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Article

Laser Doppler Flowmetry as a method of analysis for the evaluation of chemo - induced oral mucositis: A pilot study.

Flujometría por láser Doppler como método de análisis para la evaluación de la mucositis oral inducida por quimioterapia: Un estudio piloto.

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Abstract: Background: Oral mucositis (OM) is an inflammation of the oral mucosa due to cancer therapy that compromises the patient's quality of life. Laser Doppler flowmetry (LDF) is a non-invasive method to monitor microvascular blood flow (BF) in real-time. **Purpose:** Develop a method to evaluate BF in the genian region cheek in patients undergoing chemotherapy by LDF and compare the degrees of OM and pain with evaluation of BF. **Material and methods:** Evaluation of OM was performed using the World Health Organization (WHO) and Oral Mucositis Assessment Scale (OMAS) scales and the visual analog scale for pain evaluation. For flowmetry analysis, a laser Doppler flowmeter (moorVMSTM™, 780 nm wavelength and VP3 probe), fixed by an acrylic resin support was used; VP3 probe was positioned on the genian region and the patient's head was stabilized with a neck pillow for an accurate measurement. The Wilcoxon test was used to compare the flowmetry results at the studied times. The Pearson correlation coefficient was used to evaluate relationships between BF and the WHO, OMAS and visual analog scales. **Results:** Eleven patients of both sexes, aged between 30 and 78 years, with OM were included. An increase in cutaneous BF was observed at the initial times of OM, with progressive reduction during the chemotherapy cycle. There was a statistical difference ($p<0.05$) between time point T0 (first consultation) and time point T6 (last consultation). **Conclusion:** The method developed in this pilot study is effective, reliable, and reproducible, and allows the evaluation of BF dynamics in the genian region using LDF of patients undergoing chemotherapy at risk of developing OM.

Keywords: Antineoplastic agents; neoplasms; oral mucositis; laser-doppler flowmetry; microcirculation; chemotherapy.

Resumen: Antecedentes: La mucositis oral (MO) es una inflamación de la mucosa oral debido a la terapia del cáncer, que compromete la calidad de vida del paciente. La flujometría láser Doppler (FLD) es un método no invasivo para monitorear el flujo sanguíneo microvascular (FS) en tiempo real. **Objetivo:** Desarrollar un método para evaluar la FS en la mejilla de la región geniana en pacientes sometidos a quimioterapia por FLD y comparar los

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grados de MO y dolor con la evaluación del FS. **Material y Métodos:** La evaluación de la MO se realizó utilizando las escalas de la Organización Mundial de la Salud (OMS) y la Escala de Evaluación de la Mucositis Oral (OMAS) y la escala analógica visual para la evaluación del dolor. Para el análisis de flujometría se utilizó un flujómetro láser Doppler (moorVMSTM™, longitud de onda de 780 nm y sonda VP3), fijado por un soporte de resina acrílica; La sonda VP3 se colocó en la región geniana y la cabeza del paciente se estabilizó con una almohada para el cuello para una medición precisa. Se utilizó la prueba de Wilcoxon para comparar los resultados de la flujometría en los tiempos estudiados. Se utilizó el coeficiente de correlación de Pearson para evaluar las relaciones entre FS y las escalas de la OMS, OMAS y analógicas visuales. **Resultados:** Se incluyeron 11 pacientes de ambos sexos, con edades comprendidas entre 30 y 78 años, con MO. Se observó un aumento del FS cutáneo en los momentos iniciales de la MO, con reducción progresiva durante el ciclo de quimioterapia. Hubo una diferencia estadística ($p<0.05$) entre el momento T0 (primera consulta) y el momento T6 (última consulta). **Conclusión:** El método desarrollado en este estudio piloto es efectivo, confiable y reproducible, y permite evaluar la dinámica del FS en la región geniana utilizando FLD de pacientes sometidos a quimioterapia con riesgo de desarrollar MO.

Palabra Clave: *Agentes antineoplásicos; neoplasias; mucositis oral; flujometría láser-Doppler; microcirculación; quimioterapia.*

INTRODUCTION.

Oral mucositis (OM) is an inflammatory condition induced by chemotherapy (CT) and radiotherapy (RT) that consists of inflammation of the oral mucosa which can cause pain and ulcerations, interfere with quality of life, and can facilitate opportunistic infections.[1,2]

Alterations in oral microcirculation (MC) can develop immediately following CT. This can which lead to damage of the oral mucosa due to the toxicity of chemotherapeutic drugs.[1,3-5] Alterations in the MC may be important in the pathogenesis of OM and, thus, require further study.

Laser Doppler flowmetry (LDF) is a non-invasive method that allows assessment of clinical parameters of the MC through continuous blood flow (BF) monitoring in real time, instantly registering variations.[5,6] LDF is based on BF measurement by laser radiation interaction, which is generated by a helium-neon laser with a wavelength of 632.8nm, or by diode lasers releasing waves between 780 and 820nm, with power outputs between 1 and 3 mW.[6-10]

This technique has been used previously to assess oral MC in patients subjected to CT that also underwent low power laser therapy (LPL) for the treatment of OM, showing no significant changes in oral blood perfusion observed as a result of the LPL effect over the OM lesions repair.[11] The LDF technique has also been used to assess cutaneous BF in patients subjected to RT and a flow increase was observed starting at a dose of 200 cGy, which remained above the baseline value for a year after the end of treatment.[12]

One of the difficulties in performing LDF is the high variability of BF among individuals. This can be due to individual variations, such as tissue optical characteristics, emotional state, neuromuscular response, and skin color.[12] One of the unknowns related to the use of the technique is the optimal method of stabilizing the probe.

The device used cannot exert pressure on the tissue, as this would alter the results since the mechanical stimulus could modify BF.[6-8,13]There are few studies on oral MC in patients undergoing head and neck CT or RT.[11,12] Evaluation of the acute cytotoxic effects of antineoplastic therapy on oral MC by means of LDF can provide valuable information, including a correlation of BF patterns with OM pathogenesis. The aim of this study was to evaluate the genian region BF in patients undergoing CT with the risk of developing OM using LDF.

MATERIALS AND METHODS.

Selection of volunteers

In total, 11 patients of both sexes and aged between 30 and 78 years who signed the Informed Consent Form previously approved by the Ethics Committee in Research (CAAE: 41935515.6.0000.5417, University of São Paulo) were included in this study. This study was registered on the Brazilian Clinical Trials Registry Platform (RBR-2ryhcv).

The inclusion criteria were as follows: diagnosis of malignant tumor; undergoing chemotherapy treatment with high risk of developing OM; and age over 18 years.

Exclusion criteria were as follows: pregnancy; diabetes; smoking; and uncontrolled hypertension.

The consultation days for evaluation were T0 (before the beginning of the CT cycle), T1 (performed between day 1 [D1] and D3), T2 (performed between D4 and D6), T3 (performed between D7 and D9), T4 (performed between D10 and D12), T5 (performed between D13 and D15), and T6 (performed between D16 and D18), for a total of seven assessments during one CT cycle.

Assessment of the degree of OM was performed during dental care appointments by the leading researcher, previously calibrated, according to a WHO and OMAS scales.

For assessment of OM severity using the OMAS scale, the OMAS score pattern was used: MO = (∑ui/nu) + (∑ei/ne), where ∑ui is the sum of the ulcer areas; nu is the number of ulcer areas; ∑ei is the sum of erythema intensity; and ne is the number of erythema areas. Scores vary from 0 to 5.

Evaluation of pain

Oral mucosa pain assessment was conducted according to the Visual Analog Scale (VAS) in which the patient was asked to perform a pain intensity self- assessment, which was then registered into the medical record. The VAS consisted of a 10 cm plastic ruler with one of the extremities indicating "no pain" and the other "worst imaginable pain". The attendees were asked to indicate their perception of pain using the ruler at the beginning of each clinical evaluation, before LDF.

Flowmetry analysis

The Moor Instruments Laser Doppler Flowmeter® (Axminster, England), moorVMSTM™ model, which releases a diode laser at a wavelength of 780nm (infrared) at 3mW power, approximately, was used. The flowmeter Doppler band was set at 15 kHz. The flowmeter laser belongs to class 1 risk; therefore, it is safe within reasonably predictable operating conditions, does not cause damage, and there is no need for protective procedures or equipment according to the International Standard IEC 60.825-1:2007.

The VP3 probe model was used, which contains two optical fibers, an incident and receptor fiber, with 0.25mm separation, packed inside a stainless-steel tip 10mm long and with a 1.5mm diameter. The probe was calibrated monthly being used on a suspension containing microspheres in Brownian movement. The fluid used for calibration was supplied by the flowmeter manufacturer.

All measurements were conducted after a 10 min rest to stabilize BF. The room temperature during recording was kept between 23°C and 25°C. An assessment of blood pressure was conducted to control BF measurements. For the measurements, patients remained seated in a semi-supine position.

BF measurements were taken twice, for 1.5 min each, in the genian region of each patient, with the intersection of the line that extends from the external palpebral commissure with the labial trago-commissure line as a reference point. The average between these two measurements was considered the final value.

The probe was fixed in a silicon bracket manufactured with dense condensation silicon (Otoposil®) conditioned in an acrylic tube. A neck pillow was used for stabilization of the patient's head and to sustain the probe/support set. These precautions were aimed at minimizing involuntary movements that could compromise the results. (Figure 2A and Figure 2B)

The flow records were analyzed using the Moor Instruments moorVMSPC V3.1 app (England). The app shows the records in real time and allows the storage of digitized records at the rate of 40 samples per second. The app also provides the assessed BF average value and standard deviation. In each record, all the regions free from interference (produced by movements between the probe and the face) were selected and the average value for each record was calculated.

Indicators of flow variation

Recorded BF values were interpreted taking the F(AU) values obtained before the beginning of the CT or RT cycle (T0) as a reference of normality for the analysis of BF variation at T1, T2, T3, T4, T5, and T6.

BF variations for each session and each individual were analyzed using the parameter F (%), defined in the sequence: F (%) = FB/FA. 100, where FA is the initial flow value in AU (arbitrary units); FB is the flow value of subsequent sessions; and F(%) is the percentage variation of the flow from the evaluated moment compared with the initial moment, when the flow presents no alterations.

Statistical analysis

Results were statistically analyzed using the following software: SPSS V17, Minitab 16, and Excel Office 2010. The Wilcoxon test was used to compare BF records at the different timepoints (T1, T2, T3,

T4, T5, and T6) with T0 in the studied groups. The Pearson correlation coefficient was used to assess the relationship between BF and the following variables: degree of OM (WHO and OMAS scales) and degree of pain (VAS scale). For these analyses, a confidence level of 0.05 (5%) and confidence range of 95% were adopted.

Figure 1. Mean values of F (%) as a function of moments registered during CT. T0 = 100.

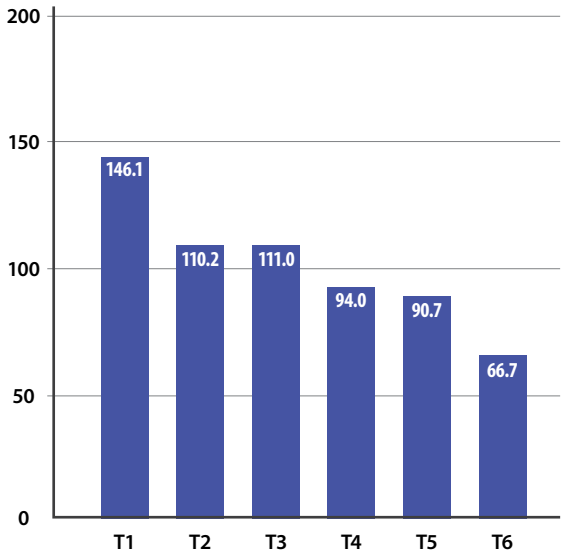
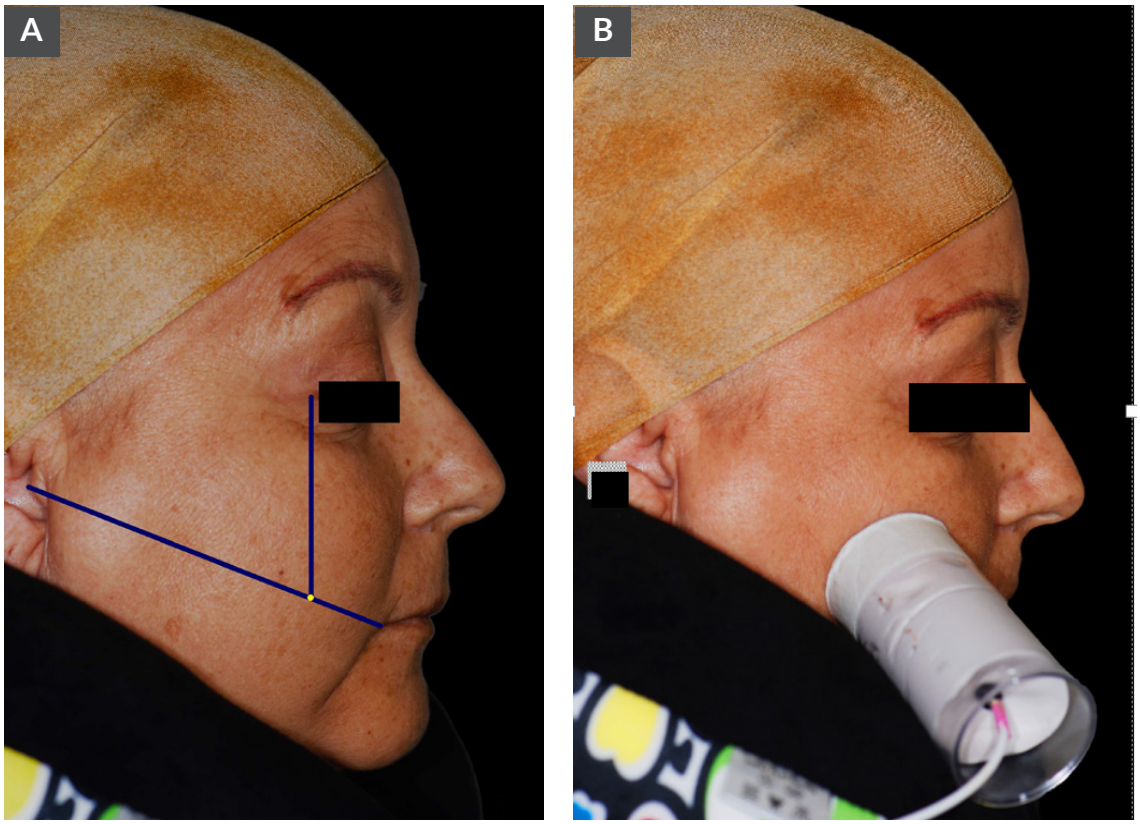


Figure 2. Measurement.



A. Reference point for measurement. B. Blood flow measurement

Table 1. Malignancies and types of chemotherapy regimens employed.

Patient	Diagnosis	Treatment type	Chemotherapeutic
1	Bowel cancer	Chemotherapy	Oxaliplatin + 5-fluorouracil (15/15 days)
2	Bowel cancer	Chemotherapy	Oxaliplatin + 5-fluorouracil (15/15 days)
3	Bowel cancer	Chemotherapy	Oxaliplatin + 5- fluorouracil (15/15 days)
4	Bowel cancer	Chemotherapy	Cisplatin + Gentamicin (7/7 days)
5	Bowel cancer	Chemotherapy	5-fluorouracil + Leucovorin (Day 1 a Day 5)/(8/28 days)
6	Bowel cancer	Chemotherapy	5-fluorouracil + Leucovorin (Day1 a Day 5)/(28/28 days)
7	Bowel cancer	Chemotherapy	5-fluorouracil + Leucovorin + Oxaliplatin (15/15 days)
8	Pancreatic cancer	Chemotherapy	5-fluorouracil + Leucovorin + Oxaliplatin (15/15 days)
9	Pancreatic cancer	Chemotherapy	5-fluorouracil + Leucovorin (15/15 days)
10	Breast cancer	Chemotherapy	5-fluorouracil + Cyclophosphamide + Methotrexate (28/28 days)
11	Ovarian cancer	Chemotherapy	Carboplatin + Paclitaxel (15/15 days)

Table 2. Comparison of flowmetry using the F% (T0) indicator with time (T1, T2, T3, T4, T5, and T6).

CT	Average	Median	Standard Deviation	n	Confidence interval	*p*-value
TO	100.00	100.00	0.00	11	-x-	- x -
T1	146.07	119.86	78.45	9	51.25	0.110
T2	110.21	122.73	43.12	11	25.48	0.374
T3	108.78	107.75	41.97	11	24.80	0.534
T4	82.38	95.45	32.75	9	21.39	0.314
T5	90.66	90.09	45.59	6	36.48	0.310
T6	66.68	66.52	9.02	4	8.84	0.043

Table 3. Comparison of flowmetry using the F(UA) indicator at T0 with time (T1, T2, T3, T4, T5, and T6).

CT	Average	Median	Standard Deviation	n	Confidence interval	*p*-value
TO	20.45	15.40	12.14	11	7.17	- x -
T1	23.12	23.20	10.13	9	6.62	0.033
T2	20.08	17.30	8.39	11	4.96	0.657
T3	22.13	13.90	15.84	11	9.36	0.563
T4	18.16	11.90	13.33	9	8.71	0.343
T5	15.79	13.66	6.02	6	4.82	0.600
T6	14.59	14.69	5.84	4	5.2	0.068

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RESULTS.

Basic disease and chemotherapy protocol.

The Table 1 shows the basic diseases and types of chemotherapy regimens performed.

In this study, 7/11 (64%) of the subjects were diagnosed with bowel cancer; 2/11 (18%) with pancreatic cancer; 1/11 (9%) with ovarian cancer; and 1/11 (9%) with breast cancer. The patients were submitted to the following chemotherapeutic regimes: 3/11 (28%), oxaliplatin and 5- fluorouracil (15/15 days); 2/11 (18%), 5-fluorouracil and leucovorin (D1 to D5, 28/28 days); 2/11 (18%), 5-fluorouracil, leucovorin, and oxaliplatin (15/15 days); 1/11 (9%), cisplatin and gentamicin (7/7 days); 1/11 (9%), 5-fluorouracil and leucovorin (15/15 days); 1/11 (9%), 5-fluorouracil, cyclophosphamide, and methotrexate; and 1/11(9%), carboplatin and paclitaxel.

BF variations during CT

The average BF values [F (%)] determined during CT are presented. (Figure 1)

Evaluation of the average BF variation in the analyzed time points compared to T0 [(F (%) = 100)] indicated that there was an increase in flow at T1, T2, and T3. However, there was no change in BF at T4 and a reduction in flow at T5, and T6. Therefore, there is an initial increase in T1 [(F (%) = 146,07)], followed by a gradual reduction in flow with further treatment, reaching the lowest value at T6, at which F (%) was 66.68. There was a significant difference only between T0 and T6 ($p<0.05$). Analysis of the F(UA) indicator showed a significant increase in BF at T1 ($p<0.05$).

The Wilcoxon test was applied to verify if the antineoplastic therapy caused an alteration in F (%) and the F(AU) average. The results are presented in (Tables II and III), respectively.

OM assessment (WHO)

Among the study subjects, 1/11 (9%) did not present any sign of OM, 3/11 (27%) presented with OM degree 1, and 7/11 (64%) presented with OM degree 2. There was no occurrence of OM degrees 3 and 4 in the present study.

OM assessment (OMAS)

Six (54%) patients presented scores between 0 and 2.9, while five (46%) patients had scores greater than 3.

VAS

Nine (64%) patients mentioned pain during the antineoplastic therapy and 2/11 (18%) patients mentioned severe pain (>7). There was a positive correlation between the OMAS ($p=0.009$), WHO ($p=0.031$), and FS [F(AU)] scales; namely, the more BF increased, the more OM evolved with proportional severity. There was no association between pain and BF.

DISCUSSION.

Previous studies investigating OM pathophysiology have focused mainly on cellular and molecular components of the oral mucosa epithelium.[14] OM evaluation, evolution, and classification were based on clinical conditions; namely, after the manifestation of OM. However, there is evidence that the MC can be an important parameter in OM pathogenesis and progression following CT.[5,15,16]

The present study is clinically relevant because it is the first and only study showing BF changes during CT and assessing the relationship between BF before and during the development of OM.

LDF can be used to evaluate BF over short and long periods.[9,10] The objective of this study was to assess subcutaneous BF as a MC parameter, before and during CT, since there is evidence that cutaneous microvascular function reflects the MC state of other locations, including the oral mucosa. However, this technique can suffer interference from the following factors: failure in the selection of equipment characteristics (calibration, band width, wavelength, and specifications of the equipment), probe positioning and stabilization, patients' emotional state, and intra- and inter- individual variabilities.[7,9,10,13]

There are few studies assessing MC alterations induced by CT. Data found in the literature suggest that there is a BF increase in the initial moments (D2 and D4 after CT) with subsequent gradual BF decrease along the CT active stage, which is consistent with the results obtained in this pilot study.[16] This two-phase BF alteration may be related to the pathophysiology of OM.[5,15-17]

According to the pathogenesis of OM, it is expected that BF alterations behave in the following manner during development and evolution of OM: vasodilation in initial manifestations, resulting in increased BF (D2) followed by increased MC permeability, leading to BF slowing and erythrocyte concentration increased in small vessels and increased blood viscosity (D4), where initial erythema and edema are clinically observed, with a lack of inflammatory infiltrate.[14,17]

From D7, BF decreased gradually. Conjunctive tissue

presents extensive tissue damage and the presence of mixed inflammatory infiltrate is observed where the damage occurred. Clinically, there is ulceration.[17]

The limitations of the present study are related to the casuistry due to the need for several evaluations in the same patient. During antineoplastic therapy, some patients presented medical complications, requiring hospital admission, which prevented the necessary outpatient evaluations. In addition, some patients died during the course of the study. We consider this a pilot study and it will be necessary to conduct further studies.

The data analysis of the present study shows a tendency for BF to increase before and during the initial stages of OM (T1 and T2) in the studied groups, with a gradual reduction in flow during the evolution of OM until its healing (T3, T4, T5, and T6). There are no studies in the literature that associate alterations in FS induced by antineoplastic therapies and MO associated pain; in this study this association was not found.

CONCLUSION.

The aim of this study was to evaluate the FM of the genian region in patients undergoing CT at risk of developing OM with the use of LDF, and the method developed in this study occurred in an effective, reliable and reproducible and allowed the evaluation of the BF dynamics in the genian region through LDF of CT patients at risk of developing OM. In this way, new studies will be able to use this methodology to evaluate the changes in FM of patients who receive different antineoplastic treatments such as CT, RT in addition to the control group, thus visualizing which are the most critical moments between FM and OM severity. An increase in cutaneous perfusion in the face at the initial times of OM was observed, with progressive reduction of BF during the CT cycle. The biphasic alteration of the observed BF is associated with the development and perpetuation of MO.

Conflict of interests: The authors declare no conflicts of interest.

Ethics approval: Institutional bioethics committee approval (CAEE 41935515.6.0000.5417).

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