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Colchicine mouth washings to improve oral mucositis in patients with hematological malignancies: A clinical trial

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ABSTRACT

Objective: Oral mucositis (OM) is a frequently encountered problem as a complication of cancer treatment. We investigated whether daily washings with colchicine solution improved mucositis in patients with hematological malignancies undergoing chemotherapy.

Methods: This study was a one-arm, nonrandomized clinical trial that used a historical control group. Patients were included in the study from the first day of mucositis and followed up until discharge. Patients received 2 mg colchicine mouthwashes daily for 5 days or saline solution. OM was assessed once daily until symptom resolution, using the WHO grading scale of 0–4 and a visual analogue scale. We determined that at least 40 patients in the colchicine group would be needed to detect a 20% difference in the duration of OM between Groups A and B, with a 95% confidence level and a power of 80%.

Results: 82 patients were included in the final analysis, 40 in the colchicine group and 42 in the control group. Median duration of OM was significantly different among groups; 9days (range 1–17days) for the control group versus 6days (range 3–13days) for those exposed to colchicine mouthwash ($p = .028$). The median days of regression of mucosal lesions were significantly different ($p = .047$) among the control group (7 days [range 3–20]) compared to the colchicine group (4 days [range 2–14]).

Significance of results: Although our findings suggest that colchicine mouthwash is helpful in reducing the severity and duration of chemotherapy-induced OM, randomized trials are needed to confirm these results.

KEYWORDS: Oral mucositis, Stomatitis, Oral ulcers, Mouthwash, Chemotherapy, Lymphoma, Leukemia

INTRODUCTION

Treatment of solid malignant tumors and hematological malignancies with cytotoxic chemotherapy and/or radiotherapy is becoming increasingly more effective, but it is associated with short- and long-term side effects. Among the clinically important acute side effects is disruption in the function and integrity of oral mucosa. These condition induced complications and may also produce discomfort and pain, poor nutrition, delays in drug administration, increased hospital stays and costs, and, in some patients' lives, threatening infection (Symonds, 1998; Plevova, 1999; Ávila et al., 2000; Shaw et al., 2000; Trotti, 2000; Worthington et al., 2004).

The molecular and cellular pathways that lead to oral mucositis (OM) are unclear. Mucosal damage is a multistep process. Once triggered directly by

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radiation or chemotherapy or indirectly by intermediate mediators initiated within cells or tissue, molecular effectors drive mucosal responses, leading to three distinct events in the oropharyngeal mucosa: keratinocyte toxicity and death, impaired mucosal immune surveillance and inflammation, and significant alterations in oral flora (Sonis, 2004; Chiappelli, 2005; Anthony et al., 2006). Among these events are clonogenic cell death, the activation of a wide range of transcription factors with the consequent expression of genes, and the production of proinflammatory cytokines, caspases, matrix metalloproteinases, leukotrienes, and ceramides (Sonis, 2004; Chiappelli, 2005; Anthony et al., 2006).

Compliance with recommended use of product is variable and there are conflicting reports of the effectiveness of diverse treatments. Various systematic reviews that focused on the prevention and treatment of OM in patients with cancer revealed different conclusions (Shaw et al., 2000; Worthington et al., 2004; Lalla et al., 2006; Stokman et al., 2006; Worthington et al., 2006). A Cochrane systematic review demonstrated that there is weak and unreliable evidence that allopurinol mouthwash, vitamin E, immunoglobulin, or human placental extract improve or eradicate mucositis and found no efficacy with the following agents: benzydamine HCl, sucralfate, tetrachlorodecaoxide, chlorhexidine, and "magic" mouthwash (lidocaine solution, diphenhydramine hydrochloride, and aluminum hydroxide suspension; Worthington et al., 2004).

A number of preclinical and clinical studies suggested that the use of anti-inflammatory agents may be a promising approach to reduce the severity of mucositis (Gatot & Tovi, 1984; Nakamura et al., 2003; Momo et al., 2005; Lalla et al., 2006). In addition, colchicine has been used to treat severe recurrent aphthous ulcers of oral mucosa in a wide rage of conditions (Ruah et al., 1988; Pico et al., 1998; Fontes et al., 2002; Altinor et al., 2003; Chang et al., 2004). An open trial that included 54 patients with aphthous stomatitis concluded that colchicine is an efficient preventive and well-tolerated treatment of severe oral ulcers (Chang et al., 2004).

We investigated whether daily washings with colchicine solution improved OM in patients with hematological malignancies undergoing high-risk chemotherapy.

METHODS

Patients

Patients enrolled in the study were adults with hematological malignancies treated with high-risk chemotherapy at the Instituto Nacional de Cancerología of Bogotá D.C., Colombia. Patient inclusion criteria were as follows: adults (over 18 years of age) with a diagnosis of lymphoma or acute leukemia treated with chemotherapy, who had the ability to read, were physically (Karnofsky >60%) and mentally capable (had the ability to understand and complete the informed consent) of participating in the research protocol, and agreed to participate. Exclusion criteria were as follows: patients with previous head or neck radiotherapy and surgery that altered the oral mucosa integrity (procedures done in the last 3 months), tumor involvement of oral mucosa, subjects included in other investigations, antecedent of salivary gland dysfunction, HIV infection, and diabetes.

During the study all patients were exposed to different co-interventions including systemic antibiotics, antimycotics, antivirals, antiemetics, analgesics (morphine and their analogs) and G-CSF support. The use of criotherapy and other oral mouthwashes was not allowed.

Study Design

The study was a one-arm, nonrandomized clinical trial that used a control group of sequentially included patients. Patients were included in the study from the first day of mucositis and follow-up until discharge from the hospital. The mouthwashes and 2-min gargling with the solutions were administered four times a day. Removable dentures had to be removed during mouthwashing, overnight, and during OM. Dental cleaning with a soft toothbrush was done two times a day. If spontaneous gum bleeding or individual intolerance occurred, only rinsing with the study solutions was recommended for oral cleaning. The study was approved by the Investigation and Ethic Committee of the Instituto Nacional de Cancerología, Bogotá D.C., Colombia, and by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Bogotá D.C., Colombia. Also, it was registered in the Latinamerican Ongoing Clinical Trials Register (LATINREC) with the number COL058.

Mouthwashes

Controls (Group A) used normal saline (NaCl 9% water solution) for oral rinsing following the same willing outline for the intervention group. Study patients (Group B) used colchicine solution with 2 mg of the medication dissolved in 500 cc of sterile water. The solutions were freshly prepared every morning and their administration was supervised by one of the researchers. Colchicine mouthwash was administered starting from the first day of the symptoms of OM until the fifth day of the disease (inflammatory phase of the mucositis); later on, the

subjects included in Group B received saline solution mouthwashes in the same way as controls.

Evaluation and Monitoring

The monitoring started on the first day of the mucositis and covered the whole inpatient stay. OM was assessed once daily until symptom resolution, using the WHO grading scale of 0–4 (0, absent; 1, slight pain, erythema; 2, sore defects, can eat solids; 3, very sore defects, requires liquid diet only; 4, alimentation not possible). Oral pain was evaluated by the patient twice a day using a visual analogue scale (VAS) scoring 0–10 (0, no pain at all; 10, intolerable pain). The tolerability of the mouthwashes was evaluated by the patient once daily using a VAS scoring 1–10 (1, very tolerable; 10, intolerable). In addition, the maximum body temperature during a day was recorded until OM resolution.

Statistical Methods

As historical data were available on the control regimen, a phase II inference about the experimental regimen was accomplished via a historical control study using the unconditional method of Makuch and Simon (Katz et al., 1994). Historical controls were enrolled prospectively and evaluated using the same methodology as with the intervention group. We determined that at least 40 patients in the colchicine group would be needed to detect a 20% difference in the duration of OM between Group A and B with a 95% confidence level and a power of 80%. *P* values compared the presence and the absence of the characteristics and values $<.05$ were considered statistically significant. The characteristics, severity, and duration of OM, length of in-patient hospitalization, the severity of OM-related pain, days of opioid consumption, the tolerability of the mouthwashes, change in oral pH (using a pHmeter), and the occurrence of infection were evaluated using the Mann–Whitney test and Fisher's exact test. Statistical analyses were performed using the SPSS 12.0 Statistical package.

RESULTS

Control and intervention groups were enrolled from October 2003 to December 2004 and from June 2005 to March 2006, respectively. Of the 88 eligible patients, 82 were included in the final analysis (2 patients refused to participate after the diagnosis of mucositis and 4 were excluded due to poor cooperation with the research team); 42 were included in study Group A (normal saline mouthwash) and 40 in Group B (colchicine mouthwash). Both groups were well balanced with no significant differences in respect of age, sex, chemotherapy regimen, and history of oral herpes infection.

Patients of Group A received a nonsignificant increased number of previous chemotherapy cycles ($p = .26$) and presented a nonsignificant higher number of previous episodes of mucositis during prior interventions ($p = .78$). The patient characteristics are shown in Table 1.

Mucositis Characteristics

No significant differences between Groups A and B were observed in median day of postchemotherapy onset of OM (day 9 [range 7–10] vs. day 8 [range 7–13] for the Groups A and B, respectively; $p = .60$). OM severity in Groups A and B was as follows: grade 1, 48% and 54% ($p = .82$); grade 2, 20% and 18% ($p = .72$); grade 3, 16% and 24% ($p = .64$); and grade 4, 16% and 4% ($p = .026$), respectively.

Mucositis Duration

Median duration of OM was significantly different among groups: 9 days [range 1–17 days] for patients treated with saline solution versus 6 days [range 3–13 days] for those exposed to colchicine mouthwash ($p = .028$). In the same way, there were significant differences regarding the day of regression of mucosal lesions (day in which there is a decrease in OM severity), day 7 for Group A (range 3–20) versus day 4 (range 2–14) for Group B ($p = .047$).

Table 1. *Characteristics of Included Patients*

Variable	Group A (saline mouthwash)	Group B (colchicine mouthwash)	*P* value
Number of patients	42	40	–
Age (years), median (range)	42 (22–74)	50 (21–70)	.36
Sex, female/male	20/22	17/23	.25
Lymphoma/leukemia	16/26	15/27	.70
Number of chemotherapy cycles within 1 year prior to study inclusion, median (range)	5 (1–7)	6 (2–9)	.26
Number of previous episodes of mucositis, median (range)	3 (0–5)	3 (0–4)	.78
Herpes infection, yes/no	12/28	9/31	.72
Weight (kg), median (range)	52 (37–78)	56 (34–72)	.28

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There were no differences between the groups concerning the duration of in-patient hospitalization (23 vs. 19 days for Groups A and B, respectively; $p = .36$), variations in weight, characteristics of the voice, salivates production, mucosal pH, and frequency and volume of oral mucosal bleeding.

Mucositis-Related Pain

Oral pain assessed with the VAS score was similar between Groups A and B (mean 5 vs. 4, $p = .58$), as was peak pain (4 [range 0–10] vs. 5 [range 0–10], $p = .64$). Grade 5 or more (moderate to severe pain) was experienced at least once by 36% of the patients ($n = 29$) with OM, 13 (31%) subjects of Group A and 16 (40%) of Group B ($p = .06$). Systemic analgesics were used for pain control in all patients (tramadol, 48 patients; morphine, 24 patients; hydromorphone, 4 patients; oxycodone, 3 patients, and transdermal phentanylum, 3 patients). There was no significant difference in the average duration of opioid consumption: 7 days (*SD* $\pm$2.4) for Group A and 6 days (*SD* $\pm$1.8) in Group B.

Tolerability of the Mouthwashes

The tolerability of the mouthwashes (assessed using VAS) was not different between the groups (grade 2 [range 1–4] vs. 2 [range 1–5], $p = .18$). Grade 5 and more (unpleasant to intolerable) was reported by 11% of patients in the control group and 14% in the colchicine group ($p = .92$). In the presence of moderate to severe OM, the frequency of use of the mouthwashes was intensified in 18% patients in the saline mothwash group and in 8% in colchicine group ($p = .037$). The median number of mouthwashes per day, however, was similar between the two groups (4 [range 1–5] vs. 5 [range 1–7], $p = .4$). No serious side effects with colchicine mouthwash were noted.

Infections

No significant differences were observed between study groups A and B in respect to the occurrence of neutropenic fever (58% vs. 61%, $p = .70$).

Risk Factors

In univariate analysis, there were no significant differences between patients with mild and moderate (grades 1–2) OM and those with severe OM (grades 3–4) regarding intervention groups, sex, age, previous mucositis events, or duration of neutropenia.

DISCUSSION

Findings

Mucositis is a significant complication of intensive chemotherapy in hematological malignancies and solid tumors. In a recent study of 599 subjects undergoing chemotherapy for solid tumors or lymphomas, 50% developed oral and/or gastrointestinal (GI) mucositis. The risk of infection in these immunosuppressed patients was significantly higher (over twofold) during cycles with mucositis than during cycles without mucositis even though the level and duration of neutropenia was similar. The risk of infection increased with growing severity of mucositis, and infection-related deaths were significantly more common during cycles with both oral and GI mucositis. During chemotherapy cycles with mucositis, the average duration of hospitalization was longer, and the requirement of liquid diets, total parenteral nutrition, fluid replacement, and antifungal or antiviral therapy were more common (Elting et al., 2003).

It was estimated that the cost of hospitalization was US$3,893 per chemotherapy cycle without mucositis, US$6,277 per cycle with oral mucositis, and US$9,132 per cycle with both oral and GI mucositis. Additionally, a reduction in the next dose of chemotherapy was twice as common after cycles with mucositis as compared to cycles without mucositis (Elting et al., 2003).

Our findings suggest that colchicine mouthwash is helpful in reducing the severity and duration of chemotherapy-induced OM; furthermore, a reduction of 12% in grade 4 OM was found, as well as a decrease of 3 days in the duration of symptoms. No differences were observed regarding the control of pain or the use of morphine and their derivates, and we did not find any adverse events related with colchicine intervention.

A number of studies had reported the benefit of colchicine to solve oral ulcers produced by some entities with similar physiopathology of OM such as Behcet disease, aphthosis, and herpes virus infection of the oral cavity (Gatot & Tovi, 1984; Katz et al., 1994; Fontes et al., 2002; Altinor et al., 2003; Elting et al., 2003; Al-Waiz et al., 2005). A recent review about the use of anti-inflammatory and immunomodulator agents in the management of mucositis suggests that those medications are a promising approach that should be further investigated (Lalla et al., 2006). A multicenter randomized clinical trial with 145 subjects evaluated the effectiveness of benzydamine mouthrinse in radiation-induced oral mucositis; the authors reported that benzidamine-treated subjects had significantly less erythema and ulceration, were more likely to remain ulcer free, and had

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significantly delayed need for systemic analgesics, compared with placebo (Epstein et al., 2001). In the same way, systemic indomethacin administration was evaluated in two studies that reported milder irradiation esophagitis and symptomatology than controls, and to delay the onset of severe OM as compared to subjects receiving placebo (Northway et al., 1980; Nicolopoulos et al., 1985).

A randomized double-blind placebo controled study tested the efficacy of alopurinol mouthwash in 5-fluoruracil-induced OM (Porta et al., 1994); this intervention reduced the mean duration of mucositis in 4.5 days, similar to our findings. A pilot study evaluated the effect of flurbiprofen on radiation-produced OM starting 1 week before the initiation of teletherapy using a historical control group; although there was no difference in the overall severity or duration of mucositis, the onset of the condition occurred later in the immunomodulator group, suggesting that NSAID therapy may an interesting strategy for investigation in future studies (Stokman et al., 2005; Lalla et al., 2006). It can be said that our findings are congruent with those of the above studies, particularly with those evaluating allopurinol.

Colchicine may interfer with neutrophil phagocytosis and chemotaxis modifying inflammatory phase of OM. Our findings demonstrate that colchicine is a low-cost and well-tolerated medication that can be easily used in developing countries.

Limitations

Despite the more rigorous scientific basis of a randomized clinical trial, the resources required to do such a study may sometimes make it impractical, where either patient's resources are limited or where the costs are prohibitive. Although the scientific basis of the historical control may be weaker, when good historical control information is available (Katz et al., 1994), it can be use as an alternative. However, well-randomized and blind clinical trials clearly have a higher evidence level. We selected this study model because we were not logistically able to perform a randomized study. On the other hand, the cost savings may still make this approach feasible in our setting. Colchicine benefits findings may be spurious, particularly due to the lack of a blinding methodology and randomization. In addition, our trial had a reduced sample size.

Implications for Research

Further randomized controlled trials are needed to confirm the efficacy and security of colchicine in oral mucositis induced by cancer treatments. Furthermore, mouthwash or orally administered colchicine, as well as other anti-inflammatory and immunomodulatory agents should be tested for the prevention and treatment of OM induced by radiotherapy or chemotherapy.

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