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Original Article

EFFICACY OF CHLORINE DIOXIDE ON ORAL LESIONS IN ACUTE MYELOBLASTIC LEUKEMIA PATIENTS UNDERGOING CHEMOTHERAPY

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ABSTRACT

Objective: The aim of this study was to describe the pharmacological management of oral lesions, particularly using chlorine dioxide agents in an acute myeloblastic leukemia (AML) patient undergoing chemotherapy.

Methods: A 9 y old girl was referred from the Department of Paediatrics at Hasan Sadikin Hospital to the Department of Oral Medicine with complaints of swelling on the lips, difficulty while eating, swallowing, and even opening the mouth. Extra oral examination showed angioedema on the lips with a prominent serosanguinolent crust. Intraoral examination revealed white plaques that could not be scrapped off in all parts of the mouth. The patient was diagnosed with AML and had received chemotherapy until the second cycle.

Results: Gauze soaked in chlorine dioxide oral rinse was applied to compress the patient's lips. Following this, 0.2% hyaluronic acid gel was also administered. In terms of intraoral treatment, chlorine dioxide was also applied by spraying it throughout the entire mouth. After one month, the lesion had completely healed, allowing the patient to open their mouth without any issues.

Conclusion: Chlorine dioxide significantly improves the oral mucosal lesions in an AML patient undergoing chemotherapy.

Keywords: Cheilitis, Angioedema, Crust, Cancer

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INTRODUCTION

Today, there has been a notable shift in the trend of human diseases, moving away from communicable diseases towards non-communicable ones. One significant non-communicable disease that has become a prominent concern is cancer. Cancer arises due to the accumulation of multiple DNA mutations, typically initiated by uncontrolled cell growth. This cancerous process stems from abnormalities in various cellular functions, including proliferation, differentiation, and growth, and is triggered by carcinogenic agents [1].

Acute myeloblastic leukemia (AML) is a cancer that affects haematopoietic cells, representing a relatively rare malignancy. The data available suggests an incidence rate of approximately 5 cases per 100,000 population.

In 2020, the new cases of this disease is about 474,519 new diagnoses cases and the mortalities is about 311,594 cases. The incidence of AML increases with age. AML is characterized by the uncontrolled proliferation of undifferentiated blood cells, known as blasts, which leads to the loss of their ability to differentiate [3].

AML have sign and symptom both systemic or locally. Generally, the patients can present fever, weakness, fatigue, anaemia, pallor, lymphadenopathy and local infections, bone and abdominal pain, bleeding [4-6]. Besides that, AML can manifest locally on the oral cavity. AML can lead to human oral changes such as petechiae haemorrhages of the tongue, lips, posterior hard and soft palate, spontaneous bleeding, mucosal pallor, and gingival overgrowth. Besides that, oral ulcerations are common found on the oral mucosa. This process due to either neutropenia or direct infiltration by leukaemic cells [4, 7-9]. Oral manifestation of acute myeloblastic leukemia in children can be gingival enlargement and gum bleeding. This is crucial sign for dentist in early detection of leukemia [10].

The oral manifestation of leukemia could be considered as early diagnostic indicators of the disease [11]. A dentist play an important role as a first man who find the diagnostic indicators from mouth. The patient can feel discomfort and more complain from their mouth. The comprehensive treatment, including pharmacology and non-pharmacology should be considered to alleviate the complaint from the patient.

Chlorine dioxide (ClO_2) is one of the material that usually used in dentistry. This material has antibacterial, antivirus dan antifungal activity. This agent is widely used to prevent plaque formation and malodour. The active agent from this medicine can penetrate through the cell and give an improvement to our mouth [13-15]. However, the efficacy of this agent in treating oral lesions is still limited. This study aims to describe the pharmacological management of oral lesions, particularly using chlorine dioxide agents in an AML patient undergoing chemotherapy.

METHODS

This study had received approval and full consent from the patient's mother for the publication of data and images. Informed consent regarding the patient's photograph and the publication had been obtained from the mother's patient. A 9 y old girl complaints of swelling on the upper and lower lips, difficulty while eating, swallowing, and even opening the mouth. The patient had a fever for three days before coming to the hospital. The swelling began with a white spot on her lips five days prior, and the complaint was worsening. There were no complaints of bleeding from the mouth. The patient had been diagnosed with AML in February 2023 and had received chemotherapy up to the second cycle with cytarabine.

The patient underwent a comprehensive examination and was generally in poor condition. She felt terrible and weak during the examination. The examination covered both extra-oral and intra-oral aspects. The extra oral examination shows angioedema on the lips with a prominent serosanguinolent crust. The intraoral examination revealed white plaques that could not be scrapped off in all parts of the mouth (fig. 1). The laboratory finding indicated abnormal results: hemoglobin: 7.2 g/dl (low), hematocrit: 20% (low), leukocytes: $0.05x10^3$/ul (very low), erythrocytes: 2.47 million/ul (low), platelets: 36 thousand/ul (very low). The patient was diagnosed with angioedema on the upper and lower labial and suspected Herpes-associated erythema Multiforme (HAEM). The patient was referred to the laboratory for IgG and Ig-M anti-HSV-1 detection. The patient was

treated with pharmacological treatment, which included applying gauze soaked in chlorine dioxide oral rinse 10 ml with a concentration 0,06 % to compress the patient's lips five times a day, followed by the administration of 0.2% hyaluronic acid gel, and was planned for observation at the next visit.

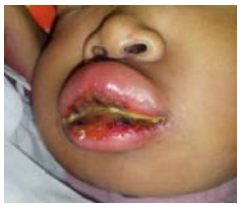

Fig. 1: Clinical feature of extra oral condition at the first day, the angioedema on the lips with prominent serosanguinolent crust and dry saliva

The second visit was held on the fourth day after the first visit. The patient showed some improvement and could open her mouth more comfortably. The swelling on the upper and lower lips had decreased, and the condition of the lips had improved. The intraoral examination revealed white plaques on the dorsal side of the tongue (fig. 2). Laboratory examination results for IgG and IgM Anti-HSV-1 indicated that the patient was not reactive to HSV-1 infection, but other laboratory results suggested a bacterial infection, with Quantitative CRP at 35.01 mg/dL (H), SGOT (AST) at 55 U/l (H), and Procalcitonin at 17.70 ng/ml (H) (>10). The Immunoglobulin E (IgE) result was within the normal limit at 150 IU/ml (<200), indicating no allergic condition. This second visit led to a revised diagnosis, including angioedema on the upper and lower labial, oral pseudomembranous candidiasis, and exfoliative cheilitis. The patient received the same previous treatment guidelines, with the addition of Vaseline album. Moreover, the pediatrician had given fluconazole 300 mg intravenous every 24 h to treat the oral pseudomembranous candidiasis.

The patient was re-examined again at the third visit, which took place on the seventh day after the first visit. The patient could open her mouth wider than before and had improved labial and intraoral mucosa (fig. 3). While the labial swelling had decreased, serosanguinolent crust remained reduced, and the intraoral condition still showed white plaques and ulceration. The patient continued to experience mouth pain. The treatment plan remained consistent, including lip compression with gauze soaked in chlorine dioxide, the application of 0.2% hyaluronic acid gel to the upper and lower lip, and systemic administration of Fluconazole 300 mg intravenously.

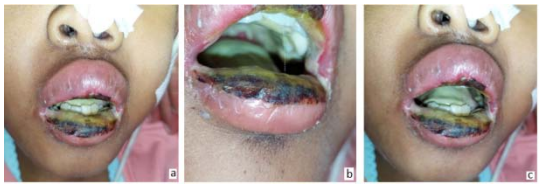

Fig. 2: Clinical features of intra-oral condition at the second visit (day 4), including (a) decreased crust on the labial, (b) white plaque on the palatum, and (c) white plaque on the dorsal of the tongue

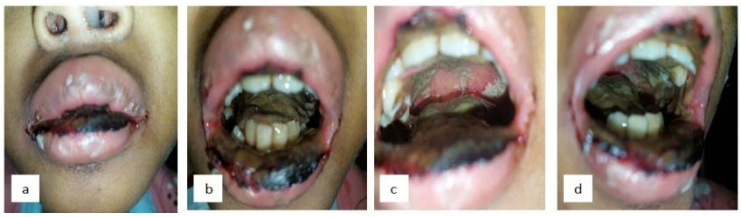

Fig. 3: Clinical features of the intra-oral condition at the third visit (7 d) showing (a) decreased crust on the labial, (b) white plaque on the dorsal side of the tongue, (c) white plaque on the palatum, and (d) white plaque on the buccal mucosa

On the tenth day after the first visit, the patient showed further improvement in labial and intraoral mucosa (fig. 4). The labial swelling had decreased, serosanguinolent crust was reduced, and the patient felt more comfortable. The patient and parents continued the treatment regularly. The patient was instructed to continue the previous treatment. The patient continued to compress the lips by using gauze soaked in chlorine dioxide and spraying it inside the mouth. Following this, 0.2% hyaluronic acid gel was also administered to the upper and lower lip. Fluconazole 300 mg intravenously was still administered systemically.

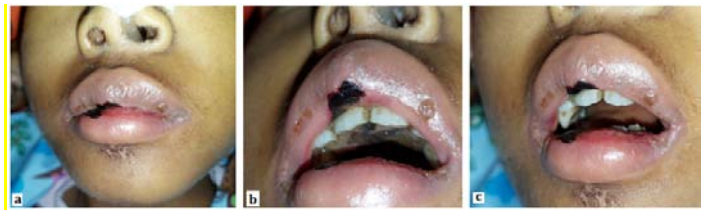

Fig. 4: Clinical feature of intra-oral condition at the eleventh day, (a) crust on the labial was decreased (b) white plaque on the palatum decreased (c) white plaque on the dorsal of the tongue decreased

Continued monitoring at the eleventh-day mark showed further improvement, with no labial swelling or serosanguinolent crust on the lips and reduced white plaque on the oral mucosa (fig. 5). The patient could chew and swallow food comfortably and was educated to maintain oral hygiene by brushing her teeth at least twice a day, after breakfast and before bedtime.

Fig. 5: Clinical feature of the intra-oral condition at the fifth visit (12th day) showing (a) no crust on the labial, (b) decreased white plaque on the palatum, and (c) decreased white plaque on the dorsal of the tongue

The patient was followed up on the next month, and her condition had significantly improved. There was no labial swelling and serosanguinolent crust on the lips, and the intra-oral mucosa appeared healthy (fig. 6). The patient could chew and swallow food comfortably and was instructed to maintain oral hygiene by brushing her teeth at least twice a day, after breakfast and before bed.

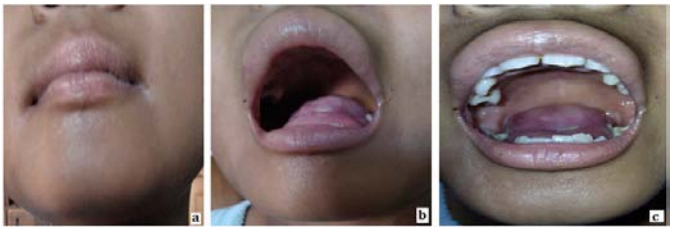

Fig. 6: Clinical features of intra-oral condition a month after the first visit. The patient revealed (a) good improvement in labial, (b) dorsum of the tongue, and (c) palatal areas

DISCUSSION

AML is one of the aggressive malignant diseases that affects the bone marrow and interferes with the production of blood cells in the human body. AML represents approximately 25% of cases of pediatric leukemia [16-18]. The etiology of these diseases is still poorly defined. The etiology that has been identified as risk factors are genetic disorders, previous chemotherapy, radiation exposure, myelodysplastic syndromes and exposure to carcinogenic chemicals [19, 20]. The main signs and symptoms that are usually found in this disease are weakness, fatigue, pallor, recurrent infections, and bleeding [9].

The oral cavity can represent the condition of AML. Oral signs and symptoms are highly frequently observed in AML patients [11, 21]. They are gingival enlargement, spontaneous gingival bleeding, and petechiae. All of these manifestations are considered the first indicator of the disease [9, 11, 17]. In this clinical study, the patient's main complaints were swelling on the upper and lower lips, difficulty while eating, swallowing, and even opening the mouth.

The patient had a fever for three days before going to the hospital. At the first visit, we suspected that the patient had a virus infection that manifested on the upper and lower labial. We found serosanguinolenta crust on the lips accompanied by fever. The patient was asked to check the Ig G and Ig M anti-HSV 1. Based on the result, the virus infection is negative. It means that there is no HSV-1 viral infection in this study. The patient got a fever because of the normal response after doing chemotherapy. Based on the information, the patient was undergoing cycle 2 chemotherapy with cytarabine. High-dose cytarabine treatment can induce a release of TNF-α followed by the sequential release of other proinflammatory cytokines in the human body. This pathway can generate fever in the patient. Fever is induced by endogenous pyrogens such as the interleukins (IL)1-α, IL-1β, IL-6, and TNF-α involved in the inflammatory response. This process also called cytarbine syndrome, which includes fever, myalgia, bone pain, maculopapular rash, conjunctivitis, malaise, and pericarditis. The inflammatory markers, including serum ferritin and CRP levels are also significantly increased at day 8 after treatment with cytarabine [22, 23].

The laboratory findings showed that the patient has underlying hematological results. AML patient usually suffers pancytopenia, which occurs systemically [9, 24]. The patient of AML suffers more blast cells in their body. The uncontrolled proliferation of blasts interferes with normal hematopoiesis. This process results in neutropenia, leukocytosis, thrombocytopenia, and increased blasts in the complete blood cell count [18, 25]. This result represents the oral manifestation of the patient [9, 24].

Angioedema on the upper and lower was found in this patient. Angioedema is self-limited subcutaneous or submucosal swelling that is caused by a localized increase in microvascular permeability. This condition is a result of increased vascular permeability in the deeper layers of the dermis in the subcutaneous tissue of the human [26-28]. Angioedema is divided into two main headlines. First, mast-cell-related angioedema develops because of allergic reactions, and the patients have accompanying urticaria. The medication for this patient is anti-histaminic therapy because of the presence of an allergic reaction. The second type is bradykinin-related angioedema. It can occur when bradykinin causes increased vascular permeability. There is no urticaria is observed in these patients. Anti-histaminic does not give the response for this disease [29].

The patient in this study revealed that there are no allergic reactions. The Immunoglobulin E (Ig E) revealed the normal value (150 IU/ml). This result is below 200. Based on the clinical condition, the patient shows angioedema related to bradykinin. The key hallmarks of bradykinin-mediated angioedema include an absence of urticaria/wheals, a more gradual onset (days versus minutes/hours), longer duration of symptoms (days versus min/h), and greater severity of swelling [30]. Bradykinin is a vasodepressor that relaxes vascular smooth muscles and, consequently, lowers blood pressure. Bradykinin causes increased vascular permeability. It has vasodilating activity corresponding to the release of 3 potent mediators, such as tissue plasminogen activator, prostacyclin, and endothelium-derived vascular relaxing factor (fig. 1) [31-34].

The patient on this study got bacterial infections. The CRP and Procalcitonin detection revealed results above the limit. The CRP result shows 35,01 mg/dl. The result is 116,7 times higher than the normal limit (<0.3 mg/dl). The Procalcitonin shows 17,70 ng/ml. It was more than the normal limit (<0,5 ng/ml bacteria develops its pathogenic effects via several toxins. The toxins can damage the tissue around them. This pathway can be assumed to play a major role even in the development of angioedema. This condition damages the tissue and induces bradykinin angioedema. The pathway is initiated when factor XII (or Hageman factor) binds to damaged tissue and converts to factor XIIa, which then converts prekallikrein to plasma kallikrein. Finally, kallikrein cleaves Human High Molecular Weight Kininogen (HMWK) to form bradykinin, which binds B2 receptors on the vascular endothelium. Bradykinin stimulates beta-2 adrenergic (B2) receptors,

which result in the release of nitric oxide and prostacyclin. The activation of Nitric oxide and prostacyclin triggers local vasodilation and increases vascular permeability, which leads to the development of angioedema. This pathway can be inhibited by biological and pharmacological inhibitors. It can be used to treat bradykinin-induced angioedema (fig. 7) [26, 35–39].

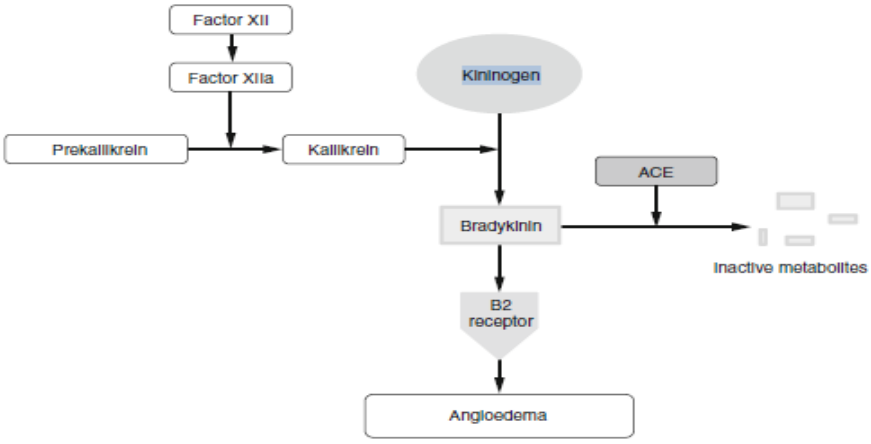

Fig. 7: The bradikin mediated pathway to angioedema [26]

The patient in this study was treated with Chlorine dioxide on the extra oral and intra-oral lesions. Chlorine dioxide is one of the most valuable materials in dentistry. Chlorine is a selective oxidizing agent. This material is a strong antioxidant that can inhibit or destroy microbes. It rapidly responds with three amino acids, such as cysteine, tyrosine, and tryptophan. Besides that, chlorine dioxide also impacts the proteins and peptides of the bacteria. This is the antibacterial effect that is produced by chlorine dioxide [13]. The scanning electron micrograph shows that chlorine dioxide changes the shape and structures of the bacteria. Chlorine dioxide causes shrinkage of bacteria and forms a wrinkled surface. There is a rupture in the cell wall of the bacteria. This process makes the cell content of the bacteria to outburst. There are two possible explanations of the mechanism of ClO_2 to the bacteria and viruses. The first mechanism is the interaction of the ClO_2 with specific biomolecules of the microorganisms, and the second mechanism of action is the effect of ClO_2 gel on the physiological functions of the microorganisms [40].

Chlorine dioxide has more advantages than other local antiseptics. A local antiseptic should fulfil the requirement. A local antiseptic acts only locally to avoid systemic poisoning and should not prevent or delay the process of healing, it means that the local antiseptic should not be cytotoxic. Besides that, a local antiseptic should be effective in relatively low concentrations and even in biofilms. A local antiseptic should not develop the resistance of microbes [13]. Chlorine dioxide can fulfil all the requirements to become a valuable local antiseptic. ClO_2 has the highest biocidal activity against microorganisms. Chlorine dioxide has antibacterial and antifungal properties. Chlorine dioxide has also strong antiviral activity. The antiviral activity is about ten times higher than sodium hypochlorite. This material can destroy all microbes including algae, plankton and protozoans. Chlorine dioxide can remove biofilm swiftly. Chlorine dioxide is highly soluble in water and can react with the extracellular polysaccharides of the biofilm. By using this process, Chlorine dioxide can penetrate biofilms rapidly to reach and kill the microbes living within the film [13, 15].

Chlorine dioxide does not trigger bacterial resistance. Chlorine dioxide is a strong material but has a selective oxidizer ability. ClO_2 reactacts rather quickly with cysteine methionine, tyrosine, tryptophan and also two inorganic ions, such as Fe^{2+} and Mn^{2+}. It means that the antimicrobial effect of ClO_2 is due to its reaction with four amino acids and their residues in proteins and peptides. Cysteine is the most reactive amino acid because of its thiol group. All the amino acids mentioned above, especially cysteine and biological thiols play a crucial role in all living systems, including microbes. Because of this process, impossible for any microbe to develop a resistance against chlorine dioxide [12, 40]. Chlorine dioxide can evaporate rapidly from its aqueous solution. This material can reach and kill bacteria even through a gas phase. Unlike the other local antiseptics, such as HOCl. This material is not significant to reduce the microorganisms. HOCl stays in disinfected area for a long time even after killing all bacteria. It can be inflammation there [42]. Chlorine dioxide has better ability with its oxidizing agent. It can steals electrons from the cell membran of the microbe. The molecular bonds will be break up, resulting in the death of the microorganisms [43].

Chlorine dioxide has antifungal effect. Most fungi live in oxygen-poor environment. This is the best condition for fungi to grow. Chlorine dioxide will provide an oxygen-rich environment. Fungi will have low tolerance for this condition. Chlorine dioxide will destroy vital part of the fungi. Chlorine dioxide will destroy the chitin of the cell wall of the candida. Chitin is synthesized by the enzyme chitin synthetase biochemically. It provides rigidity to the fungal cell wall. The mechanism is the chlorine dioxide will inhibit biosynthesis of chitin in Candida resulting in lysis from the absence of the chitin plug at the bud scar [44]. Chlorine dioxide has more advantages than other agents that usually used in dentistry. Chlorine dioxide contain complete function as antibacterial, antiviral, and antifungal activity. This material can kills microorganisms very rapidly and show significant result for the tissue healing process inside the mouth.

CONCLUSION

Chlorine dioxide significantly improves the oral mucosal lesions in an AML patient undergoing chemotherapy. A dentist should be aware of the oral condition correlates with systemic patient condition.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICT OF INTERESTS

Declared none

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