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# Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients

K.K.F. Cheng [a,*], A. Molassiotis [b], A.M. Chang [a], W.C. Wai [c], S.S. Cheung [c]

[a] *Department of Nursing, 6/F, New Teaching Block, Chung Chi College, Chinese University of Hong Kong, Shatin, Hong Kong*
[b] *School of Nursing, University of Nottingham, UK*
[c] *Department of Pediatrics, Prince of Wales Hospital, Hong Kong*

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**Abstract**

Oral mucositis is the most frequent and severe complication of chemotherapy in children with cancer that can aggravate the child's clinical condition and increase the risk of infection. This prospective comparative study was designed to determine the effectiveness of a preventive oral care protocol in reducing chemotherapy-induced oral mucositis in children with cancer. During an 8-month period, 42 children aged 6 to 17 years with haematological malignancies or solid tumours were evaluated. The 21 children who were included in the first 4-month period of the study constituted the control group. Another 21 children were enrolled in the subsequent 4 months and were assigned to the experimental group, in which they were given an oral care protocol intervention. The oral care protocol consisted of tooth brushing, 0.2% chlorhexidine mouth rinse and 0.9% saline rinse. Children in both groups were evaluated twice a week for 3 weeks. The incidence of ulcerative lesions, severity of oral mucositis and the related pain intensity were used as the main outcome variables. A 38% reduction in the incidence of ulcerative mucositis was found in children using the oral care protocol compared with children in the control group. The severity of oral mucositis ($P=0.000002$) and the related pain ($P=0.0001$) were significantly reduced with the intervention. These results support the preventive use of the oral care protocol in paediatric cancer patients who undergo chemotherapy for cancer treatment. 

*Keywords:* Oral mucositis; Chemotherapy; Oral care protocol; Paediatrics

## 1. Introduction

The success achieved over the past 30 years in improving the curative response in cancer treatment has been largely attributed to dose intensification and combination chemotherapy. However, chemotherapy-induced toxicity remains a significant clinical problem [1]. With the broad clinical use of haematopoietic growth factors (G-/GM-CSF), effects of myelosuppression have been largely overcome and are no longer dose-limiting. Oral mucositis has now become a common and primary dose-limiting toxicity of chemotherapy [2,3]. The incidence of chemotherapy-induced oral mucositis is estimated to be approximately 40% for adult patients treated with chemotherapy [4]. Patients treated with a combination of agents that are known to cause oral mucositis are more likely to suffer from this toxicity [5]. Numerous studies have also indicated that children are at higher risk of developing oral mucositis than adults [3,6,7]. Indeed, the frequency of oral mucositis has been reported to be around 65% in paediatric cancer patients [6,8]. The high prevalence, however, has not been thoroughly analysed or understood. It may be related to the higher proliferating fraction of mucosal basal cells, variations in resistance and/or the immunological status of children [3,7]. In addition, the predominant type of childhood cancer is haematological, which is proposed to lead to higher rates of oral mucositis than in patients with solid tumours [4,9].

### 1.1. Risk factors for oral mucositis

The aetiology of oral mucositis is multifactorial. Its frequency and severity can result from risk factors resulting from the therapy or associated with the patient [3,4]. However, there is lack of a large scale multivariate

* Corresponding author. Tel.: +852-2603-5667; fax: +852-2603-5269.
*E-mail address:* s980153@cuhk.edu.hk (K.K.F. Cheng).

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study to determine the association between the incidence of oral mucositis and the potential risk factors for its development. It is generally agreed that the choice of drug administered, its dose and schedule of delivery, the underlying disease, as well as the extent of myelosuppression are important variables influencing the susceptibility to oral mucositis [3,4,10].

### 1.2. Clinical manifestations and the impact of oral mucositis

The time-course of oral mucositis is well researched, and oral mucositis normally lasts for 3 weeks. It begins 3–5 days after the initiation of chemotherapy, and peaks at 7–14 days. It then slowly resolves unless complicated by infection [9,11]. Clinically, oral mucositis is characterised by erythematous, erosive and ulcerative lesions [12]. The ulcerative lesions associated with oral mucositis are the most symptomatic [13]. The literature has repeatedly highlighted that the morbidity of oral mucositis can be profound and it is very distressing to patients during cancer treatment. Besides causing intense pain and discomfort, oral mucositis can interfere with oral intake as well as the patient's ability to communicate and sleep. The most serious concern is the increase in associated risks of localised and disseminated infections resulting from the colonisation of oral micro-flora and damage to the oral tissues of patients while they are immuno-compromised [10,14–16]. Studies on bacteraemia in cancer patients have indicated that those with oral mucositis and neutropenia have a 4 times higher risk of septicaemia than individuals without oral mucositis [17,18]. Recent data has also indicated that viridans streptococci from the oral mucosal lesions are responsible for the marked increase in gram-positive bacteraemia in neutropenic cancer patients [17,19]. In addition to the morbidity and its impact on quality of life, oral mucositis may result in treatment interruptions and dose reductions with a direct impact on disease survival, including cure rates or durability of remission [10,14–16,20]. The NIH (National Institute of Health) consensus conference in 1989 emphasised the importance of minimising oral complications in order to optimise cancer treatment [16].

### 1.3. Research on oral mucositis management

There is increased attention by nurses, dentists and medical oncologists on the issues surrounding the supportive care for those with or at risk of oral mucositis. More laboratory and clinical studies have been undertaken to explain the pathogenesis and mechanisms of oral mucositis development, as well as to develop effective strategies on the prevention of oral mucositis. Although a number of strategies and products are available for the management of oral mucositis, there is, as yet, no consensus on the management of this condition other than the effective means of administering pain medication [21]. This may, in part, explain the reason for the current standard treatment for oral mucositis being symptomatic care with analgesics and nutritional support. Chin [22] also indicated that symptomatic care is all that can be provided to patients until oral mucositis resolves itself. Nevertheless, it is generally agreed in the dental and nursing literature that the institution of good and consistent oral hygiene measures is critical and may be one of the most important factors in the prevention of oral mucositis and oral infection [23,24]. The most recent biological model of oral mucositis [13] further validates the relationship of oral hygiene measures for oral mucositis, in which the endotoxin produced in association with colonising bacteria may amplify the pro-inflammatory cytokine cascade within oral mucosa and thus intensify the oral mucosal injury. Numerous studies have also supported the hypothesis that the pathogenesis of oral mucositis is partly related to a microbial interaction with the oral tissues [25,26]. In this context, reduction of oral micro-flora colonisation by ways of improvement in the quality of oral hygiene may retard the development of oral mucositis.

Many authors have noted the importance of oral care during chemotherapy treatment. There are substantial discussion papers addressing the oral care protocols used in various institutions to reduce chemotherapy-induced oral mucositis. However, as discussed in a recent systematic review, the number of well-controlled and prospective experimental studies designed to test the effectiveness of particular oral care protocols are very limited [27]. Therefore, existing research does not provide evidence of scientifically-based effective oral care regimens. Additionally, published reports on the use and efficacy of oral care protocols do not offer detailed guidance because the agents used and frequency of administration varied greatly [14,15,20,28,29]. It is noted that a large number of studies have been carried out on oral mucositis and their management without proper attention to paediatric patients. Similarly, the majority of studies on the effectiveness of oral care protocols in cancer patients deal with adults, while information about this intervention in paediatric cancer patients is limited. As pointed out by Leggott [30] and Bonnaure-Mallett and colleagues [31], the incidence of oral complications and the influence of oral care measures on oral mucositis are poorly understood in the paediatric cancer population. In addition, methodological difficulties which include small and heterogeneous populations may lead to difficulty in conducting research in children. Nevertheless, there can be little progress in the clinical care of oral mucositis of paediatric cancer patients without adequate research in this age group. Thus, the aim of the present study was to evaluate the use of a systematic preventive oral care

protocol in reducing the incidence and severity of chemotherapy-induced oral mucositis in children with cancer.

## 2. Patients and methods

### 2.1. Setting and sample

The study was conducted in a children cancer centre of a university hospital in Hong Kong after approval from the ethics committee. Enrolled in the study were children between the ages of 6 to 17 years who had received high-dose or combination chemotherapy for haematological malignancies or solid tumours. They were also capable of demonstrating the ability of tooth brushing and mouth rinsing as judged by the investigators. Patients and their parents were informed of the aim of the study and were included only after their parents had signed a consent form. All of the patients approached agreed to participate in the study (100%). The oral care protocol and control groups consisted of 21 patients each.

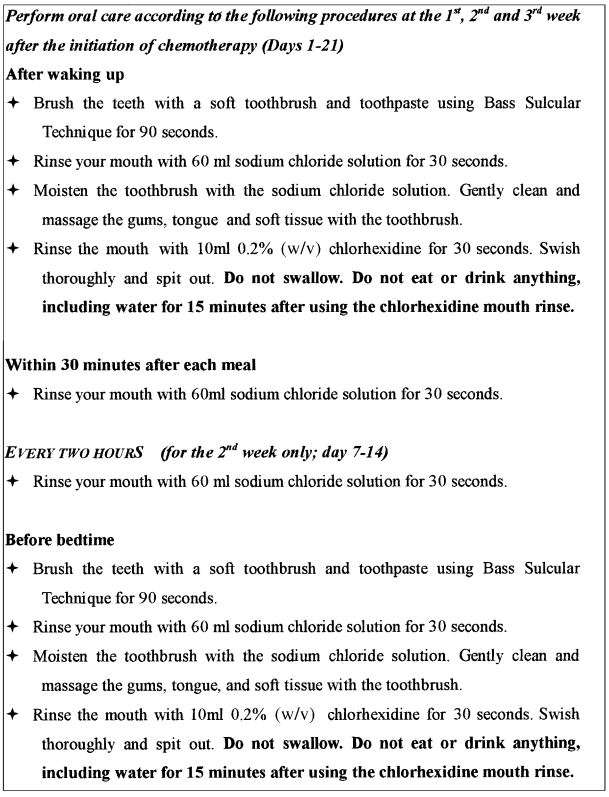
### 2.2. Study design

This was a prospective study using an intact group design. The study was conducted over 8 months. Subjects enrolled in the first 4-month period of study constituted the control group. These patients did not receive the oral care protocol intervention and the information about the importance of oral care, but when they developed oral lesions they were treated with symptomatic measures according to the routine practice at the cancer centre. It involved irregular use of 0.9% sodium chloride solution, and benzydamine hydrochloride rinse to control oral mucositis-related pain. In the subsequent 4-month period, subjects were recruited into the experimental group receiving the oral care protocol intervention (Fig. 1). The oral care protocol was developed in accordance with the clinical time-course of oral mucositis from the literature. Separating the two groups of subjects over the two periods minimised the potential contamination of the oral care procedure among control and experimental subjects. Patients in the experimental group followed the oral care protocol on the first day of chemotherapy treatment and continued for 3 weeks.

To maintain a consistent approach in implementing the intervention, patients and their parents also received a 10-min videotaped oral care programme, in which the information and instruction of the oral care protocol were provided. In addition, they were given a brochure outlining the oral care protocol. Each patient was also given an oral care practice diary where the child (or parent) recorded every oral care procedure that was performed. Compliance was monitored by assessing the frequency of oral care recorded in the diary, and by determining the amount of rinse used and left in the returned bottles. The level of oral care that was considered as adequate compliance was set arbitrarily at 80%.

### 2.3. Assessments

Clinical evaluations were performed before commencing chemotherapy and then twice per week for a 3-week period (day 1–day 21). The principal criteria for the assessment were the occurrence and severity of oral mucositis. For the purposes of the present study, the presence of oral mucositis was defined based on the clinical manifestation of ulcerative lesions in the oral mucosa. The severity of oral mucositis was measured by the Eilers' Oral Assessment Guide [32] after minor modification. The original Oral Assessment Guide was designed to assess oral mucositis in eight categories: voice, swallow, lips, tongue, saliva, mucous membrane, gingiva and teeth/denture. The Oral Assessment Guide was modified in agreement with the local experts in oncology and the following alterations were made: the category of mucous membrane was split into buccal/palate, and labial mucous membranes. The category of teeth/denture was deleted in order to permit a more accurate reflection of the severity of oral mucositis. Each descriptor for the eight categories received a score


***Perform oral care according to the following procedures at the 1st, 2nd and 3rd week after the initiation of chemotherapy (Days 1-21)***

**After waking up**

- Brush the teeth with a soft toothbrush and toothpaste using Bass Sulcular Technique for 90 seconds.
- Rinse your mouth with 60 ml sodium chloride solution for 30 seconds.
- Moisten the toothbrush with the sodium chloride solution. Gently clean and massage the gums, tongue and soft tissue with the toothbrush.
- Rinse the mouth with 10ml 0.2% (w/v) chlorhexidine for 30 seconds. Swish thoroughly and spit out. **Do not swallow. Do not eat or drink anything, including water for 15 minutes after using the chlorhexidine mouth rinse.**

**Within 30 minutes after each meal**

- Rinse your mouth with 60ml sodium chloride solution for 30 seconds.

*EVERY TWO HOURS (for the 2nd week only; day 7-14)*

- Rinse your mouth with 60 ml sodium chloride solution for 30 seconds.

**Before bedtime**

- Brush the teeth with a soft toothbrush and toothpaste using Bass Sulcular Technique for 90 seconds.
- Rinse your mouth with 60 ml sodium chloride solution for 30 seconds.
- Moisten the toothbrush with the sodium chloride solution. Gently clean and massage the gums, tongue, and soft tissue with the toothbrush.
- Rinse the mouth with 10ml 0.2% (w/v) chlorhexidine for 30 seconds. Swish thoroughly and spit out. **Do not swallow. Do not eat or drink anything, including water for 15 minutes after using the chlorhexidine mouth rinse.**

Fig. 1. Oral care protocol for paediatric cancer patients in chemotherapy.

of 1, 2 or 3 and the final score represented a sum of the categories scores. A normal mouth received a score of 8 and the highest possible score was 24. Interrater reliability of this modified scale was established using three nurses who completed four oral cavity assessments on inpatients. The agreement between the raters was high with a correlation coefficient of 0.87 ($P=0.01$).

Oral mucositis-related pain intensity was scored by the Faces Scale [33]. It consists of six cartoon faces ranging from very happy (smiling faces for no pain) to increasingly less happy faces to final sad, tearful face for worst pain. This scale was reported to be reliable and valid to measure pain in children as young as 3 years old. The other criteria of assessments were (a) the occurrence of febrile episodes which are defined as persistent pyrexia $\geqslant 38^{\circ}$ for at least 6 h during the 2nd and 3rd week after starting chemotherapy, (b) the relationship of the condition of oral mucosa and the patients in the state of neutropenia which is defined as an absolute neutrophil count (ANC) below $1\times10^9$/l. Demographic and clinical data such as gender, age, education level, usual oral care practice, underlying disease and chemotherapy regimens were recorded for each patient.

### 2.4. Data analysis

Data were analysed using the Statistical package for the Social Sciences (SPSS) program. Differences on demographic and clinical data were compared by the Chi-square test and Student *t*-test. A Chi-square test was also used to test for significant differences in the frequency of oral ulcerative lesions between the two groups. Repeated measures analysis of variance with time (prechemotherapy and days 3, 7, 10, 14, 17 and 21 after start of chemotherapy) as the within subject factor and group (with versus without oral care protocol) as the between subject factor were performed for oral mucositis and oral mucositis-related pain measures. The main effects of time and group were evaluated. Repeated contrasts were conducted for each significant time main effect to determine the source of the significance difference. Pearson's correlation coefficients were calculated between the oral mucositis scores and the pain scores. The criterion for statistical significance was considered as $P<0.05$.

## 3. Results

42 children were enrolled in the study; there were 21 children in both the control and experimental groups. The age of the children ranged from 6 to 17 years (mean age = 10.3 years, standard deviation (S.D.) = 3.19 years). Analysis of the demographic data revealed no statistically significant differences between the control and experimental groups in relation to age, gender and education level. Before the study, only 33% of the subjects performed oral care in the form of tooth brushing twice a day, and 60% of subjects performed oral care once a day. No differences were noted between these two groups in usual oral hygiene practice ($\chi^2=0.98$, $P=0.61$). The most common diagnoses were acute lymphoblastic leukaemia (48%), osteosarcoma (21%) and acute myelogenous leukaemia (14%). There were no significant differences between these two groups relative to the type of diagnosis ($\chi^2=1.53$, $P=0.676$). The more commonly used chemotherapy regimens included antimetabolites (31%) and antimetabolites + plant alkaloids (31%). No significant difference was found between the two groups of subjects with respect to the type of chemotherapy received ($\chi^2=5.8$, $P=0.122$). The two groups were comparable for prior chemotherapy received and baseline myelosuppression status (Table 1).

In this study, the predominant clinical signs of oral mucositis were erythema and ulceration. 6 patients (29%) from the experimental group did not develop erythematous and ulcerative mucosa, with their oral mucositis score remaining at 8 (normal mouth according to the Oral Assessment Guide) during the study period. However, only 1 patient (5%) in the control group experienced no erythematous and ulcerative mucosa. For both groups combined, 52% of patients developed ulcerative lesions. The distribution of subjects with ulcerative lesions was 15 out of 21 (71%) in the group not using the oral care protocol, and 7 out of 21 (33%) in the group using the oral care protocol. The difference between the two groups was statistically significant ($\chi^2=6.1$, $P=0.01$).

Fig. 2 delineates the mean oral mucositis score across all the time points evaluated for subjects in the control and experimental groups. Although the prechemotherapy mean oral mucositis score of the control group was slightly higher than that in the experimental group,

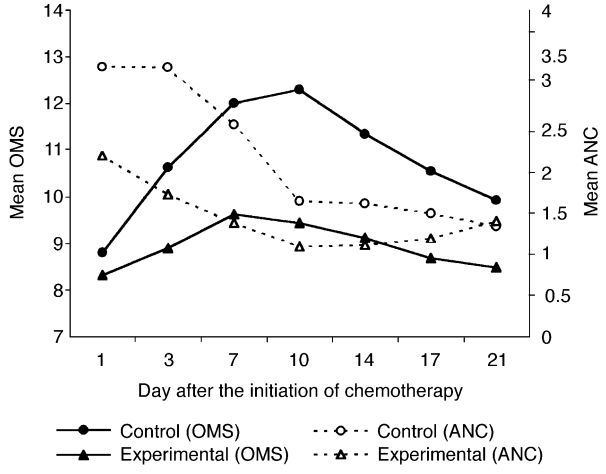



Fig. 2. Mean oral mucositis score (OMS) and absolute neutrophil count (ANC) of the control and experimental groups from days 1–21 after the initiation of chemotherapy.

Table 1
Demographic and clinical characteristics of subjects in the control and experimental groups

| | Control ($n=21$) Mean (S.D.) | Experimental ($n=21$) Mean (S.D.) | $t$ | $P$ value |
|---|---|---|---|---|
| Age (years) | 10.24 (3.2) | 10.38 (3.2) | 0.14 | NS |
| Education (years) | 4.48 (3.1) | 4.75 (3.3) | 0.27 | NS |
| | $n$ (%) | $n$ (%) | $\chi^2$ | $P$ value |
| Gender | | | | |
| Male | 14 (67) | 17 (81) | 1.1 | NS |
| Female | 7 (33) | 4 (19) | | |
| Usual oral care practice | | | | |
| Tooth brushing | | | | |
| Twice a day | 8 (38) | 6 (29) | 0.98 | NS |
| Once a day | 1 (52.4) | 14(67) | | |
| Once a week/never | 2 (10) | 1 (5) | | |
| Diagnosis | | | | |
| Haematological malignancy | 14 (67) | 14 (67) | – | – |
| Solid tumour | 7 (33) | 7 (33) | | |
| Morphological diagnosis of the cancer cases according to ICD-O | | | | |
| Leukaemia | 13 (62) | 11 (52) | 1.53 | NS |
| Lymphoma | 1 (5) | 3 (14) | | |
| Bone | 4 (19) | 5 (24) | | |
| Soft-tissue sarcoma | 3 (14) | 2 (10) | | |
| Type of chemotherapy regimen used | | | | |
| Antimetabolities | 3 (14) | 10(47) | 1.53 | NS |
| Antimetabolities + plant alkaloids | 8 (38) | 5 (24) | | |
| Antitumour Antibiotics + plant alkaloids | 7 (33) | 5 (24) | | |
| Others | 3 (14) | 1 (5) | | |
| First chemotherapy | | | | |
| No | 15 (71) | 16 (76) | 0.12 | NS |
| Yes | 6 (29) | 5 (24) | | |
| Baseline myelosuppression status | | | | |
| Non-neutropenia (ANC $\geqslant 1\times10^9$/l) | 17 (81) | 13 (62) | 0.86 | NS |
| Neutropenia (ANC $<1\times10^9$/l) | 4 (19) | 8 (38) | | |

NS, non-significant ($P>0.05$); ICD-O, International Classification Diseases for Oncology; ANC, absolute neutrophil count.

the difference was not significant ($t=1.63$, $P=0.113$). Comparison between the groups showed that the control group had a higher level of oral mucositis at all time points studied. The overall mean difference in the oral mucositis score of subjects in the control and experimental groups across all the time points evaluated was 1.85 (95% CI 1.18∼2.52). In addition, there were statistically significant differences in the mean oral mucositis score between the control and experimental groups at all the time points ($F=30.79$, $P=0.000002$).

The mean oral mucositis score of both groups varied significantly between the prechemotherapy, days 3, 7, 10, 14, 17 and 21 follow-up evaluations ($F=12.04$, $P=0.001$). Specifically, the oral mucositis scores for both groups between days 1 and 3 ($F=33.83$, $P=0.000001$), days 3 and 7 ($F=11.3$, $P=0.002$), days 10 and 14 ($F=4.41$, $P=0.042$), as well as days 14 and 17 ($F=5.73$, $P=0.02$) differed significantly from each other. In general, the pattern of oral mucositis was similar in the two groups, which appeared at about day 3, peaked on days 7–10, and started to resolve by day 14 after chemotherapy. However, the score of oral mucositis observed in the control group did not return to prechemotherapy levels at day 21. The score of oral mucositis among the subjects in the oral care protocol group returned to a level near to that of the prechemotherapy level by day 21.

Fig. 2 also shows the mean ANC of the two groups of subjects. Subjects in the experimental group experienced a lower level of neutrophil count than subjects in the control group at all time points, but this difference was not statistically significant ($F=1.73$, $P=0.196$). The mean neutrophil count of both groups varied significantly between the 7-time point evaluations ($F=7.79$, $P=0.008$). The neutrophil count dropped abruptly from around day 7, and reached the nadir at days 10 to 14. A moderate negative correlation was found to exist between the presence of oral mucosa and

the neutrophil count of the control group ($r=-0.31$, $P=0.46$) and the oral care protocol group ($r=-0.55$, $P=0.15$).

Almost all the subjects in the control group during neutropenia developed oral ulcerative lesions (8/9, 89%). Only one-third of subjects using the oral care protocol while in neutropenia developed oral ulcerative lesions (4/14, 29%). Overall, a febrile episode was recorded in 7 out of 21 (33%) and 6 out of 21 (29%) of the control and experimental subjects, respectively. The proportion of observations in which the subjects developed fever with the presence of oral ulcerative lesions was 6 out of 15 (40%) in the control group, and 1 out of 7 (14%) in the experimental group.

The intensity of oral mucositis-related pain was significantly correlated with the score of oral mucositis in the two groups of subjects ($r=0.89$, $P=0.007$). Fig. 3 shows the mean score of oral mucositis-related pain across all the time points evaluated for the control and experimental groups. Subjects in the control group reported a slightly higher pain score at prechemotherapy than subjects in the experimental group, but this difference was not statistically significant ($t=1.07$, $P=0.29$). The pain score for the control group did not return to that of the pre-chemotherapy level at day 21. In contrast, the pain scores for the experimental group decreased consistently from day 10 after chemotherapy onwards, and returned to a level lower than that of the prechemotherapy level at day 21. The results also showed that subjects in the control group reported a higher level of pain at all time points. The overall mean difference in the pain scores of subjects in the control and experimental groups across all time point evaluations was 0.65 (95% CI 0.35–0.95). There were also statistically significant differences in the mean pain score between the control and experimental groups at all the time points evaluated ($F=19.22$, $P=0.0001$).

Overall, the mean pain score of both groups varied significantly between the pre-chemotherapy, day 3, 7, 10, 14, 17 and 21 follow-up evaluations ($F=2.9$, $P=0.03$). Specifically, the pain scores for both groups of subjects between days 1 and 3 ($F=4.2$, $P=0.04$), days 3 and 7 ($F=4.32$, $P=0.04$), as well as days 17 and 21 ($F=4.9$, $P=0.03$) evaluations differed significantly from each other.

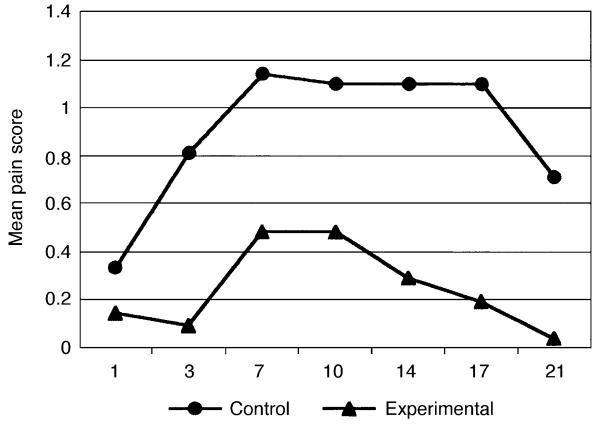



Fig. 3. Mean pain score of the control and experimental groups from days 1 to 21 after the initiation of chemotherapy.

9.5% of the subjects in the control group and 4.8% subjects in the experimental group had received a systemic analgesic (codeine) for the relief of oral mucositis-related pain. The proportion of observations in which the patient required local analgesic mouthwash (benzydamine hydrochloride) for relief of oral pain was 9 out of 21 (43%) in the control group, and 2 out of 21 (10%) in the experimental group.

All of the subjects using the oral care protocol achieved adequate compliance ($\geqslant 80\%$), and their average percentage of compliance was fairly constant throughout days 1 to 21 after starting the chemotherapy. It was 92, 95 and 90% in the 1st (days 1–6), 2nd (days 7–14) and 3rd (days 15–21) week after starting chemotherapy, respectively.

## 4. Discussion

The results provided data on the time-course of changes of the oral mucosal membrane during chemotherapy from days 1 to 21. The time-course of oral mucositis demonstrated in this study was similar to those reported in previous studies [9,10]. It is important to note that most other studies only related to the immediate or late changes of oral mucositis and not to the specific time-course of changes as presented in this study. In addition, clinical examinations were carried out on a weekly basis only in the majority of these studies [20,25,31]. This infrequent approach, however, is problematic since some ulcers that occurred had time to heal during the interval between the weekly examinations. In this context, neither the precise day of onset or resolution could be specified, nor could the responses of the oral mucosal membrane to interventions be accurately demonstrated. This may be why conflicting conclusions have been reported. As Ramirez-Amador and colleagues [34] suggest, follow-up of this patient population should be done at least twice a week in order to ensure that oral lesions are not missed.

In the present study, as well as in past studies, atrophy, erythema and ulcerative lesions were the predominant clinical characteristics of oral mucositis [29,31,34]. However, like other studies [31,34,35] we chose ulcerative lesions as a parameter for analysis because breakdown in the epithelial integrity has more clinical significance in terms of patient morbidity, potential microbial ingress, and systemic infection, when compared with epithelial atrophy or erythema. In addition, mucosal redness is often a subjective finding,

whereas an ulcerative lesion is a more objectively defined clinical endpoint [35]. Our data has shown that the oral care protocol intervention may reduce the incidence and severity of oral mucositis in paediatric cancer patients following chemotherapy. Ulceration of the oral mucosa was substantially lower in patients in the intervention group compared with those in the control group. Data from other studies indicated that 65% [6,8], 71% [7], 52% [31], or 80% [35] of paediatric cancer patients developed ulcerative oral mucositis, but only 33% of our patients who were in the oral care protocol intervention group developed ulcerative oral mucositis. In addition, fever-associated with oral mucositis was found to be lower also in these patients. The relatively low average scores of oral mucositis according to the Oral Assessment Guide in the patients using the oral care protocol further supports the preventive use of this protocol in paediatric patients who undergo chemotherapy for cancer treatment.

The length of aplastic period and low neutrophil counts are thought to be important in the development of oral lesions [36]. We also found, in agreement with other studies [8,26,35], that oral mucosa is associated with the degree of myelosuppression in patients treated with chemotherapy. For both groups, the maximum stomatotoxicity was most frequently observed at the nadir of the ANC since oral mucosal cells and leucocytes have essentially the same renewal rate [36]. However, it is noteworthy that the occurrence of ulcerative mucositis and its severity were substantially lower in patients using the oral care protocol in spite of their myelosuppression. Comparing the patients in the two groups, there was a 60% reduction in the incidence of ulcerative oral mucositis during neutropenia in the patients receiving the oral care protocol, confirming earlier reports [29].

However, these findings must be interpreted with caution because several factors could have influenced the development and severity of oral mucositis. These variables include differences in the underlying disease, doses, schedule, combination and duration of exposure to drugs, systemic clearance of drugs, degree of oral mucosal immune dysregulation, and local and microbial irritation [3,4]. However, as in other studies [14,15,28, 29,31], it was extremely difficult to control for all these variables in a single and small sample study. Nevertheless, it is important to note that patients of the same age, having the same tumour, receiving the same dose and form of chemotherapy and with an equivalent oral status were not observed to develop oral mucositis at the same frequency in the present study, supporting previous literature [13]. It seems possible that genetic influences on inflammatory response might affect the individual's capacity to tolerate chemotherapy, and thus constitute a partial explanation for the variance in patients' response to antineoplastic therapy [13].

In this study, the range of age, the distribution of patients by diagnosis and chemotherapy regimens was comparable between the two groups. Haematological malignancies constituted 57% of all childhood malignancies in the study population whose age ranged from 6 to 17 years. Several studies have suggested that oral mucositis develops more frequently in patients with haematological malignancies than in those with solid tumours [3,7,9]. This is likely to be related to the disease, drug-related myelo- and immunosuppression, as well as the frequent use of cell-cycle specific chemotherapeutic agents [3,7]. However, the validity of this presumption in paediatric cancer patients is less clear. In the present study, a similar incidence of ulcerative mucositis was observed in paediatric patients with haematological malignancies (54%) and solid tumours (50%), as described in earlier reports [7]. Similar agents are used in the treatment of childhood malignant diseases, including drugs that affect DNA synthesis, inhibit protein synthesis and inhibit mitosis, and these drugs are more frequently associated with stomatotoxicity [37].

Oral mucositis is the principle aetiology for pain in patients undergoing cancer treatment. Recent data revealed that 57.8% of pain in paediatric cancer patients was secondary to chemotherapy-induced oral mucositis [38]. Control of oral pain, therefore, is a chief concern in the management of oral mucositis. The present data has demonstrated that the oral care protocol intervention is beneficial in attenuating the severity of oral pain as the severity of oral mucositis is decreased. The patterns of oral pain observed roughly paralleled the pattern of oral mucositis development. A relationship between a high oral mucositis score and the pain score suggests that pain is exacerbated as oral mucositis becomes more severe.

It is emphasised in the literature that an oral care protocol's success depends on patient compliance [16,20]. The present data revealed that more than 90% of paediatric patients complied 100% with the oral care protocol. This is despite the fact that using a chlorhexidine rinse has led to a poor acceptance and compliance in adult patients because of its stinging, astringent taste, and discoloration of the teeth and tongue.

In conclusion, a preventive oral care protocol systematically applied to paediatric cancer patients during chemotherapy is associated with reductions in the incidence and severity of oral mucositis, as well as in the related pain. The oral care protocol was developed based on the clinical time-course of oral mucositis, which offers a detailed and specific oral care procedure that patients could follow in both clinical and home settings. In addition, various aspects of the oral care protocol, such as tooth brushing and mouth rinsing, are self-care measures that older children can learn making them more responsible for their personal health-related care.

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