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GABRIELLA LOPES DE REZENDE BARBOSA

CLASSIFICAÇÃO E AVALIAÇÃO VOLUMÉTRICA DE FISSURAS LABIOPALATINAS POR MEIO DE IMAGENS DE TOMOGRAFIA COMPUTADORIZADA DE FEIXE CÔNICO

CLASSIFICATION AND VOLUMETRIC ASSESSMENT OF CLEFT LIP AND PALATE MALFORMATIONS USING CONE BEAM COMPUTED TOMOGRAPHY

PIRACICABA
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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Radiologia Odontológica, na Área de Radiologia Odontológica.

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Orientadora: Profa. Dra. Solange Maria de Almeida Boscolo

Este exemplar corresponde à versão final da tese defendida pela aluna Gabriella Lopes de Rezende Barbosa, e orientada pela Profa. Dra. Solange Maria de Almeida Boscolo

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A Comissão Julgadora dos trabalhos de Defesa de Tese de Doutorado, em sessão pública realizada em 21 de Outubro de 2015, considerou a candidata GABRIELLA LOPES DE REZENDE BARBOSA aprovada.

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RESUMO

O presente estudo propôs-se a avaliar *in vitro* a acurácia de três métodos diferentes para mensuração do volume de fissuras orofaciais em imagens de tomografia computadorizada de feixe cônico (TCFC), e a influência do campo de visão (FOV) e voxel nessas medidas. Além disso, também objetivou-se apresentar uma classificação para fissuras alveolares e palatinas unilaterais baseada em imagens de TCFC, bem como estimar a quantidade de osso necessário para enxerto ósseo desses indivíduos e avaliar a relação desse volume com os escores atribuídos na aplicação da classificação. Para a avaliação *in vitro*, fissuras unilaterais foram simuladas em três crânios que foram subsequentemente preenchidas com cera e escaneados em equipamento de TCFC, usando quatro protocolos de aquisição variando os tamanhos de FOV e voxel. Usando três diferentes métodos, o volume do defeito/cera foi avaliado nas imagens definindo-se: (1) largura, altura e comprimento do defeito em projeção de máxima intensidade; (2) as áreas dos defeitos nas reconstruções axiais; (3) a variação dos tons de cinza da região de interesse e a segmentação do defeito. Os valores obtidos em cada método nos diferentes protocolos foram comparados ao volume real da cera (padrão ouro) por meio dos testes ANOVA e Tukey. Os métodos 2 e 3 não diferiram do padrão ouro ($p>0,05$). Contrariamente, o método 1 apresentou valores significativamente superestimados ($p<0,01$). Não foram observadas diferenças entre os diversos tamanhos de FOV e voxel ($p>0.05$). Os volumes calculados em exames de TCFC provaram ser confiáveis para avaliação volumétrica de fissuras alveolares e palatinas quando os métodos 2 e 3 foram utilizados, independentemente do tamanho de FOV e voxel. Para a avaliação *in vivo*, imagens de TCFC de 33 indivíduos com fissuras alveolares e palatinas unilaterais foram utilizadas. Três observadores avaliaram as imagens tomográficas atribuindo os devidos escores da classificação proposta pelos autores, denominada classificação GAND: defeito, arco, nasal e dental. Adicionalmente, uma avaliação quantitativa dessas fissuras foi realizada por um avaliador segmentando-se o defeito e calculando-se o volume necessário para enxerto ósseo dos mesmos. Os escores e reprodutibilidade da classificação GAND foram analisados por meio do teste Kappa ponderado. Já a associação da avaliação volumétrica com os quesitos defeito e nasal foi verificada usando-se ANOVA, enquanto a concordância intraobservador foi analisada por meio do coeficiente de correlação intraclasse (CCI). A reprodutibilidade intraobservador da classificação variou de 0,29 a 0,92 e de 0,29 a 0,91 entre os observadores. Não foram observados valores estatisticamente significantes quando avaliada a relação do volume com os parâmetros “defeito” e “nasal” da classificação GAND ($p>0,05$). A concordância intraobservador da avaliação volumétrica foi 0,97. A incorporação de imagens tomográficas no manejo de pacientes com fissuras permitiu uma maior compreensão das verdadeiras dimensões dos defeitos. A classificação GAND é um novo sistema que permite a avaliação rápida da extensão e complexidade da fenda. Para melhores resultados, recomenda-se incorporar resultados clínicos ao exame tomográfico, especialmente para o parâmetro arco. Não é possível estimar a quantidade de osso necessária para enxerto ósseo baseando-se na classificação; para tal, indica-se a segmentação individualizada para cada paciente.

Palavras-chave: Fissura Palatina. Tomografia Computadorizada de Feixe Cônico. Enxerto de Osso Alveolar.

ABSTRACT

The present study aimed to evaluate the accuracy of three different methods for volumetric assessment of orofacial clefts in cone beam computed tomography (CBCT) images, and the influence of the field of view (FOV) and voxel sizes in these measurements. In addition, it was also aimed to propose a classification for unilateral cleft lip and palate (UCLP) malformations based on CBCT images, as well as estimate the amount of bone necessary for grafting and evaluate the relation of this volume with the scores attributed in the classification. For the *in vitro* evaluation, unilateral defects were simulated in three skulls which were subsequently filled with wax and scanned in a CBCT unit using four acquisition protocols, varying FOV and voxel sizes. Using three different methods, the defect/wax volume was evaluated on the images by defining: (1) width, height and facial-palatal length of the defect in maximum intensity projection; (2) the areas of the defect on axial slices; (3) the threshold and segmentation of the region of interest. The values obtained for each method in different protocols were compared to the actual volume of the wax (gold standard) by ANOVA and Tukey tests. Methods 2 and 3 did not differ from the gold standard ($p > 0.05$). In contrast, method 1 had significantly overestimated values ($p < 0.01$). No differences were observed among different FOV and voxel sizes ($p > 0.05$). The volumes calculated on CBCT images proved to be reliable for volumetric evaluation of alveolar/palatal clefts when methods 2 and 3 are used regardless FOV and voxel sizes. For the *in vivo* evaluation, CBCT images of 33 subjects with UCLP were used. Three observers evaluated the images assigning scores proposed in GAND classification: gap, arch, nasal and dental. Additionally, a quantitative assessment of these defects was performed by one examiner who segmented the defects and estimated the amount of graft needed for posterior alveolar bone grafting. The scores and reproducibility of GAND classification was analyzed using weighted Kappa test. The association of volume assessment with the classification (gap and nasal parameters) was verified using ANOVA, while the intraobserver agreement was analyzed using Intraclass correlation coefficient (ICC). The intraobserver reproducibility of the classification ranged from 0.29 to 0.92 and ranged from 0.29 to 0.91 between the observers. There were no statistically significant values when evaluating the association of the volume with the classification ($p > 0.05$). The intraobserver agreement in the volumetric assessment was 0.97. The incorporation of CBCT imaging in the management of patients with OFC has allowed for a greater understanding of the true dimensions of the defects. The GAND classification is a novel system that allows the quick estimation of the extent and complexity of the cleft. For better results, it is recommended to incorporate clinical findings to the CBCT examination, especially for the arch parameter. It is not possible to estimate the amount of bone needed for ABG based on the classification; individualized surgical planning should be done for each patient specifically.

Keywords: Cleft palate. Cone-Beam Computed Tomography. Alveolar Bone Grafting.

SUMÁRIO

INTRODUÇÃO

A formação da face e da cavidade oral é complexa e envolve o desenvolvimento de múltiplos tecidos que devem se unir e fusionar em um processo extremamente ordenado. Distúrbios nessas etapas podem resultar em uma fissura orofacial (Neville et al., 2016). As fissuras orofaciais são malformações congênitas caracterizadas pela formação incompleta de estruturas envolvendo as cavidades nasal e oral: lábio, processo alveolar, palato duro e mole. Estas podem variar em tamanho, podendo ser apenas um defeito no palato mole até uma fenda completa que se extende por todo palato duro. Pelo fato dos lábios e palato se desenvolverem separadamente, é possível que uma criança nasça apenas com o lábio fissurado, apenas com o palato fissurado, ou uma combinação de ambos. As fissuras orofaciais estão entre os defeitos de nascimento mais comuns e tratáveis, afetando em média 1 em cada 500-750 bebês nascidos vivos anualmente no mundo (Peterson-Falzone et al., 2009). Lábio fissurado com ou sem palato fissurado é a segunda condição mais comum nos EUA, com uma prevalência de 10,63 em cada 10.000 nascimentos ou 1 em 940 nascimentos (Parker et al., 2010).

Os tipos mais comuns são: fissura labial, fissura labial completa e palatina e fissura palatina; podendo ser unilaterais, bilaterais e medianas. A maioria das crianças afetadas por esses defeitos requerem um longo e despendioso tratamento multidisciplinar para completa reabilitação. O diagnóstico clínico preciso desses pacientes, o qual não é sempre simples, é crucial para uma conduta precisa e definição das estratégias cirúrgicas (Brito et al., 2012).

Na literatura internacional não há um sistema de classificação aceito universalmente para fissuras orofaciais, geralmente utiliza-se uma simples classificação em relação à localização anatômica da fenda. Por outro lado, uma classificação proposta por Spina et al. (1972) e amplamente utilizada por profissionais no Brasil, especifica a localização da fissura e refere-se à sua origem embrionária. Quanto à conformação da fissura e efeitos nas estruturas adjacentes, não há uma terminologia e nem uma classificação estabelecidas na literatura.

A correção dessas deformidades envolvem tanto procedimentos cirúrgicos quanto ortodônticos/ortopédicos e requerem um claro entendimento, pelo cirurgião e pelo paciente e/ou família, dos objetivos terapêuticos. O profissional deve determinar prognósticos viáveis quanto à terapia proposta e um adequado planejamento deve ser feito (Steinberg et al., 2012).

Inicialmente, ainda nos primeiros meses de vida do paciente, são realizados os reparos envolvendo tecidos moles como o reparo do lábio e nariz (3 meses), seguido do fechamento do palato duro (9 meses). No entanto, por causa do significante envolvimento de defeitos ósseos no palato duro e processo alveolar da maxila em alguns indivíduos, o completo reparo de fissuras só é alcançado com enxertia óssea alveolar na região (Cobourne, 2012; Santiago et al., 2014).

Atualmente, opta-se pelo enxerto ósseo realizado durante a dentição mista (entre 8 e 10 anos), também conhecido como enxerto ósseo secundário. Essa correção da fissura alveolar é importante para restabelecer a integridade do arco dentário, estabilizar os segmentos da maxila, permitir a erupção dos dentes permanentes, promover suporte e elevação da base alar do nariz, além de fechar fístulas oro-nasais, quando presentes (Santiago et al., 2014). Geralmente, a enxertia óssea é realizada com osso autógeno retirado de sítios apropriados, sendo a crista ilíaca o principal sítio doador (Cobourne, 2012).

Durante o planejamento do tratamento, a fissura pode ser avaliada por exames de imagem e modelos de gesso. De acordo com os relatos do Encontro Internacional da Organização Mundial da Saúde em 2002, os registros clínicos dos pacientes devem ser realizados individualmente para permitir o planejamento, monitoramento do progresso e avaliação do tratamento. Nesse sentido, foi atestado que, como registro mínimo, telerradiografias laterais devem ser realizadas para monitoramento de fenda labial/palatina completa e palatina isolada aos 10 anos e também a partir dos 18 anos de idade. Nos casos de enxerto ósseo alveolar, uma radiografia intraoral (periapical ou oclusal) deve ser feita antes e 6 meses depois do procedimento.

Trindade e Silva Filho (2007) atestaram que o exame radiográfico das fissuras sempre revelam uma maior extensão do defeito ósseo alveolar do que observado no exame clínico. Como inicialmente as radiografias convencionais eram o método disponível para avaliação de fissuras, a maioria das investigações foram baseadas em medições lineares e avaliações subjetivas de radiografias panorâmica, oclusal e periapicais (Aurouze et al., 2000; Bergland et al., 1986; Helms et al., 1987; Long et al., 1995).

No entanto, as radiografias, por serem exames bidimensionais com limitações inerentes, tal como a sobreposição de imagens, apresentam restrições quanto à sua aplicabilidade e precisão. Assim, um exame tridimensional pode permitir uma melhor avaliação da extensão e forma da fissura, bem como das estruturas adjacentes graças à visualização sem sobreposição ou magnificação.

Estudos prévios reportam que a tomografia computadorizada multislice (TCMS) é uma técnica precisa na apreciação volumétrica de defeitos ósseos nas regiões palatina e alveolar, além de eficiente no cálculo do volume dos mesmos (Choi et al., 2012; Albuquerque et al., 2011; Feichtinger et al., 2007). Contudo, apesar das vantagens da TCMS, de acordo com o projeto SEDENTEXCT (2012) da União Européia de Proteção Radiológica que estabelece diretrizes para uso da tomografia, deve-se preferir a tomografia computadorizada de feixe cônico (TCFC) como método por imagem de escolha para avaliação de fendas palatinas para que a dose de radiação a que o paciente é exposto seja menor. Além disso, o menor volume exposto compatível com a situação deve ser selecionado para haver uma redução ainda maior da dose de radiação.

Os exames de TCFC têm mostrado notória relevância para diferentes objetivos no que se refere a pacientes fissurados, por exemplo para avaliar a espessura e nível de osso alveolar ao redor de dentes adjacentes às fendas (Garib et al., 2012), avaliar taxa de sucesso de enxerto ósseo alveolar e trajeto de erupção de caninos permanentes, além de caracterização do complexo maxilar (Oberoi et al., 2009; Oberoi et al., 2010; Schneiderman et al., 2009).

Pesquisas recentes vêm sendo feitas para a avaliação do volume da fissura e da quantidade de osso necessária para o enxerto ósseo e dessa forma, auxiliar no plano de tratamento e planejamento pré-operatório, aumentando a previsibillidade e diminuindo a morbidade e a necessidade de novas cirurgias de enxertia. Nesse sentido, diferentes metodologias foram empregadas para tal estimativa, tal como o uso de pontos de referência anatômicos em reconstruções volumétricas e a mensuração das área do defeito em vistas axiais, reconstrução por reconstrução, em toda a sua extensão (Quereshy et al., 2012; Feichtinger et al., 2007; Choi et al., 2012).

Diante do exposto, o presente trabalho se propôs a avaliar a acurácia de três diferentes métodos para mensuração do volume de defeitos ósseos e fissuras em imagens de TCFC, e a influência do campo de visão (FOV) e voxel nessas medidas. Além disso, também objetivou-se apresentar uma classificação para fissuras alveolares e palatinas unilaterais baseada em imagens de TCFC, bem como estimar a quantidade de osso necessário para enxerto ósseo desses indivíduos, avaliando também a relação desse volume com os escores atribuídos na aplicação da classificação.

CAPÍTULO 1

Comparison of different methods to assess alveolar cleft defects in cone beam computed tomography images

Running head: Comparison of methods to assess alveolar cleft defects in CBCT images

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ABSTRACT

Objectives: This study aimed to evaluate the accuracy of three different methods for assessing the volume of cleft defects in CBCT images. The influence of field of view (FOV) and voxel sizes was also assessed. **Methods:** Using three radiopaque plastic skulls, unilateral defects were created to mimic alveolar clefts and were filled with wax following the contralateral side contours. They were scanned in a CBCT unit using four different acquisition protocols, varying FOV and voxel sizes. Using three different methods, the defect/wax volume was evaluated on the images by defining: (1) width, height and facial-palatal length of the defect in maximum intensity projection; (2) the areas of the defect on axial slices; (3) the threshold and segmentation of the region of interest. The values obtained from each method using different acquisition protocols were compared to the real volume of the wax (gold standard) using ANOVA and Tukey's test. **Results:** Methods 2 and 3 did not differ from the gold standard ($p>0.05$). Conversely, method 1 presented statistically significant overestimated values ($p<0.01$). No differences were found among the different FOV and voxel sizes ($p>0.05$). **Conclusions:** CBCT volumes proved reliable for the volumetric assessment of alveolar cleft defects, when using methods 2 and 3 regardless of FOV and voxel sizes. It may be possible to improve surgical planning and outcomes by knowing the exact volume of grafting material needed prior to the surgical intervention.

Keywords: Orofacial Cleft, Cone-Beam Computed Tomography, Alveolar Bone Grafting

INTRODUCTION

Orofacial clefts (OFC) are congenital malformations characterized by incomplete formation of structures in the nasal and oral cavities, affecting approximately 1 child in 600 live births with considerable ethnic and geographical variations.[1] OFC can affect lip, alveolar process, hard and soft palate. It may also vary in size, as well as occur unilaterally or bilaterally.

The alveolar involvement affects 75% of the patients with clef lip.[2] This osseous defect of the alveolar process of the maxilla requires a particular osseous resolution that plays a special role in the OFC management. Alveolar bone grafting (ABG) is the method used to add bone for correction of these defects in order to restore function and form of the arch.

ABG aims to stabilize the maxillary segments,[3] provide bony support for adjacent teeth, close oronasal fistulae and improve support for the alar base.[1]

As OFC vary in size, extension and severity, patient-specific evaluation must be done during the treatment of patients with cleft. In ABG stages, the individualized preoperative planning plays an important role in the procedure. The evaluation of the shape and measurement of the size of the bone defect is useful for an accurate preoperative planning, which would result in a more predictable procedure, allowing a more precise assessment of the volume of grafting material needed and a successful ABG. This predictability may also result in decreased morbidity, reduction of total hospital stay and overall reduced cost.[4]

Initially, conventional 2D radiographs were the available method for cleft assessment before surgery. As a result, most investigations relied on linear measurements and subjective evaluations of panoramic, occlusal, and periapical radiographs.[5-8] However, the shifting from 2D to 3D approach with the incorporation of computed tomographic images in the treatment of patients with clefts allowed the visualization of the defects in all three planes without superposition of structures.

Currently, cone beam computed tomography (CBCT) is becoming increasingly more popular in dentistry and craniofacial care. This imaging modality has advantages as lower cost and lower radiation dose for the patients when compared to multislice computed tomography (MSCT). The image quality of CBCT scans and its task-specific diagnostic ability can be influenced by several variables such as the scanning unit and different acquisition parameters, such as the field of view (FOV), tube voltage, tube amperage and voxel size.[9,10] Moreover, an accurate quantitative assessment of the dimensions of the defect is possible. And, for this task, few methods have been described in the literature.

Quereshy et al., in 2012, proposed a volumetric estimation of the defect using anatomic landmarks: the cleft width, height and facial-palatal length.[11] The authors indicated this process as an accurate alternative to quantitatively assess the cleft volume. Feichtinger et al., 2007, also suggested a methodology for volumetric appraisal of the clefts.[12] In this method, the areas of the defects were determined in every axial slice that comprised the cleft and posteriorly applied to a proposed formula for volume calculation. The latter one has been used in studies of patients with cleft.[4,13]

The above mentioned methods use linear measurements and area calculation: one and two dimensional attributes, respectively. In this sense, we hypothesized that a 3D appraisal of the entire defect would be more accurate to determine its dimensions. Since segmentation is increasingly present in dental applications, it is now possible to isolate structures in the maxillofacial region even using CBCT images. Hereof, the segmentation of the cleft and calculation of its volume would be possible. It is worth mentioning that there is a paucity of literature regarding the influence of the acquisition parameters in this 3D evaluation. In this sense, the aim of the study was to evaluate the accuracy of three different methods for assessing the volume of cleft defects in CBCT images. In addition, the influence of field of view (FOV) and voxel sizes was also assessed.

METHODS AND MATERIALS

Three radiopaque plastic skulls (3B Scientific, Hamburg, Germany) were used for the study. In order to simulate an alveolar cleft, unilateral defects varying in size and shape were created, by a plastic surgeon, on the left side of the skulls using a RemB reciprocating saw (Stryker, Kalamazoo, MI, USA) and a thin extended blade (ref 5100-337-233, Stryker, Kalamazoo, MI, USA) for surgical bone removal and reshape. The clefts were filled with utility wax following the contralateral side contours.

The skulls were then scanned in a CS9300 CBCT unit (Carestream Dental, Atlanta, GA, USA) operating at 85 kVp and 4 mA. Four different acquisition protocols (Table 1) were used, varying the field of view (FOV) and voxel sizes: (1) 17x11cm FOV, 0.25mm voxel; (2) 17x11cm FOV, 0.5mm voxel; (3) 17x13.5cm FOV, 0.3mm voxel; (4) 17x13.5cm FOV, 0.5mm voxel.

Table 1 - Imaging protocols used in the research.

Protocol	FOV (cm)	Voxel (mm)	kVp	mA	Time (s)	DAP (mGy.cm^2)
1	17 x 11	0.25	85	4	6.4	770
2	17 x 11	0.50	85	4	6.4	770
3	17 x 13.5	0.30	85	4	11.3	1359
4	17 x 13.5	0.50	85	4	11.3	1359

The 12 resultant CBCT DICOM volumes (3 skulls x 4 protocols) were saved in DICOM files. The assessments were performed in a secluded room with dim light by an oral and maxillofacial radiologist with experience in tomographic appraisal and cleft management. Three different methods were used to evaluate the volume of the cleft/wax in the images:

(1) The first one, proposed by Quereshy et al., 2012, was performed using inVivo software (Anatomage Inc, San Jose, CA). Initially, the three dimensional (3D) reconstruction in maximum intensity projection (MIP) was created. Using landmarks, linear measurements corresponding to the cleft width, height and facial-palatal length were collected. These values were used to calculate the estimated volume of the defect (Figure 1).

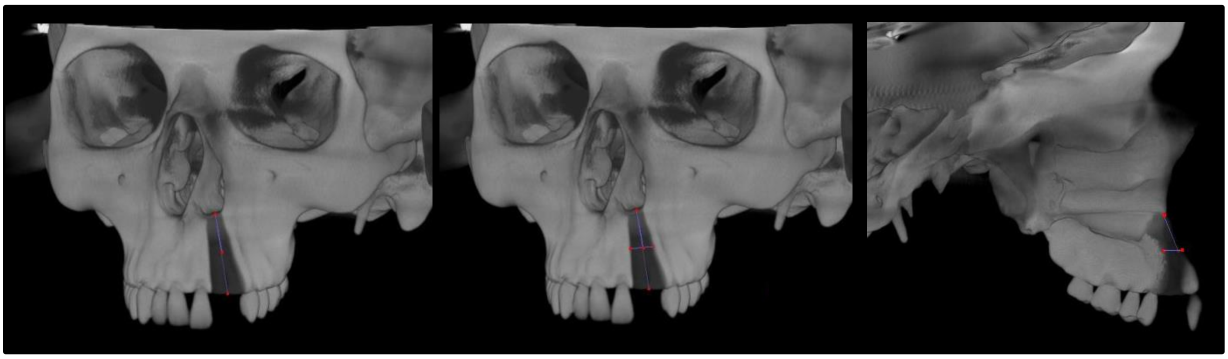

Figure 1 – Method 1: Measurement of the height, width and facial-palatal length of the cleft in MIP projection.

(2) The second method, first described by Feichtinger et al., 2007, was also executed using inVivo software (Anatomage Inc, San Jose, CA). In this technique, the defects were outlined on each axial slice and the area was automatically given. After determination of the area in every slice that comprised the cleft, the volume was calculated using the following formula: Volume = [A1 × S]+[A2 × S]+. . . +[An × S] (A, area; S, thickness of the slice; n, number of slices) (Figure 2).

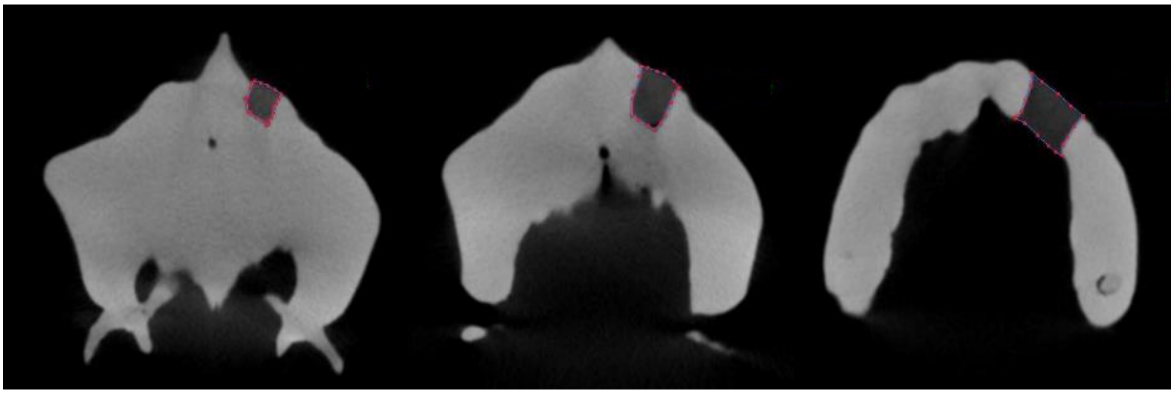

Figure 2 – Method 2: Measurement of the area of the cleft slice by slice on axial view.

(3) The third method consisted in a 3D evaluation using Mimics software (v16.0, Materialise Medical, Leuven, Belgium). For this, the threshold comprising the region of

interest (cleft/wax) was defined. The volumetric region of interest (VOI) was cropped to comprise only the cleft for posterior segmentation. After threshold selection, a three dimensional editing was used to obtain refined surfaces of the segmentation, resulting in a VOI that was rendered into a shaded surface mesh and the segmented volume was calculated (Figure 3).

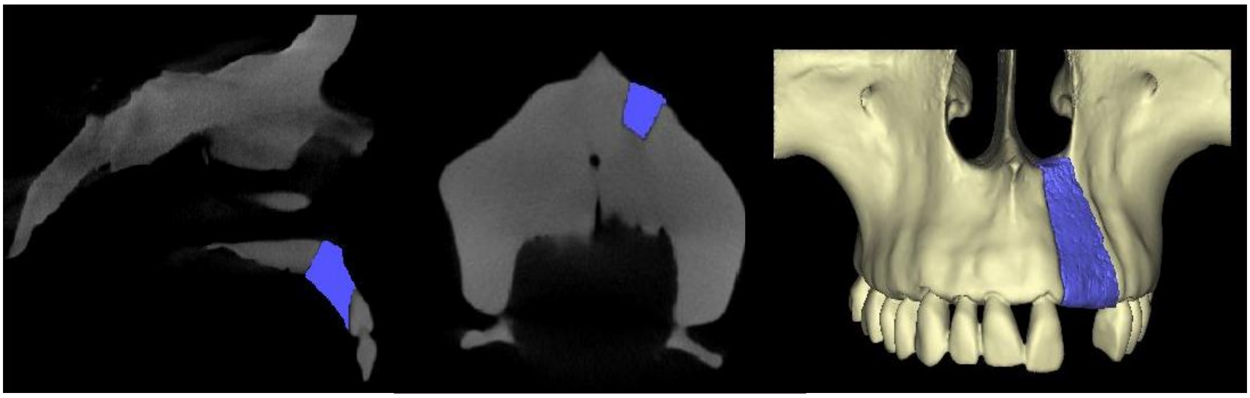

Figure 3 – Method 3: Segmentation and volumetric measurement of the cleft.

In order to compare the methods, the calculation of the real volume of the wax was selected as the gold standard of the study. For this assessment, the skull was immersed in warm water and the entire wax was carefully removed using a dental floss. Next, a graduated cylinder was filled with water up to a reference line. The entire wax model was then submerged into the cylinder and the new volume occupied by the water was delimited. The real volume was measured using Archimedes’ principle of water displacement. This analysis was performed twice for each wax model by one well-trained evaluator using a digital caliper. After a month interval, the evaluations of all CBCT images were repeated to evaluate intraobserver reliability.

After data collection, the values obtained from each method using different acquisition protocols were compared to the real volume of the wax using two-way analysis of variance (ANOVA) and Tukey’s test, using BioEstat for Windows (v.5.0; Bioestat, Belém, PA, Brazil). For intraobserver analysis, Pearson's correlation coefficient was performed using SigmaStat for Windows (v. 3.5; Systat Software Inc., Erkrath, Germany). The level of significance was set at $p < 0.05$. The values for agreement evaluation were interpreted as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61– 0.80) or almost perfect (0.81+).

RESULTS

The final sample of the study consisted of 12 CBCT DICOM volumes of 3 skulls with simulated unilateral alveolar defects scanned under 4 different protocols each, varying FOV and voxel sizes.

Intraobserver values indicated almost perfect agreement for all methods (method 1: 0.98, method 2: 0.99, method 3: 0.98).

The overall values of the volumetric measurements for each skull and method are summarized in Table 2. In relation to the comparison among the methods for assessment of the cleft volume, methods 2 and 3 did not differ from the gold standard ($p>0.05$). Conversely, method 1 presented statistically significant overestimated values ($p<0.01$).

Table 2 - Average volumes of the simulated defects according to the methods (mm^3).

	Gold Standard	SD	Method 1	SD	Method 2	SD	Method 3	SD
Skull 1	1384.40 A	0.10	1410.47 B	58.03	1355.57 A	37.39	1406.58 A	56.82
Skull 2	1582.80 A	0.08	2540.19 B	125.22	1471.84 A	37.89	1501.71 A	51.57
Skull 3	760.70 A	0.02	1117.70 B	46.75	680.25 A	14.61	681.33 A	28.66

Means followed by different letters on the same line are significantly different ($p<0.05$).

In relation to the influence of different acquisition parameters, no differences were found among the selected protocols. The variation of FOV and voxel sizes did not influence the reliability of the methods ($p>0.05$).

DISCUSSION

OFC are the most common birth defects, which can affect lip, hard palate, soft palate and alveolar process. The presence of cleft in the alveolar region poses a challenge in the osseous reconstruction of the affected region by ABG.[1] The adequate care of these patients requires the dedication of a well-prepared interdisciplinary team throughout years of treatment and management, as well as the incorporation of technological advances and constant updating of the team. Moreover, society as a whole is affected by the quality of the care provided as the contribution of these patients to the community is inevitably influenced by the adequacy of their treatment.[14] In this sense, improvement in the treatment planning of the patients with cleft is also of great importance. At first, most preoperative and follow-up investigations, for example of ABG procedures, were done by conventional radiographs, such as panoramic and occlusal images.[5-8] However, the inherent limitation of imaging a 3D structure in a 2D exam has limited the proper assessment of the bone defects in these examinations. The increased utilization of faster computed tomographic exams of lower cost allowed the increase in referrals for CBCT exams by dental practitioners.[15,16]

Additionally, an important advantage of CBCT is the decrease of radiation dose to which the patients are exposed. Reductions up to 12.3-fold in the effective dose are observed when compared to MSCT.[17] This reduction is especially relevant for patients with craniofacial anomalies since they are children and adolescents exposed to an extensive number of exams along years of treatment. According to SEDENTEXCT guidelines, CBCT exams should be preferred in cases of patients with cleft instead of MSCT in an attempt to reduce radiation exposure.[18] In the present study, the two different adopted FOV resulted in variation in exposure doses. The smallest FOV had a dose-area product (DAP) of 770 mGy.cm^2 while the largest one presented an estimation of 1359 mGy.cm^2 (Table 1). It is true that these values are estimated dose values provided by the manufacturer without weighting based on tissues. Even so, such values can provide an overall idea for the health practitioners and improve exam indication and selection of parameters.

Based on our results, the variation of FOV did not influence the methods' performance ($p>0.05$). For this reason, a protocol of lower dose exposure should be selected in accordance with SEDENTEXCT guidelines. Also, in several CBCT units, such as the one used in the present study, when a larger FOV is used, the scanning time increases and more likely the patient will move during image acquisition, leading to artifact movements and image degradation. In our study, only the two extended FOVs available in the CBCT unit were evaluated. They are the indicated volume for scanning patients with clefts in the Craniofacial Center where the study was conducted, as well as in many other centers. It allowed the clinical and practical application of our results, being the smallest volume size compatible with the situation and most indicated for scanning the 17x11cm FOV.

In relation to the voxel size, its influence on image resolution and diagnostic ability of different diseases has been object of study of several reports.[9] In the evaluated CBCT unit, two options of voxel size per FOV are provided by the acquisition software. When using the 17x11cm FOV, 0.25mm and 0.5mm voxel sizes can be selected; and with the 17x13.5cm

FOV, 0.3mm and 0.5mm voxel sizes. In our study we tested all the available possibilities, and as observed for FOV, the voxel size did not influence the performance of all three methods.

It is well known that CBCT linear measurements are accurate and don't show difference in relation to anatomical truths,[19,20] even when acquisition parameters are altered in a range of acceptable image quality.[21,22] These reports of the literature corroborate our findings that the imaging parameters did not influence the results when the methods that use linear measurements were performed (methods 1 and 2). However, as little has been studied regarding the influence of acquisition parameters in the accuracy of 3D models for volumetric assessment, the present study aimed to evaluate the scanning possibilities in order to provide a better indication of these exams for this purpose. The results observed disagrees with the findings of da Silveira et al., 2014 who detected that protocols with different voxel sizes in CBCT significantly changed volumetric measurements.[23] However, these authors evaluated such measures in simulated internal root resorptions, lesions of much smaller dimensions than the defects assessed in our study. It is possible, or even probable, that voxel sizes do have an influence on accuracy in small defects. Furthermore, the lack of influence observed in method 3 can be the foundation for further research for practitioners of craniofacial teams that aim to incorporate the segmentation in the treatment of patients with cleft. Moreover, no reports in the available English literature regarding the influence of acquisition protocols in the assessment of cleft volumes were found.

Regarding the comparison of methods for volume assessment of clefts, method 1 presented overestimated values, not being suitable for this purpose. This result disagrees with the reports of the study that suggested the method.[11] However, differently from our study, this previous report did not have a gold standard with known dimension for comparison. An overestimation of the necessary amount of bone for ABG would lead to unnecessary bone removal from the donor site, increasing morbidity.[1]

Conversely, methods 2 and 3 proved reliable in our study. This finding is in agreement with previous studies.[4,12,13] Nonetheless, Feichtinger et al., 2007 and Choi et al., 2012 used images from patients that underwent ABG, and did not have a gold standard for comparison of the obtained volume and proper evaluation of the method itself. Even with the reports of Albuquerque et al., 2011 regarding the reliability of these methods using the same gold standard as our study, it was important to evaluate this methodology using CBCT images, since the technology is becoming increasingly more present in the treatment of clefts. Along with Albuquerque et al., 2011, the cited studies evaluated the method in MSCT images, which vary significantly in quality and resolution when compared to CBCT, which could lead to different results in different imaging modalities.

With reference to method 3, no reports were found using the exact same method and software. However, studies that evaluate cleft volumes by 3D methods also found values that did not differ from a gold standard.[24,25] The edition of boundaries and volume of interest in previous reports was done slice by slice in the study of Amirlak et al., 2013 and applying an algorithm in the study of Kasaven et al., 2013. These studies were similar to ours in that they used simulated defects in skulls but differed from our study in the methodology and software selected for volume assessment. The use of skulls for this type of research is a double-edged sword: the possibility of having a gold standard with accurate known dimensions at one side; on the other, the potential shortcoming of reproducing the true clinical situation. In studies similar to the present one, the evaluation of a method's reliability by a gold standard is mandatory, which makes the use of models such as skulls necessary and is also a limitation of the study at the same time.

Currently, the validation of assessments based on segmentation and 3D models of CBCT exams is essential considering that such images were easily produced only by MSCT. The production and evaluation of these virtual models is a big advance for all types of treatment. Additionally, Hamada et al., 2005 stated that these images would be especially advantageous for preoperative imaging of the morphology of residual alveolar clefts.[26]

CONCLUSION

CBCT volumes proved reliable for the volumetric assessment of alveolar cleft defects, when using methods of area determination in axial reconstructions and segmentation with 3D rendering of the volume, regardless of FOV and voxel sizes, in the evaluated methodology. It may be possible to improve surgical results by knowing the exact volume of grafting material needed prior to the surgery itself.

REFERENCES

1. Cobourne MT. Cleft lip and palate: epidemiology, aetiology, and treatment (vol 16). Front Oral Biol. Basel: Karger, 2012.

2. Bell WH, Proffit WR, White RP. Residual alveolar and palatal cleft. In: Bell WH, Proffit WR, White RP (ed). Surgical correction of dentofacial deformities. Philadelphia,PA: WB Saunders, 1980, pp 1329–1367.

3. Turvey TA, Vig K, Moriarty J, Hoke J. Delayed bone grafting in the cleft maxilla and palate: a retrospective multidisciplinary analysis. Am J Orthod 1994; 86:244–256.

4. Choi HS, Choi HG, Kim SH, Park HJ, Shin DH, Jo DI, Kim CK, Uhm KI. Influence of the Alveolar Cleft Type on Preoperative Estimation Using 3D CT Assessment for Alveolar Cleft. Arch Plast Surg 2012; 39(5):477-482.

5. Aurouze C, Moller KT, Bevis RR, Rehm K, Rudney J. The presurgical status of the alveolar cleft and success of secondary bone grafting. Cleft Palate Craniofac J 2000; 37(2):179-184.

6. Bergland O, Semb G, Abyholm FE. Elimination of the residual alveolar cleft by secondary bone grafting and subsequent orthodontic treatment. Cleft Palate J 1986; 23(3):175-205.

7. Helms J, Speidel M, Denis K. Effect of timing on long-term clinical success of alveolar cleft bone grafts. Am J Orthod 1987; 92:232–240.

8. Long RE, Spangler BE, Yow M. Cleft width and secondary alveolar bone graft success. Cleft Palate J 1995; 35:420–427.

9. Spin-Neto R, Gotfredsen E, Wenzel A. Impact of voxel size variation on CBCT-based diagnostic outcome in dentistry: a systematic review. J Digit Imaging 2013; 26(4):813-820.

10. Kamburoglu K, Murat S, Kolsuz E, Kurt H, Yuksel S, Paksoy C. Comparative assessment of subjective image quality of crosssectional cone-beam computed tomography scans. J Oral Sci 2011; 53:501–508.

11. Quereshy FA, Barnum G, Demko C, Horan M, Palomo JM, Baur DA, Jannuzzi J. Use of cone beam computed tomography to volumetrically assess alveolar cleft defects--preliminary results. J Oral Maxillofac Surg 2012; 70(1):188-191.

12. Feichtinger M, Mossböck R, Kärcher H. Assessment of bone resorption after secondary alveolar bone grafting using three-dimensional computed tomography: a three-year study. Cleft Palate Craniofac J 2007; 44(2):142-148.

13. Albuquerque MA, Gaia BF, Cavalcanti MG. Oral cleft volumetric assessment by 3D multislice computed tomographic images. Int J Oral Maxillofac Surg 2011; 40(11):1280-1288. doi: 10.1016/j.ijom.2011.05.015.

14. Parameters for evaluation and treatment of patients with cleft lip/palate or other craniofacial anomalies. Official publication of the American Cleft Palate-Craniofacial Association. November 2009 Available from: http://www.acpa-cpf.org/uploads/site/Parameters_Rev_2009.pdf

15. Mozzo P, Procacci C, Tacconi A, Martini PT, Andreis IA. A new volumetric CT machine for dental imaging based on the cone-beam technique: preliminary results. Eur Radiol 1998; 8(9):1558-1564.

16. Scarfe WC, Farman AG, Sukovic P. Clinical applications of cone-beam computed tomography in dental practice. J Can Dent Assoc 2006; 72(1):75-80.

17. Ludlow JB, Ivanovic M. Comparative dosimetry of dental CBCT devices and 64-slice CT for oral and maxillofacial radiology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106(1):106-114.

18. SEDENTEXCT guidelines. Safety and Efficacy of a New and Emerging Dental X-ray Modality. Radiation protection no. 172: cone beam CT for dental and maxillofacial radiology (evidence-based guidelines). 2012. Available from: http://www.sedentexct.eu/files/radiation_protection_172.pdf.

19. Ganguly R, Ruprecht A, Vincent S, Hellstein J, Timmons S, Qian F. Accuracy of linear measurement in the Galileos cone beam computed tomography under simulated clinical conditions. Dentomaxillofac Radiol 2011; 40(5):299-305.

20. Stratemann SA, Huang JC, Maki K, Miller AJ, Hatcher DC. Comparison of cone beam computed tomography imaging with physical measures. Dentomaxillofac Radiol 2008; 37(2):80-93.

21. Torres MG, Campos PS, Segundo NP, Navarro M, Crusoe-Rebello I. Accuracy of linear measurements in cone beam computed tomography with different voxel sizes. Implant Dent 2012; 21:150–155.

22. Vasconcelos TV, Neves FS, Queiroz de Freitas D, Campos PS, Watanabe PC. Influence of the milliamperage settings on cone beam computed tomography imaging for implant planning. Int J Oral Maxillofac Implants 2014; 29(6):1364-1368.

23. da Silveira PF, Vizzotto MB, Liedke GS, da Silveira HL, Montagner F, da Silveira HE. Detection of vertical root fractures by conventional radiographic examination and cone beam computed tomography— an in vitro analysis. Dent Traumatol 2013; 29(1):41-46.

24. Kasaven CP, Ivekovic S, McIntyre GT, Gillgrass T, Thomson DA, Menhinick A, Mossey PA. Validation of the volumetric measurement of a simulated maxillary alveolar bone defect using cone-beam computed tomography. Cleft Palate Craniofac J 2013; 50(6):e115-120.

25. Amirlak B, Tang CJ, Becker D, Palomo JM, Gosain AK. Volumetric analysis of simulated alveolar cleft defects and bone grafts using cone beam computed tomography. Plast Reconstr Surg 2013; 131(4):854-859.

26. Hamada Y, Kondoh T, Noguchi K, Iino M, Isono H, Ishii H, Mishima A, Kobayashi K, Seto K. Application of limited cone beam computed tomography to clinical assessment of alveolar bone grafting: a preliminary report. Cleft Palate Craniofac J 2005; 42(2):128-137.

CAPÍTULO 2

GAND classification and volumetric assessment of unilateral cleft lip and palate malformations using cone beam computed tomography

Short title: CBCT based classification for UCLP

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ABSTRACT

The study aimed to propose a classification for unilateral cleft lip and palate (UCLP) malformations based on CBCT images, as well as estimate the amount of bone necessary for grafting and evaluate the relation of this volume with scores attributed in the classification. CBCT images of 33 subjects with UCLP were evaluated according to gap, arch, nasal and dental parameters (GAND classification). Additionally, these defects were segmented and the amount of graft needed for later alveolar bone grafting was estimated. The reproducibility of GAND classification was analyzed by weighted Kappa test. The association of volume assessment with the classification (gap and nasal parameters) was verified using ANOVA, while the intraobserver agreement was analyzed using Intraclass correlation coefficient. The intraobserver reproducibility of the classification ranged from 0.29 to 0.92 and the interobserver ranged from 0.29 to 0.91. There were no statistically significant values when evaluating the association of the volume with the classification ($p>0.05$). The GAND classification is a novel system that allows the quick estimation of the extent and complexity of the cleft. It is not possible to estimate the amount of bone needed for alveolar bone graft based on the classification; individualized surgical planning should be done for each patient specifically.

INTRODUCTION

Orofacial clefts (OFC) are congenital malformations characterized by incomplete formation of structures involving the nasal and oral cavities: lip, alveolus, hard and soft palate. OFC may also vary in size, from a defect limited to the soft palate to a complete cleft that extends through the hard palate, alveolar process, nasal floor and lip. OFC can affect one side (unilateral) or both sides (bilateral) of the patient[1]. The pathogenesis of cleft lip and cleft palate is complex and the most widely accepted model to account for the development of OFC is the multifactorial inheritance, according to which this pathology is connected to the interplay of genetic and environmental factors[2].

Non-syndromic orofacial cleft is the most common congenital malformation affecting 1 in 600 live newborns on an annual worldwide average[1]. Treatment of cleft lip and palate deformities requires several staged surgical procedures and a multidisciplinary approach. The medical and non-medical providers count on the completeness and accuracy of the medical records and images to develop comprehensive treatment plans. Several systems of classification have been used with the objective to facilitate communication among providers and describe the location and extent of the deformities. Most of the classifications available to date identify patterns of cleft phenotypes based on clinical records, photographs, intra-oral models and two-dimensional (2D) images[3-6].

There is an increasing need to move from 2D assessment and grading systems to 3D-based systems. The cone beam computed tomography (CBCT), in particular, allows the assessment of craniofacial abnormalities, with doses to children lower than multislice CT, and has increasingly become important in treatment planning and diagnosis of these conditions[7]. CBCT imaging provides 3D volumetric data of the entire maxillofacial region with high resolution and accuracy[8]. Moreover, the request of these exams for treatment of patients with OFC is justified according to the guidelines of the European Commission in Radiation Protection of CBCT (SEDENTEXCT), allowing the incorporation of CBCT images in OFC management, especially for assessment of alveolar bone grafting, dental implants installation and orthodontic treatment of the cleft-adjacent teeth[3,9].

Regarding OFC, the most accepted classification was developed by Kernahan and Stark (1958), and describes the cleft palate in relative terms by using the incisive foramen as a dividing point[10]. The classification adequately described the most common types of clefts: the complete unilateral cleft lip and palate and the isolated posterior cleft palate. Since then, several modifications and new classifications have been described in the literature[11-14]. However, with the development of CBCT images, the assessment of the cleft using 3D imaging is now feasible and allows medical and dental providers to exchange patient information and improve treatment plans, especially before secondary alveolar bone grafting (ABG).

In this sense, there is a growing need for new methods for cleft assessment and classification based on tomographic images. The present study presents a classification for unilateral alveolar and palatal clefts, based on CBCT images to assist providers in all aspects of treatment planning. It consists on the evaluation of four parameters: **G**ap; **A**rch form; **N**asal floor; and **D**ental features, establishing the GAND classification. This classification proposes a qualitative assessment using scores to evaluate each parameter, being a method to aid clinicians to quickly estimate the extent and magnitude of the cleft. The higher the scores, the higher is the complexity of the cleft.

Regarding the **Gap** or cleft size, it would benefit preoperative planning in the sense that surgeons would be able to estimate the size of the defect and amount of bone necessary for grafting and whether an additional donor area would be needed. This parameter ranges from notched alveolar process to large clefts; these differences may change the type and amount of the selected graft. A successful treatment of notch in the alveolar process can be achieved by small amounts of bone graft that could be obtained from allograft, alloplast or xenograft material[15]. However, for small clefts, autogenous bone from chin, ramus or iliac crest may be indicated; and for large clefts, iliac crest or tibia would be the ideal donor areas[1,16].

In relation to the **Arch** form assessment, it would allow the determination of the position of the lesser segment in relation to the greater segment; and it can be aligned or anteriorly and/or posteriorly constricted. This conformation is directly related to the need for expansion prior to bone grafting since, ideally, the arch should be aligned before surgery avoiding orthodontic expansion of the recently placed bone graft[17,18].

The **Nasal** parameter, estimates the size of the defect present in the nasal base region / piriform margin and helps to determine the need for nasal floor augmentation during preoperative planning. The nasal floor augmentation may improve the position of the alar base on the cleft side and the overall nasal symmetry[19].

The assessment of **Dental** features assists all dental professionals in the craniofacial team in making a decision regarding tooth extractions and space maintenance. It is important, prior to surgical interventions in the cleft region, to determine the presence of supernumerary or malformed teeth that may be extracted at the same procedure[20-23]. In cases of teeth that will erupt in the graft area or patients with missing teeth in the cleft region, the space should be maintained for eruption or for future implant placement with implant-supported dental prosthesis[24-26].

With the incorporation of segmentation and volumetric assessments when processing CBCT images, a quantitative evaluation of the gap and estimations for surgical procedures is also possible. It is worth mentioning that an adequate volume of bone grafted during ABG is crucial for the success of the procedure, and also strongly related to donor site morbidity[27]. This information is increasingly requested by craniofacial teams to improve preoperative planning and procedure predictability.

Previous studies evaluated the bone volume necessary for secondary ABG in the alveolar cleft using surgical simulation software and observed a significant correlation between the preoperative measurements with the actual volume of the bone graft used in the surgical procedure. Consequently, the assessment of the amount of bone needed using CBCT images would be advantageous for cases of cleft repair[27,28].

In this sense, this paper has two distinct purposes: (1) present a classification for unilateral alveolar and palatal clefts based on CBCT images (GAND classification) and evaluate its reliability; (2) estimate the amount of bone graft needed prior to ABG surgeries of these subjects and (3) evaluate the relation of the volumetric values obtained with the Gap and Nasal parameters attributed using the GAND classification.

MATERIAL AND METHODS

After approval of the study by the Institutional Review Board (IRB#11-1560), subjects with UCLP who underwent CBCT examination comprised the research sample. The tomographic exams were acquired for purposes unrelated to the study.

The inclusion criterion consisted of the presence of a unilateral cleft. The exclusion criteria were patients with any diagnosed craniofacial syndrome, previous orthodontic expansion treatment, previous secondary ABG and CBCT exams with excessive scattering and motion artifacts. A total of 50 CBCT exams were inspected for selection of the sample and 17 subjects were excluded from the sample due to orthodontic treatment (n = 11), previous ABG (n = 1) and insufficient image quality (n = 5); obtaining a final sample of 33 subjects.

The enrolled subjects ranged in age from 6 to 11 years old, with average age of 8.03 years old. The study population consisted of 15 females and 18 males, presenting with 11 right unilateral clefts and 22 left defects. Informed consent regarding the use of CBCT data afterwards was obtained from all patients.

For image acquisition, a CS9300 CBCT unit (Carestream Health, Atlanta, GA, USA) operating at 60–90 kVp, 2–15 mA, 17x13.5cm field of view and 0.3 mm voxel size was used. All data were saved in DICOM files for subsequent evaluation in a secluded room with dim light. The study involved two different approaches for distinct purposes: GAND classification and volumetric assessments.

Gand classification assessment

For the first assessment, the images were imported into InVivo software (Anatomage, San Jose, CA, USA) and scored according to the proposed GAND classification. The region of interest in the exam could be observed in multiplanar reconstruction (MPR) using the three planes (axial, sagittal, coronal), as well as using three dimensional reconstruction in maximum intensity projection (MIP). Each CBCT image was classified qualitatively according to the four parameters of the GAND classification based on the position of the lesser segment in relation to the greater segment: G (size of the gap); A (arch form); N (nasal base defect); and D (dental assessment). The classification was previously introduced to the examiners for calibration before image evaluation (Figure 1), as follows:

Gap

The size of the gap should be assessed qualitatively, and it need to be observed in its totality in the MIP reconstruction. The slices may also be observed in order to confirm the extension and boundaries of the defect. The gap is classified as: G1 – Notch of the alveolar process; G2 - Small defect; G3 – Large defect.

Arch Form

The assessment of the arch form should be based on the position of the lesser segment. The arch form can be better visualized in the axial plane in MPR or in MIP reconstructions, clipping the mandible and observing the 3D model in inferosuperior view. The arch form is classified as: A1 – Maxillary arch aligned; A2 – Lesser segment anteriorly constricted; A3 – Lesser segment anteriorly and posteriorly constricted.

Nasal Floor

The magnitude of the defects extending to the nasal floor can be clearly seen on MIP reconstructions, giving a 3D notion in relation to the adjacent structures. The nasal floor is classified as: N1 – Notch of the nasal floor; N2 – Small defect of the nasal floor; N3 – Large defect of the nasal floor.

Dental

For evaluation of teeth and possible alterations, an initial panoramic reconstruction based on the CBCT exam can be done to give an overall view. Next, the slices, should be observed in all three planes to confirm possible diagnosis regarding the number and integrity of teeth adjacent to the cleft. The MIP can also be evaluated. The dental assessment is as follows: D1 – no missing teeth and no malformation; D2 – presence of malformed or supernumerary teeth in the regions adjacent to the cleft; D3 – missing permanent teeth in the regions adjacent to the cleft.

The first evaluation of the classification, used as the gold standard, consisted of a consensus between two authors of the study that designed and proposed the classification (one oral and maxillofacial radiologist and one prosthodontist). After, for the second appraisal, three observers (two oral and maxillofacial radiologists and one prosthodontist) were selected to evaluate the same parameters for validation and replicability of the suggested classification. All five evaluators had experience in cleft assessment. After an interval of two weeks, all observers repeated the same evaluation with the entire sample.

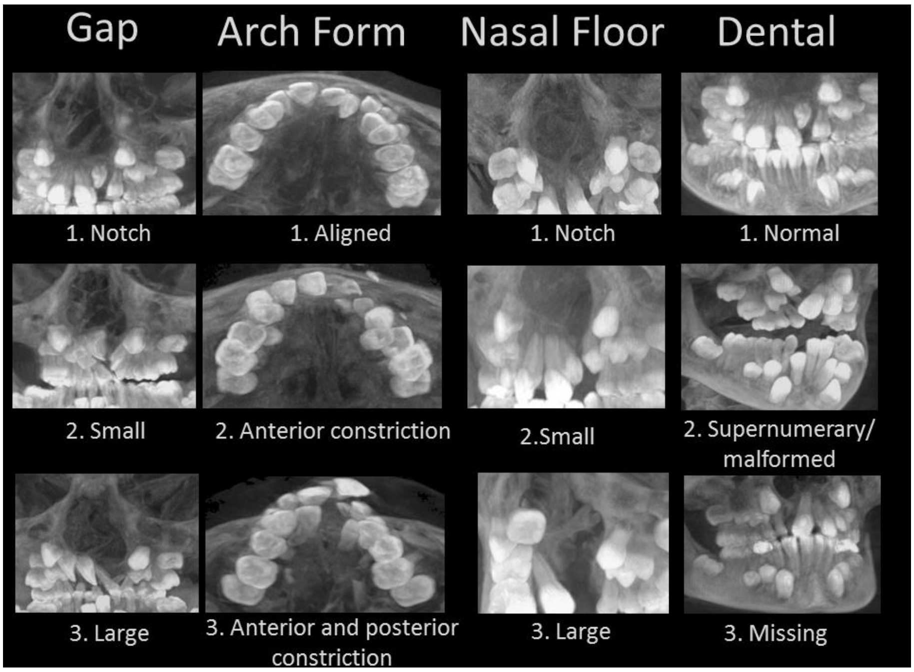

Figure 1 –Examples for each parameter of the GAND classification.

Volumetric evaluation

For this assessment, the images were imported into Mimics software (version 16.0, Materialize Medical, Leuven, Belgium) and appraised by one single observer, an oral and maxillofacial radiologist with experience in tomographic evaluation and segmentation. First, the maxilla was segmented based on threshold selection and manual editing. Once the volumetric model of the cleft region was obtained, a simulation of bone graft filling was performed. First, the threshold of the air/defect was selected, and a combination of 2D and 3D manual editing was performed, following the maxillary contralateral side contours. The boundaries of the filling were a continuation of the cleft margins, thus a continuation of the alveolar process inferiorly, anteriorly and posteriorly and a continuation of the nasal margins superiorly.

The definition of the region that should be filled with bone was elucidated by the surgeons of the craniofacial center during preoperative simulation of those subjects. Once the volume was defined, a 3D model was created and its volume was automatically given by the software in mm^3. After a two-week interval, the same volumetric evaluation was repeated with 25% of the sample.

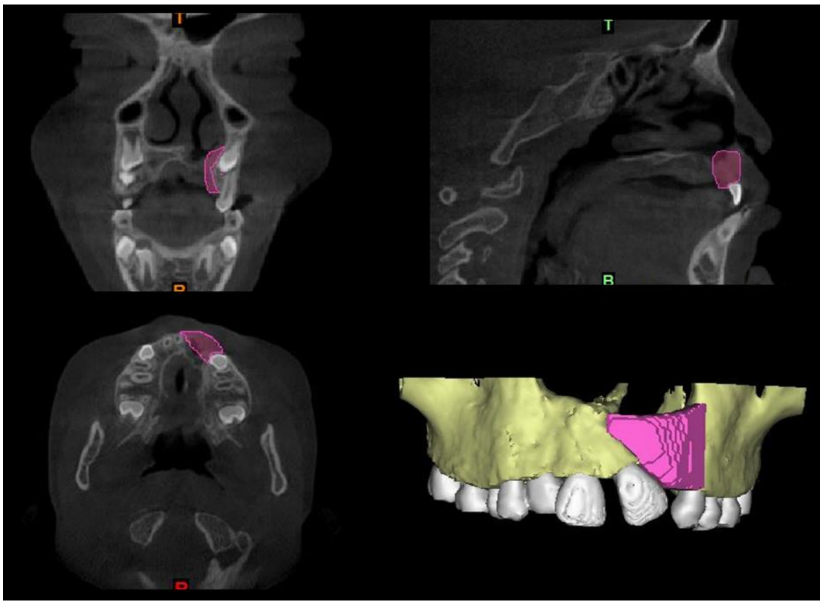

Figure 2 – Segmentation of the maxilla and region that will be filled with bone graft (pink volume).

Statistical analysis

GAND classification scores and the reproducibility among the observers were assessed by weighted Cohen's kappa with 95% confidence intervals (CI). Intra and inter observer reproducibility examination were performed using MedCalc software version 11.2.1.0 (MedCalc Software, Mariakerke, Belgium). Observer agreement was categorized by kappa values as poor (<0.0), slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), or almost perfect (0.81-1.00) (Landis e Koch, 1977)[29].

In relation to the volumetric evaluation and its association with parameters of the GAND classification, analysis of variance (ANOVA) was performed by SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA); p values < 0.05 were considered statistically significant.

Intraobserver agreement in volumetric evaluation was calculated by intraclass correlation coefficients (ICC) using MedCalc software version 11.2.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

The final sample of the study consisted of 33 CBCT exams of subjects presenting with unilateral cleft. The gender distribution of the sample was balanced (54.54% male and 45.45% female). It was observed a significant higher number of defects affecting the left side (66.66%) than the right side (33.33%).

Reproducibility Analysis

The intraobserver agreement values obtained by weighted Kappa analysis ranged from 0.69 to 0.87 for Observer 1, from 0.29 to 0.79 for Observer 2 and from 0.39 to 0.92 for Observer 3, representing substantial to almost perfect, fair to substantial and fair to almost perfect agreement for each evaluator respectively (Landis e Koch,1977)[29]. It can be observed that the lowest values were obtained in the arch assessment, and the highest, in the dental assessment (Table 1).

The kappa values for the interobserver agreement ranged from 0.29 to 0.91, with a confidence interval of 95%. The detailed results can be observed in Table 1.

In the GAP parameter evaluation, the kappa values ranged from 0.56 to 0.81, representing moderate to almost perfect agreement. For the ARCH parameter, the values ranged from 0.29 to 0.52, a fair to moderate agreement. For the NASAL parameter, the values ranged from 0.503 to 0.638, a moderate to substantial agreement. And, for the DENTAL assessment, values ranging from 0.67 to 0.91 were observed, representing substantial to almost perfect agreement.

Volume association Analysis

The mean volume of the sample was 0.86cm^3 ± 0.35 cm^3, ranging from 0.34 to 1.97 cm^3. The intraobserver agreement value according to the ICC was 0.97 (with a CI ranging from 0.85 to 0.99), demonstrating an excellent correlation of the evaluator, according to ICC interpretation by Szklo and Nieto (2000)[30].

ANOVA test showed no statistical significant differences when the volumes were compared among Gap (0.21) and Nasal (0.34) parameters scores of the GAND classification. However, even without statistical significance, a tendency to higher volumes in higher scores was found and it can be observed in the presented boxplots (Figure 3 and 4).

Table 1 – Kappa values for intra and inter observer agreement for GAND classification.

Parameter	Evaluator	Gold standard		1		2		3	
		Kappa	CI 95%	Kappa	CI 95%	Kappa	CI 95%	Kappa	CI 95%
GAP	1	0.71	(0.50 - 0.92)	0.69	(0.45 - 0.93)	*	*	*	*
	2	0.72	(0.52 - 0.92)	0.81	(0.62 - 0.99)	0.60	(0.32 - 0.88)	*	*
	3	0.62	(0.40 - 0.84)	0.63	(0.41 - 0.85)	0.56	(0.33 - 0.79)	0.67	(0.44 - 0.90)
ARCH	1	0.52	(0.29 - 0.76)	0.70	(0.49 - 0.91)	*	*	*	*
	2	0.40	(0.17 - 0.63)	0.50	(0.25 - 0.75)	0.29	(-0.005 - 0.58)	*	*
	3	0.40	(0.16 - 0.63)	0.54	(0.25 - 0.84)	0.29	(-0.011 - 0.59)	0.39	(0.05 - 0.72)
NASAL	1	0.64	(0.42 - 0.86)	0.69	(0.47 - 0.92)	*	*	*	*
	2	0.63	(0.41 - 0.86)	0.59	(0.35 - 0.83)	0.67	(0.45 - 0.90)	*	*
	3	0.56	(0.34 - 0.77)	0.59	(0.38 - 0.80)	0.50	(0.29 - 0.72)	0.46	(0.26 - 0.65)
DENTAL	1	0.66	(0.50 - 0.83)	0.87	(0.74 - 1)	*	*	*	*
	2	0.91	(0.78 - 1)	0.67	(0.49 - 0.85)	0.79	(0.63 - 0.95)	*	*
	3	0.77	(0.61 - 0.93)	0.88	(0.75 - 1)	0.78	(0.61 - 0.95)	0.92	(0.80 - 1)

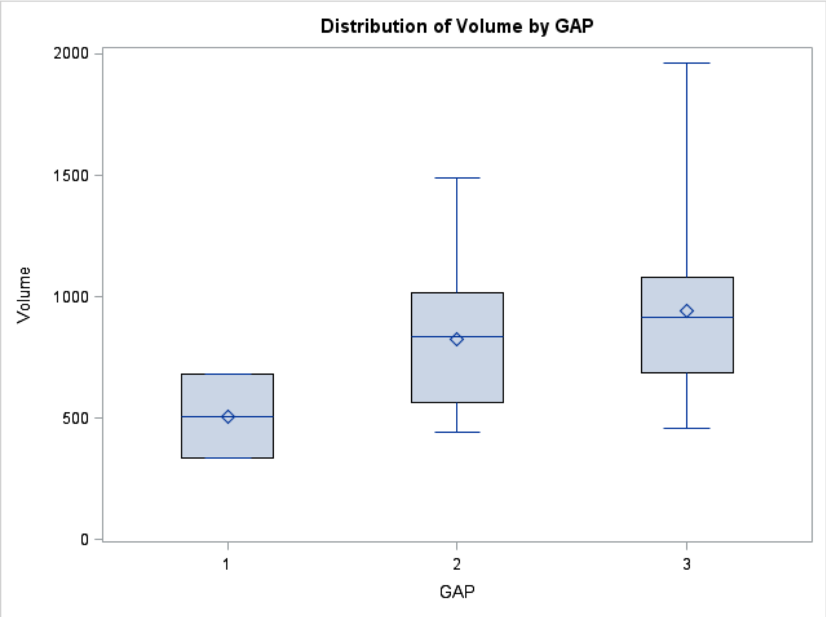

Figure 3 – Distribution of the volumes by gap parameter scores

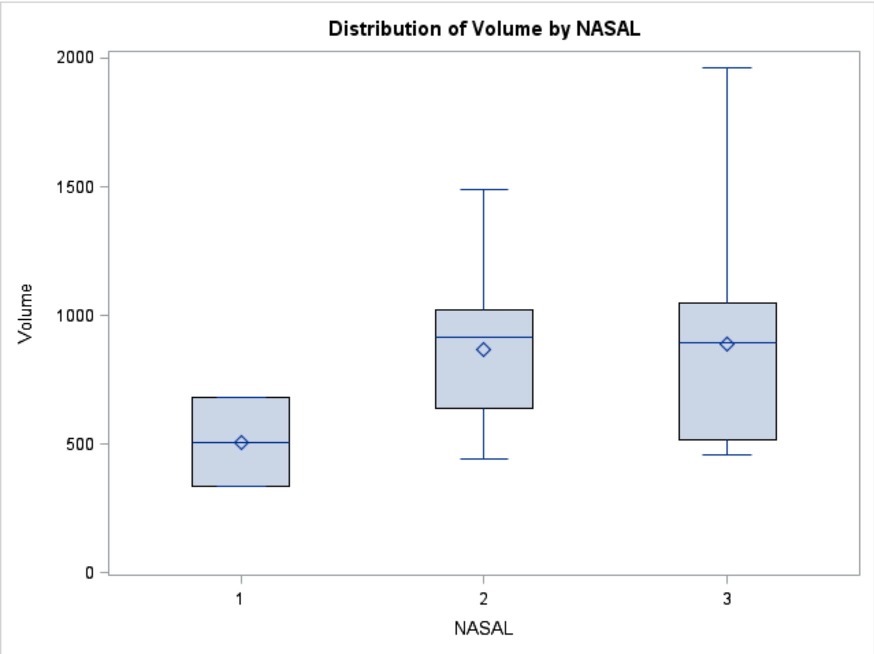

Figure 4 – Distribution of the volumes by nasal parameter scores

DISCUSSION

Documentation in dental, surgical, orthodontic and prosthodontic treatment of individuals born with craniofacial anomalies has historically been based on photographs, radiographs (panoramic, cephalometric, occlusal and periapicals) and stone casts, allowing only a limited degree of 3D assessment[3-6]. With the development of CBCT, greater diagnostic information is available resulting in its increasing importance in the diagnosis and treatment of craniofacial anomalies[31,32]. New possibilities for assessing craniofacial abnormalities are being proposed, highlighting the studies regarding preoperative planning for ABG.

Currently, CBCT exams are frequently requested at some point of the treatment of patients with OFC by the health care providers of craniofacial teams all over the world. In this sense, a classification based on tomographic images would improve diagnosis and communication. These are desirable characteristics in cleft classification schemes; however they are, in general, deficient in providing information that helps to define future steps in treatment planning[33]. In this regard, the assessment of bone graft volume prior to ABG procedures increases predictability and the possibility to reduce surgical time and morbidity. Prior estimates of bone volume were not based on objective diagnostic criteria, thus the extracted amount could be excessive or deficient[27,28]. Moreover, the extension of the defect and involvement of adjacent structures can change the treatment and prognosis.

When a new classification or index is proposed, it must be easy to score and become intuitive. Also, it is important to calculate its reproducibility to evaluate if it gives repeatable results when the same subject is assessed by different observers at different time points. The kappa values from Gap, Nasal and Dental parameters were satisfactory/excellent. These assessments were proved reliable and can be used for tomographic interpretation of patients with unilateral clefts.

The lowest kappa values of the study were observed in the arch assessment (Table 1). This might be explained by the confusion caused by the presence of multiple teeth adjacent to the cleft region due to mixed dentition and dental crowding. Also, it was observed that, in some cases, the arch was classified as anteriorly and posteriorly constricted but in fact it was aligned with severe maxillary deficiency, causing misinterpretation. However, it must be mentioned that kappa values tend to be low if data are much skewed, even if agreement is close to 100%.

Nevertheless, the arch form and maxillomandibular relationship are well diagnosed by clinical examination which would eliminate possible misinterpretations of this parameter. It is important to report these features in the patient chart to improve later multidisciplinary treatment planning and team discussion. In an attempt to improve the amount of information during team meetings, it is also possible to incorporate intraoral scanning generating virtual models of the patient and even perform treatment simulations. Since low kappa values were observed for this parameter, it can also be suggested that quantitative assessments would be beneficial, adding information to it and helping in the final diagnosis. One possible alternative that has to be further tested is the use of linear measurements assessing, posteriorly, the distance between first permanent molars and, anteriorly, the distances between primary first molars. Specific ratios between these measurements would differ between aligned and constricted arches.

The defect extension in the nasal region was selected as a parameter of the classification since one of the main goals of secondary ABG is to provide support to the alar base[1,34]. It helps to increase the position of the nasal base and to improve overall nasal symmetry, consequently improving facial esthetics, as it induces changes in the soft tissue profile. Previous studies have demonstrated that the nostril sill is elevated after ABG, and in addition, the height of the upper lip can also be elongated[34]. Nevertheless, care should be taken to avoid excessive bony augmentation under the alar base, which can occlude the ipsilateral nostril, causing functional breathing problems, and can distort alar symmetry.

Dental assessment for GAND classification takes into consideration the presence of supernumerary, missing or malformed teeth. These criteria were defined since it is reported that the most frequently observed dental anomaly in UCLP subjects is tooth agenesis, with incidence of 92.5%[21]. Also, high occurrence of supernumerary tooth, morphological anomalies in both dentitions, delayed tooth development and eruption and microdontia have been described[22]. It is worth mentioning that the prevalence of these alterations is greater in patients with OFC than in children without clefts[20,35].

Based on the gold standard evaluation, from the total sample of the present study, only 6.06% subjects were classified as not having any type of dental anomalies, 45.45% as having supernumerary or malformed teeth and 48.48% as having any missing teeth in the cleft region, which is in agreement with occurrences reported in the literature.

This dental assessment aims to improve treatment planning prior to surgical interventions in the cleft region, to determine the need of extractions at the same procedure. The higher kappa values were observed in this assessment (Table 1), probably because it is the feature that the evaluators are more familiar with.

However, even with an excellent correlation, a quantitative evaluation can be combined adding more information and reducing the subjectivity of the process. In this sense, incorporating information regarding the eruption process of teeth in the cleft region is a possible alternative and would benefit the diagnosis and decision of ABG timing. Though chronological age (usually between 8 and 10 years of age) is an important part of the decision-making process, the state of the developing dentition is the primary factor to guide this decision[16]. The timing of secondary ABG is widely discussed, but many consider it appropriate to graft prior to canine eruption, during eruption of the central and lateral incisors, when present. In this regard, it is possible to evaluate the canine position in relation to the thirds of the incisors roots and anatomical crest of the alveolar bone, using a paracoronal view in CBCT images[36].

In relation to the volumetric evaluation, the average volume of the sample was 0.86 cm^3 (±0.35), a similar value when compared to the average volumes described by Choi et al., 2012[27], and lower when compared to the study of Shirota et al., 2010[28]. This can be explained by the difference in the mean age of the sample studies; the present study has a sample with mean age comparable to Choi et al., 2012, while Shirota et al., 2010 had a sample 14 years older. These previous studies calculated the volume by different methods, delimiting the area of the defect slice by slice, whereas the present research had a three dimensional approach that was also proved reliable and accurate. Moreover, the technique used allows the 3D view of the combination maxilla-defect for better understanding of the filling shape, with smooth margins delimited by hard tissues.

Differently from previous studies[27,28], it was not possible to correlate the simulation with the actual volume used. This was because the surgeons on the team where the present study was conducted support that different pressure on the syringe plunger can affect the volume and thus the precise measurement of bone. In agreement, it is reported that methods for accurately measuring this volume during surgery still have to be established[28].

The purpose of assessing the correlation between volumetric assessment and the classification (Gap and Nasal parameters) was to establish a volume range for each one of the three scores (G1/G2/G3 and N1/N2/N3). A positive correlation would lead to an estimation of the amount of bone graft needed prior to ABG surgeries, without the time consuming segmentation and volumetric appraisal. No association was observed, still, even without statistically significance, it could be observed a growing trend in the boxplots (Figures 3 and 4) and that the bigger the defects, the larger the volumes. However, since no statistical significance was observed, an individualized volumetric assessment for preoperative planning is recommended for each subject that will undergo ABG, improving the predictability of the procedure.

The incorporation of 3D imaging in the management of patients with OFC has allowed a greater understanding of the true dimensions of the defects and new classifications based on these exams should be developed. The GAND classification is a novel system that allows the quick estimation of the extent and complexity of the cleft and it can be used as a communication tool. For better results, it is recommended to incorporate clinical findings with the tomographic examination, especially for the arch parameter. The study also concludes that it is not possible to estimate the amount of bone needed for ABG based on the classification; individualized segmentation and virtual surgical planning should be done for each patient specifically.

REFERENCES

1. Cobourne MT. Cleft lip and palate: epidemiology, aetiology, and treatment (vol 16). Front Oral Biol. Basel, Karger, 2012.

2. Mangold E, Ludwig KU, Nöthen MM. Breakthroughs in the genetics of orofacial clefting. Trends Mol Med 2011: 17(12):725-733.

3. Hamada Y, Kondoh T, Noguchi K, Iino M, Isono H, Ishii H, Mishima A, Kobayashi K, Seto K. Application of limited cone beam computed tomography to clinical assessment of alveolar bone grafting: a preliminary report. Cleft Palate Craniofac J 2005: 42(2):128-137.

4. Bergland O, Semb G, Abyholm FE. Elimination of the residual alveolar cleft by secondary bone grafting and subsequent orthodontic treatment. Cleft Palate J 1986: 23:175–205.

5. Long RE Jr, Spangler BE, Yow M. Cleft width and secondary alveolar bone graft success. Cleft Palate Craniofac J 1995: 32:420–427.

6. Kindelan JD, Nashed RR, Bromige MR. Radiographic assessment of secondary autogenous alveolar bone grafting in cleft lip and palate patients. Cleft Palate Craniofac J 1997: 34:195–198.

7. Zamora N, Cibrián R, Gandia JL, Paredes V. A new 3D method for measuring cranio-facial relationships with cone beam computed tomography (CBCT). Med Oral Patol Oral Cir Bucal 2013:1;18(4):e706-713.

8. Periago DR, Scarfe WC, Moshiri M, Scheetz JP, Silveira AM, Farman AG. Linear accuracy and reliability of cone beam CT derived 3-dimensional images constructed using an orthodontic volumetric rendering program. Angle Orthod 2008: 78(3):387-395.

9. SEDENTEXCT guidelines. Safety and Efficacy of a New and Emerging Dental X-ray Modality. Radiation protection no. 172: cone beam CT for dental and maxillofacial radiology (evidence-based guidelines), 2012 Available from: http://www.sedentexct.eu/files/radiation_protection_172.pdf.

10. Kernahan DA, Stark RB. A new classification for cleft lip and cleft palate. Plast Reconstr Surg Transplant Bull 1958: 22(5):435-441.

11. Kernahan DA. The striped Y--a symbolic classification for cleft lip and palate. Plast Reconstr Surg 1971: 47(5):469-470.

12. Elsahy NI. The modified striped Y--a systematic classification for cleft lip and palate. Cleft Palate J 1973: 10:247-250.

13. Smith AW, Khoo AK, Jackson IT. A modification of the Kernahan "Y" classification in cleft lip and palate deformities. Plast Reconstr Surg 1998: 102(6):1842-1847.

14. Schwartz S, Kapala JT, Rajchgot H, Roberts GL. Accurate and systematic numerical recording system for the identification of various types of lip and maxillary clefts (RPL system). Cleft Palate Craniofac J 1993: 30(3):330-332.

15. Paganelli C, Fontana P, Porta F, Majorana A, Pazzaglia UE, Sapelli PL. Indications on suitable scaffold as carrier of stem cells in the alveoloplasty of cleft palate. J Oral Rehabil 2006: 33(8):625-629.

16. Cho-Lee GY, García-Díez EM, Nunes RA, Martí-Pagès C, Sieira-Gil R, Rivera-Baró A. Review of secondary alveolar cleft repair. Ann Maxillofac Surg 2013: 3(1):46-50.

17. Vig KW. Alveolar bone grafts: the surgical/orthodontic management of the cleft maxilla. Ann Acad Med Singapore 1999: 28(5): 721-727.

18. McIntyre GT, Devlin MF. Secondary alveolar bone grafting (CLEFTSiS) 2000-2004. Cleft Palate Craniofac J 2010: 47(1):66-72.

19. Ahuja RB. Primary definitive nasal correction in patients presenting for late unilateral cleft lip repair. Plast Reconstr Surg 2002: 110(1): 17-24.

20. Wu TT, Chen PK, Lo LJ, Cheng MC, Ko EW. The characteristics and distribution of dental anomalies in patients with cleft. Chang Gung Med J 2011: 34(3):306-314.

21. Celikoglu M, Buyuk SK, Sekerci AE, Cantekin K, Candirli C. Maxillary dental anomalies in patients with cleft lip and palate: a cone beam computed tomography study. J Clin Pediatr Dent 2015: 39(2):183-186.

22. Haque S, Alam MK. Common dental anomalies in cleft lip and palate patients. Malays J Med Sci 2015: 22(2):55-60.

23. Santiago PE, Schuster LA, Levy-Bercowski D. Management of the alveolar cleft. Clin Plast Surg 2014:41(2):219-232.

24. Yilmaz S, Kiliç AR, Keles A, Efeoğlu E. Reconstruction of an alveolar cleft for orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2000: 117(2):156-163.

25. Rosenstein SW, Grasseschi M, Dado DV. A long-term retrospective outcome assessment of facial growth, secondary surgical need, and maxillary lateral incisor status in a surgical-orthodontic protocol for complete clefts. Plast Reconstr Surg 2003: 111(1):1-13; discussion 14-6.

26. Sedlackova K, Duskova M, Strnadel T, Kotova M, Haas M. Using dental implants in the prosthetic rehabilitation of patients with cleft defect type II. Cleft Palate Craniofac J 2011: 48(1):98-102.

27. Choi HS, Choi HG, Kim SH, Park HJ, Shin DH, Jo DI, Kim CK, Uhm KI. Influence of the Alveolar Cleft Type on Preoperative Estimation Using 3D CT Assessment for Alveolar Cleft. Arch Plast Surg 2012: 39(5):477-482.

28. Shirota T, Kurabayashi H, Ogura H, Seki K, Maki K, Shintani S. Analysis of bone volume using computer simulation system for secondary bone graft in alveolar cleft. Int J Oral Maxillofac Surg 2010: 39(9):904-908.

29. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977: 33(1):159-174.

30. Szklo R, Nieto FJ. Epidemiology beyond the basis. Annapolis: Aspen Publications; 2000: 343–404.

31. Oberoi S, Knueppel S. Three-dimensional assessment of impacted canines and root resorption using cone beam computed tomography. Oral Surg Oral Med Oral Pathol Oral Radiol 2012: 113(2):260-267.

32. Seth V, Kamath P, Vaidya N. Cone beam computed tomography: third eye in diagnosis and treatment planning. Int J Orthod Milwaukee 2012: 23(2):17-22.

33. Liu Q, Yang ML, Li ZJ, Bai XF, Wang XK, Lu L, Wang YX. A simple and precise classification for cleft lip and palate: a five-digit numerical recording system. Cleft Palate Craniofac J 2007: 44(5):465-468.

34. Kim SW, Park SO, Choi TH, Hai do T. Change in upper lip height and nostril sill after alveolar bone grafting in unilateral cleft lip alveolus patients. J Plast Reconstr Aesthet Surg 2012: 65(5):558-563.

35. Tortora C, Meazzini MC, Garattini G, Brusati R. Prevalence of abnormalities in dental structure, position, and eruption pattern in a population of unilateral and bilateral cleft lip and palate patients. Cleft Palate Craniofac J 2008: 45(2):154-162.

36. Suomalainen A, Åberg T, Rautio J, Hurmerinta K. Cone beam computed tomography in the assessment of alveolar bone grafting in children with unilateral cleft lip and palate. Eur J Orthod 2014: 36(5):603-611.

DISCUSSÃO

As fissuras orofaciais estão entre os defeitos de nascimento mais comuns e tratáveis, afetando em média 1 em cada 600 bebês nascidos vivos anualmente no mundo (Peterson-Falzone et al., 2009). O tamanho e extensão dos defeitos, bem como o comprometimento das estruturas adjacentes, podem variar de indivíduo para indivíduo, envolvendo estruturas das cavidades nasal e oral. As fissuras são tradicionalmente classificadas por sua posição anatômica e origem embrionária, não havendo, no entanto, classificações que levem em consideração a conformação da fissura e efeitos nas estruturas adjacentes, motivando assim a busca por uma nova classificação que também leve em consideração outros parâmetros e não a fissura isoladamente, gerando um dos objetivos da presente pesquisa.

A maioria das crianças afetadas por esses defeitos requerem um longo e despendioso tratamento multidisciplinar, que se inicia pelo reparo de tecidos moles e geralmente culmina na enxertia óssea alveolar na região para o completo reparo dos defeitos ósseos da fissura. O adequado planejamento do enxerto ósseo é de grande importância, uma vez que uma enxertia com quantidade insuficiente de osso leva a futuras intervenções para finalizar-se o reestabelecimento ósseo da região, tanto na região alveolar quanto nasal. Além disso, a superestimação da quantidade de osso necessária a ser colhida gera uma remoção desnecessária no sítio doador aumentando a morbidade (Cobourne, 2012).

Para o planejamento desses procedimentos eram utilizados modelos de gesso e exames por imagem bidimensionais, como radiografias periapicais, oclusais e panorâmicas. No entanto, com o crescente uso dos exames tomográficos na prática odontológica e em centros craniofaciais para tratamento de indivíduos com malformações, planejamentos por meios tridimensionais são viáveis, inclusive sendo possível a estimação do volume do defeito por meio das imagens. Para essa finalidade, diferentes métodos foram propostos na literatura, como a mensuração baseada em pontos de referência e nas áreas do defeito ao longo das reconstruções axiais (Quereshy et al., 2012; Feichtinger et al., 2007). Além disso, a incorporação da tomografia computadorizada de feixe cônico (TCFC) no tratamento de pacientes com fissuras permitiu a realização de segmentação volumétrica para diversas finalidades como por exemplo a avaliação de vias aéreas (Pimenta et al., 2014).

Nesse sentido, a presente pesquisa objetivou comparar tais métodos propostos com um padrão ouro, para assim indicar as melhores técnicas para a estimação de volume dos defeitos ósseos. Apenas o método proposto por Quereshy et al., 2012 mostrou-se inadequado para a avaliação, apresentando volumes superestimados, provavelmente pela conformação particular de cada defeito, sendo improvável ter-se uma medida acurada de seu volume apenas baseando-se na altura, largura e profundidade da fissura.

Ainda com relação ao crescente uso da TCFC como método por imagem durante o planejamento do tratamento de pacientes com fissuras, novas classificações com base nesses exames devem ainda ser desenvolvidas. O presente estudo propõe a classificação GAND com o intuito de ampliar a incorporação das informações obtidas pela TCFC nas discussões dos profissionais e gerar um maior entendimento da conformação tridimensional da fissura.

Além disso, a presente pesquisa buscou correlacionar o volume das fissuras com dois dos quatro parâmetros da classificação GAND (Defeito e Nasal / Gap e Nasal), para se estimar o volume ósseo necessário para o enxerto na região sem a mensuração volumétrica do defeito, obtendo-se uma previsibilidade baseada em avaliação subjetiva. No entanto, os resultados obtidos no estudo refletem uma tendência de maiores volumes nos maiores escores da classificação, sem significância estatística. Assim, para que haja uma acurada estimação do volume ósseo necessário deve-se realizar a avaliação volumétrica objetiva, tanto pelo método de segmentação quanto pela medida das áreas do defeito que se mostraram acurados em relação ao padrão ouro, independentemente dos tamanhos do campo de visão e voxel empregados na aquisição da imagem.

A classificação proposta também incorpora a avaliação dos dentes adjacentes à fissura uma vez que são reportadas na literatura taxas bastante elevadas quanto à presença de anomalias dentárias nos indivíduos com fissuras. Alterações como agenesia, dente supranumerário, erupção e desenvolvimento tardios, microdontia e alterações morfológicas são reportadas (Haque e Alam, 2015). Assim, no parâmetro Dental (Dental), deveriam ser observadas tais alterações, o que gerou um percentual de apenas 6,06% dos indivíduos da amostra sem nenhum tipo de anomalia dentária.

Com relação ao parâmetro Arco (Arch), baseando-se nos valores de kappa, indica-se a incorporação das informações obtidas no exame clínico intraoral com a observação tridimensional da conformação do arco no exame tomográfico, para assim ter-se maior entendimento da complexa organização dessas estruturas. Pode-se inclusive incorporar o escaneamento intraoral para a melhor discussão entre os integrantes da equipe multidisciplinar do centro craniofacial além de permitir o arquivamento digital tridimensional dessa informação.

Assim, com base nos resultados do estudo, percebe-se que a incorporação de imagens tridimensionais no manejo de pacientes com fissuras permitiu uma maior compreensão das verdadeiras dimensões dos defeitos e seus efeitos nas estruturas adjacentes.

CONCLUSÃO

A classificação GAND é um novo sistema que permite a avaliação rápida da extensão e complexidade da fenda. Para melhores resultados, recomenda-se incorporar resultados clínicos com o exame tomográfico, especialmente para o parâmetro arco. Não é possível estimar a quantidade de osso necessária para enxerto ósseo baseando-se na classificação GAND, indicando-se segmentação individualizada para cada paciente. Nesse sentido, para a realização de um acurado plano de tratamento e simulação pré-cirúrgica, métodos baseados na segmentação tridimensional da região de interesse ou na mensuração das áreas do defeito em cortes axiais podem ser usados para o cálculo do volume de fissuras alveolares/palatinas, independentemente do tamanho de FOV e voxel empregados na aquisição da imagem.

REFERÊNCIAS*

Albuquerque MA, Gaia BF, Cavalcanti MG. Oral cleft volumetric assessment by 3D multislice computed tomographic images. Int J Oral Maxillofac Surg. 2011;40(11):1280-8.

Aurouze C, Moller KT, Bevis RR, Rehm K, Rudney J. The presurgical status of the alveolar cleft and success of secondary bone grafting. Cleft Palate Craniofac J. 2000; 37(2):179-84.

Bergland O, Semb G, Abyholm FE. Elimination of the residual alveolar cleft by secondary bone grafting and subsequent orthodontic treatment. Cleft Palate J. 1986;23(3):175-205.

Brito LA, Meira JG, Kobayashi GS, Passos-Bueno MR. Genetics and management of the patient with orofacial cleft. Plast Surg Int. 2012;2012:782821.

Choi HS, Choi HG, Kim SH, Park HJ, Shin DH, Jo DI, et al. Influence of the alveolar cleft type on preoperative estimation using 3d ct assessment for alveolar cleft. Arch Plast Surg. 2012;39(5):477-82.

Cobourne MT. Cleft lip and palate: epidemiology, aetiology, and treatment (vol 16). Front Oral Biol. Basel: Karger; 2012.

Feichtinger M, Mossböck R, Kärcher H. Assessment of bone resorption after secondary alveolar bone grafting using three-dimensional computed tomography: a three-year study. Cleft Palate Craniofac J. 2007;44(2):142-8.

Garib DG, Yatabe MS, Ozawa TO, da Silva Filho OG. Alveolar bone morphology in patients with bilateral complete cleft lip and palate in the mixed dentition: cone beam computed tomography evaluation. Cleft Palate Craniofac J. 2012;49(2):208-14.

Haque S, Alam MK. Common dental anomalies in cleft lip and palate patients. Malays J Med Sci 2015;22(2):55-60.

Helms J, Speidel M, Denis K. Effect of timing on long-term clinical success of alveolar cleft bone grafts. Am J Orthod. 1987; 92(3):232–40.

Long RE, Spangler BE, Yow M. Cleft width and secondary alveolar bone graft success. Cleft Palate J. 1995;32(5):420–7.

Neville BW, Damm DD, Allen CM, Chi AC. Oral and maxillofacial pathology. 4th Ed. St Louis: Saunders, 2016.

Oberoi S, Chigurupati R, Gill P, Hoffman WY, Vargervik K. Volumetric assessment of secondary alveolar bone grafting using cone beam computed tomography. Cleft Palate Craniofac J. 2009;46(5):503-11.

* De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors. Abreviatura dos periódicos em conformidade com o Medline.

Oberoi S, Gill P, Chigurupati R, Hoffman WY, Hatcher DC, Vargervik K. Three-dimensional assessment of the eruption path of the canine in individuals with bone-grafted alveolar clefts using cone beam computed tomography. Cleft Palate Craniofac J. 2010;47(5):507-12.

Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. National Birth Defects Prevention Network. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010;88(12):1008-16.

Peterson-Falzone SJ, Hardin-Jones MA, Karnell MP. Cleft Palate Speech. 4th ed. United States of America: Mosby Elsevier; 2009.

Pimenta LA, de Rezende Barbosa GL, Pretti H, Emodi O, van Aalst J, Rossouw PE, et al. Three-dimensional evaluation of nasopharyngeal airways of unilateral cleft lip and palate patients. Laryngoscope. 2015 125(3):736-9.

Quereshy FA, Barnum G, Demko C, Horan M, Palomo JM, Baur DA, et al. Use of cone beam computed tomography to volumetrically assess alveolar cleft defects--preliminary results. J Oral Maxillofac Surg. 2012;70(1):188-91.

Santiago PE, Schuster LA, Levy-Bercowski D. Management of the alveolar cleft. Clin Plast Surg. 2014:41(2):219-32.

Schneiderman ED, Xu H, Salyer KE. Characterization of the maxillary complex in unilateral cleft lip and palate using cone-beam computed tomography: a preliminary study. J Craniofac Surg. 2009;20 Suppl 2:1699-710.

SEDENTEXCT guidelines. Safety and efficacy of a new and emerging dental x-ray modality. radiation protection no. 172: cone beam CT for dental and maxillofacial radiology (evidence-based guidelines), 2012 Disponível em: http://www.sedentexct.eu/files/radiation_protection_172.pdf.

Spina V, Psillakis JM, Lapa FS. Classificação das fissuras lábio-palatinas: sugestão de modificação. Rev Hosp Clin Fac Med São Paulo. 1972;27:5-6.

Steinberg B, Caccamese J Jr, Padwa BL. Cleft and craniofacial surgery. J Oral Maxillofac Surg. 2012;70(11 Suppl 3):e137-61..

Trindade IEK, Silva Filho OG. Fissuras labiopalatinas. Brasil: Livraria Santos Editora; 2007.

World Health Organization. Global strategies to reduce the health-care burden of craniofacial anomalies. Report of WHO Meetings on International Collaborative Research on Craniofacial Anomalies: WHO Human Genetics Programme; Geneva,Switzerland; 2002.

APÊNDICE 1 - Metodologia expandida

O presente trabalho consistiu em dois estudos, um *in vitro* e um *in vivo*. Para o estudo *in vitro* foram confeccionados defeitos unilaterais para simular uma fissura alveolo palatina em crânios plásticos. Usando três crânios feitos de material radiopaco (3B Scientific, Hamburg, Germany), os defeitos foram criados por um cirurgião plástico no lado esquerdo variando a forma e o tamanho usando uma lâmina de serra fina (ref 5100-337-233, Stryker, Kalamazoo, MI, USA) para remoção e remodelação óssea cirúrgica acoplada a uma micro serra recíproca RemB (Stryker, Kalamazoo, MI, EUA).

Após a confecção dos defeitos, foi realizado o acabamento dos mesmos utilizando uma broca maxicut de tungstênio em peça de mão em baixa rotação para que fossem removidos os restos de plástico na região, bem como regularizar e remover os ângulos retos criados pela micro serra. Uma vez finalizados os defeitos, eles foram totalmente preenchidos com cera utilidade vermelha (Kerr Dental Laboratory Products, Orange, CA, EUA) seguindo os contornos maxilares contralaterais para que houvesse uma continuidade dos processos alveolares e palatinos.

Cada crânio foi posicionado no tomógrafo computadorizado de feixe cônico CS9300 (Carestream Dental, Atlanta, GA, EUA) para aquisição das imagens tomográficas, de forma que a linha de orientação sagital coincidisse com o plano sagital mediano e a linha de orientação axial ficasse paralela ao plano de Frankfurt.

Inicialmente, um scout (imagem inicial adquirida em um exame de tomografia computadorizada, semelhante a uma radiografia, com a finalidade de orientar o posicionamento do paciente/objeto dentro do campo de visão) foi obtido para posicionamento do crânio, de forma que a maxila estivesse centralizada dentro dos limites do *Field of View* ou Campo de Visão (FOV). Ajustes no posicionamento eram realizados, caso necessário.

As imagens foram adquiridas empregando-se dois tamanhos de FOV grande disponíveis no aparelho e dois tamanhos de voxel que eram disponibilizados automaticamente quando o tamanho do FOV era selecionado, gerando assim, quatro protocolos de aquisição (Tabela 1).

A quilovoltagem-pico (kVp) e a miliamperagem (mA) foram mantidas a 85 kVp e 4 mA em todos os protocolos. O tempo de exposição e a *dose area product* (DAP) variaram automaticamente de acordo com o tamanho de FOV selecionado.

Tabela 1 – Protocolos de imagem utilizados na pesquisa

Protocolo	FOV (cm)	Voxel (mm)	kVp	mA	Tempo (s)	DAP (mGy.cm^2)
1	17 x 11	0.25	85	4	6.4	770
2	17 x 11	0.50	85	4	6.4	770
3	17 x 13.5	0.30	85	4	11.3	1359
4	17 x 13.5	0.50	85	4	11.3	1359

Após a aquisição, as imagens foram exportadas no formato DICOM e importadas para o programa inVivo (Anatomage Inc, San Jose, CA) e Mimics (Materialise Medical, Leuven, Belgium), nos quais foram empregados três métodos para avaliação do volume do defeito/cera utilizando computador independente àquele de aquisição. Um cirurgião-dentista radiologista com experiência em avaliação tomográfica foi o avaliador do estudo. As avaliações foram realizadas de forma randomizada e sem conhecimento prévio quanto ao protocolo de aquisição da imagem observada.

O primeiro método avaliado, proposto por Quereshy et al. (2012), baseou-se em reconstruções tridimensionais que foram geradas em projeção de máxima intensidade (MIP) no programa inVivo. Usando a ferramenta de mensuração linear, as medidas correspondentes à largura, altura e profundidade vestibulo-palatina foram obtidas. Multiplicando-se esses valores, calculou-se o volume estimado do defeito.

O segundo método, descrito por Feichtinger et al. (2007), também foi executado no programa inVivo. Nessa técnica, o região do defeito visualizada em cada reconstrução axial foi delimitada utilizando-se a ferramenta de mensuração de área do programa. Depois da delimitação, o valor correspondente àquela área era automaticamente fornecido. Tal mensuração foi realizada em todas as reconstruções axiais ao longo de toda a altura do defeito, com 1mm de espessura de corte. Usando a fórmula proposta pelos autores (Volume = [A1 × S]+[A2 × S]+. . . +[An × S], onde A = área; S = espessura de corte e n = número de cortes), o volume estimado do defeito foi obtido.

Já o terceiro método consistiu em uma avaliação tridimensional e foi desenvolvido no programa Mimics. Primeiramente, o *threshold* (variação dos tons de cinza da imagem) da maxila era selecionado, editado bi e tridimensionalmente e um modelo 3D correspondente à maxila era gerado. Em seguida, o *threshold* da região de interesse (defeito/cera) era definido e restringido à região do defeito. Uma combinação de edições foi realizada para obter as superfícies adequadas do defeito. Uma vez englobado todo o volume de interesse na máscara do programa, um modelo 3D era gerado e seu volume era automaticamente fornecido.

As três avaliações tomográficas foram repetidas com toda a amostra após intervalo de um mês para posterior análise intraobservador.

O padrão ouro do estudo foi obtido por meio da avaliação do volume do próprio bloco de cera. Para tanto, primeiramente o crânio foi imerso em um balde com água morna e com a ajuda de um fio dental, todo o bloco de cera foi removido sem perda do material. Em seguida, um cilindro graduado foi preenchido com água até uma linha de referência demarcada com marcador preto. O bloco de cera foi então imerso no cilindro e o novo volume ocupado pela água e a cera foi delimitado com o mesmo marcador. A variação entre a delimitação inicial da água e novo nível com a cera foi avaliada por um observador usando-se um paquímetro digital (Figura 1). As medidas foram realizadas duas vezes para cada bloco. O volume real da cera foi então calculado pelo princípio de Arquimedes de deslocamento de líquidos.

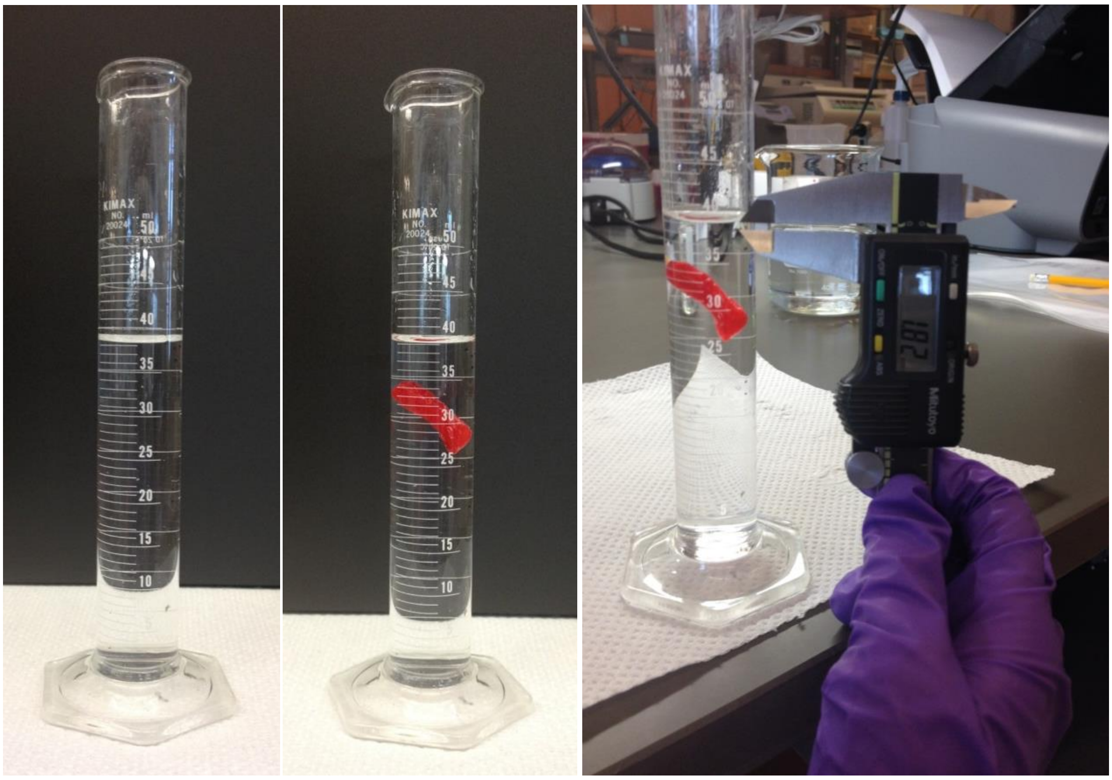

Figura 1 – Avaliação do volume do bloco de cera pela avaliação do deslocamento do volume de água em cilindro milimetrado pelo princípio de Arquimedes.

Depois de finalizadas as avaliações, os valores obtidos nos três métodos baseados nos diferentes protocolos de aquisição da imagem foram comparados ao padrão ouro usando a análise de variância dois fatores e teste de Tukey, usando o programa BioEstat (Bioestat, Belém, PA, Brasil).A análise intraobservador foi calculada pela correlação de Pearson usando o programa SigmaStat (Systat Software Inc., Erkrath, Alemanha). Os valores obtidos foram interpretados como fraco (0–0,20), regular (0,21–0,40), moderado (0,41–0,60), substancial (0,61– 0,80) e quase perfeito (0,81+).

Para o estudo *in vivo* foram usados exames tomográficos de indivíduos com fissuras labiopalatinas unilaterais (FLPU) que foram submetidos ao exames por propósitos não relacionados à pesquisa.

Indivíduos diagnosticados com síndrome, submetidos à tratamento ortodôntico expansor ou enxerto ósseo alveolar (EOA) prévio e exames de TCFC com excesso de artefatos foram excluídos da amostra. Um total de 50 exames de TCFC foram inspecionados para seleção da amostra e 17 indivíduos foram excluídos por tratamento ortodôntico (n=11), EOA prévio (n=1) e qualidade de imagem insuficiente (n=5), obtendo-se uma amostra final de 33 indivíduos.

A idade dos indivíduos variou de 6 a 11 anos de idade, com média de 8,03 anos. A amostra consistiu em 15 indivíduos do sexo feminino e 18 do sexo masculino, apresentando 11 FLPU afetando o lado direito e 22 o lado esquerdo.

A imagens tomográficas foram adquiridas no mesmo tomógrafo computadorizado de feixe cônico CS9300 (Carestream Dental, Atlanta, GA, EUA), operando a 60–90 kVp, 2–15 mA, FOV de 17x13.5cm e voxel de 0,3 mm. As imagens foram salvas em formato DICOM para subsequente avaliação em sala com iluminação reduzida. O estudo envolveu duas diferentes abordagens com objetivos distintos: classificação GAND e avaliação volumetrica.

A primeira etapa consistiu na avaliação da Classificação GAND, em que as imagens tomográficas foram importadas para o programa InVivo (Anatomage, San Jose, CA, EUA) e escores foram atribuídos para cada quesito proposto na classificação. A região de interesse poderia ser observada em reconstrução multiplanar (MPR) usando os três planos (axial, sagital e coronal), bem como usar a reconstrução tridimensional de projeção em máxima intensidade (MIP).

Cada imagem tomográfica era classificada qualitativamente, baseando-se na posição do menor segmento maxilar em relação ao maior, quanto aos aspectos do defeito, arco, assoalho nasal e dentes (gap, arch, nasal e dental). A classificação foi previamente descrita aos avaliadores para que eles já estivessem habituados antes da avaliação das imagens.

Quanto ao defeito, seu tamanho deveria ser avaliado qualitativamente observando-se a fissura em sua totalidade na reconstrução MIP. As reconstruções multiplanares também poderiam ser visualizadas para confirmar-se a extensão e limites do defeito. O quesito defeito (Gap) deveria ser classificado em G1 – Pequena descontinuidade no processo alveolar; G2- Pequeno defeito e G3 – Grande defeito.

Quanto ao formato do arco, a posição do menor segmento em relação ao maior deveria ser avaliada, podendo-se observar em reconstução axial em MPR ou em vista inferosuperior do modelo 3D gerado na reconstrução MIP, após remover-se a mandíbula da imagem. O quesito arco (Arch) deveria ser classificado em A1 – Arco maxilar alinhado; A2 – Segmento menor anteriormente constrito; A3 - Segmento menor constrito anterior e posteriormente.

Quanto à avaliação do assoalho nasal, deveria-se observar a extensão dos defeitos nessa região, podendo ser observada na reconstrução MIP, promovendo um noção tridimensional em relação às estruturas adjacentes. O quesito nasal (Nasal) deveria ser classificado em N1 – Pequena descontinuidade do assoalho nasal; N2 - Pequeno defeito do assoalho nasal e G3 – Grande defeito do assoalho nasal.

Quanto à avaliação dentária, uma reconstrução panorâmica baseada no volume tomográfico pode ser realizada para promover uma visão geral dos arcos. Em seguida, as reconstruções em MPR deveriam ser observadas nos três planos para confirmar possíveis diagnósticos quanto ao número e integridade dos dentes adjacentes à fissura. A reconstrução MIP também poderia ser observada. O quesito dental (Dental) deveria ser classificado em D1 – sem ausência dentária e sem malformações; D2 – presença de dente malformado ou supranumerário na região adjacente à fissura e D3 – ausência dentária nas regiões adjacentes à fissura.

As imagens foram primeiramente avaliadas por dois autores do trabalho que propuseram a classificação e que observando as imagens, chegaram a um consenso com relação a todos os quesitos de toda a amostra. Esses dois observadores eram cirurgiões dentistas, um radiologista e um protesista. Em seguida, para uma segunda avaliação, três observadores (dois radiologistas e um protesista) foram selecionados e avaliaram a amostra quanto aos quesitos propostos na classificação GAND. Todos os cinco observadores tinham experiência em avaliação de fissuras. Após duas semanas, todos os observadores repetiram a mesma avaliação com a amostra inteira.

Os escores da classificação GAND e a reprodutibilidade entre os observadores foi avaliada pelo teste kappa de Cohen com intervalo de confiança de 95%. A reprodutibilidade intra e interobservadores foi calculada pelo programa MedCalc (MedCalc, Mariakerke, Bélgica). Os valores obtidos foram interpretados como fraco (0–0,20), regular (0,21–0,40), moderado (0,41–0,60), substancial (0,61– 0,80) e quase perfeito (0,81+).

A segunda etapa do estudo consistiu na avaliação volumétrica das fissuras dos indivíduos da amostra, e para isso, as imagens tomográficas foram importadas no programa Mimics (Materialize Medical, Leuven, Bélgica) e avaliadas por um único observador, radiologista, com experiência em avaliação e segmentação de imagens tomográficas.

Para a segmentação da região de interesse, primeiramente deveria-se segmentar a maxila e para tanto, selecionar o *threshold* correspondente à região de osso cortical e trabecular maxilar, obtendo-se assim uma máscara correspondente a esses valores. Em seguida, uma combinação de edição corte por corte (bidimensional) e volumétrica (tridimensional). Uma vez delimitada toda a região de interesse da maxila, o modelo tridimensional (3D) da maxila era gerado para servir como base para a segmentação da fissura.

Para obter-se o modelo do defeito, primeiramente deveria-se selecionar o *threshold* da fissura, o mesmo das regiões aéreas do exame, gerando uma nova máscara, de coloração e valores distintos. Em seguida, edições corte a corte e volumétricas foram realizadas seguindo os contornos maxilares do lado contrário. Os limites desse preenchimento consistiram na continuação das margens da fissura, sendo uma continuação do processo alveolar inferior, anterior e posteriormente e uma continuação das margens nasais superiormente. A definição da região que seria preenchida por osso em posterior EOA foi elucidada por cirurgiões do centro craniofacial durante a simulação pré-cirúrgica desses indivíduos. Uma vez que a máscara correspondente ao defeito englobava somente a região de interesse, um modelo 3D era gerado e seu volume era automaticamente fornecido pelo programa em mm^3. Após um intervalo de duas semanas, a mesma avaliação volumétrica foi repetida com 25% da amostra.

A reprodutibilidade intraobservador da avaliação volumétrica do estudo foi calculada pelo coeficiente de correlação intraclasse (CCI) usando o programa MedCalc (MedCalc, Mariakerke, Bélgica).

O estudo também objetivou avaliar a associação dos volumes obtidos na segmentação dos defeitos com dois escores da classificação GAND, os parâmetros defeito e nasal (Gap e

Nasal). Para tanto, a análise de variância (ANOVA) foi realizada usando o programa SAS (SAS Institute Inc., Cary, NC, EUA), com valores de $p<0,05$ considerados estatisticamente significantes.

ANEXO 1 – Aprovação do protocolo de pesquisa pelo Institutional Review Board (IRB)

THE UNIVERSITY *of* NORTH CAROLINA *at* CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
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Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: Luis Andre Pimenta
Dental Ecology

From: Biomedical IRB

Approval Date: 3/12/2015
Expiration Date of Approval: 3/11/2016
RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Renewal
Expedited Category: 5.Existing or non-research data
Study #: 11-1560

Study Title: 3D Volumetric Evaluation of Cleft Lip and Palate Patients

This submission has been approved by the IRB for the period indicated.

Study Description:

Purpose: This is a preliminary study designed to evaluate cleft patients with 3-dimensional volumetric software using cone beam CT. Previous evaluation of cleft related patients were done based on two dimensional x-rays including panoramic and cephalometric films. Cone beam CT provides a 3-dimensional craniofacial imaging. Their hypothesis is that cone beam CT scan will give information about soft tissue and hard tissue that is much more useful than the previous 2-dimensional xrays; this will include information about patients' airway, palate function, maxillofacial growth and the relation between the hard tissue and the soft tissue in all dimensions of growth. The cone beam CT has been considered the examination of choice in many instances, since it provides high-resolution imaging, diagnostic reliability, and risk-benefit assessment. Cleft patients suffer growth disturbances in anterior-posterior, transverse and vertical dimensions. Their goal is to assess these craniofacial deformities using a new 3D technology software package referred to as Dolphin. Participants: 70 patients with cone beam studies will be enrolled in their study. All of these studies have already been completed through the Craniofacial Center at the UNC School of Dentistry. All of the participants have the diagnosis of unilateral complete cleft lip and palate and are patients at the UNC Craniofacial Center. No exclusions will be made for gender, race and ethnicity. Procedures (methods): They will evaluate 70 subjects that already have had Conebeam CT images taken as part of their routine treatment. The radiological studies will be analyzed for volumetric measurement of the airway, including hard tissue and soft tissue using the Dolphin software (which is already present at the UNC Orthodontics Department) and MIMICS software.

Submission Description:

In this submission, we are requesting the change of the study PI and updating research personal. Dr. John Van Aalst has left UNC, Dr. Luiz Pimenta will be the new study PI. We are also asking to add Dr. Vivaldi and Dr. Lima as co-investigators to the research.

Regulatory and other findings:

This research meets criteria for waiver of informed consent for research [45 CFR 46.116(d)] and waiver of

HIPAA authorization [45 CFR 164.512(i)(2)(ii)].

This research is closed to enrollment and remains open for data analysis only.

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Your approved consent forms and other documents are available online at
http://apps.research.unc.edu/irb/index.cfm?event=home.dashboard.irbStudyManagement&irb_id=11-1560.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at http://irbis.unc.edu.

The current data security level determination is Level II. Any changes in the data security level need to be discussed with the relevant IT official. If data security level II and III, consult with your IT official to develop a data security plan. Data security is ultimately the responsibility of the Principal Investigator.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40CFR 26 (EPA), where applicable.

CC:
Marziye Eshghi, Allied Health Sciences
Thiago Lima, Dental Ecology
Beatriz Paniagua, Psychiatry
Martin Styner, Psychiatry
Daniela Vivaldi, Dental Ecology
David Zajac, Dental Ecology

ANEXO 2 – Carta de confirmação da submissão do artigo intitulado “Comparison of different methods to assess alveolar cleft defects in cone beam computed tomography image” ao periódico Dentomaxillofacial Radiology

Print Close

From: **DMFR Office** (em@editorialmanager.com)
Sent: Wednesday, October 14, 2015 10:23:43 AM
To: Gabriella Lopes de Rezende Barbosa (gabriellalopes@live.com)

Dear Ms. Barbosa,

You are receiving this e-mail as you are listed as the corresponding author or as a co-author on the submission entitled "Comparison of different methods to assess alveolar cleft defects in cone beam computed tomography images", which has been received by Dentomaxillofacial Radiology.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an Author at http://dmfr.edmgr.com/

You will be informed by email of the manuscript reference number in due course.

If you do not think you should be listed as an author of this work, please get in touch with the editor (rschulze@uni-mainz.de)

Thank you for submitting your work to DMFR.

Kind regards,
DMFR Office

ANEXO 3 – Carta de confirmação da submissão do artigo intitulado "GAND classification and volumetric assessment of unilateral cleft lip and palate malformations using cone beam computed tomography" ao periódico International Journal of Oral and Maxillofacial Surgery

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