McGaw W.T. and Belch A.: 
Oral complications of acute leukemia: Prophylactic impact of a chlorhexidine mouth rinse regimen. 
Oral Surg., 1985, 60 (3), 275-280
Oral complications of acute leukemia: Prophylactic impact of a chlorhexidine mouth rinse regimen

Wm. T. McGaw and A. Belch, Edmonton, Alberta, Canada

CROSS CANCER INSTITUTE

The prophylactic value of twice-daily mouth rinses with a solution of 0.1% chlorhexidine gluconate in minimizing oral complications during remission-induction chemotherapy was tested in sixteen patients with acute myeloblastic leukemia. The study design was double blind with a placebo control. Standardized measurement indices were employed to assess the dental plaque levels and the degree of gingivitis and mucositis during remission-induction. The treatment group demonstrated superior oral health on the basis of each of these measurement parameters. A moderate increase in tooth staining was observed in the treatment group. The results also suggested the potential value of chlorhexidine mouth rinses in the prophylaxis of oral candidiasis in the myelosuppressed patient.


The oral and dental complications arising in cancer patients can be divided into those that are attributable to the malignant disease itself and those that are attributable to the various modalities of cancer therapy. The greatest oral morbidity is associated with the treatment of oral cancers by radiotherapy and/or surgery. However, the problem is not restricted to oral cancer patients, and patients with malignant conditions that do not involve the head and neck may develop significant oral complications in relation to their disease or its therapy.

Up to 40% of all patients receiving cancer chemotherapy develop ulcerative, hemorrhagic, or infectious oral complications either as a result of direct toxicity of the cytotoxic drugs to the rapidly dividing oral mucosal epithelium or secondary to the effects of myelosuppression.1 Because there is often very little margin of safety between the therapeutic and stomatotoxic doses of these drugs,2 oral complications are often inevitable. However, efforts must be made to keep these within tolerable and safe limits.

The severity and duration of stomatitis caused by cancer chemotherapeutic agents have been shown to be correlated with pre-existing levels of dental plaque and periodontal disease.3,4 There are good a priori reasons, as well as preliminary reports in the literature,5,6 to suggest that preventive treatment in the form of oral hygiene instruction and periodontal scaling and prophylaxis may reduce the severity of oral complications. This might have particular benefit for patients with acute leukemia in whom approximately 28% of all acute infections developing during remission-induction chemotherapy represent acute exacerbation of pre-existent periodontal disease.1 Unfortunately, the profound thrombocytopenia and neutropenia that these patients experience during remission-induction may preclude conventional preventive dental measures in light of the risk of bleeding or bacteremia. Therefore, alternate approaches must be sought.

Johnson and Rozanis,4 in reviewing chemical approaches to dental plaque control, concluded that chlorhexidine gluconate appears to be the most suitable agent to prevent dental plaque accumulation and the development of gingivitis. Several long-term clinical investigations have established the safety and effectiveness of chlorhexidine in this regard.5,8 In addition to the effect on dental plaque and gingivitis, bacterial counts in the saliva are reduced by up to 95% in the course of a few days' use of a chlorhexidine mouth rinse regimen.11 The antifungal effect of chlorhexidine has been demonstrated in both in vitro and in vivo studies and is comparable to that of specific topical antifungal agents.12,14

The main disadvantages of the chlorhexidine rinse are poor acceptance and compliance by patients because of its astringent taste, which can temporarily
interfere with the taste of other foodstuffs, and the potential for staining of the teeth, tongue, and esthetic dental restorations.\textsuperscript{3, 7, 15, 16}

The aim of this study was to assess the efficacy of a chlorhexidine mouth rinse regimen as a prophylactic measure in preventing or reducing oral complications during remission-induction chemotherapy for acute myeloblastic leukemia.

**MATERIALS AND METHODS**

A group of sixteen patients with acute myeloblastic leukemia preparing to undergo remission-induction chemotherapy at the Cross Cancer Institute consented to participate in the trial. The group consisted of ten male and six female patients with an age range of 17 to 54 years (mean age, 33 years). Participation was restricted to patients with periodontal pockets that did not exceed 4 mm in depth.

The trial design was of a double-blind type with patients randomized into two experimental groups. The protocol and informed consent were reviewed and approved by the Institute's Ethics Committee. All patients received a prechemotherapeutic clinical and radiographic dental examination. Dental treatment deemed necessary to eliminate foci of infection or mechanical irritation (that is, provisional restoration of gross decay, removal of calculus deposits, smoothing of sharp restorations or cusps, and endodontic treatment of nonvital teeth) was performed as required, with appropriate precautions.

The chemotherapy regimen employed for remission-induction was identical in all patients (Table 1). During chemotherapy and throughout their hospital admission, one group rinsed twice daily for 2 minutes with 10 ml of a 0.1% aqueous solution of chlorhexidine gluconate.\textsuperscript{a} The second group rinsed with a placebo solution containing identical colouring and flavouring agents and into which was incorporated 0.1% quinine chloride. The latter component was added to produce a slightly astringent quality comparable to that of the 0.1% chlorhexidine solution. No other active oral hygiene measures were undertaken.

At the initiation of chemotherapy and on alternate days over the course of the hospital admission, dental plaque levels and gingivitis were assessed via the standardized measurement indices of Loe and Silness.\textsuperscript{10, 11} The degree of oral mucositis was assessed daily by means of a standardized index developed by Hickey.\textsuperscript{4} A standardized index was developed to grade the degree of tooth staining as Grade 0 (no staining), Grade 1 (mild staining), Grade 2 (moderate staining), or Grade 3 (marked staining).

The dental plaque, gingivitis, and tooth-staining indices were assessed as individual units on the buccal and lingual aspects of the maxillary right first molar, maxillary right lateral incisor, maxillary left first premolar, mandibular left first molar, mandibular left lateral incisor, and mandibular right first premolar. The average of all of these unit values was recorded as the index score for each respective variable on any given measurement day.

In addition to these oral parameters, the total number of febrile days during the measurement period was recorded for each patient.

Descriptive statistics and frequency distributions were determined for every variable, and tests of comparison were made to determine whether significant differences existed between groups. Febrile days were compared by means of a paired $t$ test, while the nonparametric variables were analysed by the Mann-Whitney-Wilcoxon test.\textsuperscript{19}

**RESULTS**

At the initiation of remission-induction chemotherapy, no significant differences existed between groups for any of the measurement indices.

Patients accepted both mouth rinse formulations well, and the level of compliance with the mouth rinse regimen was judged to be excellent.

Total length of admission ranged from 3 to 8 weeks, with an average length of 33 days. Only one patient was hospitalized for less than 4 weeks, and in no instance was a hospitalization period of greater than the average length of 33 days the result of oral complications. Therefore, data were analyzed serially over a 4-week period, with the average parameter values calculated weekly for each patient (Figs. 1 to 4). The single patient in the chlorhexidine group whose hospitalization was limited to 24 days did not return for re-evaluation on day 28. Therefore, the average parameter values recorded for the fourth week in this case were calculated on the basis of the last day of hospitalization.

Significantly lower average dental plaque scores and gingivitis scores were recorded in the chlorhexidine group over the 4-week measurement period (Figs. 1 and 2).

The average mucositis scores were similar in both groups during the first 2 weeks following initiation of

\textsuperscript{a}Corsodyl (I.C.I.)—diluted to half strength in water.
chemotherapy (Fig. 3). The scores were slightly higher during this interval in the control group, but this difference could not be shown to be statistically significant. However, during the third and fourth weeks the average mucositis scores were significantly higher in the control group. Four of the eight patients in the control group had Grade 3 mucositis for a total of 10, 10, 12, and 13 days, respectively, while only two of the patients in the chlorhexidine group experienced this severity of mucositis for 4 and 5 days, respectively.

Four patients in the control group developed oral pseudomembranous candidiasis, two requiring systemic antifungal therapy with parenteral amphotericin B. None of the patients in the treatment group developed overt oral candidiasis. However, routine oral mucosal smears for the demonstration of candidal organisms were not performed in all patients; nor were salivary titers of *Candida albicans* determined.

The average number of febrile days during the measurement period was lower in the chlorhexidine group (16.3 ± 3.4 days) than in the control group (20.0 ± 5.6 days), but statistical analysis did not show this difference to be significant.

In three patients using the chlorhexidine rinse noticeably increased discoloration of the dorsal surface of the tongue developed. A slight increase in the average tooth-staining index was measured in the chlorhexidine group (Fig. 4). This increase was attributable to slight discoloration of composite restorations on anterior teeth. This degree of discoloration was not deemed to be a matter of significant concern by these patients, whose overall subjective appraisal of the formulation was favorable. Only three patients voiced negative comments regarding the taste of the chlorhexidine formulation, and in none of these persons did the taste discourage their compliance with the mouth rinse regimen.

**DISCUSSION**

It has previously been shown in healthy volunteers that, in the absence of all other active oral hygiene measures, a chlorhexidine mouth rinse regimen effectively prevents the development of dental plaque and gingivitis. It has been shown that in the presence of deep periodontal pockets with subgingival plaque and calculus, chlorhexidine is less effective in maintaining periodontal health—and then only if initially preceded by mechanical scaling.

Therefore, this pilot study was limited to patients with periodontal pocket depths that did not exceed 4 mm.

The mouth rinse regimen provided good control of dental plaque and gingival inflammation in the chlorhexidine group. Those Grade 2 plaque levels
that were noted in this group were found almost exclusively on the labial surface of the mandibular incisor teeth of three of the first patients entered in the chlorhexidine group. This is an area that may not be well irrigated during normal mouth rinsing action. When patients were subsequently instructed specifically to consciously direct the rinse into the labial vestibule as part of the rinsing action, improved plaque control was observed in this area.

The standard chlorhexidine mouth rinse regimen generally described in the literature recommends rinsing twice daily for 1 minute with 10 ml of a 0.2% solution.\textsuperscript{7,10,15} In the present study a 0.1% concentration was selected in an effort to minimize the risk of adverse effects. A review of more than 20 years of experience with chlorhexidine mouth rinses in Europe reveals fewer than ten reported cases of mucositis.\textsuperscript{20} These infrequent desquamative mucosal reactions were associated in each case with use of the conventional 0.2% concentration. In several of these cases there were features to suggest that other factors, such as viral infection, may indeed have been the actual cause of the observed mucosal changes. However, the plaque-controlling effect of 0.1% chlorhexidine solutions has been shown to be satisfactory without any reported adverse mucosal effects.\textsuperscript{6,15} This provided the rationale for selection of the lower concentration in the present study. In an effort to compensate for the lower concentration, an empirical decision was made to require the patients to rinse for 2 minutes rather than for 1 minute.

With regard to considerations of toxicity associated with the use of chlorhexidine mouth rinses, the risk of systemic toxicity is negligible, as radiolabeling studies have shown that systemic absorption is minimal and does not result in detectable blood levels.\textsuperscript{21} In patients employing daily chlorhexidine mouth rinses over a 2-year period, extensive clinical laboratory investigations demonstrated no aberrations; nor were any systemic adverse effects reported.\textsuperscript{1}

The risk of adverse mucosal effects of a chlorhexidine mouth rinse is very low; such effects occur as relatively infrequent idiosyncratic responses.\textsuperscript{4,21} Laboratory studies have demonstrated a cytotoxic effect of chlorhexidine, in concentrations as low as 0.02%, in cultures of HeLa cells\textsuperscript{22} or in human gingival fibroblasts.\textsuperscript{22} However, when these in vitro toxicology studies are repeated with the addition of serum or salivary glycoproteins to the culture medium, a protective influence can be demonstrated.\textsuperscript{22}

At a clinical level, histologic and histochemical studies of human mucosal biopsy material taken after 18 months of daily exposure to chlorhexidine have not revealed any adverse effect of chlorhexidine on the oral mucosa.\textsuperscript{24} Chlorhexidine rinses have proved beneficial in enhancing repair following periodontal surgery\textsuperscript{25} and accelerating healing of aphthous ulcers.\textsuperscript{26} Both of these effects are presumably mediated through the control of secondary infection.

The marked reduction in oral bacterial counts that occurs in patients on a chlorhexidine mouth rinse
regimen\(^\text{11}\) raises a concern regarding the possibility of superinfection by resistant organisms. However, long-term use of the mouth rinse has been associated with neither detectable population shifts in the oral flora nor changes in microbial susceptibility.\(^4\)\(^,\)\(^7\)

The yellow-brown discoloration of teeth and soft tissues that is often described in the literature was not a source of concern to any of the patients in this study. Admittedly, these patients were employing the mouth rinse over a relatively short interval in comparison with the long-term use with which unacceptable levels of staining have generally been described.\(^8\)\(^,\)\(^9\) The precise nature of this extrinsic staining has not been established, but dietary factors have been implicated and certain beverages are chromogenic in the presence of chlorhexidine.\(^4\)

The incidence and severity of mucositis were similar in the two patient groups during the first 2 weeks following the initiation of remission-induction chemotherapy. In the third and fourth weeks, however, the average mucositis score was significantly lower in the chlorhexidine group. These observations can be readily understood if the mechanisms of chemotherapy-associated stomatotoxicity are considered. Chemotherapy-induced stomatitis can represent both a direct cytotoxic action of the drugs on the oral mucosal cells and an indirect result of myelosuppression. Adriamycin, cytosine arabinoside, and amsacrine are all agents that can produce significant direct stomatotoxicity. Direct stomatotoxicity is usually observed within 4 to 7 days following administration of the agents\(^9\) and, barring secondary infection, is usually self-limiting, with spontaneous resolution occurring approximately 2 to 3 weeks from the time chemotherapy was initiated.

Indirect stomatotoxicity is usually observed 12 to 16 days following the initiation of chemotherapy, when the white blood cell count is at its nadir.\(^8\)\(^,\)\(^9\) Clinically, the effects of neutropenia are often most marked in the marginal gingiva, where they presumably represent exacerbation of pre-existing chronic periodontal infection.\(^11\)

It would not be reasonable to expect the chlorhexidine mouth rinse regimen to preclude the direct toxic effects of cancer chemotherapeutic agents on the oral mucosa. With the possible exception of citrovorum rescue for methotrexate-induced toxicity, there is no antidote for the direct toxicity of these agents. The beneficial effects of chlorhexidine observed in this study, as reflected by reduced severity and duration of mucositis, presumably reflect decreased secondary infection of the direct stomatotoxic lesions and reduction of dental plaque and periodontal infection during the high-risk interval of profound neutopenia. The interval of most severe mucositis in the control group corresponded to the nadir of the white blood cell count. This direct relationship between the peripheral blood counts and oral mucosal status has been described previously.\(^9\)

More than 80% of all leukemic patients have been shown to be oral "carriers" of Candida albicans.\(^12\) Opportunistic fungal infections remain a major cause of early treatment failures in acute myeloblastic leukemia. In the present study, overt oral candidiasis was only encountered in four patients in the control group who developed pseudomembranous candidiasis. While the fungicidal effect of chlorhexidine has previously been demonstrated in both in vitro and in vivo studies,\(^13\) its prophylactic value has not been established. Daily mouth rinses with 0.2% chlorhexidine have not proved effective in producing a sustained reduction in the titers of Candida albicans in the saliva of leukemic patients.\(^12\) While salivary titers of Candida albicans were not performed in the present study, the clinical observations suggest that the chlorhexidine mouth rinse regimen may have valuable applications in the prophylaxis of oral candidal infections in myelosuppressed patients.

REFERENCES


Reprint requests to:
Dr. Wm. T. McGaw
Room 5084
Dentistry-Pharmacy Building
University of Alberta
Edmonton, Alberta, Canada T6G 2N8