Buccodental health and oral mucositis. Clinical study in patients with hematological diseases

Mª del Mar Sabater Recolons [1], José López López [2], Mª Eugenia Rodríguez de Rivera Campillo [1], Eduardo Chimenos Küstner [2], José María Conde Vidal [3]

(1) Profesor Asociado de Medicina Bucal
(2) Profesor Titular de Medicina Bucal
(3) Catedrático de Medicina Bucal. Facultad de Odontología. Universidad de Barcelona

Correspondence:
Dra. Mª del Mar Sabater
C/ Mandri nº 21,3º1º
08022 Barcelona
E-mail: 20365msr@comb.es

ABSTRACT

Objectives: The objective of the present study is to assess whether a good buccodental status (evaluated by means of dentogingival indices), is associated with a lower incidence and severity of oral mucositis in patients with hematological diseases who receive treatment with chemotherapy or bone marrow transplant.

Study design: The study was carried out on 97 patients admitted to the Hematology Service of the Hospital Duran y Reynals in Barcelona during 2002-2003. These patients received treatment with chemotherapy or conditioning prior to bone marrow transplant. A descriptive study was made, analyzing oral hygiene, one dental index, and two gingivales indices, and evaluating their relationship with the appearance of mucositis.

Results: The patients with high plaque (PI) and gingival (GI) indices during chemotherapy presented a higher percentage of mucositis (77.4% and 65.7% respectively) against those who had little or no visible plaque. In the case of the PI, the differences were statistically significant (p=0.015). Likewise, patients who brushed their teeth 3 times/day presented mucositis in only 26.7% of cases, against those who did not brush, or brushed only once a day (65.9% and 68.4%), these differences also being statistically significant (p=0.013). The CAO showed similar results in patients with or without mucositis (7.59 and 7.03 respectively).

Conclusions: In our study, a good gingival status as well as good oral hygiene during chemoradiotherapy is associated with a lower incidence and severity of mucositis.

Key words: Malignant hematological diseases, chemoradiotherapy, mucositis, buccodental status.

RESUMEN

El objetivo del presente trabajo fue valorar si un buen estado buco-dental (valorado mediante índices dento-gingivales), se asociaba a una menor incidencia y gravedad de mucositis oral en pacientes con enfermedades hematológicas que iban a recibir tratamiento con quimioterapia o un trasplante de médula ósea.

Diseño del estudio: El estudio se llevó a cabo en 97 pacientes ingresados en el Servicio de Hematología del Hospital Duran y Reynals en Barcelona en los años 2002-2003. Estos pacientes recibían tratamiento con quimioterapia o bien el acondicionamiento previo a un trasplante de médula ósea. Se realizó un estudio descriptivo analizando un índice dental, dos índices gingivales y la higiene oral y su relación con la aparición de mucositis.

Resultados: Los pacientes que durante la quimioterapia mostraron valores elevados del índice de placa (IP) y gingival (IG) presentaron un mayor porcentaje de mucositis (77.4% y 65.7% respectivamente) frente a los que tenían poca placa o ésta no era visible. En el caso del IP las diferentas fueron estadísticamente significativas (p=0.015). Asimismo los pacientes

que cepillaban los dientes 3veces/día sólo presentaron mucositis en un 26.7% de los casos, frente a los que no cepillaban o lo hacían una vez al día (65.9% y 68.4%), siendo estas diferencias también estadísticamente significativas (p=0.013). El ICAO mostró resultados similares en los pacientes con o sin mucositis (7.59 y 7.03 respectivamente).
Conclusiones: En nuestro trabajo, un buen estado gingival así como una buena higiene oral durante la quimiorradiote-rapia, se asocian a una menor incidencia y gravedad de mucositis.

Palabras clave: *Enfermedades hematológicas malignas, quimiorradioterapia, mucositis, estado buco-dental.*

INTRODUCTION
Oral mucositis is one of the most frequent side effects of oncological treatment. The prevalence oscillates between 30-70% after chemotherapy, and can increase to 90% in the case of a bone marrow transplant (1-3). It is a significant cause of morbidity during antineoplastic therapy. It affects the patient's quality of life since it proceeds with intense pain and ulcers that hinder feeding, swallowing and speech (1,3). Likewise, it is associated with prolonged fever, parenteral alimentation, administration of opiates, and a higher risk of infection (4,5).
Mucositis is an inflammatory reaction that affects the entire gastrointestinal tract, although with a greater involvement of the oropharyngeal area. Clinically it appears between approximately the fifth and seventh day from the start of chemotherapy, the lesions being located fundamentally in the non-keratinized oral mucosa (1,6). In patients who receive a bone marrow transplant (BMT), the lesions can begin at 24 to 48 hours of the infusion (7).
Mucositis can present different grades of severity, from a minimal erythema, edema or burning sensation, to large and painful ulcers that limit basic oral functions and can even interrupt the oncological treatment (7-9).
The etiopathogenesis of mucositis is not entirely clear. Classically, it has been linked to the so-called "theory of direct-indirect toxicity", by which, on the one hand, the mucositis would result from the direct action of the chemotherapy on the cells of the basal layer of the epithelium, and on the other, it would be due to the secondary myelosuppression of the oncological treatment (10). At the end of the nineties, Sonis (2) established a new etiopathogenic hypothesis in which he described mucositis as a complex biological process that would proceed in four phases: inflammatory / vascular, epithelial, ulcerative / bacterial and healing phase. This is the current hypothesis, and diverse authors are carrying out in-depth investigations into the characteristics of the different cellular and molecular phenomena that are produced.
In addition, a series of risk factors have been described in association with the appearance of mucositis, among which, those related with the chemotherapy regime and those related with the individual (age, nutritional, buccodental and hematological status among others) are highlighted (1,4,10). On the other hand, it has been suggested that mucositis would not only affect the epithelium, but rather some cellular and molecular phenomena would be located in the submucosa, principally the vascular endothelium (2,4). Recent studies also point out a possible genetic basis for the appearance and severity of mucositis (1).

It has been demonstrated that the type of chemothera-peutic regime is a very important factor in relation to the appearance of mucositis, so much so that some authors (3,6,10) describe it as an independent risk factor. Regimes that involve busulphan, melphalan, cyclophosphamide, and etoposide, or conditioning prior to BMT in which the patient also receives the so-called total body irradiation (TBI), present elevated stomatotoxicity (4,5,10).
Regarding patient-dependent factors, we focus on the buccodental status. Some studies have associated the condition of the oral cavity to the appearance of mucositis (2,6,11). However, few studies exist that objectively evaluate oral health during chemotherapy. Most studies have been carried out by nursing staff who have assessed oral hygiene protocols and oral care (12,13), or by oncologists or interns (14-16), there being very few that register dental or gingival indices (17,18). In most cancer hospitals, the patient is usually recommended to visit the stomatologist before beginning chemoradiotherapy. However, in many cases the urgency to begin treatment of the basic disease means that it is not possible to carry out all the required odontological treat-ment. On the other hand, maintaining the oral cavity under the best hygienic conditions and with minimum gingival inflammation during oncological treatment should lead to fewer mucosal complications (7).
The above argument and the lack of studies in relation to this topic have motivated this clinical study of oral mucositis and its association with the buccodental status.

OBJECTIVES
The objective of this study was to verify if a good buccoden-tal condition (correct oral hygiene, absence of cavities, den-tal plaque and gingival inflammation) during oncological treatment is associated with a lower incidence and severity of oral mucositis in patients with hematological disease who receive chemotherapy or a bone marrow transplant.

STUDY DESIGN
The study was carried out in the Hematology Service of the Hospital Duran y Reynals, Barcelona between May 2002 and December 2003.
The sample was made up of 97 patients diagnosed with some type of hemopathy and scheduled to receive treatment with standard chemotherapy or conditioning prior to bone marrow transplant.
This is a descriptive, longitudinal study. Descriptive statis-tics of the sample and the clinical findings were performed, calculating the different means and their corresponding

standard deviations with a confidence interval of 95%. The chi-square test was used for qualitative variables and the Student's t-test for the quantitative variables in the analysis of possible associations between mucositis and the independent variables, with a significance level of 0.05%.

The data were collected in an Excel table and the statistical calculation was carried out using the SPSS program version 11.0 for Windows.

PATIENTS AND METHODS

Patients

Patients participating in the study had previously been admitted to the hospital Hematology Service. Informed consent was given prior to being included in the study. The inclusion criteria were as follows: aged over 17 years, male or female, diagnosed with hematological disease, treatment with chemotherapy and/or BMT, voluntary participation in the study. The following exclusion criteria were selected: serious deterioration in general health, low cognitive level, simultaneous presence of any mucocutaneous disease, graft versus host disease, and refusal to participate in the study.

Methods

The visit to the patients was programmed for the seventh day following initiation of chemotherapy or conditioning for BMT. A special protocol was designed to register the data obtained. Both the anamnesis and the buccodental exploration were performed by the same examiner in all patients with the purpose of reducing any possible subjectivity. Examinations were carried out in the patient's own room or in the ITU (Intensive Therapy Unit), with the patient either in bed or sitting in a chair. For the examination of the oral cavity, we used: gloves, mask, dental light for intraoral illumination and a WHO sterile examination set containing two dental mirrors, some dental forceps, an examination probe and a periodontal probe.

In the anamnesis, the following fundamental data were registered: age, sex, hematological disease, chemotherapy regime, BMT and type, other systemic diseases, drug treatments and analytic parameters.

The buccodental state was evaluated by means of the following indices:
- CAOD index (19)
- Silness-Löe plaque index (20)
- Löe-Silness gingival index (20)
- Oral hygiene (good, 3 times a day; regular, twice a day; bad, once or not at all) supervised by the hospital nursing staff

Furthermore, other parameters were registered:
- The type of mouthwash used by the patient
- The oral pain measured on a visual analogical scale (VAS) (0-no pain, 10-maximum pain)
- The degree of mucositis according to the WHO classification (21)

When carrying out the statistical analysis of the data for both the plaque and the gingival indices, because of the low number of patients in each of the grades it was decided to regroup the different categories of variables. The variables were regrouped as follows: Plaque index (PI) - 2 groups: patients with visible or abundant plaque, and patients with no visible plaque or without plaque, gingival index (GI) - 2 groups: patients with healthy gums or slight inflammation, and patients with moderate or severe inflammation.

RESULTS

Of the 97 patients that participated in the study, 47 were male (48.5%) and 50 female (51.5%). The mean age was of 48.5 years, standard deviation 15.25 years, and range 17-72.

The most frequent hematological diseases present in the sample were acute myeloid leukemia (37.1%), non-Hodgkin's lymphoma (20.6%) and multiple myeloma (12.4%). To a lesser degree: chronic myeloid leukemia and the Hodgkin's lymphoma, (7.2% each one) medullary aplasia and acute lymphatic leukemia (6.2% each one) and finally chronic lymphocytic leukemia (3.1%).

The most used chemotherapeutic regimes were DAE (daunorubicin, ara-C, etoposide) (26.8%), followed by CHOP (cyclophosphamide, doxorubicin, leurocristine (vincristine sulfate), prednisone), IDICE (idarubicin, cyclophosphamide, etoposide) and busulphan / melphalan (14.4% each one respectively).

Of the 97 patients, 42 (43.3%) received a bone marrow transplant, while the remaining 55 (56.7%) did not. Of the 42 transplants, 22 were autologous and 20 allogenic.

Evaluating of pain on the VAS obtained the following results: the initial mean pain was 2.75 with a median of 2.0 and a standard deviation of 2.44. Twenty-eight percent of patients were not in pain during the visit.

Regarding the type of mouthwash, 27.8% of patients were not using mouthwash at the time of the visit, while the remaining 72.2% were. Of these, 38.1% used bicarbonate and 32.0% used multiple mouthwashes (bicarbonate, chamomile, chlorhexidine, nystatin).

The results of the descriptive study of the mucositis are described below. The appearance of mucositis is described both in function of the chemotherapy regime and in relation with the dental and gingival indices, and oral hygiene.

The prevalence of mucositis in our study was 60.8%. Most patients (44.3%) only presented erythema / edema (WHO grade I), while the most serious forms (WHO grades II, III, IV) appeared less frequently (7.2%, 6.2%, 3.1% respectively).

The relationship between mucositis and chemotherapy regime: the patients treated with busulphan / melphalan presented mucositis in 71.4% of cases, followed by the IDICE, DAE and CHOP regimes with percentages of 64.3%, 61.5% and 57.1% respectively. However, the differences were not statistically significant.

Relationship between mucositis and CAO index: the CAO index for patients with mucositis was 7.59 and 7.03 for those without it. The differences were not statistically significant.

Relationship between mucositis and plaque index (PI): patients without plaque presented mucositis in 48.0% of the cases; patients with no visible plaque presented mucositis

in 55.0%; patients with visible plaque, 77.8%; and patients with abundant plaque, 75.0%. Given the low number of patients in each group and the clear tendency for patients with visible or abundant plaque to present higher mucositis percentages, the data for this variable was grouped into two categories: patients with visible or abundant plaque and patients with no or no visible plaque. The patients with visible or abundant plaque presented mucositis in 77.4%, on the other hand those with no plaque or where this was not visible, presented mucositis in only 52.3% of cases. This difference was statistically significant (p=0 .015).

Relationship between mucositis and gingival index (GI): patients with healthy gums presented mucositis in 46.2% of cases; patients with slight inflammation, in 60.0%; patients with moderate inflammation, 69.2%; and patients with severe inflammation, presented 100% mucositis. In this case, and also for the same reasons, the variable was grouped into two categories. Thus, the patients with gingival inflammation presented 65.7% mucositis; and the patients with healthy gums presented 46.2% mucositis. Despite this tendency, the differences were not significant (p=0 .067).

Relationship between mucositis and oral hygiene: patients with good oral hygiene presented mucositis in only 26.7% of cases. Those with poor oral hygiene presented in 65.9% of cases and those with normal oral hygiene in 68.4%. These differences were statistically significant (p=0 .013).

Relationship between mucositis and oral mouthwashes: patients who did not use mouthwash, presented only 37% mucositis. On the other hand, mucositis did appear in 71% of those who used multiple mouthwashes and in 67.6% of those who rinsed with bicarbonate, with statistically significant differences (P=0 .015).

DISCUSSION

Chemotherapy and/or BMT are the current treatments for diverse types of malignant diseases, not just hematological, because of the good therapeutical results offered. For this reason, the number of patients subjected to these therapies has increased in recent years, and the control and handling of its complications is fundamental. Given that the oral cavity is one of the most frequent locations for side effects of chemoradiotherapy, and one that causes the patient much discomfort, a close collaboration aimed at minimizing these effects should exist between the stomatologist and the other health-care professionals involved in treating the patient.

The prevalence of mucositis found in our study was 60.8%. This high frequency corresponds with that referred by other authors such as Epstein et al. (1), Gabriel et al. (4) or Sonis (2).

We observed no significant differences between the type of chemotherapy regime and the presence of mucositis. However, there is a tendency for patients treated with certain cytostatics to present a higher rate of mucositis, as was found in the case of regimes based on busulphan / melphalan, results that coincide with those of Wardley et al. (5) and Barasch et al. (10).

When it comes to evaluating the remaining results, we find ourselves, as mentioned in the introduction, with few options. On one hand, few studies in the literature evaluate the gingival and dental status, and on the other, the existence of different classifications for mucositis can occasionally hinder the comparison. In our study, we have used the WHO classification (21), one of the most used, especially in clinical studies (0: normal mucosa, 1: erythema, edema, 2: erythema, small aphthae, 3: large ulcers, only liquids allowed, 4: large ulcers, pseudomembranes, ingestion is not possible).

The mean CAOD index in our study did not show significant differences in connection with the presence of mucositis. In any case, it is well known that patients with active caries, radicular remains and septic foci of dental origin, have a higher risk of presenting pain and oral infections during chemotherapy (mainly in the neutropenic phase). We also highlight that the CAO index value of 7.73 found in the current study is somewhat lower than that observed in a study published by our group in 2000: 10.7 (17).

Some studies have tried to evaluate the oral state noting parameters such as visits to the dentist or oral treatments received. Dodd et al. (13), registered a mean of 15 months from the last visit to the dentist and 10.7 months since the last scaling in a group of 50 breast and colon cancer patients who developed mucositis during chemotherapy, which could give some idea of the possible presence of dental alterations, calculus and plaque. Epstein et al. (1), point out that oral hygiene, and thus the removal of dental plaque, would be an indirect form of reducing the risk of bacteremia and periodontitis.

With regard to studies registering dental or gingival indices and their relationship with mucositis, we will comment on two: that of the year 2000 mentioned above, and another from 2002. In the first, López et al. (17) observed a decrease of PI and GI (significant in the case of GI) in patients who attended the dentist before beginning chemotherapy. In the second, Lugliè et al. (18) carried out a scaling or curettage and administered a 0.2%chlorhexidine mouthwash to 27 patients, obtaining a statistically significant decrease for both PI and GI during chemotherapy against a control group. Mucositis presented in only 20% of patients in their treatment group. On the other hand, McCarthy et al. (22), in patients with solid tumors, observed results contrary to most studies, included ours, finding no relationship between oral hygiene and accumulated plaque, and the presence of mucositis.

A highly controversial topic is that of dental brushing during chemotherapy since many hospitals prohibit it because of the possible risk of bacteremia and bleeding in the neutropenia and platelet deficiency phases. In the present study, we evaluate oral hygiene in function of the number of times per day that the patient brushes. We were aware of the probable subjectivity of the parameter and that it could depend on the individual's own ability; although brushing teeth more than once a day should, in our opinion, usually indicate greater interest by the patient for their oral hygiene and thus better plaque removal. The Greene Vermillion, 1960 oral hygiene index (OHI) (20) was not used since it

requires a dual evaluation: the extent of debris and of tartar, the scale is similar to the plaque index and its values increase with age. The significant result we observed in patients who brushed 3 times a day from the beginning of chemotherapy, is close to that of authors such as Kennedy et al. (15), Cheng et al. (23), and Bonnaure-Mallet et al. (24), the last two in an infant population.

It has also been observed that good oral hygiene that includes dental brushing reduces the incidence and severity of mucositis without increasing the risk of bacteremia, not even in neutropenic patients, since the presence of plaque and abundant calculus are considered potentially more dangerous (7,15,23). However, these authors point out that once used, the dental brush is quickly colonized by oral bacteria and they therefore recommend discarding the brush after each use or soaking in a 2% chlorhexidine solution and rinsing in sterile saline serum before reuse. Stiff (25) on the other hand, does not recommend brushing during the post-transplant mucositis phase, although they would allow antiseptic mouthwashes and anesthetics. Epstein et al. (26), affirm that the 25-50% sepsis in immunocompromised patients originates in the oral cavity, although they do not observe that brushing per se increases the risk of bacteremia.

The use of an oral mouthwash during chemotherapy, either preventatively or as treatment, is widespread. In fact, it forms part of the preventive and therapeutic protocol for the oral complications of chemoradiotherapy in most cancer hospitals. However, the literature does not recommend their widespread use, since in many cases there is limited scientific evidence for their effectiveness (1,8,27). Kenny (12) compares two protocols for oral care in hematological patients, one with bicarbonate and the other with saline serum finding no differences between them with regard to evolution of mucositis. Furthermore, the topical application of 0.2% chlorhexidine in aqueous solution has been used in different studies with controversial results. Pitten et al. (28) in leukemia patients and Dodd et al. (13) in patients with breast and colon neoplasia observed that using chlorhexidine reduced neither the incidence nor the severity of the mucositis. Pitten (28) also points out, the possibility of side effects such as irritation of the oral mucosa and dental staining, although he indicates that chlorhexidine would reduce the oral microbial load. On the other hand, Rutkauskas et al. (29) obtained positive results for mucositis after administering chlorhexidine mouthwash in patients who were to receive a BMT, and Lugliè et al. (18), refer that chlorhexidine could have influenced the reduction of the mucositis observed in their study, although the patients also received periodontal treatment. In addition, Caribé et al. (30) include chlorhexidine in their protocol for the treatment of mucositis secondary to radiation therapy in patients with oral cancer.

In our study, patients that did not use mouthwash developed less mucositis than those who used multiple mouthwashes (chlorhexidine, bicarbonate, camomile, fungicidin/nystatin). These results, which at first sight may seem contradictory, would indicate that patients who rinsed presented a more serious oral mucositis and therefore more oral symptomatology, and to reduce this would we believe use all available solutions. That is to say, it would be a typical example of a non-causal relationship, in that possibly those patients who did not present mucositis, did not need to use a mouthwash, and not that the mouthwash was the cause of the mucositis.

CONCLUSIONS

In conclusion, it should be emphasized that from the results obtained in our study, maintaining a healthy oral cavity during oncological treatment, with little plaque or gingival inflammation, is a factor that would condition a lower and less serious incidence of mucositis. In addition, dental brushing becomes the most effective method for the removal of dental plaque.

On the other hand, we believe further studies where the buccodental status and mucositis are randomly evaluated over time with a larger group of patients are necessary. Likewise, it is essential to deepen our studies of the remaining risk factors and the etiopathogenesis of mucositis, since better understanding will help to develop new treatments in the future and to improve the quality of life for the cancer patient.

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