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Streptococcal bacteremia in patients submitted to hematopoietic stem cell transplantation: The role of tooth brushing and use of chlorhexidine

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Abstract

A retrospective evaluation of 73 consecutive recipients of hematopoietic stem cell transplantation (HSCT) was conducted to investigated the role of oral care and incidence of streptococcal bacteremia in patients submitted to hematopoietic stem cell transplantation. Patients were retrospectively evaluated and divided into group A (GA=38) and group B (GB=35). During hospitalization patients from GA performed oral hygiene daily with extra soft toothbrush and toothpaste besides performing mouth cleaning with an ethanol-free 0.12% chlorhexidine solution tree times a day. In contrast GB patients performed mouth cleaning with extra soft toothbrush and toothpaste, but no chlorhexidine was used. Using the Chi square test it was observed that all patients from GA presented negative blood culture for alpha-hemolytic Streptococcus viridans and *Candida albicans* and only 1 patient without oral mucositis from GB presented positive blood cultures for Streptococcus intermedius (p=0.48). The results indicate that methodology used for oral care before the HSCT and the practice of tooth brushing during the period were effective in preventing streptococcal bacteremia. Moreover, our data suggest that the mouth cleaning with chlorhexidine during HSCT may be not mandatory.

Key words: *Bacteremia, chlorhexidine, hematopoietic stem cell transplantation, oral hygiene.*

Introduction

During hospitalization, patients who undergo a myeloablative chemotherapy protocol for hematopoietic stem cell transplantation (HSCT) develop neutropenia and therefore have a tendency to septicemia that can be originated in many sites of the organism (1). During the 70s, gram-negative organisms were isolated with more frequency in blood cultures exams than the gram-positive (1-3). Since early 80s the scenario has changed, predominating gram-positive bacteria in blood cultures, especially α-hemolytic viridans streptococci varying from 10 to 70% (1) and coagulase-negative staphylococci (mainly Staphylococcus epidermidis) have been observed (2).

The mouth bacteria field is made of several species of bacteria and fungi (4). Dental plaque formed by them has been defined by as "the nonmineralized microbial accumulation that adheres tenaciously to tooth surface, restorations, and prosthetic appliances, shows structural organization with predominance of filamentous forms, is composed of an organic matrix derived from salivary glycoproteins and extracellular microbial products, and cannot be removed by rinsing or water spray" (4). They present a complex composition with more than 500 species and some are identified as the main causes of caries, gingivitis and periodontal disease. The maximum concentration is found in bacterial plaque, where it is estimated that there are between 10^{11} and 10^{12} microorganisms per gram of wet weight though there are also abundant bacteria on the back of the tongue and in the cheek and palatal mucosa. Although there are differences among the different oral ecosystems, globally the most abundant microorganisms are streptococci of the viridans group (5). Consequently, the thicker the plaque the greater to risk of infection (6). With a rich bacteria site in the oral cavity, specially gram-positive, there is a serious source of infection for the patient submitted to HSCT, since besides undergoing a severe immune suppression, patients may suffer from oral mucositis (OM) that serves as a open door to micro organisms (2,7,8). Considering that oral and gastrointestinal mucositis may occur in up to 100% of the patients undergoing high-dose chemotherapy with HSCT (9), there is a high possibility for HSCT patients to acquire septicemia generated in the oral cavity.

The oral infection prevention must begin with the effort to reduce bacterial plaque and this can be achieved by the preparation of patients before hospitalization for the HSCT, through oral hygiene instructions, proper conditioning of the oral cavity, removal of gum calculus, making necessary restorations and extracting teeth with bad prognostic (10). In the oral care before hospitalization for the HSCT, a mouthwash with an ethanol-free 0.12% chlorhexidine solution has become standard due to its efficacy in bacteria and fungi elimination (7,9).

In the current study, we investigated the role of oral care and incidence of streptococcal bacteremia in patients submitted to hematopoietic stem cell transplantation.

Patients and Methods

This was as retrospective study, performed from January 4, 2004, and May 20, 2005. All patients (73) submitted to HSCT at the "Centro de Transplante de Medula Óssea do Instituto Nacional de Câncer" (CEMO-INCA) were included. Patients were divided into group A (GA=38 patients) and group B (GB=35 patients). The study was conducted according to the resolution 196/96 from the National Health Council and was approved by the local Ethics Committee. All patients signed an informed consent and received all clarifications and orientations.

Inclusion and exclusion criteria

The criteria for inclusion in the study was defined as age ≥ 18 years old, patients with hematological disease and indication to HSCT, patients able to perform mouth cleaning (oral hygiene). Patients unable to perform mouth cleaning were excluded.

** Method:*

Oral care before hospitalization

All patients (GA e GB) were previously evaluated by the dentist and received dental care, whenever necessary. Dental care included educating patients about oral hygiene; panoramic radiograph; oral examination with attention to soft tissues and bones; tooth and periodontal exam; removal of sub and supragingival calculus; elimination of sources of trauma caused by orthodontic bands and brackets, teeth, or prosthesis; extraction of teeth with signs or symptoms indicative of potentially bad prognosis (active periodontal disease, teeth requiring endodontic treatment or with extended caries and coronary destruction) (9,10). All patients from both groups performed oral hygiene after meals with toothpaste with fluoride and mouth washing with an ethanol-free 0.12% chlorhexidine solution during 15 days before hospitalization for the transplant, three times a day (morning, afternoon, and night). Patients from both groups received 5 vials of chlorhexidine for a 15-day period. Drug countability of chlorhexidine was performed, as well as, registration of the use in the patient charts.

Oral care during hospitalization

Patients from group A had participated in a phase III trial analyzing the impact of low power laser in the prevention of oral mucositis, and they followed the protocol in which toothpaste and toothbrush were provided in the day of hospitalization. Further they performed with extra-soft toothbrushes, dental paste with a peroxidase system after every meal and mouth washing with an ethanol-free 0.12% chlorhexidine solution, 20 ml three times a day (morning, afternoon, and night), from the

conditioning (D-7) until neutrophil recovery (presence of 500 neutrophils in the peripheral blood for two consecutive days) (9).

Patients from group B underwent HSCT in the same period of the year, performed oral hygiene every meal at their discretion using extra-soft toothbrushes and toothpaste without peroxidase system but with fluoride and did not use mouth washing with an ethanol-free 0.12% chlorhexidine solution during the time of hospitalization. It should be emphasized that patients from group B were not included in the LPLT trial at random due to accrual limitations. The interventions in groups A and B are summarized in (Fig. 1).

Chemoprophilaxy

The patients from both groups used intravenously fluconazol 200 mg every 12 hours, acyclovir 500 mg/m² every 8 hours, both from D–2 until neutrophil recovery, sulfametoxazol + trimetropin every 12 hours from the hospitalization day until D-2 in order to prevent infection by Pneumocistis jirovecci (carini). There was no antibiotic prophylaxis specific for gram-positive and gram-negative in neither group.

Systemic infection evaluation (Bacteremia)

Bacteremia was defined with the presence of at least one aerobic, anaerobic bacteria and fungi positive blood culture sample. Blood cultures were collected in both group patients during the first fever episode and subsequent.

Blood cultures exam and microorganism identification

The analyses of the positive feature in the blood exam was made by automatic method with a BACTEC 9240 (Becton Dickinson) and the identification were made by automatic method with a VITEK® (bioMérieux).

Statistic analyses

The data were obtained through observation of results of the blood cultures during fever and correlated to the study group with the presence of OM (G2, G3 e G4-Oral Mucositis Index of the World Health Organization) (11) and use of the mouth washing with an ethanol-free 0.12% chlorhexidine solution during the time of hospitalization, using the chi-square test (χ^2) and with the hospitalization time using the Student test. The statistical test applied to analyze the patient's characteristics were Student test and chi-square test (χ^2). A p-value ≤ 0.05 was considered significant.

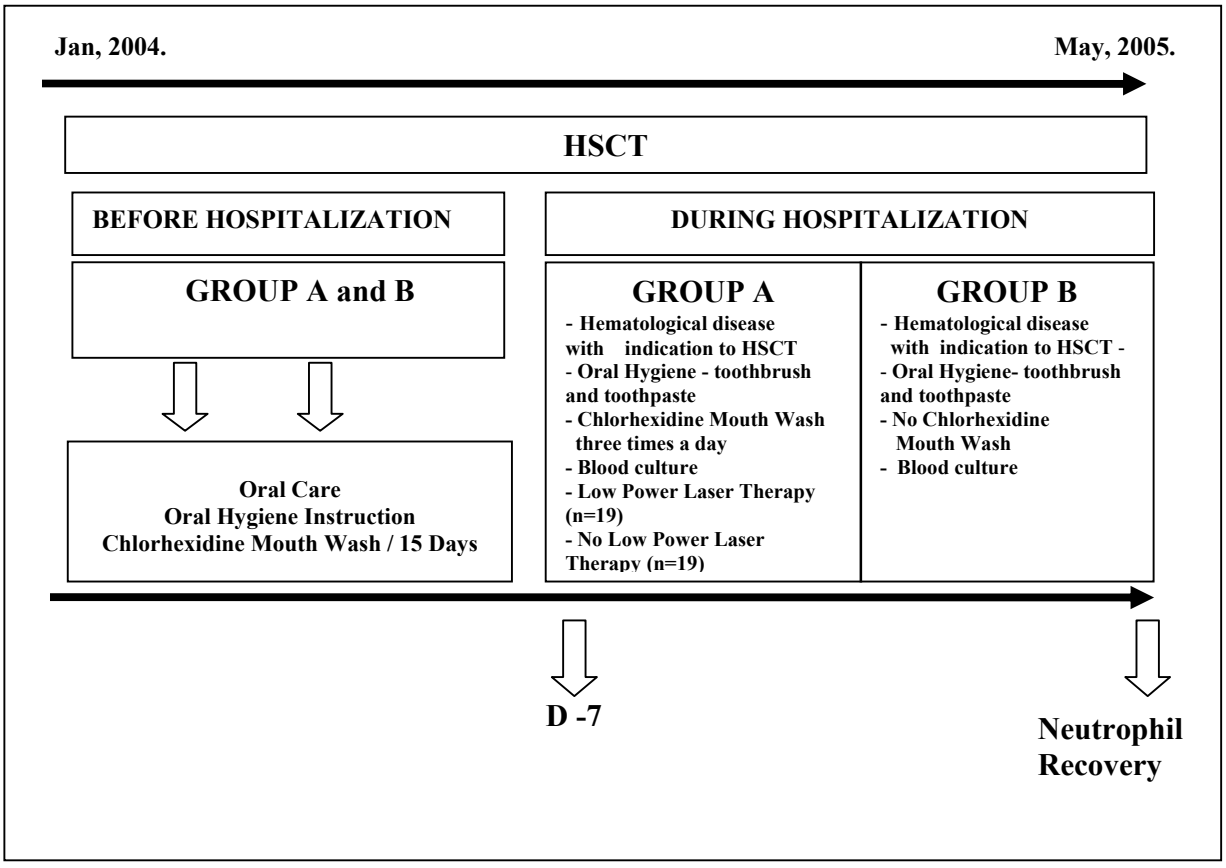

Fig. 1. Characteristics of protocols. HSCT: Hematopoietic stem cell transplantation.

Results

Patient characteristics

The study group A consisted of 38 patients (28 Allogeneic and 10 Autologous), 23 male and 15 female, ranging in age from 19 to 57 years (mean age, 36.7 years). Cancer diagnoses in this group included acute lymphoblastic leukemia (n=1), acute myeloblastic leukemia (n=6), chronic myeloblastic leukemia (n=16), Hodgkin's lymphoma (n=8), Non-Hodgkin's lymphoma (n=4) and myelodisplasic syndrome (n=3). The study group B consisted of 35 patients (21 Allogeneic and 14 Autologous), 18 male and 17 female, ranging in age from 19 to 64 years (mean age, 34.1 years). Cancer diagnoses in this group included acute lymphoblastic leukemia (n=3), acute myeloblastic leukemia (n=4), chronic myeloblastic leukemia (n=4), Hodgkin's lymphoma (n=13), Non-Hodgkin's lymphoma (n=8) and myelodisplasic syndrome (n=3). When the age (p=0.23), gender (p=0.43), HSCT (p=0.21) was compared between GA and GB no significant difference was observed. When the primary neoplasia (leukemia versus lymphomas versus myelodisplasic syndrome) was compared between GA and GB a significant statistical difference was observed (p= 0.04).

Table 1. Positive blood cultures.

Blood cultures and OM	GROUP A n=38	GROUP B n=35	p
Positive blood cultures with OM	5	7	0.43
Positive blood cultures without OM	4	3	0.77
TOTAL	9 (23.6%)	10 (28.6%)	0.63

OM: Oral mucositis.

Blood culture

All patients presented fever at some point and so had blood samples collected for culture, which is a routine at CEMO. In total, 480 blood cultures (GA=245, GB=235) were performed with median of 5 exams for patient in GA and GB, respectively. The incidence of positive blood culture in both groups was not statistically different (p=0.63), (Table 1).

Blood culture, oral mucositis and use of the chlorhexidine

Out of 38 patients in GA and 35 patients in GB only 9 (23.6%) and 10 (28.6%) presented positives blood cultures, respectively (p=0.63).

In GA α-hemolytic viridans streptococci and fungi were not isolated, however in GB α-hemolytic viridans streptococci was isolated in 1 patient (p=0.48).

When the positivity of blood culture were compared between GA (with chlorhexidine) and GB (without chlorhexidine), considering the patients with OM G2, G3 e G4 (p=0.43) and without OM G2, G3 e G4 (p=0.77) no significant difference was observed (Table 1). The results showed that 5 patients from GA and 7 from GB that had OM and positive blood cultures results did not present positive results for viridans streptococci. The microorganisms isolated in patients with OM were: Bacillus species, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Staphylococcus haemolyticus, Staphylococcus epidermidis, Stenotrophomonas maltophilia. Further positive results for Streptococcus intermedius was observed in 1 patient without OM in GB (p=0.48).

Oral mucositis and hospitalization length

When a correlation was established between patients submitted to HSCT allogeneic and autologous with OM, bacteremia and the hospitalization length, although patients submitted to HSCT allogeneic that presented bacteremia had a trend for a longer hospitalization (excess of 4 days) than those without bacteremia, no significant difference was seen (Table 2); p=0.107).

Table 2. Duration of Hospital Stay Compared across HSCT.

HSCT, n	N	Median (Max-Min)	Mean (SD)	p
Allogeneic with positive blood cultures	13	34 (74-20)	39.62 (17.50)	.107
Allogeneic with negative blood cultures	30	30 (68-18)	30.83 (8.98)	
Allogeneic with oral mucositis	33	30 (70-21)	34.06 (11.62)	.596
Alogeneic without oral mucositis	10	30.5 (74-18)	31.60 (16.13)	
Autologous with positive blood cultures	4	19 (21-18)	19.25 (1.26)	.525
Autologous with negative blood cultures	19	20 (32-17)	20.42 (3.52)	
Autologous with oral mucositis	14	20.5 (32-17)	21.14 (3.71)	.088
Autologous without oral mucositis	9	18 (22-17)	18.78 (1.64)	
Allogeneic (death)	6	----------	----------	----------
Autologous (death)	1	----------	----------	----------

Discussion

Even though the results of HSCT have been encouraging, infectious complications still result in significant morbidity and mortality and remain major obstacles to further improvement of survival rates. Infections following HSCT are determined in part by the sequential events that occur in the process of marrow ablation, hematopoietic engraftment and immunologic recovery. Moreover, most of the bacteria and yeasts enter the host via a damaged integument either through or gut or via an intravascular device or the oral cavity (2).

Although different strategies of oral care have been evaluated in patients submitted to HSCT the impact of this oral care on Streptococcal bacteremia have been neglected.

In this context, the aim of the present study was to evaluate in a retrospective manner the impact of oral care on Streptococcal bacteremia in patients submitted to HSCT. The oral hygiene protocol used in all patients for oral conditioning before the hospitalization for the HSCT included oral hygiene orientation, supplementation of toothpaste and toothbrush and the use of an ethanol-free 0.12% chlorhexidine solution during 15 days. The protocol used during hospitalization included toothpaste, toothbrush and use or not of chlorhexidine (GA and GB, respectively).

The goal of this strategy was to reduce the microorganisms from the mouth to the background that comes from Listgarten (4) who quotes that the higher the dental plaque volume, the higher the quantity and quality of microorganisms. Goodson et al. (6) also states that the effectiveness of the mechanical cleaning associated with the hygiene instruction in the recovery or maintenance of oral health and that the mechanical removal diminishes the quantity of bacteria but it does not alter the dental plaque composition.

It was chosen to use 0.12% chlorhexidine solution to alter the quantity of microbiota and inhibit the dental plaque formation and consequently prevent gum diseases. The activity of chlorhexidine has been defined elsewhere, with activity against gram-positive, gram-negative and some fungi. Further when used as mouthwash at 0.12%, it reduce several species of the bacteria in saliva (12).

In the current study, blood cultures results showed that there were no statistically significant difference between patients who used chlorhexidine during hospitalization (GA=23.6%) and patients that did not use chlorhexidine (GB=28.6%). When the incidence of positive blood cultures was evaluated in patients with OM and those ones who did not present OM in GA and GB, it was also observed that there was no statistically significant differences in the Groups. This data was contrary to data presented by other studies quoting OM as a cause of the bacteremia (1, 13-16). It is worth mentioning that out of 19 (26%) positive blood cultures in 73 patients, only 1 (1.36%) was positive for α-hemolytic viridans streptococci *(Streptococcus intermedius)* and that happened in a patient from GB, who did not presented OM. It must be pointed out that patients from this study did not receive antibacterial prophylaxis for gram-negative and gram-positive. This is contrary to data presented by Bilgrami et al. (13) who observed an incidence of 17.5% of streptococci isolated from blood cultures in patients using prophylactic ampicillin and 19% in those without it. These authors also mention that all patients submitted themselves to: ciprofloxacin 500 mg, twice a day from D-10 till recovery neutrophil or the beginning of parenteral antibiotics, acyclovir 250 mg/m² from the conditioning until recovery neutrophil, mouthwashes with chlorhexidine 15 ml twice a day, mouthwash with nystatin, 1 million units 4 times a day and hydrogen peroxy diluted 4 times a day, but there was no information about tooth brushing.

The patients from both groups (A and B) did not present other issues as gum diseases, dental fracture, abscess both periapical and periodontal and the ones with OM presented positive blood cultures for some microorganisms common in other sites, but that may be isolated in the oral cavity but we can not indicate their origin for not accomplishing oral swab. We observe that OM was not directly correlated to positive bacteremia streptococci, although evidence suggest that the breaking of oral mucous permits the penetration of microorganisms, which justifies the importance of the oral care, fact that was seen by Ruescher et al. (1), observed OM in 63% of patients with positive blood cultures for α-hemolytic streptococci, compared to only 36% of OM in patients without it. The authors assert that OM is a risk factor for bacteremia (odds ratio of 3:1) when compared to patients with intact mucous. It was also seen by Marron et al. (14), in patients with cancer, that quoted an incidence of 18% of positive blood cultures for α-hemolytic viridans streptococci, in 485 episodes of bacteremia and when they isolated the following species: *Streptococcus mitis* (72 cases), *Streptococcus salivarius (7), Streptococcus sanguis (5), Streptococcus milleri (3),* and *Streptococcus mutans (2).* Thus, as the previous results, these authors did not refer to how the oral cavity was prepared before the HSCT. Graber et al. (15), stated all patients had dental evaluation and treatment as well as panoramic radiography before the HSCT. In that study the patients received norfloxacin 400 mg / day from D-7 till the neutrophil recovery. This author did not provide information about oral hygiene during HSCT and the results of this study showed an incidence of 33.9% (19 in 56) for α-hemolytic viridans streptococci.

It should be highlighted that oral care for both groups before HSCT was equal for all patients and they all brushed their teeth during hospital stay. Although toothpastes were different, its composition may not have in-

terfered on the results. Inconclusive evidence exists in the literature with regard to the additional (beneficial) mechanical effect of a dentifrice on plaque removal. Paraskevas et al. (17,18) affirm that the use of toothpaste did not contribute to mechanical plaque removal during manual toothbrushing and it seemed that the mechanical action provided by the toothbrush was the main factor in the plaque-removing process. Addy et al. (19) in 80s already showed that the triclosan toothpastes containing the copolymer and chlorhexidine solution, produced significant reductions on salivary bacterial counts and to correlate it with plaque inhibitory properties of antimicrobial compounds. Assuming groups A and B were homogeneous in age, gender, HSCT protocol, oral care before hospitalization and that low power laser therapy (LPLT) is not bactericide, the relevant difference between the groups was the use of mouthwash with 0,12% chlorhexidine during hospitalization in the GA. It should be highlighted though that LPLT is bactericide when used with photosensitizer (dye) as an anti-microbial photodynamic therapy (20). The excellent results concerning bacteremia α-hemolytic viridans granted to the preparation of the oral cavity before HSCT and the maintenance of oral hygiene with toothbrush during HSCT.

In this study all patients undergoing an HSCT either allogeneic or autologous with or without OM presented no difference in the time for hospitalization, regardless of the presence of bacteremia. This is in contrast to Ruescher et al. (1) who says that when independently analyzed the patients with OM stayed hospitalized for a longer period (39.7 days) than those without OM (34.4 days).

In our hands, the patients submitted to HSCT allogeneic that presented bacteremia had a trend for a longer hospitalization, however this was not statistically significant, probably due to small sample size. This is in line with Ruescher et al. (1) who states that patients with sepsis stayed in hospital 10 days more than those without it and Vera-Llonch et al. (16) refer that there was a 14-day difference in the length of hospital stay between patients with the highest OM grade and those with OM grade 0. In a conservative evaluation on a hypothetical population of 100 patients, Ruesher et al. (1) estimates that 15% of transplanted patients presented infection with streptococci and that 45% presented OM. It also says that patients with OM and sepsis, when compared to patients with OM without sepsis, has the hospital stay increased in 11 days, resulting in an additional cost of U$ 544,500 e U$4500 per day/patient. Following the same line Vera-Llonch et al. (16) also observed a cost increase in cases that the patient presented OM (U$ 437,421) against the ones without OM (U$ 213,995). They state that the patient with OM has other co-morbidity as: e.g., gastrointestinal bleeding, volume depletion, cardiac failure. Although it may represent a flaw in our study we chose not to estimate eventual cost increase because we understand that the transplanted patient presents other co-morbidity which may interfere in the length of hospital stay such as the recovery neutrophil, graft-versus-host disease, cardiac insufficiency, hepatic insufficiency, kidney insufficiency, gastrointestinal bleeding since these data was not collected prospectively its evaluation could lead to a bias.

In conclusion, no significant difference for streptococcal bacteremia between GA and GB, moreover overall a lower incidence was observed. Despite the non-randomized nature of this study, our data suggests that the dominant factor for this result was the oral care approach before the hospitalization for HSCT based in the practice of necessary dental treatment and adequate oral hygiene measurements (toothbrushing and the mouth washing with 0.12% chlorhexidine) and maintenance of the oral hygiene with the toothbrush during it. The proceeding of mouth washing with 0.12% chlorhexidine during the length of hospital stay for HSCT may be unnecessary. It would be interesting to confirm that in a randomized trial addressing also potential cost-effectiveness implications.

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