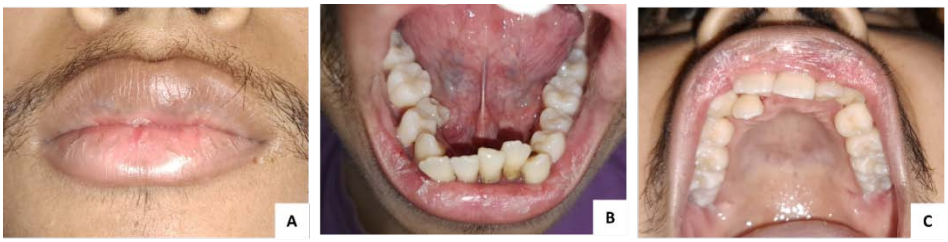

Fig. 3: Clinical features of the patient's lips and oral cavity at the final visit, (A) the hematoma on the lower lip was healed, (B) bleeding gums on the mandibular anterior gingiva healed, and (C) Petechiae on the palate healed

Table 1: Laboratory examination results

Hematology	First visit	Final Visit	Normal Range
Haemoglobin	5.7 g/dl	7.7 g/dl	14–17.4 g/dl
Hematocrit	17.2%	23.6%	41.5–50.4%
Erythrocytes	2.04 million/µl	2.80 million/µl	4.5–5.9 million/µl
Leukocytes	2.41 x 10^3/µl	1.50 x 10^3/µl	4.4–11.3 x 10^3/µl
Platelets	12 x 10^3/µl	33 x 10^3/µl	150-450 x 10^3/µl

DISCUSSION

The patient in this study, was previously diagnosed with chronic myeloid leukemia (CML). CML is a myeloproliferative neoplasm derived from abnormal multiple-potential stem cells. Imatinib mesylate (Gleevec, Glivec, formerly STI571) treatment has been received by the patient since the initial CML diagnosis. Although the drug was generally well tolerated by the patient's body, there have been a number of hematological side effects reported. Severe adverse hematological effects of imatinib are very rare, but this patient developed severe bone marrow aplasia following imatinib therapy, resulting in aplastic anemia. Fatal bone marrow aplasia is a rare case finding, as is aplastic anemia in this study [14–16]. The exact mechanism of how imatinib induces antiproliferative effects and bone marrow injury remains unexplained. Studies have shown that imatinib significantly inhibits monocyte/macrophage development from normal bone marrow progenitors *in vitro*, whereas neutrophil and eosinophil development is less affected. A prospective study of CML patients taking high-dose imatinib for one year showed highly significant changes in serum immunoglobulin G

and immunoglobulin M levels, suggesting an immune-mediated mechanism. Myelosuppression has been identified as an independent adverse risk factor for achieving a cytogenetic response. Various degrees of myelosuppression can occur in CML patients treated with imatinib. Myelosuppression can occur at any time during imatinib therapy [14].

Oral manifestations in aplastic anemia patients that are directly related to pancytopenia in this study include gingival bleeding, hematoma, petechiae, and pallor of the mucosa [1, 4]. Meanwhile, the localized chronic marginal periodontitis that was also found was more related to local factors due to poor oral hygiene. Gingival bleeding and petechiae are oral manifestations associated with decreased platelet levels, although thrombocytopenia may not indicate the degree of bleeding petechiae. These lesions are most likely due to blood clotting disorders caused by thrombocytopenia leading to excessive bleeding even after minor trauma due to normal oral function. Advanced or progressive cases of periodontitis may result from prolonged neutropenia which may be due to several qualitative and quantitative neutrophil abnormalities, such as neutropenia, agranulocytosis, and leucocyte adhesion deficiency [2]. Gingivitis and periodontitis, which occur in 36.36% of patients with Fanconi aplastic anemia, do not have an association with lower platelet counts but rather are caused by poor oral hygiene [1, 2, 14].

The management to stop the bleeding in this study was a collaborative pharmacological therapy from the internal medicine department with the oral medicine division. Therapy from the internal medicine department was systemic therapy consisting of polypharmacy, namely paracetamol, folic acid, *granulocyte colony-stimulating factor* (G-CSF), cefixime, calcium carbonate, and potassium chloride, as well as blood transfusion. Meanwhile, therapy from our division, the oral medicine division, focuses on dental care and topical therapy which consists of cleaning calculus with manual equipment, using 5% tranexamic acid mouthwash, chlorine dioxide mouthwash, and petroleum jelly.

The choice of tranexamic acid therapy used in this study is in topical form, namely by compressing it on the source of bleeding in the gingiva. Mouthwashes containing tranexamic acid have been widely used in the field of dentistry, their use also does not require inpatient monitoring and is economical. The importance of using tranexamic acid has already been discussed in several clinical studies [10]. The Food and Drug Administration of the USA (FDA) approved the use of tranexamic acid for heavy menstrual bleeding, short-term prevention in hemophilia patients, tooth extraction, and menorrhagia in hemophilia patients [17]. Tranexamic acid is an antifibrinolytic agent and inhibits thrombus degradation, so it can help stop bleeding [10]. In addition, tranexamic acid is a synthetic reversible competitive inhibitor of the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin (the activated form of plasminogen) from binding to and ultimately stabilizing the fibrin matrix [13, 17-19]. Pharmacokinetic studies of blood and salivary levels after oral tablet administration and 5% tranexamic acid solution showed that oral tablet administration showed plasma levels reached maximum values after 120 min, but no tranexamic acid was detected in saliva. Rinsing the mouth with 10 ml of 5% tranexamic acid for two minutes produced therapeutic salivary levels that persisted for more than two hours but without therapeutic plasma levels. There were no differences in treatment outcomes from the use of tranexamic acid preparations made either from vial products (intravenous injection solution) or from tablet preparations after use as a mouth rinse for two minutes [13].

Topical use of tranexamic acid can also minimize the side effects of this drug. Tranexamic acid is well tolerated by the body, but there are still some reported side effects of the drug [10]. Unexpected effects of tranexamic acid use include seizures, headache, back pain, abdominal pain, nausea, vomiting, diarrhea, fatigue, pulmonary embolism, venous thrombosis, anaphylaxis, and visual disturbances [17]. An increased risk of thrombosis with this drug has not been proven in all clinical trials [10]. Topical use can reduce the risk of thromboembolic events associated with systemic administration of antifibrinolytic agents [20].

Other topical pharmacological therapies were used in the treatment of oral lesions in this study. Chlorine dioxide antiseptic mouthwash and petroleum jelly were used to maintain lip moisture. Chlorine dioxide has antibacterial, antiviral, antifungal, pain relief, and tissue healing effects [21–23]. Its diverse effectiveness makes chlorine dioxide often used in dental practice, including to relieve pain after wisdom tooth extraction, improve the healing process after oral surgical procedures, effective endodontic irrigation materials, treatment for periodontal disease, and halitosis [22, 24]. Chlorine dioxide dissolves well in water and penetrates biofilms well [22, 23]. Chlorine dioxide is a selective oxidizing agent. It reacts poorly with most substances in living organisms but reacts rapidly with three amino acids, namely cysteine, tyrosine, and tryptophan. The antibacterial activity is derived from its reaction with those three amino acids, their acidic residues in proteins, and peptides preventing bacteria resistance. The compound also oxidizes precursors of volatile sulfur compounds (VSC) so it functions as an anti-halitosis [23-25]. Cell viability tests show that chlorine dioxide is only toxic at very high concentrations, to human gingival fibroblasts [21, 22].

Petroleum jelly is one of the most widely used topical agents for antimicrobial peptide upregulation, skin barrier improvement, and hydration [26, 27]. Petroleum jelly was first discovered by Robert Chesebrough, a chemist working in Titusville, Pennsylvania in 1859. He found that workers were using a product called "rod wax" to treat open wounds [26]. Petroleum jelly is a rare semisolid mixture of branched and cyclic saturated hydrocarbons with varying lengths of more than 25. It is a complex combination of liquid (mineral oil) and solid (paraffin wax and microcrystalline wax) components [26, 27]. The substance is tasteless, almost odorless and non-irritative. Petroleum jelly is an anhydrous occlusive moisturizer with the ability to reduce trans-epidermal water loss (TEWL) by 50% to 99%. Comparative studies have shown that petroleum jelly reduces TEWL by almost 50% within 40 min, which is much greater than other oily water creams. Human studies have shown that petroleum jelly accelerates skin barrier repair while increasing stratum corneum thickness in acetone-induced skin barrier disorders. As an emollient, it works as an exfoliant by loosening desquamated keratinocytes when applied to the skin. In atopic dermatitis, petrolatum-occluded skin shows increased expression of barrier proteins, filaggrin, and loricrin and upregulation of antimicrobial peptides, including human b-defensin 2, and LL-37 [26]. Human studies have also reported the benefits of using petroleum jelly on wound healing. Petrolatum also has a variety of other uses in dermatology, namely as a patch test instrument, carrier of medicinal ointments, and self-medication [26, 27].

CONCLUSION

Tranexamic acid mouthwash along with manual scaling of calculus, which is a predisposing factor for gingival bleeding, as well as blood transfusion, have an important role in the successful comprehensive management of gingival bleeding due to pancytopenia in patients with aplastic anemia.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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