

Prevention of Oral Mucositis in Paediatric Patients with Acute Lymphoblastic Leukemia undergoing Chemotherapy: A randomized controlled, cross-over trial using 0.12% Chlorhexidine Gluconate and 1% Povidone Iodine Mouthwash

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Abstract

Title:

Prevention of oral mucositis in paediatric patients with acute lymphoblastic leukemia undergoing chemotherapy: a randomized controlled, cross-over trial using 0.12% chlorhexidine gluconate and 1% povidone iodine mouthwash.

Rationale

One of the most debilitating complications of chemotherapy is oral Stomatitis. It occurs in up to 52-80% of children undergoing chemotherapy. Standard oral hygiene includes several mouthwashes that may be chosen for prophylactic and therapeutic use. However, there are only a few studies which compare their efficacy in Paediatric acute lymphoblastic Leukemia (ALL). A consensus protocol regarding prophylaxis and treatment of oral Mucositis is needed for this population of patients.

Objectives

General

To compare the efficacy of 0.12% Chlorhexidine Gluconate and 1% Povidone Iodine mouthwash in the prevention of Oral lesions in children with ALL receiving Chemotherapy.

Specific

1. To determine the demographic and clinical data of the participants as to: a) sex b) age c) type of leukemia d) phase of chemotherapy 2. To determine the effect of 0.12% chlorhexidine gluconate mouthwash and 1% povidone iodine mouthwash in the prevention and treatment of oral lesions in acute lymphoblastic leukemic children receiving chemotherapy as to: a) incidence b) severity of oral lesions c) duration of symptoms 3. To determine any side effects or complications of using either mouthwash.

Study Design

Prospective, randomized controlled, non-blinded, two period cross-over trial

Subjects

Children between 6 and 18 years old diagnosed with ALL who are undergoing Induction, Consolidation, or Re-induction chemotherapy at USTH-BCI from August 2013 to December 2014

Methodology

The study was conducted at the University of Santo Tomas Hospital and Benavides Cancer Institute (USTH-BCI). Twenty-one eligible children ages 6 to 18 years diagnosed with ALL who are undergoing chemotherapy were divided into two groups. Group 1 was instructed to rinse with 10 mL of 0.12% chlorhexidine gluconate mouthwash twice daily, and Group 2 with 10 mL of 1% povidone iodine mouthwash twice daily, for 14 days or until lesions healed if present at the 14th day of study. Alkaline saline mouthrinse was used by the subjects during the 2 week 'washout' time between the two periods of study. The two groups then switched mouthrinses during the second study period. The occurrence of ulcerative lesions and severity of mucositis were measured at baseline and twice weekly of each study period, using the Oral Mucositis Assessment Scale (OMAS) and World Health Organization (WHO) Grading Scale. Statistical analysis includes descriptive statistics using percentage, mean, and standard deviation, frequencies, and percentages. Generalized linear models for testing treatment difference on mean WHO and OMAS scores. Paired t-test was used to test for difference in mean duration. McNemar's test was used to test for difference in incidence of OM between the two treatments.

Results

Four (19%) subjects experienced mucositis while using 0.12% chlorhexidine mouthwash, while 2 (9.5%) developed mucositis while using 1% povidone iodine mouthwash. Chlorhexidine gluconate mouthwash has a higher mean score than 1% povidone iodine mouthwash on both dependent variables (WHO and OMAS scores), which means that 1% povidone iodine mouthwash has more beneficial effect. The mean duration of mucositis while using chlorhexidine is 9.5 days (3-16 days) while for povidone iodine, 6 days (3-9 days). If we base our conclusion on the 95% confidence interval of the treatment difference and the p-value (<0.05), the differences are not statistically significant. No side effects or complications were observed with the use of either mouthwash.

Conclusion

Both 0.12% chlorhexidine gluconate and 1% povidone iodine mouthwash have similar effects in the prophylaxis and treatment of oral mucositis for pediatric patients with acute lymphoblastic leukemia. Either mouthwash may be recommended in a consensus protocol for oral mouth care in this subset of patients during chemotherapy.

Keywords: Chemotherapy; Paediatric Patients; Acute Lymphoblastic Leukaemia; Diseases

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in childhood. In the Philippines, ALL accounts for 65% of all leukaemias in children 0-14 years old [1]. According to the Philippine Paediatric Society registry of diseases, it ranks #21 in the top cases seen in accredited hospitals from May 2006 to February 2013. Out of 1,847,754 cases reported, ALL accounts for 16,400 [2]. It is important to note that based on data from the Philippine Cancer Registry-Manila Cancer Registry, there were 1500 registered cases of paediatric leukaemia and lymphoma cases in the National Capital Region from 1996-2005.

The primary treatment of acute lymphoblastic leukaemia is chemotherapy. One of the most debilitating complications of chemotherapy is oral stomatitis which interferes with eating, patient compliance to therapy, and potential risk of oral infection. It occurs in up to 52-80% of children undergoing chemotherapy [3]. It can start from the third to fifth day after initiation of chemotherapy and lasts about 3 weeks [4]. It occurs most often between the seventh and fourteenth day after chemotherapy [5]. Clinically, oral mucositis presents with an initial mucosal erythema, which often progresses to patchy mucositis, and then extensive ulceration and desquamation [6].

The probable mechanisms involve complex biological events mediated by a number of inflammatory cytokines and the direct effect of the chemotherapeutic drug on the basal epithelium and connective tissue, and the oral microbial environment [7]. Several therapy- and patient-specific factors, including the chemotherapeutic drug itself, the type of malignancy, age, neutrophil count, and level of oral care, are part of the etiology of oral mucositis. To a large extent, the severity of the condition is related to the specific chemotherapeutic agents used. The chemotherapeutic agents that are highly stomatotoxic are: methotrexate, fluorouracil, doxorubicin, and etoposide [8]. Other chemotherapeutic agents that have a high potential for precipitating oral mucosal damage are alkylating agents such as; antimetabolites such as cytosine arabinoside, 6-mercaptopurine, and vinca alkaloids such as vincristine [9].

It has been shown that cancer treatment causes alterations in oral microbiota which may lead to the emergence of potential pathogens. Studies are lacking to show how different cancer treatments affect oral microbiota as a whole [10]. Thus, it is important to individualize oral treatment care in cancer patients and study treatment effects of subgroup populations. A recent systematic review of basic oral care for the management of oral mucositis in cancer, done in 2019 by Hong et al. [11] noted that the implementation of multi-agent combination oral care protocols is beneficial for the prevention of oral mucositis during chemotherapy.

Oral mucositis remains an unresolved clinical problem in Paediatric for oncology. Standard oral hygiene includes several mouthwashes that may be chosen for prophylactic and therapeutic uses, however, there are only a few studies which compare their efficacy in paediatric acute lymphoblastic leukaemia. A consensus protocol regarding prophylaxis and treatment of oral mucositis is needed for this population of cancer patients.

In a systematic review of articles published between January 2000 and January 2015 (Macedo et al.) [12], it was found that chlorhexidine gluconate is able to decrease the frequency and intensity of oral mucosa

injuries in patients with acute leukemia but that other therapeutic agents may present better results.

The aim of the present study is to compare the efficacy of 0.12% chlorhexidine gluconate and 1% povidone iodine mouthwash in the prevention of oral lesions in acute lymphoblastic leukemic children receiving chemotherapy.

Objectives

General Objective

To compare the efficacy of 0.12% chlorhexidine gluconate and 1% povidone iodine mouthwash in the prevention of oral lesions in children with acute lymphoblastic leukemic receiving chemotherapy.

Specific Objectives

A. To determine the demographic and clinical data of the participants as to:

a) sex b) age c) type of leukemia d) phase of chemotherapy

B. To determine the effect of using 0.12% chlorhexidine gluconate mouthwash in the prevention and treatment of oral lesions in acute lymphoblastic leukemic children receiving chemotherapy as to: a) incidence b) severity of oral lesions c) duration of symptoms

C. To determine the effect of using 1% povidone iodine mouthwash in the prevention and treatment of oral lesions in acute lymphoblastic leukemic children receiving chemotherapy as to: a) incidence and b) severity of oral lesions c) duration of symptoms

D. To determine any side effects of 0.12% chlorhexidine gluconate mouthwash and 1% povidone iodine mouthwash.

Methodology

Study Design

Prospective, randomized controlled, non-blinded, two period cross-over trial. This design was based on the fact that it is extremely difficult to control for all therapy- and patient-specific variables in a single-center study, and on the practical difficulty of obtaining a sufficient number of participants, given the low incidence of childhood acute lymphoblastic leukaemia. In addition, the distinguishable colour, taste, and amount used of 0.12% chlorhexidine gluconate and 1% povidone iodine oral rinses makes blinding not considered feasible.

Subjects

Twenty-one children ages 6 to 18 years old diagnosed with Acute Lymphoblastic Leukaemia.

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Sampling

Randomized (computer generated using Microsoft Excel software)

Setting

University of Santo Tomas Hospital and Benavides Cancer Institute

Inclusion Criteria

Children ages of 6 to 18 years old diagnosed with Acute Lymphoblastic Leukaemia who are undergoing Induction, Consolidation, or Re-induction chemotherapy (based on the Modified Berlin-Frankfurt-Munster Acute Lymphoblastic Leukaemia Protocol) or Induction or Intensification chemotherapy (based on the Children's Cancer Group Protocol, CCG-1941: Bone Marrow Transplantation versus Prolonged Intensive Chemotherapy for Children with Acute Lymphoblastic Leukaemia after an Initial Bone Marrow Relapse) and seeking consult at STUH-BCI, and are capable of tooth-brushing and mouth-rinsing as judged by the principal investigator.

Exclusion Criteria

Children with oral mucositis or any oral lesion at initial assessment are having following conditions like hypersensitivity to iodine, hyperthyroidism, and mental retardation.

Withdrawal Criteria

Those patients who have persistent lesions beyond 21 days will be advised to switch mouthwashes. If lesions persist despite two weeks of treatment using the second type of mouthwash, the patient will be off study. Those who fail to adhere to the follow-up schedule or complete the two study periods, experience hypersensitivity reaction to the mouthwash, develop complications that will not allow them to toothbrush or mouthrinse, withdraw from the chemotherapy cancer treatment protocol, or expire due to complications of leukaemia, will be off study.

Procedure

The study was conducted at the Santo Tomas University Hospital and Benavides Cancer Institute (STUH-BCI) after approval from the Institutional Review Board. Twenty-one children between the ages of 6 and 18 years old diagnosed with acute lymphoblastic leukaemia who are undergoing Induction, Consolidation, or Re-induction phase chemotherapy (based on the Modified Berlin-Frankfurt-Munster Acute Lymphoblastic Leukaemia Protocol) or Induction or Intensification phase chemotherapy (based on the Children's Cancer Group Protocol, CCG-1941: Bone Marrow Transplantation versus Prolonged Intensive Chemotherapy for Children with Acute Lymphoblastic Leukaemia after an Initial Bone Marrow Relapse) were enrolled in the study. The children are all capable of tooth-brushing and mouth-rinsing as judged by the principal investigator.

It is important to note that the phase of treatment of the subjects is not a significant factor in the results since Induction, Consolidation, and Re induction phases are considered intensive chemotherapy and involve the use of chemotherapeutic agents that have a common side effect of oral mucositis. This may be compared to the Maintenance phase in which the chemotherapeutic agents do not usually cause oral mucositis. The studies by Cheng et al. [13], Setiawan et al. [14], Darwish et al. [15] and Soares et al. [16], all used subjects in various phases of intensive chemotherapy.

Written informed consent that was approved by STUH Institutional Review Board (IRB) was obtained from the parents. Participants at

least 15 years old to 18 years old co-signed the informed consent form with the parents. Verbal assent was obtained for participants 7 to under 12 years old, and a simplified assent form was obtained for those 12 to 14 years old. No assent was obtained for those younger than 6 years old, but a sign of dissent on the part of the child will be respected and documented.

Participants and the parents were given instructions by the principal investigator on standard oral hygiene measures with regards to brushing, rinsing, and flossing. They were instructed to maintain strict oral hygiene during the entire study period.

The principal investigator and two paediatric residents evaluated each patient at the start of the study for mucositis. Those with mucositis will not be eligible for the study, as well as those with the following conditions: hypersensitivity to iodine, hyperthyroidism, and mental retardation.

Eligible participants were randomly assigned to two groups. Group 1 was instructed to rinse with 10 mL of 0.12% chlorhexidine gluconate mouthwash twice daily, 30 minutes after breakfast and 30 minutes after the last meal at night, while Group 2 was instructed to do the same with 15 mL of 1% povidone iodine mouthwash, for 14 days during the first period of study. The PI and two paediatric residents evaluated each subject every three days for the appearance of oral mucositis. The World Health Organization and Oral Mucositis Assessment Scale scores given by the PI and two paediatric residents were recorded, and the average score was considered the final score.

Those who developed oral mucositis during the first period continued to use the same mouthwash assigned to their group if the lesions persisted beyond 14 days. They used the same mouthwash until lesions completely healed. Children's Oncology Group Supportive Care Guidelines were followed: regular tooth-brushing with a soft bristle toothbrush, mouthwash-use, and if indicated, intravenous hydration, hyperalimentation, effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy, and empiric antiviral and antifungal therapy. A topical anesthetic (aluminum hydroxide solution plus diphenhydramine) and a coating agent (sucralfate suspension) were applied to lesions. Those who required admission for chemotherapy and/or complications of chemotherapy such as febrile neutropenia were continued to be monitored for oral mucositis and ulcers.

Since oral lesions usually start 3-5 days after chemotherapy and lasts about 3 weeks, persistent lesions beyond 21 days may indicate that the assigned mouthwash is not effective for the subject. In this regard, subjects were advised to switch mouthwashes. (Group 1 used 1% povidone iodine mouthwash while Group 2 used 0.12% chlorhexidine mouthwash.) If lesions persisted despite two weeks of treatment using the second type of mouthwash, the patient was removed from the study.

There is a two week 'wash-out' time between the two periods of study. During the 'washout' time, alkaline saline mouthrinse (15 mL twice daily, 30 minutes after breakfast and 30 minutes after the last meal at night) will be used by the subjects. (Alkaline saline solution can be made by mixing half a teaspoon each of salt and baking soda in 1 pint or 473 mL of water.) The 'washout' time commenced after at least 14 days from the start of the first period of study and oral lesions have healed if any appeared. The 'wash-out' time of two weeks is based on the cross-over study by Cheng et al. (2004) which used a period of 1-2 weeks 'wash-out' time between the use of the two different mouthwashes that were being compared. Two weeks is a sufficient interval period to avoid over-lapping effects of the mouthwash since the effects of mouthwash are acute.

If oral mucositis developed during the 'wash-out period', the subjects stopped using the alkaline rinse solution and resumed the use of the mouthwash that was assigned to them during the first study period. If the lesions were not healed by two weeks using the assigned mouthwash, subjects switched to the second type of mouthwash. If the lesions did not heal by two weeks using the second type of mouthwash, the patient was removed from the study. Subjects resumed the use of alkaline mouthrinse solution once lesions completely healed (Figure 1).

Following the 'wash-out' period, Group 1 then used the 1% povidone iodine mouthwash during the second period of study, while Group 2 used 0.12% chlorhexidine gluconate mouthwash. If oral mucositis/ulceration developed during the second study period, the subjects continued to use the mouthwash assigned to their group until lesions healed. If lesions persisted beyond 21 days of use of the assigned mouthwash, subjects were advised to switch mouthwash until lesions healed (Figure 2). If lesions persisted for two more weeks despite using the second type of mouthwash, the patients were removed from the study. Children's Oncology Group supportive guidelines were followed at all times (Figure 3).

Participants were instructed by the principal investigator to rinse their mouths using a ballooning and sucking motion of the cheeks without swallowing for 30 seconds. Both the child and parent were also interviewed by the principal investigator at each assessment visit about the performance of oral care. Each participant was given a notebook diary for monitoring the frequency of mouthwash rinsing. Compliance was monitored by the principal investigator. The frequency of oral care recorded in the diary was counter-checked by recording the number of returned empty or partially-used mouthwash bottles at the end of each study period.

The occurrence of ulcerative lesions and severity of mucositis was measured at baseline and twice weekly (Days 0,3,6,9,12,15 of each study period), using the Oral Mucositis Assessment Scale and World Health Organization Grading Scale (Table 1). Those who developed oral mucositis were monitored every 3 days until lesions completely healed. Monitoring was done by paediatric haematology-oncology fellows and 2 paediatric residents. Ramirez-Amador and colleagues suggest that two time points per week for assessment are sufficient to obtain estimates of oral mucositis and to ensure that oral ulcerative lesions are not missed [17]. Monitoring for adverse effects also ended once the participant completed the two study periods.

Oral Mucositis Assessment Scale (OMAS)

OMAS will be used in assessing the following oral cavity regions: lip (upper and lower), cheek (right and left), right ventral and lateral tongue, left ventral and lateral tongue, floor of mouth, soft palate, and

hard palate. Erythema is rated on a scale 0-2 (0=none, 1= not severe, 2= severe), and ulceration/pseudomembrane is a combined category rated on scores based on estimated surface area involved (0=no lesion, 1= <1 cm², 2= 1 to 3 cm², and 3= more than 3 cm²), and summed giving a possible score range of 0 to 45.

The world health organization grading scale for mucositis

- Grade 0 (none): None
- Grade 1 (mild): Soreness +/-erythema, no ulceration
- Grade 2 (moderate): Erythema, ulcers. Patients can swallow solid diet
- Grade 3 (severe): Ulcers, extensive erythema. Patients cannot swallow solid diet
- Grade 4 (life-threatening): Oral mucositis to the extent that alimentation is not possible

Those who failed to adhere to the follow-up schedule or failed to complete the two study periods, and those who experienced hypersensitivity reaction to the mouthwash, or developed complications that would not allow them to toothbrush and mouthrinse, as well as those who withdrew from chemotherapy cancer treatment, or expired due to complications of leukaemia, were removed from the study.

Patients who were placed off study or completed the study may use mouthwash of choice at their own expense. Patients were still treated for leukaemia and its complications unless the patient decided to withdraw from the chemotherapy treatment protocol or expired due to complications of leukaemia. Children's Oncology Group supportive care guidelines on oral mucositis continued to be followed.

With regards to mechanism of action, chlorhexidine gluconate (0.12%) is designed to reduce dental plaque and oral bacteria. It is incorporated into the bacterial membrane and has been shown to have an immediate bactericidal action and a prolonged bacteriostatic action due to adsorption onto the pellicle-coated enamel surface. If it is not deactivated, chlorhexidine lasts longer in the mouth than other mouthwashes [18].

Similarly, povidone-iodine mouthwash (1%) has wide antiseptic effects including antiviral, antibacterial, and antifungal efficacy. It has good tolerability as well. In contrast to other antiseptic agents, povidone-iodine does not lead to any irritation or damage to the oral mucosa [19].

A main difference between 0.12% chlorhexidine gluconate and 1% povidone iodine mouthwash is that 0.12% chlorhexidine gluconate is absorbed at the tooth surface, plaque, and oral mucosa, thus slowly

Location	Erythema ^a			Ulceration/Pseudomembrane ^b			Total
Upper lip	0	1	2	0	1	2	3
Lower lip	0	1	2	0	1	2	3
Right cheek	0	1	2	0	1	2	3
Left cheek	0	1	2	0	1	2	3
right ventral and lateral tongue	0	1	2	0	1	2	3
left ventral and lateral tongue	0	1	2	0	1	2	3
Floor of mouth	0	1	2	0	1	2	3
Soft palate	0	1	2	0	1	2	3
Hard palate	0	1	2	0	1	2	3

^aErythema: 0=none; 1= not severe; 2= severe

^bUlceration/pseudomembrane:

0=no lesion; 1= <1 cm²; 2= 1 to 3 cm²; and 3= more than 3 cm²

Table 1: Oral Mucositis Assessment Scale and World Health Organization Grading Scale

released in 24 hours after use during the time the saliva concentration decreases. Povidone iodine (1%) is not absorbed at the tooth surface, plaque, and oral mucosa, so does not have the additional benefit of 0.12% chlorhexidine gluconate mouthwash [20].

Results

Twenty-two patients were eligible for the study, however one patient refused chemotherapy treatment, hence he was not included in the study. A total of 21 subjects were included, with no drop-outs. The mean age of the patients is 10.8 years, with a standard deviation of 3.88. There were 14 (66.7 %) males and 7 females (33.3 %). Of the 21 subjects, 18 (85.7 %) are diagnosed with immunophenotype pre-B ALL, 1 (4.8%) with pre-T cell, and 2 (9.5 %) with T-cell. Fifteen (71.4 %) entered the study during induction, 2 (9.5%) during intensification, and 4 (19.1 %) during reinduction (Table 2). Thirteen patients were assigned to Group 1 and started with the use of 0.12% chlorhexidine mouthwash, while eight patients were assigned to Group 2 and started with the use of 1% povidone iodine mouthwash.

Four (19%) subjects experienced mucositis while using 0.12% chlorhexidine mouthwash, while 2 (9.5%) developed mucositis while using 1% povidone iodine mouthwash. The mean duration of mucositis while using chlorhexidine is 9.5 days (3-16 days) while for povidone iodine, 6 days (3-9 days). There were no side effects or complications with the use of either mouthwash.

Based on the crude and model-adjusted means, 0.12% chlorhexidine mouthwash has a higher mean score than 1% povidone iodine mouthwash on WHO and OMA scores which means that povidone iodine mouthwash has more beneficial effect. In terms of duration, Chlorhexidine has higher mean duration. The incidence of oral mucositis is higher in the Chlorhexidine group. However, if we base our conclusion on the 95% confidence intervals of the treatment difference and the p-values (all values are greater than 0.05 level), the differences between the two treatment groups are not statistically significant (Table 3).

Neither side effects nor complications were observed with the use of either mouthwash.

Scope and Limitations

The scope of this study is to do a comparative study on two mouthwashes that are both accepted as standard of care in paediatric patients with acute lymphoblastic leukaemia so as to provide supportive evidence for a consensus protocol regarding prophylaxis and treatment of oral mucositis in this population of patients.

This research is limited to the study of a subset population of paediatric patients' ages 6 to 18 years old diagnosed with acute lymphoblastic leukaemia. It is important to note that most studies on prophylactic therapies for chemotherapy-induced mucositis include

Demographic and Clinical Characteristic		
Age (years)	Mean SD	10.8 3.88
Sex, n (%)	Male Female	14 (66.7) 7 (33.3)
Sequence group, n (%)	Chlorhexidine – Povidone iodine Povidone iodine – Chlorhexidine	13 (61.9) 8 (38.1)
Type of acute lymphoblastic Leukemia, n (%)	Pre-B cell Pre-T cell T-cell	18 (85.7) 1 (4.8) 2 (9.5)
Chemotherapy phase, n (%)	Induction Intensification Reinduction	15 (71.4) 2 (9.5) 4 (19.1)

Table 2: Summary of the demographic and clinical characteristics

	Chlorhexidine	Povidone iodine	Treatment comparison
WHO score			
• Crude mean (SD)	0.333 (0.7303)	0.143 (0.4781)	
• Model-adjusted mean*	0.293	0.139	
• Treatment difference (95% confidence interval)			0.1538 (-0.2608, 0.5684)
• p-value			0.447
Oral mucositis assessment			
• Crude mean (SD)	0.619 (1.5322)	0.286 (0.9562)	
• Model-adjusted mean*	0.524	0.279	
• Treatment difference (95% confidence interval)			0.2452 (-0.6309, 1.1213)
• p-value			0.565
Duration			
• Crude mean (SD)	1.000 (2.7386)	0.571 (2.0389)	
• Treatment difference (95% confidence interval)			0.4286 (-1.1454, 2.0026)
• p-value			0.576
Incidence of oral mucositis			
• Frequency (%)	4 (19.0)	2 (9.5)	
• p-value			0.317

*adjusted for period effect

Table 3: Comparative Statistical Analysis of the Treatments

both adult and paediatric subjects, as well as both hematologic and solid tumour malignancies. There are only a few studies directed to paediatric acute lymphoblastic leukaemia patients as the sole subjects. Furthermore, previous studies on mouthwash use in paediatric acute lymphoblastic leukaemia involve subjects as young as two years of age. It is important to note that the effectiveness of mouthwash use for children less than 6 years of age may not be accurate since this age group may not be able to use proper techniques in the use of mouthwash.

Patients younger than 6 years old are not included since mouthwash-use in this age group is not recommended due to their inability to use proper mouth-rinsing techniques, as well as to avoid the possibility of complications if swallowed.

Excluded in this study is information regarding the presence and degree of neutropenia of the patients during the periods of study and patients' preference regarding which mouthwash they will continue to use after the study period. Survival outcome and event-free survival rate of the patients is beyond the scope of this study.

Conclusion

Both 0.12% chlorhexidine gluconate and 1% povidone iodine mouthwash have similar effects in the prophylaxis and treatment of oral mucositis for paediatric patients with acute lymphoblastic leukaemia. Either mouthwash may be recommended in a consensus protocol for oral care in this subset of patients during chemotherapy since both are equally effective. The cost of each mouthwash and patient preference should be taken into consideration when determining which mouthwash is to be used.

Recommendations

The study is a subset analysis and has a relatively small subject population, which limits the ability to generalize from the data, so more comprehensive evaluations, including patient preference, with a larger population, are required to confirm our findings. Since there is generally a low incidence of childhood acute lymphoblastic leukaemia, multi-institutional collaborative research is needed in order to define further the optimal regimen for oral care in children and provide the basis for the best practice in relation to oral mucositis.

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References

1. Laudico AV, Medina V, Lumague MRM, Mapua CA, Redaniel MTM, et al. (2010) Philippine Cancer Facts and Estimates.
2. Alfiler CA, Atienza MA, Atienza MM and Bautista MS (2013) Philippine Pediatric Society.
3. Mallet MB, Bunetel L, Doleux ST, Guérin J, Bergeron C, et al. (1998) Oral complications during treatment of malignant diseases in childhood. *Eur J Cancer* 34: 1588-1591.
4. Cheng KK, Molassiotis A, Chang A, Wai WC, Cheung SS, et al. (2001) Evaluation of an oral care protocol intervention in the prevention of chemotherapy induced oral Mucositis in Pediatric Cancer Patients. *Euro J Cancer* 37: 2056-2063.
5. Little JW, Miller C, Rhodus NL and Falace D (2001) Dental management of the medically compromised patient, 6th ed.
6. Amador VR, Pedraza LE, Mohar A, Gómez ER and Fernández PV, et al. (1996) Chemotherapy-associated oral mucosal lesions in patients with leukemia or lymphoma. *Euro J Cancer B Oral Oncol* 32: 322-327.
7. Sonis ST (1998) Mucositis as a biological process: A new hypothesis for the development of chemotherapy-induced Stomatotoxicity. *Oral Oncol* 34: 39-43.
8. Weitman (1996) Cancer chemotherapy and pharmacology in children. *Principles of Antineoplastic Drug Development and Pharmacology*.
9. Perry MC, Doll DC, Freter CE (1997) *The Chemotherapy Source Book*.
10. Meurman JH (2010) Oral microbiota and cancer. *J Oral Microbiol*.
11. Hong C H L, Gueiros LA, Fulton JS, Cheng KKF and Kandwalet A et al. (2019) Systematic review of basic oral care for management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 27: 3949-3967.
12. Macedo RA, Morais EF, Dantas AN, Morais MLSA (2015) Chlorhexidine to treat oral mucositis in patients with acute leukemia: Systematic review. *Rev Dor* 16: 221-226.
13. Cheng KKF, Chang AM and Yuen MP (2004) Prevention of Oral Mucositis in Paediatric Patients treated with Chemotherapy: A randomised crossover trial comparing two protocols of oral care. *Euro J Cancer* 40:1208-1216.
14. Setiawan AS, Reniarti L and Oewen RR (2006) Comparison effects of Chlorhexidine Gluconate and Povidone Iodine mouthwashes to Chemotherapy-induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia. *Int J Oral-Med Sci* 5: 1-5.
15. Darwish AM, Salama MAS, Basiouny MS and Arafa NM, et al. (2011) Effect of Chlorhexidine in Prevention of Oral Lesions in Leukemic Children Receiving Chemotherapy. *Journal of American Science* 7.
16. Soares AF, Luz de Aquino AR, Pereira de Carvalho CH, Weege Nonaka CF and Almeida D, et al. (2011) Frequency of Oral Mucositis and Microbial Analysis in Children with Acute Lymphoblastic Leukemia Treated with 0.12% Chlorhexidine Gluconate. *Brazil Dentistry Journal* 22: 312-316.
17. Amador VR, Pedraza LE, Mohar A, Gómez ER, Fernández PV, et al. (1996) Chemotherapy-associated oral mucosal lesions in Patients with Leukemia or Lymphoma. *Eur J Cancer Oral Oncol* 32: 322-327.
18. Lang NP and Brex MC (1986) Chlorhexidine digluconate- an agent for chemical plaque control and prevention of gingival inflammation. *Journal of Periodontal Research*.
19. Alterio D, Jereczek-Fossa BA, Fiore MR, Piperno G (2007) Cancer treatment-induced mucositis. *Anticancer Research*.
20. Fishman et al. (2005) Mouthrinses and tooth whiteners. *Primary Preventive Dentistry*.