VINICIUS RABELO TORREGROSSA

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THE INFLUENCE OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION ON SALIVARY FLOW

Piracicaba
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Universidade Estadual De Campinas
Faculdade de Odontologia de Piracicaba

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba, da Universidade Estadual de Campinas, como parte dos requisitos exigidos para a obtenção do título de Mestre em Estomatopatologia, área de concentração em Estomatologia.

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Orientador: Professora Doutora Maria Elvira Pizzigatti Corrêa

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Profa. Dra. MARIA ELVIRA PIZZIGATTI CORRÊA

Profa. Dra. VANESSA ROCHA LIMA SHCAIRA

Prof. Dr. FRANCISCO JOSÉ PENTEADO ARANHA

RESUMO

INTRODUÇÃO: A disfunção salivar é uma complicação oral comum ao Transplante de Células-Tronco Hematopoéticas (TCTH) alogênico. Diversos estudos relacionaram alterações salivares qualitativas e quantitativas à presença da Doença do Enxerto-Contra-Hospedeiro (DECH) crônica. Entretanto, ainda não foi completamente compreendida a influência da toxicidade dos regimes de condicionamento sobre as alterações precoces do fluxo salivar. O primeiro capítulo deste trabalho teve como objetivo avaliar as alterações precoces do fluxo salivar induzidas pelo TCTH alogênico e, no segundo capítulo, objetivou-se validar critérios clínicos utilizados para o diagnóstico de hipossalivação nesta população de pacientes. PACIENTES E MÉTODOS: *Capítulo 1* – Foi realizado um estudo prospectivo que envolveu 69 pacientes adultos submetidos ao primeiro TCTH entre os anos 2010 e 2014, na Unidade de Transplante de Células-Tronco Hematopoéticas, Hemocentro de Campinas/Hospital de Clínicas, Unicamp. Amostras de saliva não estimulada foram coletadas, e os pacientes foram submetidos à avaliação da saúde oral, e da secreção salivar através da aplicação de critérios clínicos específicos para o diagnóstico de hipossalivação, previamente ao início do regime de condicionamento, e entre os dias D+8-10 pós-TCTH. A avaliação da condição de saúde oral incluiu a obtenção do índice de Dentes Cariados, Perdidos e Obturados (CPOD), Índice Gengival (IG), e do Índice de Placa (IP). Além disso, foi realizada a avaliação do grau de mucosite oral entre os dias D+8-10 pós-TCTH, de acordo com os critérios da Organização Mundial de Saúde (OMS). Os critérios clínicos de hipossalivação avaliados envolveram quatro critérios objetivos e quatro questões subjetivas, considerando-se hipossalivação quando o Fluxo Salivar Não Estimulado (FSNE) ≤0,2 mL/min. As variáveis categóricas foram analisadas pelo teste de associação Qui-quadrado, e pelos testes de Fisher e de Mann-Whitney. O teste t pareado foi utilizado na comparação das variáveis contínuas nos diferentes períodos. *Capitulo 2* – Foi realizado um estudo de corte transversal que envolveu 120 pacientes não consecutivos submetidos ao primeiro TCTH alogênico entre os anos 2006 e 2014. Os pacientes foram submetidos a avaliações orais, que incluíram a coleta de saliva

não estimulada, e a utilização de oito critérios clínicos para o diagnóstico de hipossalivação em diferentes períodos pós-TCTH. O teste alfa de Cronbach foi aplicado para medir a consistência interna e confiabilidade dos oito critérios aplicados. Foram selecionados 5/8 critérios clínicos de hipossalivação, e um Sistema de Pontuação para Boca Seca (SPBS) foi construído. O teste de Mann-Whitney e a correlação de Pearson foram utilizados na análise da distribuição do FSNE em relação às pontuações dicotomizadas. RESULTADOS: *Capítulo 1* - Foi observado um aumento do fluxo salivar e piora do grau de inflamação gengival entre os dias D+8-10 pós-TCTH (p=0,03 e p=0,03, respectivamente). O aumento do fluxo salivar neste período foi correlacionado à gravidade da mucosite oral (p=0,02), à presença de vômito (p=0,03), e ao uso de nutrição parenteral total (p=0,03) nos dias das coletas de saliva. Apesar da hipossalivação não ter sido um achado frequente no período estudado, mulheres e pacientes com doenças de alto risco apresentaram um menor fluxo salivar (p=0,01 e p=0,03, respectivamente). *Capítulo 2* - Os cinco critérios clínicos de hipossalivação validados (*1.Alta aderência da espátula de madeira na mucosa jugal; 2.Ausência de lago sublingual*; *3.Saliva espessa e viscosa*; *4.Ausência de secreção salivar após ordenha do ducto parotídeo*; 5. *Você sente sua boca seca?*) foram considerados essenciais para a construção do SPBS. Após a dicotomização das pontuações obtidas no SPBS, 66 (55%) pacientes apresentaram pontuações de 0-1, com uma média do FSNE de 0,65 mL/min (0,1-9,0 mL/min), e 54 (45%) pacientes apresentaram pontuações de 2-5 com uma média do FSNE de 0,34 mL/min (0,01-6,7 mL/min). Maiores pontuações no SPBS foram correlacionadas a um FSNE reduzido (p=0,006, r=-25%), confirmado pelo teste de Mann-Whitney (p<0,0001). CONCLUSÕES: *Capítulo 1* - Houve um aumento do FSNE nos dias D+8-10 pós-TCTH, e este achado pode estar relacionado à intensa reação inflamatória e dano tecidual induzido pela toxicidade dos regimes de condicionamento (mucosite oral). *Capítulo 2*- O SPBS provou ser uma ferramenta confiável para o diagnóstico de hipossalivação na população estudada.

Palavras-chave: transplante de células-tronco hematopoéticas, saliva, xerostomia

ABSTRACT

INTRODUCTION: Salivary dysfunction is a common complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Many studies related qualitative and quantitative salivary changes to the presence of chronic Graft-Versus-Host Disease (GVHD). However, it was still not completely understood the influence of the conditioning regimens toxicity on the very early salivary flow changes. The first chapter of this study aimed to evaluate the very early salivary flow changes induced by allo-HSCT, and, the second chapter aimed to validate the clinical criteria used for the diagnosis of hyposalivation in this patient population. PATIENTS AND METHODS: *Chapter 1* – This was a prospective study that enrolled 69 adult patients undergoing their first allo-HSCT between the years 2010 to 2014, at the HSCT Unit, Hematology and Blood Transfusion Center of Campinas/Clinical Hospital, University of Campinas. The unstimulated whole saliva was collected and patients were assessed for their oral health status, and salivary secretion through the application of specific clinical criteria for the diagnosis of hyposalivation, before the start of the pretransplant conditioning regimens and between the days D+8-10 posttransplantation. The oral health exam included the evaluation of Decayed-Missing-Filled teeth (DMFT) index, Gingival Index (GI), and Plaque Index (PI). Furthermore, the degree of oral mucositis (OM) was assessed between the days D+8-10 posttransplantation, according to the World Health organization (WHO) criteria. The clinical assessment of hyposalivation was composed by four objective clinical criteria and by four subjective questions, considering hyposalivation when the unstimulated whole saliva flow rate (UWSFR) was ≤ 0.2 mL/min. Categorical variables were analyzed by the chi-square association test, ant by the Fischer's test, besides of the Mann-Whitney *U* Test. Pared T-test was used to compare continuous variables in different periods. *Chapter 2*- A cross-sectional study was conducted involving 120 non-consecutive patients undergoing their first allo-HSCT between the years 2006 to 2014. Patients underwent oral health exams, which included the unstimulated whole saliva collection, and the use of 8 clinical criteria for the diagnosis of hyposalivation at different periods post-HSCT. Cronbach's alpha test was applied in order to measure the internal consistency and satisfactory reliability of all eight criteria

used. Five of eight clinical criteria of hyposalivation were selected, and a scoring system called Oral Dryness Score (ODS) was built. Mann-Whitney *U* test and the Pearson's correlation coefficient were applied to analyze the UWSFR distribution among the dichotomized ODS scores. RESULTS: An increase of the UWSFR, and the worsening of the gingival index were observed at days D+8-10 posttransplantation (p=0.03, and p=0.03, respectively). A positive correlation was found between the increase of UWSFR and OM severity (*p*=0.02), with vomiting episodes (*p*=0.03), and with the use of total parenteral nutrition (TPN) (*p*=0.03) at the days of saliva collection. Although hyposalivation was not a frequent finding among the studied population, a reduced UWSFR was observed in women, and in the group of patients with a high risk underlying disease (*p*=0.01, and *p*=0.03, respectively). *Chapter 2*- The five validated clinical criteria of hyposalivation (*1.Higher adherence of the wood spatula to the jugal mucosa*; *2.No saliva pooling in the anterior floor of mouth*; *3.Increased viscosity and thickness of saliva*; *4.Absence of salivary secretion of the parotid duct under manual pressure; 5.Does your mouth feels dry?)* were considered essential for the ODS building. After dichotomizing the ODS scores, 66 (55%) patients presented 0–1 scores, with a UWSFR median of 0.65 mL/min (0.1–9.0 mL/min), and 54 (45%) patients presented 2–5 scores with a UWSFR median of 0.34 mL/min (0.01–6.7 mL/min). A higher ODS was correlated with a decreased UWSFR (p=0.006, r=-25%), confirmed by the Mann-Whitney U test (p<0.0001). CONCLUSIONS: *Chapter 1*- An increase of the UWSFR was found between the days D+8-10 posttransplantation, and it may be related to the intense inflammatory reaction and tissue damage induced by the conditioning regimens toxicity (oral mucositis). *Chapter 2* - The ODS proved to be a reliable tool for the diagnosis of hyposalivation in the studied population.

Key Words: hematopoietic stem cell transplantation, saliva, xerostomia

SUMÁRIO

DEDICATÓRIA

Dedico este trabalho à minha querida avó Joanina Tourinho Rabelo (*In Memoriam)*. Por ser uma mulher de fibra e feição marcante, não era de se esperar que possuísse aquele característico olhar complacente e sorriso acalentador. Mas era.

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LISTA DE ABREVIATURAS E SIGLAS

ASSPDUMP	*Absence of Saliva Secretion of the Parotid Duct Under Manual Pressure*
BMI	*Body Mass Index*
CCB	Camila Cominato Boer
CPOD	Índice de Dentes Cariados, Perdidos e Obturados
CsA	*Cyclosporine*
DECH	Doença do Enxerto-Contra-Hospedeiro
DMFT	Decayed-Missing-Filled Teeth Index
FSNE	Fluxo Salivar Não Estimulado
GI	*Gingival Index*
GVHD	*Graft-Versus-Host Disease*
HLA	*Human Leucocyte Antigen*
allo-HSCT	*allogeneic Hematopoietic Stem Cell Transplantation*
ICT	Irradiação Corpórea Total
IG	Índice Gengival
IP	Índice de Placa
MMF	*Mycophenolate Mofetil*
MTX	*Methotrexate*
ODS	*Oral Dryness Score*
OM	*Oral Mucositis*
OMS	Organização Mundial de Saúde
PI	*Plaque Index*
SPBS	Sistema de Pontuação para Boca Seca
TBI	*Total Body Irradiation*
TCTH	Transplante de Células-Tronco Hematopoéticas
TPN	*Total Parenteral Nutrition*
UWSFR	*Unstimulated Whole Saliva Flow Rate*
VRT	Vinicius Rabelo Torregrossa
WHO	*World Health organization*

INTRODUÇÃO

Descrita como o “espelho do corpo”, a saliva é um dos mais complexos, versáteis, e importantes fluidos biológicos (Farnaud et al., 2010). A sua presença é essencial para o adequado funcionamento e bem-estar do organismo humano (Jonsson et al., 1993; Spielmann & Wong, 2011).

A saliva contém uma variedade de componentes orgânicos incluindo imunoglobulinas, enzimas, mucinas, hormônios, e citocinas (Zelles et al., 1995; Rehak et al., 2000; Malamud, 2011). Também podem ser encontrados eletrólitos como o sódio, potássio, cálcio, magnésio, bicarbonato, e fosfato (Humphrey & Williamson, 2001). A presença destes componentes caracteriza a saliva humana como um produto biológico único, capaz de participar de importantes funções fisiológicas relacionadas à manutenção da homeostase e controle ecológico adequado da cavidade oral (Humphrey,& Williamson, 2001; Malamud, 2011).

Diversas funções são desempenhadas pela saliva, incluindo a lubrificação e limpeza da mucosa orofaríngea; o auxílio na degustação dos alimentos; na atividade digestiva enzimática; na formação e deglutição do bolo alimentar; na atividade antibacteriana, antifúngica e antiviral; na atividade reparadora tecidual; na modulação do pH do biofilme bacteriano, e na participação do processo de remineralização do esmalte dental (Jonsson et al., 1993; Fenoll-Palomares et al., 2004; Mese & Matsuo, 2007; Malamud, 2011; Spielmann & Wong, 2011).

Por definição, a saliva é um complexo misto de secreções provenientes das diferentes glândulas salivares, do fluido crevicular gengival, das células epiteliais descamadas, de microorganismos, de restos alimentares, e das secreções nasais e brônquicas (Rudney, 1995). A maior parte da saliva é produzida pelos três pares de glândulas salivares maiores, sendo essas as parótidas, submandibulares e sublinguais, e por centenas de glândulas salivares menores espalhadas pela cavidade oral (Humphrey,& Williamson, 2001; Dodds, Johnson, Yeh, 2005).

As glândulas salivares são órgãos altamente especializados, que possuem três segmentos celulares distintos com características morfofuncionais definidas. Os três tipos de células presentes nas glândulas salivares são: mioepiteliais, acinares, e ductais (Humphrey,& Williamson, 2001; Dodds et al., 2005). As células mioepiteliais estão envolvidas na contração acinar através da estimulação neural. As células acinares são responsáveis por secretar um fluido plasmático primário, que pode ser seroso, mucoso, ou misto. Por fim, as células dos ductos salivares estão envolvidas na modificação do fluido plasmático primário durante a passagem pela porção estriada do sistema celular ductal (Humphrey,& Williamson, 2001).

A secreção salivar pode ser definida como “um movimento unidirecional de líquido, eletrólitos e macromoléculas para dentro da saliva, em resposta à estimulação apropriada” (Edgar, O’Mullane & Dawes, 1996). Fisiologicamente, o mecanismo de secreção salivar divide-se em dois estágios: (1) em um primeiro momento há a secreção de um fluido plasmático primário aquoso e isotônico pelas células acinares e, em seguida, (2) ocorrem trocas iônicas no sistema celular ductal, responsáveis por transformar a saliva excretada em um fluido hipotônico (Garrett et al., 1991; Dodds, Johnson, Yeh, 2005; Mese & Matsuo, 2007). De uma forma geral, a capacidade de secreção de fluido pelas células acinares é maior do que a capacidade de reabsorção de eletrólitos pelo sistema celular ductal. Isto pode explicar a relação existente entre a velocidade do fluxo salivar e a variação da composição da saliva excretada (Edgar, O’Mullane & Dawes, 1996). Este fato permitiu a categorização da saliva em dois tipos reconhecidamente distintos: a saliva estimulada e não estimulada (Sreebny, 2000).

Todo o processo de secreção salivar é controlado pelo sistema nervoso autônomo que, através da transdução de sinais estimulatórios, ativam receptores específicos para mecanismos de trocas iônicas e secreção proteica nas glândulas salivares (Dodds, Johnson, Yeh, 2005). Existem três tipos principais de estímulos desencadeadores envolvidos na secreção salivar: (1) a mastigação, (2) o paladar, (3) e o olfato (Humphrey,& Williamson, 2001). A estimulação colinérgica gerada

por um destes estímulos é capaz de induzir à secreção profusa de uma saliva serosa, primariamente associada à função digestiva, categorizada como saliva estimulada. Já a saliva não estimulada é secretada na ausência de estímulos e, apesar de não apresentar função digestiva, é a principal responsável pela lubrificação da mucosa oral e orofaringe ao longo do dia. Esta última possui como principal característica uma constituição viscosa, devido à alta concentração de mucinas de baixo e alto peso molecular (Sreebny, 2000; Mese & Matsuo, 2007).

Outros fatores podem afetar a secreção salivar, tanto em volume quanto em sua composição (Edgar, O'Mullane & Dawes, 1996; Humphrey,& Williamson, 2001). O uso de medicamentos, idade, gênero, ciclo circadiano, fatores psíquicos, endócrinos, nutricionais e metabólicos. Além disso, doenças locais e/ou sistêmicas que afetam as glândulas salivares foram relacionadas a alterações salivares quantitativas e qualitativas (Dawes, 1972; Farnaud et al., 2010).

Nos últimos anos, diversos trabalhos publicados deram ênfase às alterações salivares relacionadas ao Transplante de Células-Tronco Hematopoéticas (TCTH) (Nagler et al., 1996; Nagler & Nagler, 2003; Nagler & Nagler, 2004; Alborghetti et al., 2005; Soares et al., 2005; Coracin et al., 2006; Imanguli et al., 2007; Laaksonen et al., 2011; Bassim et al., 2012; Hull et al., 2012; Daikeler et al., 2013; Paczesny, 2013; Soares et al., 2013; Barrach et al., 2014; Gomes et al., 2014; Boer et al., 2015).

O TCTH é uma modalidade terapêutica amplamente utilizada para a cura de doenças hematológicas ou de outros tecidos, de insuficiências medulares, e dos distúrbios congênitos da hematopoiese (Thomas, 1975). O TCTH tem como base a substituição de uma medula óssea doente ou deficiente por uma medula nova e sadia, através da infusão de células progenitoras hematopoéticas (Thomas, 1975; Santos, 1983; Ferrara & Deeg, 1991).

O TCTH pode ser classificado quanto ao tipo de doador (alogênico, singênico, autólogo); quanto ao grau de parentesco (aparentado ou não-aparentado); quanto ao grau de histocompatibilidade humana (HLA – *Human Leucocyte Antigen)*; quanto à fonte das células progenitoras hematopoéticas

infundidas (sangue periférico, medula óssea, e cordão umbilical); e quanto ao regime de condicionamento empregado (mieloablativo, ou de intensidade reduzida) (Amos & Gordon, 1995).

Apesar dos avanços alcançados ao longo das últimas décadas no campo do TCTH alogênico, esta modalidade de tratamento ainda está associada a significativa morbidade (Majhail et al., 2008; Gratwohl et al., 2010).

A cavidade oral é um sítio altamente susceptível a efeitos diretos e indiretos relacionados ao TCTH (Raber-Durlacher et al., 2004). Cerca de 80% dos pacientes submetidos a este procedimento podem apresentar complicações orais (Woo et al., 1993). Estas podem ser classificadas em agudas e tardias de acordo com o momento em que se manifestam e o tipo de sequela gerada (Schubert & Peterson, 2004). As complicações orais agudas mais frequentes incluem: mucosite oral, infecções recorrentes, dor, e sangramento. Tardiamente, a Doença do Enxerto-Contra-Hospedeiro crônica (DECHc) oral, cáries disseminadas, disfunções do paladar, além da disfunção salivar são as alterações mais observadas (Hull et al., 2012; Daikeler et al., 2013; Barrach et al., 2014; Haverman et al., 2014).

Alterações salivares no contexto do TCTH alogênico foram relacionadas em grande parte aos regimes de condicionamento empregados, à Irradiação Corpórea Total (ICT), às medicações utilizadas no tratamento de suporte, e principalmente à presença da DECH crônica (Chaushu et al., 1995; Barrach et al., 2014; Haverman et al., 2014). Vários trabalhos mostraram que estas alterações salivares são decorrentes de modificações do padrão histológico das glândulas salivares, que podem apresentar fibrose acinar, alterações ductais, e perda de parênquima (Nagler & Nagler, 2003; Alborghetti et al., 2005; Soares et al., 2005; Shulman et al., 2006; Soares et al., 2013)

As principais manifestações clínicas orais relacionadas às alterações salivares em pacientes submetidos ao TCTH alogênico incluem: hipossalivação e xerostomia (Daikeler et al., 2013); a perda ou alterações do paladar (Boer et al., 2010); cáries generalizadas (Castellarin et al., 2012); infecções fúngicas, virais e

bacterianas recorrentes (Palmason et al., 2011); além de outras complicações comumente observadas em pacientes com um fluxo salivar reduzido (Sreebny, 2000). Essas complicações aumentam significativamente a morbidade dos pacientes afetados, que apresentam uma significativa redução de sua qualidade de vida, além de estarem associadas a aumentos expressivos nos custos do tratamento de suporte (Raber-Durlacher et al., 2004; Daikeler et al., 2013).

O Grupo de Odontologia e Medicina Oral da Unidade de Transplante de Células-Tronco Hematopoéticas, Hemocentro de Campinas/Hospital de Clínicas – Unicamp, vem, ao longo das últimas décadas, estudando as alterações orais em pacientes submetidos ao TCTH alogênico (Alborghetti et al., 2005; Soares et al., 2005; Coracin et al., 2006; Pereira et al., 2007; Boer et al., 2010; Pimentel et al., 2010; Mawardi et al., 2011; Noce et al., 2011; Soares et al., 2013, Gomes et al., 2014; Noce et al., 2014; Boer et al., 2015;). Esses estudos tiveram como objetivo também o reconhecimento das alterações em glândulas salivares associadas ao TCTH alogênico, correlacionando os aspectos histopatológicos e imagiológicos*, com sua repercussão clínica.

Embora estudos tenham descrito a presença de alterações salivares quantitativas após o TCTH alogênico (Chaushu et al., 1995; Laaksonen et al., 2011; Hull et al., 2012; Daikeler et al., 2013), a sua influência sobre as alterações precoces** do fluxo salivar não foi completamente compreendida. Soma-se a isso a inexistência de um critério padronizado para a avaliação clínica da hipossalivação nesta população de pacientes, o que dificulta a análise clínica diagnóstica do envolvimento das glândulas salivares na DECH crônica.

Portanto, o objetivo deste trabalho foi o de avaliar a influência do TCTH alogênico sobre as alterações precoces do fluxo salivar, e, secundariamente, validar critérios clínicos utilizados para o diagnóstico de hipossalivação nesta população de pacientes.

Nota do autor:

* O termo imagiológico é relativo a imagiologia, “conjunto de técnicas utilizadas na obtenção de imagens para estudo do corpo humano”.

** O termo precoce será empregado no sentido de “mais cedo do que o esperado”, “adiantado”.

CAPÍTULO 1

Very early salivary flow changes in allogeneic hematopoietic stem cell transplantation

Abstract

Objective. *Salivary dysfunction is a recognized complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). The aim of this study was to analyze the influence of allo-HSCT on the very early salivary flow changes.*

Study Design. *This was a prospective study that enrolled 69 adult patients undergoing their first allo-HSCT between the years 2010 to April 2014. The unstimulated whole saliva and clinical data were collected before patients started on the pretransplant conditioning regimens and between the days D+8-10 posttransplantation. In addition, patients were submitted to an oral health exam, and to a clinical assessment of hyposalivation in both studied periods. Oral mucositis (OM) severity was evaluated according to the WHO criteria. Chi-square or Fischer's test, besides of the Mann-Whitney U Test were applied according to the variable type. Pared T-test was used to compare continuous variables in different periods.*

Results. *An increase of the unstimulated whole saliva flow rate (UWSFR), and the worsening of gingival index were observed at days D+8-10 posttransplantation. A positive correlation was found between an increase of the UWSFR and a greater severity of OM, the use of total parenteral nutrition and with vomiting episodes. Although hyposalivation was not a frequent finding among the studied population, a reduced UWSFR was observed in women, and in the group of patients with a high risk underlying disease.*

Conclusion. *The clinical impact of the conditioning regimens toxicity showed through the OM severity seemed to have influenced the very early salivary flow changes. If the influence of HSCT on the very early salivary changes could be better characterized, as well as its correlation with short and long-term oral outcomes of HSCT patients, the proper clinical management could be improved.*

Key words: *salivary dysfunction; xerostomia; allogeneic hematopoietic stem cell transplantation*

Introduction

Saliva plays a critical role in oral homeostasis[1]. Disruptions in the quantity and composition of salivary secretions may lead to deleterious consequences for the oral health[2].

Salivary dysfunction is a recognized complication of allo-HSCT [3-5]. In this population, salivary dysfunction can be found as a result of initial damage caused by the conditioning regimens toxicity, alone or in combination with total-body irradiation (TBI), and to the presence of oral chronic graft-versus-host disease (cGVHD)[6-8].

In allo-HSCT patients, late histological alterations in salivary glands are mostly associated with the presence of cGVHD, leading to hyposalivation, oral dryness and other mucosal pathologies[9-12]. According to the *NIH Consensus Criteria* (2006), the presence of lymphocytic infiltration, damaged intralobular ducts, fibroplasia in periductal stroma, and inflammation with subsequent destruction of acinar tissue are considered histological characteristics for the diagnosis of cGVHD in minor salivary glands[13]. However, interstitial fibrosis was also observed in minor salivary gland biopsies at the onset of cGVHD, suggesting to be an effect of an earlier salivary gland injury, probably due to the conditioning regimens toxicity, as previously mentioned[6-8;10;11].

Symptoms of oral dryness arise as a relevant issue potentially harmful for the quality of life in HSCT patients[14]. When a reduced salivary flow rate was present in this group of patients, xerostomia[15], recurrent oral infections[12], increased salivary viscosity[16], oral pain[17], taste disorders[18], and other common sequelae of patients with hyposalivation were reported at different periods of transplantation[6;16;19]. It brings difficulties in defining the proper clinical management of these oral complications, related to salivary changes.

The aim of the present study was to analyze the influence of allo-HSCT on the very early salivary flow changes.

Materials and methods

Study population

A prospective study was performed from September 2010 to April 2014 at the HSCT Unit, of the University of Campinas, São Paulo, Brazil. The study enrolled 69 non-consecutive adults patients, with malignant and non-malignant hematological diseases undergoing their first related or unrelated allogeneic HSCT. The graft source was from the bone marrow or from peripheral blood. Conditioning regimens and GVHD prophylaxis were selected according to ongoing protocols at the University Hospital. Overall patient and transplant characteristics are shown in **Table 1**.

Demographics, underlying disease, donor characteristics, GVHD prophylaxis, conditioning regimens protocols, body mass index at admission, use of total parenteral nutrition (TPN), blood and/or platelets transfusions, and the presence of fever or vomiting episodes at evaluations days were obtained from medical records, available either through paper or by electronic registries.

A written informed consent was obtained from all participants or from their legal representatives before participation. Patients who did not consent to their participation in the study and those who had previously received head and neck radiation therapy were excluded. The study was approved by the Research Ethics Committee from the School of Medical Sciences, at University of Campinas, São Paulo, Brazil (process n. 1297/2010).

Oral health exam

Oral health examinations were performed before the patients were started on the pretransplant conditioning regimens for HSCT (baseline data) and between the days D+8-10 posttransplantation.

Table 1. Characteristics of 69 allogeneic HSCT patients

Characteristics	***n* = 69**
Age at transplant, median (range)	46 (21-68)
Male, no. (%)	39 (57)
Diagnosis	
Acute leukemias / Myelodysplastic syndrome, no. (%)	30 (44)
Chronic leukemias and Myelofibrosis, no. (%)	13 (19)
Lymphomas and Multiple Myeloma, no. (%)	19 (27)
Non-malignant disease*, no. (%)	6 (9)
Other	1 (1)
Disease risk	
Standard, no. (%)	30 (43)
High risk**, no. (%)	39 (57)
Donor characteristics	
Age, median (range)	42 (20-72)
Female→ Male, no.(%)	17 (24.6)
Donor Source	
Bone marrow, no. (%)	21 (30)
Peripheral blood, no. (%)	48 (70)
HLA-match	
HLA-identical related, no. (%)	57 (83)
HLA-matched unrelated, no. (%)	12 (17)
Conditioning regimen	
Myeloablative, no. (%)	41 (59)
Reduced intensity, no. (%)	28 (41)
TBI-based, no. (%)	15 (22)
GVHD prophylaxis	

CsA/MTX, no. (%)	58 (84)
CsA/MMF, no. (%)	11(16)

HLA human leukocyte antigen, *TBI* total-body irradiation, *GVHD* graft-versus-host disease, *CsA* cyclosporine, *MTX* methotrexate, *MMF* mycophenolate mofetil.

*Non-malignant disease included aplastic anemia and paroxysmal nocturnal hemoglobinuria

**High risk diseases included acute leukemias in second remission after a short first remission (<3 years for patients with acute lymphocytic leukemia, and <1 year for patients with acute myelocytic leukemia), or in third remission and beyond, or in relapse chronic myelogenous leukemia in accelerated phase, juvenile myelomonocytic leukemia, or lymphoma in relapse or refractory disease

The oral health status was clinically assessed through the evaluation of all permanent teeth using the Decayed-Missing-Filled Teeth (DMFT) index[20]; by the presence of superficial debris and plaque thickness on the gingival one third areas of six selected teeth according to Silness and Löe Plaque Index (PI)[21], and by the degree of gingival inflammation of six selected teeth, according to Silness and Löe Gingival Index (GI)[22]. Oral Mucositis (OM) severity was evaluated according to the World Health Organization (WHO) criteria[23].

Patients were instructed to maintain the oral hygiene, which consisted in teeth brushing, regular flossing, and use of 0.12% non-alcoholic chlorhexidine mouthwashes until discharge. Patients were regularly followed by the oral medicine team during and after the studied period. In this study, all oral examinations were done by authors VRT and CCB.

Study of salivary secretion

The unstimulated whole saliva was collected before patients started on the pretransplant conditioning regimens (baseline data) and between the days D+8-10 posttransplantation. Saliva samples were collected during the morning period (10 a.m. to 11 a.m.) in order to avoid the influence of the circadian rhythm[24]. Patients were advised to prevent eating, drinking (except water), smoking, brushing teeth or using any type of chewing gum at least one hour prior to saliva collection[25].

Once asked to sit, patients were requested to swallow the entire volume of saliva present in their mouths, and to avoid speaking or swallowing during the procedure. The Unstimulated Whole Saliva Flow Rate (UWSFR) was determined by spitting every 30 seconds for 5 minutes into a pre-weighed sterilized glass tube. The whole saliva volume collected was then measured, and assuming that 1g = 1mL, the UWSFR was expressed in mL/min[26;27]. Hyposalivation was considered when the UWSFR was ≤ 0.2 mL/min[28].

Clinical assessment of hyposalivation

The clinical assessment of hyposalivation, was performed in both studied periods, which was composed by four objective clinical criteria and by four subjective questions[11;18]. The objective clinical criteria included: *1.Higher adherence of the wood spatula to the jugal mucosa*; *2.No saliva pooling in the anterior floor of mouth*; *3.Increased viscosity and thickness of saliva*; *4.Absence of salivary secretion of the parotid duct under manual pressure* (ASSPDUMP). The subjective questions included: *1.Does your mouth feels dry? 2.Do you have any pain in your mouth? 3.Did you feel any change in taste? 4.Did you have any oral hypersensitivity during food intake?.*

Statistical analysis

Chi-square or Fischer's test, besides of the Mann-Whitney U Test were applied according to the variable type. Pared T-test was used to compare continuous variables in different periods. P-value ≤ 5% was considered as significant. Statistical analysis was performed using SPSS software (v.15; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Sixty-nine patients were enrolled with a median age of 46 years old (range 21-68), and 39 (57%) patients were males. Forty-one (59%) patients received a myeloablative conditioning regimen. Total-body irradiation (TBI) was administered in 15 (20%) patients as part of the conditioning regimen protocol. Forty-eight (70%) patients received peripheral blood cells as graft source, and GVHD prophylaxis was specific to the underlying disease. Thirteen (19%) patients had been previously submitted to an autologous HSCT.

Oral health exam

No variation was observed in the mean DMFT score during the studied periods, 17.8 (4-32). The mean Plaque Index (PI) was 0.5 (0-3), and 0.67 (0-3) at baseline and at days D+8-10, respectively, (p=0.12). The mean Gingival Index (GI) was 0.4 (0-3), and 0.55 (0-3) at baseline and at days D+8-10, respectively (p=0.03).

Oral mucositis

Forty-six out of 69 (67%) patients developed oral mucositis (OM), and 27/69 (39.1%) patients presented a severe OM (grade III-IV, *WHO* criteria). Higher scores of OM were significantly correlated with Myeloablative conditioning regimens (p=0.006), with TBI exposure (p=0.01), and with four clinical criteria of hyposalivation: *oral pain*, *oral hypersensitivity during food intake*, *an altered taste perception*, *increased viscosity and thickness of saliva*, and with the *higher adherence of the wood spatula to the jugal mucosa*, ($p<0.05$).

Study of salivary secretion

Hyposalivation, as previously defined as UWSFR ≤0.2 mL/min, was not a frequent finding in the studied periods, including in patients who have received a previous autologous HSCT. Hyposalivation was found only in 5/69 (7.2%) patients at baseline, and in 8/69 (11.6%) patients at days D+8-10. Overall, a reduced UWSFR was observed in women (p=0.02), and in the group of patients with a high

risk underlying disease (p=0.03). When age was dichotomized into two groups (21-44, and ≥45 years), a decreased UWSFR was observed in the group of patients with ≥45 years old, however, with no statistical difference.

The mean UWSFR at baseline was 0.54 mL/min (range 0.11-1.22) and at days D+8-10 was 0.8 mL/min (range 0.03-6.7), showing a significant increase of the UWSFR at the second salivary assessment (p=0.03) (**Fig. 1, Table 2**). The increase of the UWSFR was significantly correlated with OM severity (p=0.02), with TPN (p=0.03), and with vomiting episodes (p=0.03) at the day of saliva collection.

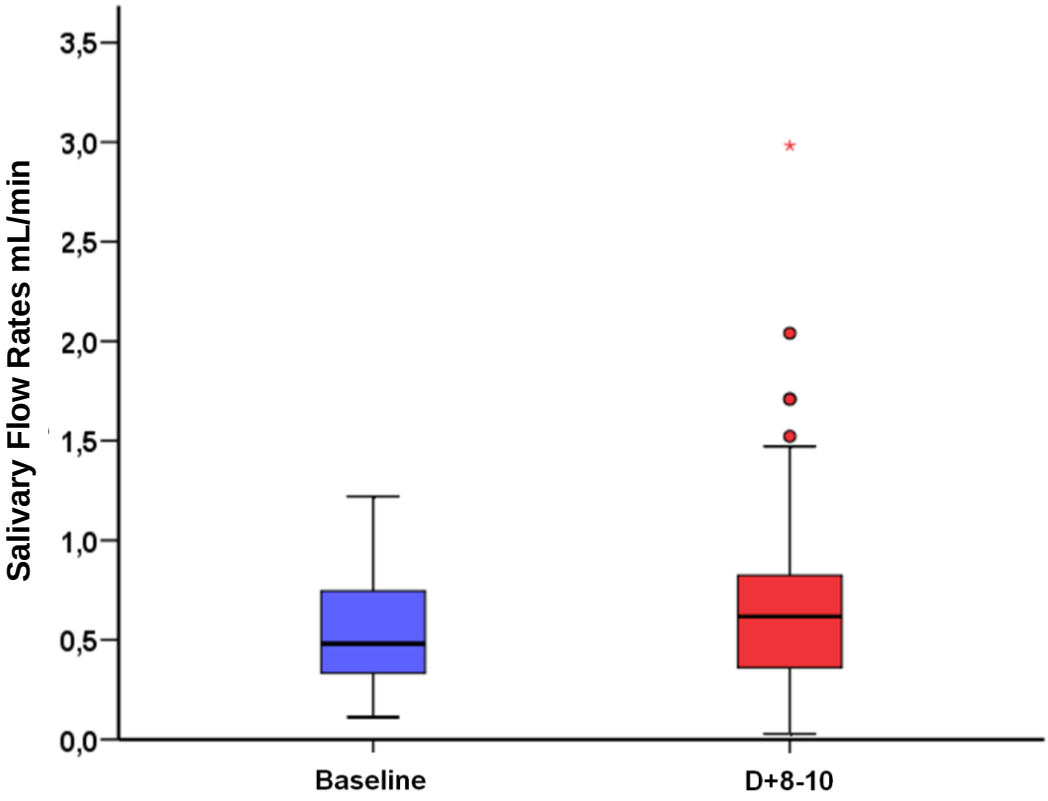

Figure 1 - Unstimulated whole saliva flow rates (mL/min) according to baseline and D+8-10 assessments (p=0.03).

Table 2 Clinical assessment of hyposalivation in 69 allogeneic HSCT patients pre (baseline) and post-HSCT (days D+8-10).

Objective parameters	**Pre-HSCT (baseline)**	**Post-HSCT (days D+8-10)**	***p – value***
UWSFR, mean (mL/min)	0.54	0.8	**0.03**
Higher adherence of the wood spatula, no. (%)	49 (71)	49 (83)	**0.001**
No saliva pooling in the anterior floor of mouth, no. (%)	19 (28)	14 (24)	0.17
Increased viscosity and thickness of saliva, no. (%)	9 (13)	33 (56)	0.44
ASSPDUMP, no. (%)	32 (46)	29 (49)	**0.009**
Missing data, no. (%)	0	10 (14)	**-**
Subjective parameters			
Oral pain, no. (%)	3 (4)	38 (63)	0.99
Altered taste perception, no. (%)	9 (13)	28 (47)	0.45
Oral hypersensitivity during food intake, no. (%)	2 (3)	43 (72)	0.99
Xerostomia, no. (%)	19 (28)	30 (50)	0.77
Missing data, no. (%)	0	9(13)	-

UWSFR unstimulated whole saliva flow rate, *ASPDUMP* absence of the saliva secretion of the parotid duct under manual pressure

No significant correlation was found between the UWSFR variation and the conditioning regimens protocols, neither with TBI exposure, nor with the graft source. Also, overweight (BMI>25), the presence of fever and blood or platelets transfusions at the day of salivary assessments had no influence on the salivary flow rates results.

Clinical assessment of hyposalivation

The observer's clinical impression of the objective parameters of hyposalivation showed that the *higher adherence of the wood spatula to the jugal mucosa* was the most noted clinical criteria in both periods. Although not statistically significant, the objective parameter *increased viscosity and thickness of saliva* ranged from 9/69 (13%) patients to 33/69 (56%) patients between the two assessments. A decreased UWSFR was correlated with the clinical criteria of hyposalivation: a*bsence of salivary secretion of the parotid duct under manual pressure* (p=0.05), and with n*o saliva pooling in the anterior floor of mouth*, (p=0.02), at baseline and at days D+8-10, respectively.

Xerostomia was the main patient´s complaint at baseline. It was present in 19/69 (28%) patients, followed by a*n altered taste perception* 9/69 (13%), *oral pain* 3/69 (4%), and o*ral hypersensitivity during food intake* 2/69 (3%). *Oral hypersensitivity during food intake* was the main patient´s complaint at days D+8-10, affecting 43/69 (72%) patients, followed by *oral pain* 38/69 (63%), *xerostomia* 30/69 (50%), and *an altered taste perception* 28/69 (46.7%). Overall results of the clinical assessment of hyposalivation were summarized on **Table 2.**

Discussion

Changes in salivary secretion and constitution in acute stages following allo-HSCT are predominately attributed to conditioning regimens and TBI exposure[6]. Common oral complications of these salivary changes can be expressed through the development of xerostomia and hyposalivation slightly before transplantation, and mostly as an oral late effect related to cGVHD[3;14]. However, Chausu et al.

(1995) observed a reduced salivary secretion toward the end of the preconditioning period, followed by a gradual salivary flow rate reconstitution over the first 5 days posttransplantation. This observation are consistent with the findings of the herein study, which demonstrated an increase of the UWSFR on days D+8-10 posttransplantation when compared to baseline assessments. It may suggest the influence of conditioning regimens toxicity on the salivary gland function at the very early phase posttransplantation. In addition, vomiting and use of TPN at the days of saliva collection were also correlated with an increase of the UWSFR. Vomiting and use of TPN are well known adverse events of HSCT[29]. The results found in this study may reinforce the role of the conditioning regimens toxicity in modulating acute events in HSCT.

Inflammatory processes are the key in the pathobiology of the most oral complications in HSCT[30]. Oral Mucositis (OM) is an inflammatory-driven process of the oral mucosa considered one of the most important oral complications of cancer therapy[30;31]. OM can affect 75-100% of HSCT patients and its severity is associated with myeloablative conditioning regimens and TBI exposure[32]. In this present study, OM was observed in 46/69 (67%) patients and it was correlated with an increase of the UWSFR (p=0.02), with myeloablative conditioning regimens (p=0.006), with TBI exposure (p=0.01), and with the worsening of gingival index (p=0.03). The association between the salivary flow and the development and progression of OM is unclear[2]. Several studies discussed the possibility of an increased salivary flow playing a role in OM severity[2;33-35]. It is explained by the saliva carrier properties, which can transport chemotherapeutic drugs used in conditioning regimens for HSCT[33]. Thus, the direct diffusion to the basal epithelium of cytotoxic drugs contained in saliva can affect the rapidly dividing cells[2]. In the other hand, the opposite was showed by McCarthy *et al* (1988), which observed an association between a reduced salivary flow and the occurrence of OM episodes[35;36]. Despite that, we speculate that the association found in this present study between the increase of the UWSFR and OM severity may be related to changes in salivary constitution. Immunoglobulins, proteins,

electrolytes and non-specific host defenses present in saliva can be changed in the setting of HSCT[37;38]. These changes can result in a more viscous saliva during the OM period[16], besides the worsening of the swallowing physiology[39], followed by increasing the salivary resting volume in the oral cavity[15]. It may be confirmed in the present study by the positive correlation between the OM severity and the hyposalivation criteria: *increased viscosity and thickness of saliva* (p=0.009), and by the increase of the *higher adherence of the wood spatula to the jugal mucosa (*p=0.001) at days D+8-10. Thus, although the swallowing physiology of patients was not the objective of this study, these alterations may reflect the clinical impression of an increased salivary secretion due to the presence of a more viscous saliva in the oral cavity observed at days D+8-10 posttransplantation.

Subjective symptoms of oral dryness, such as xerostomia, oral pain, and an altered taste perception have a significant impact on the quality of life in HSCT population[3;14;16]. Although xerostomia was one of the most frequent patients' complaints in both studied periods (28% and 50%, at baseline and at days D+8-10, respectively), its presence was concomitant with an increase of the UWSFR at the second salivary assessments. Xerostomia can occur when the salivary flow rate is less than the rate of fluid loss from the mouth by evaporation during mouth breathing, and by absorption through the oral mucosa[40]. In this studied group, the increased xerostomia complaint at the very early phase of transplantation could be related to the changes in saliva constitution, to the alterations in the absorption capacity of the oral mucosa, and/or by the increased mouth breathing due to the presence of oral pain and OM at the days D+8-10. These factors could contribute to an increased absorption and evaporation of saliva water, besides the lower capacity of saliva lubrication, leading to symptoms of oral dryness.

Variations in salivary flow rates had been linked to individual patient characteristics, such as age, gender, body mass index (BMI), or with some diseases, which leads to differences in salivary secretion[25;28;41]. Agreeing with this, in the present study, a lower overall UWSFR was correlated with the group of patients with a high risk disease (p=0.03), and with women (p=0.02). Nevertheless,

within the limits of the present study, the influence of other factors, such medications, could not be analyzed, but this important topic remains for further investigations.

Conclusions

In summary, hyposalivation was not a frequent finding among the studied population in both evaluated periods. An increased UWSFR was observed at day D+8-10 posttransplantation. Also, a positive correlation was found between an increase of the UWSFR and a greater severity of oral mucositis, the use of total parenteral nutrition, and with vomiting episodes. These results may demonstrate the clinical impact of the conditioning regimens toxicity on the very early salivary flow changes. Further studies should be performed in order to better characterize the influence of HSCT on the early salivary changes, and its implication on short and long-term oral outcomes, as well as its proper clinical management.

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The authors declare no conflicts of interest.

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CAPÍTULO 2

Validation of clinical criteria for the diagnosis of hyposalivation and development of an oral dryness score in allogeneic hematopoietic stem cell transplant patients

Abstract

Background: *Hyposalivation is a common oral complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT).*

Objective: *To validate eight clinical criteria used for the diagnosis of hyposalivation in the allo-HSCT population.*

Methods: *This was a cross-sectional study that enrolled 120 patients undergoing their first allo-HSCT between the years 2006 and 2014. The oral dryness assessments were performed using four objective clinical criteria and four subjective questions during different periods of the HSCT. The unstimulated whole saliva flow rate (UWSFR) was measured from each patient after the clinical evaluation. Hyposalivation was defined when UWSFR was <0.2 mL/min. Cronbach's alpha test was applied in order to measure the internal consistency and satisfactory reliability of the eight clinical criteria.*

Results: *Five of the eight clinical criteria of hyposalivation were correlated with a decreased UWSFR. A scoring system called Oral Dryness Score (ODS) was developed using the five selected criteria, with each criterion scored as one point for a total score of 0–5. The ODS was dichotomized between 0–1 and 2–5 scores, respecting its behavior according to the UWSFR. After dichotomization, 66 (55%) patients presented 0–1 scores, with a UWSFR median of 0.65 mL/min (0.1–9.0 mL/min), and 54 (45%) patients presented 2–5 scores with a UWSFR median of*

0.34 mL/min (0.01–6.7 mL/min). A higher ODS was correlated with a decreased UWSFR (p=0.006, r=-25%), confirmed by the Mann-Whitney U test (p<0.0001).

Conclusion: *The ODS was correlated with a decreased UWSFR, proving to be a reliable tool for the diagnosis of hyposalivation in the allo-HSCT population.*

Key words: *salivary flow rate; xerostomia; allogeneic hematopoietic stem cell transplantation*

Introduction

Despite the great advances made over the past decades in the field of allo-HSCT, this procedure is still associated with significant morbidity and mortality[1]. Allo-HSCT is also associated with debilitating long-term effects involving oral tissues and/or salivary glands, such as graft-versus-host disease (GVHD)[2]. The assessment of glandular function was included, among other oral complications, in the NIH Consensus Project (2005) as part of the routine oral evaluation for chronic GVHD diagnosis[3]. Although early and late salivary changes were studied in allo-HSCT patients[4–9], there is no validated method for oral dryness assessment in this population that could be simple and easy-to-perform by different health care professionals directly involved in the care of these patients. In this study, we aimed to perform a validation of eight hyposalivation criteria that have been used during the past several years in our HSCT Unit as a clinical tool for the diagnosis of hyposalivation.

Methods

This was a prospective cross-sectional study that enrolled non-consecutive patients undergoing their first allo-HSCT during the years 2006 to 2014 at the HSCT Unit, of the University of Campinas (UNICAMP), São Paulo, Brazil. This study was approved by the Research Ethics Committee from the School of Medical Sciences, at the University of Campinas (processes n. 497/2005 and n. 1297/2010). In addition, a written informed consent was obtained from all patients or from their legal representatives before participation. Patients who did not consent to their participation in the study and those who had previously received head and neck radiation therapy were excluded.

Patients were submitted to a regular oral examination at different periods, between five to 4407 days after allo-HSCT, as a part of the long-term monitoring standardized assessments done by VRT and CCB, from the Oral Medicine team. The clinical assessment of hyposalivation was performed using four objective

clinical criteria and four subjective questions[6;10]: The objective clinical criteria included: *1.Higher adherence of the wood spatula to the jugal mucosa; 2.No saliva pooling in the anterior floor of mouth; 3.Increased viscosity and thickness of saliva; 4.Absence of the salivary secretion of the parotid duct under manual pressure* (ASSPDUMP). The subjective questions included: *1.Does your mouth feels dry?; 2.Do you have any pain in your mouth?; 3.Do you feel any change in taste?; 4.Did you have any oral hypersensitivity during food intake?.*

After the assessment of hyposalivation, the unstimulated whole saliva was collected. Saliva samples were collected during the morning period (10 a.m. to 11 a.m.) in order to avoid the influence of the circadian rhythm[11]. Patients were previously advised to prevent eating, drinking (except water), smoking, brushing teeth or using any type of chewing gum at least one hour prior to saliva collection.

Once asked to sit, patients were requested to swallow the entire volume of saliva present in their mouths, and to avoid speaking or swallowing during the procedure. The unstimulated whole saliva flow rate (UWSFR) was determined by spitting every 30 seconds for five minutes into a pre-weighed sterile glass tube. The whole saliva volume collected was then measured, and assuming that 1g = 1mL, the UWSFR was expressed in mL/min[12;13]. Hyposalivation was considered when the UWSFR was <0.2 mL/min[14].

Statistical analysis

The median and range were used to summarize the criteria, and a box plot was created to depict the results. Cronbach's alpha test was used in order to measure the internal consistency and satisfactory reliability of all clinical criteria of hyposalivation[15]. Considering a minimum value of 0.5 for the Cronbach's alpha coefficient, a 5-item screening tool was selected from all criteria of hyposalivation. The five selected clinical criteria of hyposalivation included: *1.Higher adherence of the wood spatula to the jugal mucosa; 2.No saliva pooling in the anterior floor of*

mouth; 3.Increased viscosity and thickness of saliva; 4.Absence of the salivary secretion of the parotid duct under manual pressure; 5.Does your mouth feels dry?.

One point was given for each item on the 5-point scoring system, now called the Oral Dryness Score (ODS). Mann-Whitney *U* test was applied to analyze the UWSFR distribution among the dichotomized scores, in addition to the Pearson's correlation coefficient. All analyses were carried out using SPSS software (v.15; SPSS Inc., Chicago, IL, USA).

Results

A total of 120 patients were enrolled with a median age of 45 years old (14-68), and 69 (58%) patients were males. Myeloablative conditioning protocols were given to 83 (69%) patients. The majority of patients (63%) received peripheral blood stem cells as the graft source, and GVHD prophylaxis was specific to the underlying disease. Twenty-three patients (19%) presented oral chronic GVHD during the oral examinations. Overall patient and transplant characteristics are shown in **Table 1**.

Table 1 – Patient and Transplant Characteristics

Characteristics	**n = 120**
Age at transplant, median (range)	44 (14.2–68)
Male, no. (%)	69 (58)
Diagnosis	
Acute leukemias/Myelodysplastic disorders, no. (%)	51 (43)
Chronic leukemias and Myelofibrosis, no. (%)	35 (29)
Lymphomas and Multiple Myeloma, no. (%)	24 (20)

Non-malignant diseases*, no. (%)	10 (8)
Conditioning regimen	
Myeloablative	83 (69)
Reduced Intensity	37 (31)
Source of stem cells	
Peripheral blood, no. (%)	76 (63)
Bone marrow, no. (%)	44 (37)
GVHD prophylaxis	
CsA/MTX, no. (%)	101 (84)
CsA/MMF, no. (%)	19 (16)

GVHD Graft-Versus-Host Disease, *CsA* cyclosporine, *MTX* methotrexate, *MMF* mycophenolate mofetil.
*Non-malignant disease included severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, and sickle cell anemia.

The *higher adherence of the wood spatula to the jugal mucosa* was the most expressed clinical criteria of hyposalivation, present in 91 (76%) patients. This was followed by ASSPDUMP (53%), *increased viscosity and thickness of saliva* (50%), and by *no saliva pooling in the anterior floor of mouth* (42%). *Oral hypersensitivity during food intake* was the main complaint, reported by 70 (58%) patients, followed by *an altered taste perception* (54%), *xerostomia* (53%), and by *oral pain* (46%).

The overall distribution of the ODS was as follows: score of 0, 1, 2, 3, 4, and 5 were present in 13 (11%), 16 (13%), 25 (21%), 24 (20%), 28 (23%), and 14 (12%) patients, respectively. The overall UWSFR median was 0.52 mL/min (0.01–9.0 mL/min). The ODS was dichotomized between 0–1 scores and 2–5 scores, respecting its behavior according to UWSFR (**Figure 1**). After dichotomization, 66

(55%) patients were included in the 0–1 scores, with an UWSFR median of 0.65 mL/min (0.10–9.0 mL/min), and 54 (45%) patients were included in the 2–5 scores with an UWSFR median of 0.34 mL/min (0.01–6.7 mL/min). Thus, patients presenting a higher ODS tend to have decreased UWSFR (p=0.006, r=-25%), as confirmed by the Mann-Whitney *U* test (p<0.0001). The overall distribution of the ODS groups and its relationship to UWSFR is shown in **Table 2**.

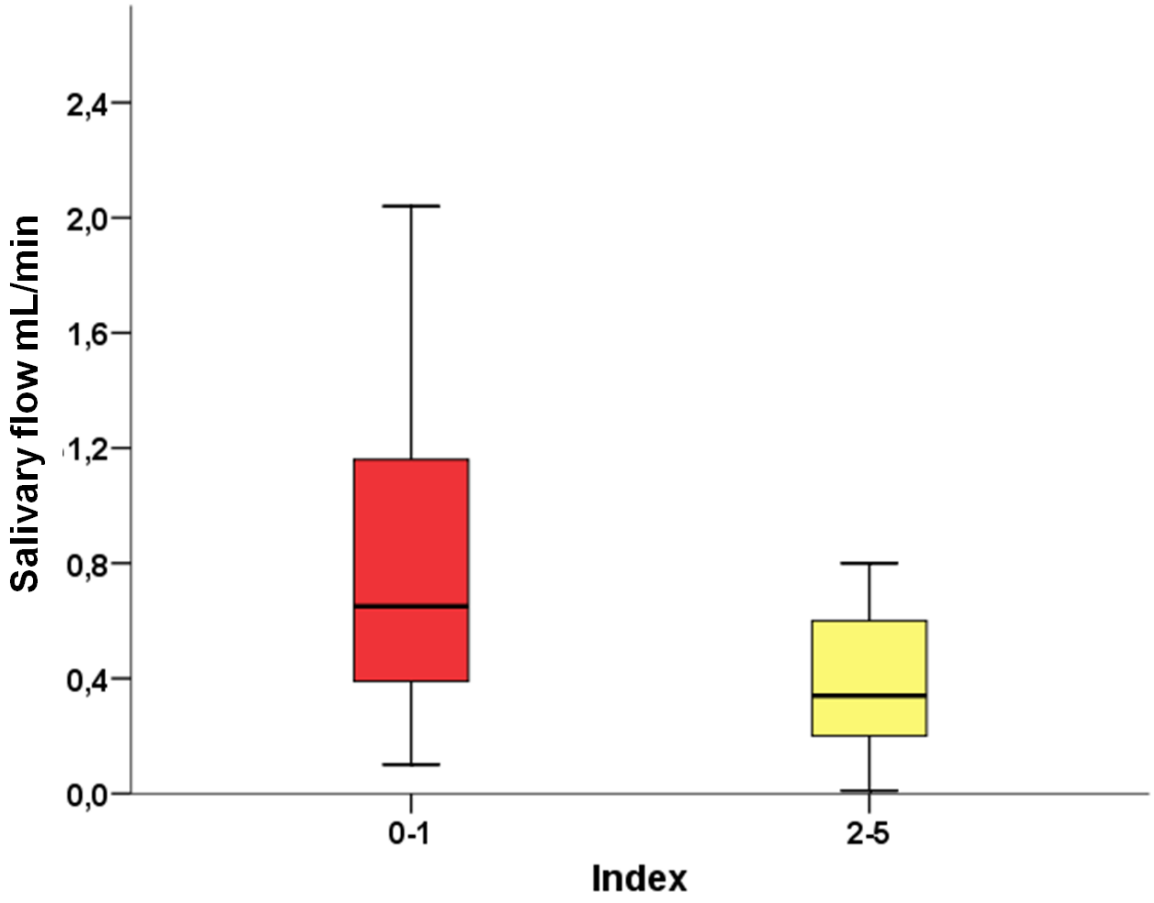

Figure 1 - Unstimulated whole saliva flow rates (mL/min) distribution, according to the 0–1 and 2–5 Oral Dryness Score (*p*=0.0001).

Table 2 – *Oral Dryness Score* (ODS) distribution according to dichotomization of the scores and its relationship to unstimulated whole saliva flow rates.

ODS	n (%)	Mean Salivary flow rate (mL/min)
0–1 scores	66 (55)	0.65 (0.10–9.0)
2–5 scores	54 (45)	0.34 (0.01–6.7)
Total	120 (100)	0.52 (0.01–9.0)

Discussion

This study aimed to validate eight clinical criteria for the diagnosis of hyposalivation used in our institution over the past several years. The results showed that five of eight clinical criteria used regularly had a positive correlation with a decrease of the UWSFR measurements, regardless the moment that the test was applied. The five selected clinical criteria were composed by four objective criteria and by a subjective question: *1.Higher adherence of the wood spatula to the jugal mucosa; 2.No saliva pooling in the anterior floor of mouth; 3.Increased viscosity and thickness of saliva; 4.Absence of the salivary secretion of the parotid duct under manual pressure; 5.Does your mouth feels dry?*. Thus, the selected criteria were grouped and validated as an Oral Dryness Score (ODS).

There are already some questionnaires and indices for the assessment of hyposalivation in the literature[12;16]. Most of them consider a lot of items for possible evaluation, as well as specific tests commonly performed by dentists and/or by oral medicine specialists. Nevertheless, in an HSCT unit, dentists and/or oral medicine specialists are not the only ones that can examine the oral cavity. Hence, a reliable score system that could be performed by different health care professionals directly involved in the HSCT patient's care would be welcomed. The

ODS could be considered a simple method for making a criteria-based diagnosis of hyposalivation. The ODS was shown to be able in indicating patients with a decreased UWSFR and could be performed by different health care professionals that are part of the HSCT team.

It is important to note that, in this study, the transplantation characteristics, such as the conditioning regimens, the source of progenitor cells, age, sex, medications used and other oral or systemic diseases, such as chronic GVHD, which could have a direct influence on salivary flow rates, were not considered. Despite the influence of these conditions in salivary flow rates, the objective of this study was to validate the clinical criteria for the diagnosis of hyposalivation used on an everyday basis in the HSCT population, regardless of the day that the exam was performed.

The major limitation of this study could be the number of patients included. On the other hand, this study was just a part of an ongoing research project conducted by our team. The ongoing project has the intention to study salivary changes in the allo-HSCT context[6;8–10;17].

Having analyzed samples from different periods after allo-HSCT, our results minimize the weight of the evaluation period from transplantation. In summary, the ODS was built from the five validated clinical criteria of hyposalivation used over the past several years in our HSCT Unit. The ODS seems to be a reliable tool in identifying hyposalivation, regardless of the day of evaluation in patients who underwent allo-HSCT.

Conclusion

The five validated clinical criteria of hyposalivation (*1.Higher adherence of the wood spatula to the jugal mucosa; 2.No saliva pooling in the anterior floor of mouth; 3.Increased viscosity and thickness of saliva; 4.Absence of the saliva secretion of the parotid duct under manual pressure; and the question 5.Does your*

mouth feels dry?) were considered essential for building the ODS. A higher ODS was correlated with a decreased UWSFR.

An accurate diagnosis of a reduced salivary flow rate in allo-HSCT patients using an easy-to-perform and reliable clinical score may facilitate the early management of oral complications related to hyposalivation and minimize their impact on the quality of life of allo-HSCT survivors. More studies using these validated criteria as a scoring system should be performed in other HSCT groups.

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The authors declare no conflicts of interest.

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CONCLUSÕES

- O aumento do fluxo salivar observado nos dias D+8-10 pós-transplante pode estar relacionado ao impacto clínico gerado pela toxicidade aguda dos regimes de condicionamento utilizados no TCTH alogênico, que pôde ser observada através da prevalência e severidade da mucosite oral, e de outros eventos agudos como o uso de nutrição parenteral total e episódios de vômito.
- A hipossalivação não foi um achado comum na população estudada, mesmo naqueles pacientes que já haviam sido submetidos previamente a um TCTH autólogo.
- Os cinco critérios clínicos validados para o diagnóstico de hipossalivação (*1.Alta aderência da espátula de madeira na mucosa jugal; 2 Ausência de lago sublingual; 3.Saliva espessa e viscosa; 4.Ausência de secreção saliva após ordenha do ducto parotídeo; 5.Você sente sua boca seca?)* foram considerados essenciais para a construção do Sistema de Pontuação para Boca Seca (SPBS).
- O SPBS provou ser uma ferramenta confiável para o diagnóstico de hipossalivação na população estudada.
- Mais estudos devem ser realizados no intuito de se melhor compreender a influência do TCTH sobre as alterações salivares precoces, relacionando-as com as complicações orais agudas e tardias presentes em pacientes submetidos ao TCTH alogênico.
- Um diagnóstico precoce das alterações quantitativas salivares, aliado à análise individual do risco de complicações orais, poderá permitir um manejo preventivo adequado, essencial para o suporte de pacientes submetidos ao TCTH.

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APÊNDICE 1

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Eu, _____, autorizo o Cirurgião Dentista *Vinicius Rabelo Torregrossa*, aluno de pós-graduação devidamente matriculado no Programa de Pós-graduação em Estomatopatologia da Faculdade de Odontologia de Piracicaba, Universidade Estadual de Campinas (FOP-UNICAMP), a realizar a coleta de meus dados necessários para a pesquisa intitulada: "**Estudo da saliva como fonte de biomarcadores no Transplante de Células Tronco-Hematopoéticas".** Foram discutidos comigo os detalhes da pesquisa, que incluem a coleta de dados específicos, exame físico intrabucal e avaliação da condição salivar, tendo em vista identificar de forma precoce sinais clínicos de Hipossalivação e alterações no fluxo salivar relacionadas ao Transplante de Células Tronco-Hematopoéticas.

*Todas as avaliações serão realizadas por um Cirurgião Dentista treinado da equipe de Odontologia do Hemocentro-Campinas, em diversas fases, que incluirão coletas pré e pós-transplante.

CONDIÇÕES A SEREM AVALIADAS:

1. **Índice de Placa (IP), Índice Gengival (IG) e CPOD:** Será avaliado o IP, IG e CPOD através do exame físico intrabucal realizado por um Cirurgião Dentista com um espelho odontológico, sonda exploradora e sonda periodontal do tipo OMS;
2. ***Hipossalivação:*** Avaliações em diferentes períodos pré e pós-transplante, onde parâmetros de boca seca serão avaliados com uma espátula de madeira e luz artificial, e a saliva do paciente será coletada visando a mensuração do fluxo salivar não-estimulado.
3. ***Grau de mucosite****: Avaliação conforme de acordo com os critérios d*a Organização Mundial de Saúde (OMS), *entre os dias* D+ 8 e D+10, durante o período de internação para a realização do transplante;
4. ***Coleta de saliva:*** Para as coletas das amostras de saliva o paciente deverá cuspir toda a saliva contida em sua boca a cada 30 segundos até completar o tempo de 05 minutos em um recipiente graduado fornecido pela equipe de Odontologia do Hemocentro-Campinas, após um intervalo mínimo de uma hora da última refeição ou da última higiene bucal, preferencialmente na posição sentada. Esse exame será realizado nos períodos pré e pós-transplante e incluirá a avaliação da quantidade de saliva e de seus componentes bioquímicos.

Desconfortos, riscos previsíveis e benefícios esperados: Estou ciente de que um Cirurgião Dentista treinado da equipe de Odontologia do Hemocentro-Campinas realizará a coleta da minha saliva e exames periódicos em minha boca.

Não existem riscos previsíveis relacionados a este procedimento. O paciente poderá apresentar desconforto durante o exame bucal no caso de apresentar feridas em sua boca em decorrência da manifestação de mucosite oral ou de outras patologias na cavidade oral.

Todos os participantes desta pesquisa receberão atendimento odontológico no Ambulatório de Odontologia do Hemocentro-Campinas, sendo devidamente encaminhados para outros Centros de Atendimento Odontológico da rede pública de saúde, quando o procedimento necessário não for

passível de ser realizado neste Ambulatório. Não haverá beneficio financeiro para os participantes do estudo.

Forma de acompanhamento e assistência: Os pesquisadores estarão à disposição para quaisquer esclarecimentos adicionais pessoalmente, por telefone ou e-mail (modo de contato abaixo).

Ressarcimento e indenização: Não há gastos previstos pela participação na pesquisa e, portanto, não há previsão de ressarcimento pelos gastos referentes ao seu deslocamento, tendo em vista que os indivíduos serão avaliados no mesmo dia e período segundo o agendamento de sua consulta médica. Não há riscos previsíveis pela participação na pesquisa e, portanto, não há previsão de indenização. Você receberá uma cópia deste Termo de Consentimento Livre e Esclarecido.

Todas as minhas perguntas sobre a pesquisa foram respondidas, não restando dúvidas. Essas avaliações serão feitas sem qualquer custo para mim. Terei total liberdade de retirar minha autorização a qualquer momento e deixar de participar do estudo, conforme determinação da Resolução 196/96 do Conselho Nacional de Saúde do Ministério da Saúde sem prejudicar a continuação do meu tratamento. Fui avisado sobre a possibilidade de armazenamento do material biológico para estudos futuros, desde que aprovados pelo Comitê de Ética em Pesquisa, de acordo com as normas da Resolução 347/2005.

Autoriza o armazenamento do material biológico coletado (sangue, urina, saliva e /ou biópsia)?

☐ SIM ☐ NÃO

Serei informado sobre os resultados dos exames, sendo mantido sigilo sobre a minha identidade quando forem expostas e publicadas as conclusões da pesquisa.

Campinas, _____/_____/ _____ Ciente:_____

Responsável: Vinicius Rabelo Torregrossa – Fone: (19) 98805-9651 – viniciusrabelotorregrossa@gmail.com

Orientador(a): Dra. Maria Elvira Pizzigatti Corrêa – Fone: (19) 35218729 – elvira@unicamp.br

ATENÇÃO: A sua participação em qualquer tipo de pesquisa é voluntária. Em caso de dúvidas quanto aos seus direitos, escreva para o Comitê de Ética em Pesquisa da FCM - UNICAMP. (Endereço: Cidade Universitária Zeferino Vaz – Barão Geraldo- Campinas – São Paulo – Brasil). Caixa postal - 611 - CEP - 13083-970 - **Fone: (19) 35218936**

APÊNDICE 2

FICHA DE AVALIAÇÃO CLÍNICA

Avaliação **"A"** (Pré-Transplante)

PACIENTE: No._____ Data: ____/____/____ D: _____ HC:_____ Sexo: _____

Nome do Paciente:_____Data de nascimento (_____/_____/_____) Idade: (_____)

Endereço:_____

Telefone para contato:_____ (Falar com: _____)

Raça: _____

História da doença atual (queixa principal e duração):

_____

Uso de medicamentos de rotina? S ☐ N ☐
Quais?_____

Fuma? S ☐ N ☐ Quanto?_____ Tipo? _____ Bebe? S ☐ N ☐ Quanto?_____ Tipo? _____

AVALIAÇÃO CLINICA ORAL: Exame da cavidade Oral

IP 0 – sem placa; 1 - placa detectada por sondagem; 2 - placa visível; 3 - placa espessa (+ 1mm); X - dente ausente

☐ 16 ☐ 12 ☐ 24 ☐ 36 ☐ 32 ☐ 44

IG 0 - gengiva norma;l 1 - gengiva c/ inflamação leve; 2 - gengiva c/ inflamação moderada; 3 - gengiva c/ inflamação severa; X- ausente

☐ 16 ☐ 12 ☐ 24 ☐ 36 ☐ 32 ☐ 44

CPOD: _____ 0- Hígido; 1- Cariado; 2– Restaurado com cárie; 3– Restaurado sem cárie; 4– Ausente por cárie; 5– Pilar prótese

18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

Exame Clínico Bucal - Variações da Normalidade e Lesões Secundárias

Lesão : S ☐ N ☐ Descrição da lesão: _____

Localização: _____
AVALIAÇÃO DO FLUXO SALIVAR

Valor Peso Final _____ g (-) Valor Peso Inicial _____ g (/5) = Valor obtido: _____ ml/min.

AVALIAÇÃO DE HIPOSALIVAÇÃO

PARÂMETROS	Pré- TCTH	D+8-10
Alta aderência da espátula de madeira na mucosa jugal		
Ausência de Lago sublingual		
Saliva espessa e viscosa		
Ausência da secreção salivar após ordenha do ducto parotídeo		
Você sente sua boca seca?		

Conduta
____

____

Avaliação **"B"** (Fase de mucosite oral: D +8-10)

Uso de medicamentos de rotina? S ☐ N ☐ Data: ____/____/____ D: ______

Quais?____

AVALIAÇÃO CLINICA ORAL: Exame da cavidade Oral

IP 0 – sem placa; 1 - placa detectada por sondagem; 2 - placa visível; 3 - placa espessa (+ 1mm); X - dente ausente

☐ 16 ☐ 12 ☐ 24 ☐ 36 ☐ 32 ☐ 44

IG **0 - gengiva norma;l 1 - gengiva c/ inflamação leve; 2 - gengiva c/ inflamação moderada; 3 - gengiva c/ inflamação severa; X- ausente**

☐ 16 ☐ 12 ☐ 24 ☐ 36 ☐ 32 ☐ 44

CPOD: __________ 0- Hígido; 1- Cariado; 2– Restaurado com cárie; 3– Restaurado sem cárie; 4– Ausente por cárie; 5– Pilar prótese

18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

Exame Clínico Bucal - Variações da Normalidade e Lesões Secundárias

Lesão : S ☐ N ☐ Descrição da lesão: _____

Localização: _____

AVALIAÇÃO DO FLUXO SALIVAR

Valor Peso Final _____ g (-) Valor Peso Inicial _____ g (/5) = Valor obtido: _____ ml/min.

AVALIAÇÃO DE HIPOSALIVAÇÃO

PARÂMETROS	Pré- TCTH	D+8-10
Alta aderência da espátula de madeira na mucosa jugal		
Ausência de lago sublingual		
Saliva espessa e viscosa		
Ausência de secreção salivar após ordenha do ducto protídeo		
Você sente sua boca seca?		

Avaliaçao da Mucosite - (OMS):

Grau da Mucosite:

0 – Ausência de sintomatologia;

1 – Dor e Eritema;

2 – Eritema e úlceras (ingestão habitual de líquidos e sólidos);

3 – Úlceras (somente ingestão de líquidos);

4 – Úlceras (incapaz de se alimentar por via oral).

Conduta

_____

_____

ANEXO 1

Adendo em projeto previamente aceito no Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP (CEP/FCM), parecer Nº 1297/2010.

UNICAMP

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

http://www.fcm.unicamp.br/fcm/pesquisa/comite-de-etica-em-pesquisa

CEP, 28/05/13.
(PARECER CEP: N° 1297/2010)

PARECER

I - IDENTIFICAÇÃO:

PROJETO: **"AVALIAÇÃO PROSPECTIVA DAS ALTERAÇÕES CLÍNICAS ORAIS E DA PROETÔMICA SALIVAR EM PACIENTES SUBMETIDOS AO TRANSPLANTE DE CÉLULAS TRONCO-HEMATOPOIÉTICAS ALOGÊNICO".**

PESQUISADOR RESPONSÁVEL: Patrícia do Socorro Queiroz Feio

II – PARECER DO CEP.

O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP tomou ciência e aprova a validação das proteínas e o estudo da proteômica salvar dos pacientes, que será desenvolvida pelo aluno de mestrado Vinicius Torregrossa e a alteração da pesquisadora responsável para Maria Elvira P. Corrêa, referente ao protocolo de pesquisa supracitado.

O conteúdo e as conclusões aqui apresentados são de responsabilidade exclusiva do CEP/FCM/UNICAMP e não representam a opinião da Universidade Estadual de Campinas nem a comprometem.

III – DATA DA REUNIÃO.

Homologado na V Reunião Ordinária do CEP/FCM, em 28 de maio de 2013.

Profa. Dra. Fátima Aparecida Böttcher Luiz
COORDENADORA do COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

ANEXO 2

Comprovante de submissão do artigo intitulado "*Validation of clinical criteria for the diagnosis of hyposalivation and development of an oral dryness score in allogeneic hematopoietic stem cell transplant patients*" no periódico científico "*Brazilian Journal of Hematology and Hemotherapy*".