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RESEARCH ARTICLE

Extended oral care can prevent oral mucositis in immunocompromised acute lymphoblastic leukemia ghildren

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ABSTRACT

Background: Oral mucositis is a serious complication of chemotherapy. The incidence of chemotherapy induced mucositis ranges from 40%-76% with many studies suggesting that children are more susceptible than adults. **Aim:** We aimed at evaluating pretreatment dental rehabilitation in protecting from oral mucositis in acute lymphoblastic leukemia children. **Patients and Methods:** An open labeled randomized controlled study including 50 newly diagnosed patients with dental caries was conducted. They were classified into a group (A) using standard oral care and group (B) undergoing extended oral care using dental rehabilitation by a pediatric dentist before induction chemotherapy. **Results:** No differences were observed between both groups regarding mucositis development or severity. Mucositis was more among patients with lower neutrophil count, platelet count and poor compliance to daily oral care (P value <0.001, 0.01 and <0.001) respectively. A positive correlation between mucositis grade and Decayed; Missing and Filled Teeth (DMFT) score and a negative correlation between mucositis grade and neutrophil count were noticed with statistical significance. **Conclusion:** Although dental rehabilitation before induction chemotherapy did not seem to reduce either the occurrence or grade of oral mucositis, the positive correlation between mucositis severity and DMF score supports the importance of pretreatment dental assessment and rehabilitation in such immunocompromised patients. Neutropenia, thrombocytopenia and poor oral care were found to be risk factors for oral mucositis.

Keywords: Acute lymphoblastic leukemia, ALL, Chemotherapy, Dental rehabilitation; Extended oral care; Immunocompromised children, Mucositis; Standard oral care

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INTRODUCTION

Oral mucositis is a serious dose limiting complication of chemotherapy (Elting et al., 2007). Severe mucositis can significantly interfere with malignant disease management and patient survival rates, as it often results in interruption of therapy, secondary infection and sepsis (Childers et al., 1993). For acute lymphoblastic leukemia patients treated with standard and high dose chemotherapy, the incidence of chemotherapy induced mucositis ranges from 40% to 76%. Previous studies have shown that children are more likely than adults to develop oral mucositis during chemotherapy (Childers et al., 1993; Nemes et al., 2018). The predisposing factors of mucositis are not fully understood in patients undergoing malignant disease treatment. It has been suggested that several risk factors contribute to mucositis; treatment related, genetic associated and microorganisms related factors (Burrows &Thorpe, 1994; Sonis, 2010; Santos de Faria, et al., 2014). Treatment of mucositis requires integrated oral care, including regular oral care protocols, dental assessment and rehabilitation before and during cancer therapy and the use of different mouth rinses e.g. normal saline or sodium bicarbonate (Rubenstein et al., 2004). In this study we aimed primarily at studying the impact of applying extended oral care using

dental rehabilitation method before induction chemotherapy on preventing or decreasing the severity of oral mucositis in acute lymphoblastic leukemia children. Also we analyzed the effect of other predisposing factors on the occurrence or severity of oral mucositis as a secondary objective.

PATIENTS AND METHODS

Study design and patients enrollment

An open labeled randomized controlled trial including consecutive 50 newly diagnosed acute lymphoblastic leukemia (ALL) children with dental caries with an age ranging from 4 to 18years was conducted over 18months.

Patients were consecutively enrolled in to two groups

Control group (a): consisted of 25 newly diagnosed ALL Children during the induction phase of chemotherapy using standard oral care (applied at our institution) using normal (1: 1) saline mouthwash at least 4 times a day and tooth brushing twice a day with fluoride toothpastes prescribed by a dentist) and intervention group (b):consisted of the next 25 newly diagnosed ALL Children undergoing extended oral care (dental rehabilitation before starting chemotherapy) by a pediatric dentist in addition to standard oral care protocol. Patients planned for teeth extraction were provided with prophylactic platelet transfusion if their platelet count was less than 40.000/mm^3, and prophylactic antibiotics if the absolute neutrophil count was less than 1500/mm^3. Patients belonging to this interventional group should not have any acid - base or electrolyte disturbances or any of the oncologic emergencies. Patients during further phases of ALL treatment beyond the induction phase, uncooperative or those with mental disabilities were excluded from the study. Also patients initially presented with an oncologic emergency that necessitated urgent medical intervention or intensive care unit admission (e.g. hyper leukocytosis, superior vena cava or tumor lysis syndromes) were excluded from the experimental group (B).

Ethical consideration

The study was conducted in accordance with the declaration of Helsinki (WMA, 1964). Written consents were obtained from either parents of each child before being enrolled in the study. The study was approved by local the institutional review board on 27th March, 2017.

METHODOLOGY

All patients underwent dental examination using Decayed; Missing and Filled Teeth (DMFT) index for permanat teeth and (dmft) for primary teeth for evaluating caries experience (Larmas, 2010).

Assessment of patients' compliance

Each patient was provided with a patient diary to document patient's compliance: patients fulfilling more than 75% of the standard oral care instructions were considered good compliants, while those fulfilling from 50-75% were assigned as faire compliants and those who failed to fulfill at least 50% of the standard oral care instructions were called poor compliants.

Screening and assessment of mucositis grade

The patients were examined daily since the beginning of induction chemotherapy protocol (ALL-BFM 90) (Schrappe et al., 1994) for the development of oral mucositis (starting day, grading and duration). The grade of mucositis was determined according to the WHO rating scale for oral toxicity as shown in Table 1.

Table 1. WHO rating scale for oral toxicity (WHO, 1979).

Grade	Symptom
0	No symptom
1	Soreness and erythema
2	Erythema, ulcers; can eat solid food
3	Ulcers, requires liquid diet only
4	No possible alimentation

RESULTS

Patient demographics and clinical characteristics were similar in both groups regarding age, sex, body mass index and type of leukemia (Table 2). All patients (n= 50) had dental caries; of them 6 with missed teeth and 9 with filled teeth in group (A) versus 5 and 8 in the group (B) respectively. Among the extended oral care group (B) 21 patients underwent teeth extraction, 2 teeth filling and another 2 patients underwent both teeth extraction and filling. Table 3 compares mucositis occurrence, onset, grade, frequency and duration between standard group (A) and extended care group (B) without statistical differences between them.

Table 2. Patients' demographics and clinical characteristics of the studied groups

Patient Demographics	Standard Oral Care Group (A)	Extended Oral Care Group(B)	Test of significance	p-value
Age (years) Median (Min- Max)	7.50(4-16)	10(4-17)	Z=1.792	0.073
Sex Male Female	16(64.0%) 9(36.0%)	12(48.0%) 13(52.0%)	χ^2=1.29	0.254
BMI Mean ±SD	19.64±4.01	19.32±4.52	t=0.264	0.793
Diagnosis Pre B ALL T ALL	18(72.0%) 7(28.0%)	16(64%) 9(36%)	χ^2=0.00	0.91
Dental problems: Decayed teeth Missed teeth Dental plaque	25 6 9	25 5 8	χ^2=1.13	0.82
Dental rehabilitation: Teeth Extraction Teeth Filling Teeth Extraction & Filling	- - -	21 2 2		

BMI: Body mass index**,** Z: Z test, t: student sT test, χ^2 : Chi Square test

Table 3. Comparison between standard (A) and extended (B) oral care groups regarding mucositis occurrence and characteristics

Mucositis	Group (A) (25)	Group (B) (25)	Test of significance	P -value
Occurrence Yes No	20 5	18 7	χ^2=0.00	0.9
Onset of mucositis 1st week 2nd week 3rd week	12(60%) 6(30%) 2(10%)	10(50%) 5(25%) 5(25%)	χ^2=1.58	0.459
Grade of mucositis 1 2 3 4	5(25%) 4 (20%) 8(40%) 3 (15%)	6 (30%) 8 (40%) 6 (30%) 0	MC	0.19
Mucositis frequency: Once Twice Three times	15(75.0%) 2(10.0%) 3(15.0%)	16(70%) 4(30%) 0(0%)	MC	0.085
Duration of mucositis (days) Median(Min-Max)	10.00(3.00-21.00)	10.0(5.00-20.00)	Z=0.205	0.83

Z: Z test , MC: Monte Carlo test , χ^2: Chi Square test

Table (4) highlighted potential risk factors for oral mucositis. The occurrence of mucositis was more among patients with a lower neutrophil count, platelet count and those who were poorly compliant to daily oral care (who did not fulfil at least 50% of the daily oral hygiene instructions as mentioned in the patients and method section) with statistical significance (P value <0.001, 0.01 and <0.001) respectively. While patients' age, sex, maternal education, DMFT score and dental rehabilitation did not differ significantly between patients who developed mucositis and those who did not have mucositis.

A positive correlation between mucositis grade and DMFT score (r= 0.38, p =0.01) was observed as shown in Figure 1, while negative correlation between mucositis grade and ANC (r= -0.33, p = 0.036) was found in Figure 2.

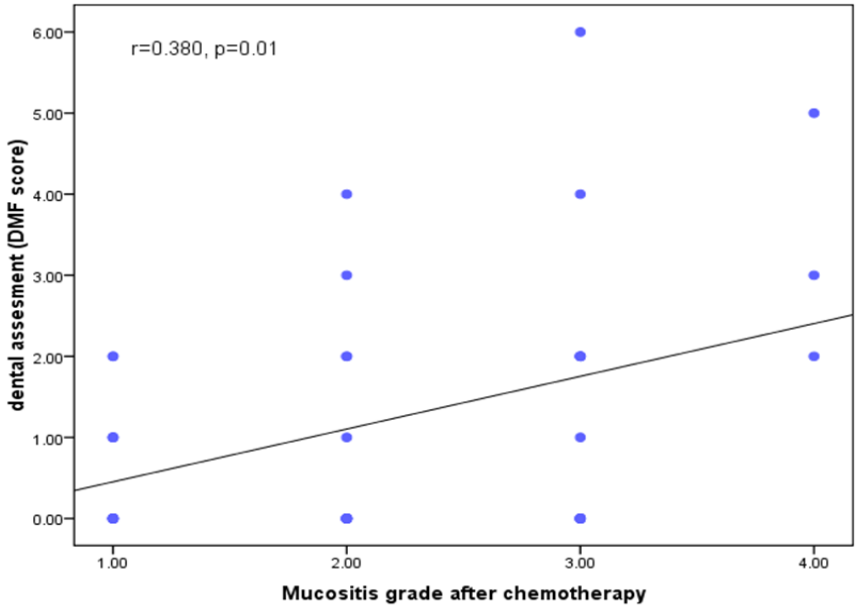

Figure 1. Correlation between mucositis grades and dental assessment score (DMF score).

DISCUSSION

Chemotherapy-treated children are more vulnerable to experiencing mucositis. Since mucositis adversely affects the quality of life through decreasing food intake, hospitalization and increasing risk of infection, it is considered one of the main non-hematological chemotherapy- related complications (Vadhan-Raj et al., 2013). Therefore, adequate oral hygiene is badly needed to reduce morbidity and to improve the patient's general condition (Azher and Shiggaon, 2013).

More than half of the patients among both categories (22/40) experienced mucositis in the first week of chemotherapy. This seemed to be related to the direct toxic effect of chemotherapy resulting in damage of the mucosal cells and increasing vascular permeability, so enhancing cytotoxic drug uptake into the oral mucosa (Sonis et al., 1994).

The median period of oral mucositis was10 days which is consistent with the rapid turnover of the oral mucosal cells, usually ranges from 7 to14 days unless there are wound-disrupting factors such as mechanical irritation or infection which may postpone the healing phase (Sonis, 1998).

In the present study, no differences were found between both study groups regarding either mucositis occurrence or characteristics (onset, grades, frequency and duration). This highlights the multifactorial process of mucositis with chemotherapy rather than a single dental factor. Furthermore, the type of dental rehabilitation done for most of the patients in the current study was teeth extraction, with a small number undergoing teeth filling while other types of rehabilitation like repair defective restorations and polish teeth with sharp edges were not feasible because of limited permissible time for dental procedures before starting chemotherapy which represents an emergent treatment.

According to an extensive systematic review published by McGuire et al**.** (2013) the protective role of dental care provided by a professional against mucositis cannot be overemphasized because of insufficient or conflicting results, however few studies support the effectiveness of intensive dental care in decreasing the severity of mucositis (de Morales et al., 2001; Melkos et al., 2003; Djuric et al., 2006). Nevertheless, in our study the DMFT score was positively correlated with mucositis severity. This result is supported by the guidelines panel of Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recommending pre-treatment evaluation and management of any active oral/dental lesions for patients who are

expected to become immunocompromised because of their cancer therapies (Rubenstein et al., 2004 ; Keefe et al., 2007).

Neutropenia was found to be a risk factor for the development of oral mucositis and negatively correlated to its severity grade. It seems that oral mucosal cells regeneration rate is parallel to leucocytes recovery making the researchers hypothesize that oral mucositis appears near the lowest point of neutrophil count (nadir), with its resolution is correlated with the recovery of neutrophils (Verdi, 1993; Khan & Wingard, 2001). In addition, it is thought that reduction of neutrophil count results in impaired epithelial cell proliferation and increases damage of oral mucosa making it more susceptible to bacterial colonization, viral and fungal invasions that aggravate oral mucositis (Cheng et al., 2011; Cinausero et al., 2017). This finding comes in agreement with previous studies that reported higher risk of mucositis (~3 times) in patients with low neutrophil count (Gandhi et al., 2017; Damascena et al., 2020).

Mucositis was observed more among patients with much a lower platelet count. Patients with severe thrombocytopenia are at greater risk of gingival bleeding which is considered a good media for bacterial growth. Also gum bleeding renders them less compliant to oral care. This is in agreement with Mendonça et al. (2015) reporting significant association between severity of mucositis and a low platelet count at day 14 of induction chemotherapy for ALL children. However, the association between thrombocytopenia and occurrence of severe oral mucositis remains a conflicting issue as other studies did not find a significant relationship between both variables (Damascena et al., 2020; Pires et al., 2020).

Poorly compliant patients to routine oral care experienced oral mucositis more than those who were classified as fair and good compliants to routine oral care. This emphasizes the importance of good oral hygiene in protecting immunocompromised patients against oral mucositis. This is matched with Mattos et al. (2020) who demonstrated that patients who did not adhere to dental treatment were at higher risk of developing oral complications compared with other children and adolescents with full adherence to dental care. In addition, poor oral health has been accompanied by a higher rate of oral complications during chemotherapy and radiotherapy especially among children and adolescents (Cheng et al., 2008; Glenny et al., 2010; Hong, 2010).

In conclusion, the results of this study suggest that although no significant differences regarding the occurrence or the severity of mucositis were found between patients undergoing invasive dental rehabilitation before induction chemotherapy and those undergoing standard oral care only, DMFT score was found to be positively correlated with mucositis grades. This emphasizes the importance of pretreatment dental assessment and providing professional dental care for active lesions in patients who are expected to be immunocompromised because of cancer therapy. Also neutropenia, thrombocytopenia and poor oral hygiene were found to be risk factors for oral mucositis.

Study limitation

The study faced some limitations as a small patient group, from a single center and few types of dental rehabilitation were done because of limited permissible time.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTION

AG Collected the clinical data of the patients, arranged patients'' transfer from the Oncology inpatient ward to dental clinic at Faculty of Dentistry and approved the final version of manuscript submitted. SA suggested the research idea, wrote the manuscript. HS was responsible for the dental work for the patients,

revised and the manuscript revision. AM revised the clinical work and approved the final version of the manuscript.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article. More detailed data is available from corresponding author on reasonable request.

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