



## Prevention of oral lesions in children with acute lymphoblastic leukemia

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### KEYWORDS

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**Summary** Acute lymphoblastic leukemia (ALL) is the most common form of cancer in children and is responsible for severe stomatologic complications. Treatment consists of four phases of chemotherapy, the main side effect of methotrexate, the drug most used during the intensification phase, is oral mucositis.

**Objective:** To evaluate the clinical aspects of the oral mucosa of children with ALL and to determine the effect of 0.12% chlorhexidine gluconate on the prevention of stomatologic complications in these patients.

**Patients and methods:** Thirty-three children treated for ALL ranging in age from 2 to 15 years, without distinction of gender or race, were submitted to visual examination, digital palpation of the oral mucosa and cytologic examination of the buccal mucosa, and divided into two groups: group I consisted of 23 children using an oral solution of 0.12% chlorhexidine gluconate twice a day, and group II consisted of 10 children who did not receive this solution. All children received daily oral hygiene care guided by the dentist throughout treatment.

**Results:** Mucositis was observed in six children of group I and eight of group II, and was characterized by erythema, edema and ulcers. Uniform cytologic findings were

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obtained for the two groups, with a clear predominance of cells of the intermediate layer in all smears, in addition to a perinuclear halo in 18% of the smears.

*Conclusion:* The present results suggest that systematic preventive treatment with 0.12% chlorhexidine gluconate and oral hygiene care reduce the occurrence of oral complications in children with ALL undergoing antineoplastic chemotherapy.

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## 1. Introduction

Leukemia is a disease resulting from the malignant transformation of stem cells whose proliferation starts in the bone marrow [1]. In acute lymphoblastic leukemia (ALL), the proliferating abnormal lymphoid cell clones can exhibit characteristics of B or T lymphocytes [2]. This type of cancer most frequently affects children between the ages of 2 and 5 years [3,4]. Chemotherapy is the treatment of choice for ALL, with methotrexate being among the drugs most frequently used [5].

Stomatologic complications are frequent in these patients and may result from the clinical course of the tumor itself or may be a side effect of antineoplastic therapy [6–8]. Oral mucositis is a frequent stomatologic complication in patients under antineoplastic chemotherapy, especially in those with leukemias. Mucositis is a complex condition resulting from the interaction between antineoplastic agents and epithelial cells, the action of proinflammatory cytokines, oral microbiota, overlapping local trauma, unsatisfactory oral hygiene conditions, and the deficient immune status of the patient [8–12].

Initially, oral mucositis is characterized by a burning sensation, followed by inflammatory changes in the mucosa that generally manifest as erythema and subsequent ulceration [10,13,14]. This clinical presentation generally starts around the fifth to tenth post-chemotherapy day and tends to regress within 2–3 weeks [15]. Oral mucositis can occur in any region of the mouth, but more frequently affects non-keratinized regions such as the jugal mucosa, soft palate and floor of the mouth [8,16,17]. Its occurrence can be associated with other lesions such as candidiasis [8,18].

In view of the discomfort caused by these clinical symptoms, the interference with treatment protocols and the risk of life for the patients, measures are necessary to minimize or even prevent the occurrence and severity of oral mucositis. These measures range from the intensification of oral hygiene care [19] to the use of different substances including sodium bicarbonate [20], saline solution, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, herbal medicines such as *Oren-gedoku-to* and *Syousaikotou*

[21,22], and chlorhexidine, among others [10,16,20,23,24].

The objective of the present study was to analyze the clinical and cytologic aspects of the oral mucosa of children with ALL submitted to antineoplastic chemotherapy at the Center of Children Oncology and Hematology (COHI), Varela Santiago Children's Hospital, Natal, Rio Grande do Norte, Brazil, who received daily mouth rinses of 0.12% chlorhexidine gluconate and oral hygiene care.

## 2. Patients and methods

In a descriptive and experimental study, 33 children with ALL of both sexes ranging in age from 2 to 15 years, without distinction of race, hospitalized at the Varela Santiago Children's Hospital, Natal, RN, Brazil, were submitted to clinical and cytologic evaluation of the oral mucosa. At diagnosis, the patients were classified into low and high risk according to clinical and laboratory criteria. Next, the patients were submitted to a chemotherapy regimen for 24 weeks during an initial phase, followed by a period of maintenance chemotherapy for 1 year and a half. This initial phase was divided into periods and blocks until the occurrence of total remission and was followed by the maintenance phase for the conclusion of therapy. In each period or block, a specific combination of drugs was administered with the objective to achieve cure according to the standard Brazilian protocol for the treatment of acute leukemia proposed by the Brazilian Society of Pediatric Oncology [25]. Methotrexate was one of the drugs used in this therapy and 0.12% chlorhexidine gluconate was administered for 10 consecutive days after each infusion of methotrexate during chemotherapy intensification.

The patients were divided into two groups: group I consisted of 23 children who received 0.12% chlorhexidine gluconate in the form of mouth rinses or applied with a cotton pad immersed in the solution for one minute 30 min after breakfast and after the last night meal; group II consisted of 10 children who did not receive this treatment.

All patients were submitted to clinical examination of the oral cavity and digital palpation of the

oral mucosa, and cytologic smears were obtained from the buccal mucosa at the beginning of chemotherapy intensification for the determination of oral health conditions. The cytologic smears were stained by the modified Papanicolaou technique and then examined by light microscopy. Mucositis was diagnosed according to the criteria established by Epstein et al. [26].

The children of the two groups received the same daily oral hygiene care. The data obtained for the two groups were analyzed statistically using Fisher's exact test and the odds ratio.

The study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte, Brazil. The parents or responsible persons were informed about the character and objectives of the study and signed a free informed consent form.

### 3. Results

Six (26%) of the 23 children of group I developed mucositis. Mucositis persisted after 7 days of treatment with 0.12% chlorhexidine solution but showed no signs of ulceration (Figs. 1 and 2). The remaining 17 children presented no clinical signs of oral mucosal alterations.

In group II, 8 (80%) of the 10 children developed mucositis, initially characterized by the presence of erythema in the buccal and labial mucosa and then by the formation of edemas and ulcers (Figs. 3 and 4). Oral candidiasis was diagnosed in one of these children. The mucositis lesions developed within 2–4 days after the administration of methotrexate (intensification phase) and were painful, impairing normal alimentation of the children.

The cytologic findings showed no expressive variations. There was a clear predominance of cells of the intermediate layer in all cases, and in 18% of the smears the cells presented a perinuclear halo.



**Fig. 1** Normal aspect of oral mucosa in a patient of group I 10 days after administration of methotrexate.



**Fig. 2** Oral mucositis in a patient of group I, characterized by erythema 10 days after administration of methotrexate.



**Fig. 3** Patient of the group II with oral mucositis characterized by erythema and edema.

Comparison of the two groups by Fisher's exact test revealed a lower frequency of mucositis in group I, with this difference being statistically significant ( $p=0.007$ ). The odds ratio of 11.3 (CI: 1.86–69.11) indicates that patients not receiving preventive intervention presented an 11 times higher chance of contracting mucositis.



**Fig. 4** Patient of group II with oral mucositis characterized by erythema, edema and ulceration.

## 4. Discussion

The present study showed a high frequency of mucositis in children with ALL who did not received chlorhexidine (80%). The lesions appeared 2–4 days after the administration of methotrexate (intensification phase), and were preferentially located on the labial and buccal mucosa, completely disappearing about 10 days after their appearance.

Evidence indicating that oral hygiene care favors the general condition of patients with ALL [19] supports the importance of increasing this care, although oral hygiene care alone is ineffective in the control of mucositis. However, the present results demonstrate that oral hygiene in combination with mouth rinses with 0.12% chlorhexidine gluconate was effective in the prevention of oral mucositis in children of group I, since the frequency of mucositis was markedly lower (26%) in these patients.

Fidler et al. [27] admitted that there is no absolutely safe intervention for the prevention of oral mucosal lesions in patients undergoing antineoplastic chemotherapy. Various chemical substances have been tested for this purpose [10,16,20,23,24,28] and chlorhexidine has shown excellent results regarding the promotion of oral health, reducing the severity and duration of mucositis in patients with ALL submitted to chemotherapy and in a state of severe neutropenia [29–31]. However, chlorhexidine should be used at concentrations proven to be therapeutic due to its damaging effect on the epithelium of the oral mucosa as reported by Pereira Pinto et al. [32].

Despite these observations, Spijkervet et al. [33] and Epstein et al. [34] reported no positive results with the *in vivo* or *in vitro* use of chlorhexidine. However, there are variables that might interfere with the *in vivo* action of chlorhexidine solution, altering its results and therefore somehow impairing the interpretation of studies that analyze the efficacy of chlorhexidine.

Cytologic analysis of the oral mucosa showed a marked predominance of cyanophilic cells in the smears which may have caused the loss of cells of the superficial layer of the oral epithelium as a result of the disease itself, thus leading to the exposure of cells of the intermediate layer which will then exhibit new surface receptors. This fact permits the adhesion of pathogenic microorganisms to the epithelial surface favored by the compromised immunologic state of the patient due to ALL. This picture tends to be complicated by the institution of antineoplastic chemotherapy because of the damaging effect of methotrexate on cells of the oral epithelium whose interaction with factors inherent

to the disease and conditions of the oral environment culminate in mucositis. In this respect, 0.12% chlorhexidine gluconate may break an important link in the course of events that lead to mucositis due to its effective action as an antiseptic agent which interferes with the adhesion of pathogenic microorganisms.

The observation of one case of candidiasis in the present study agrees with the finding of Gordón-Núñez and Pereira Pinto [17] who observed one case of oral mucositis associated with pseudomembranous candidiasis among 40 children with cancer analyzed.

The present results demonstrate that chlorhexidine as used here was effective in the control of oral mucositis by clearly reducing the number of cases, thus fulfilling its important role in the prevention of the complex presentation of oral mucositis.

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