SHORT COMMUNICATION

Topical contrast agents to improve soft-tissue contrast in the upper airway using cone beam CT: a pilot study

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The purpose of this study is to explore the topical use of radiographic contrast agents to enhance soft-tissue contrast on cone beam CT (CBCT) images. Different barium sulphate concentrations were first tested using an airway phantom. Different methods of barium sulphate application (nasal drops, syringe, spray and sinus wash) were then tested on four volunteers, and nebulized iodine was tested in one volunteer. CBCT images were performed and then assessed subjectively by two examiners for contrast agent uniformity and lack of streak artefact. 25.0% barium sulphate presented adequate viscosity and radiodensity. Barium sulphate administered *via* nasal drops and sprays showed non-uniform collection at the nostrils, along the inferior and/or middle nasal meatuses and posterior nasal choana. The syringe and sinus wash showed similar results with larger volumes collecting in the naso-oropharynx. Nebulized iodine failed to distribute into the nasal cavity and scarcely collected at the nostrils. All methods of nasal application failed to adequately reach or uniformly coat the nasal cavity beyond the inferior nasal meatuses. The key factors to consider for optimum topical radiographic contrast in the nasal airway are particle size, flow velocity and radio-opacity. *Dentomaxillofacial Radiology* (2013) **42**, 20130022. doi: 10.1259/dmfr.20130022

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Introduction

Upper airway analysis has gained considerable attention in the medical and dental fields, especially in breathing disorders such as obstructive sleep apnoea. Three-dimensional (3D) models of the upper airway segmented from cone beam CT (CBCT) scans are emerging as a means to visualize and assess the upper airway. Segmentation (manual, automatic or semi-automatic) refers to the extraction of structural information of particular interest from surrounding images. This analysis tool is essential because it defines the contours and boundaries of anatomy or pathology for visualization or characterization.¹

Although CBCT provides less radiation than multi-detector CT (MDCT), CBCT presents with a lower signal-to-noise ratio. The larger amounts of scattered radiation from the X-ray source in CBCT enhance noise in the reconstructed images, affect the low-contrast detectability and thus may influence image quality and tissue segmentation accuracy.² Adding to the difficulty is the complex anatomy of the nasal airway, which will affect boundary definition, grey-level thresholding, accuracy of the 3D model and any resultant quantitative analysis.³

Contrast agents are employed by many imaging modalities and can easily improve signal-to-noise ratio by improving tissue contrast. Several studies used contrast agents, namely iodine, in the nasal and paranasal sinuses to assess nasal/sinus drug delivery using MDCT,^{4,5} nuclear medicine⁶⁻⁸ and CBCT.⁹ To our knowledge, topical

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Figure 1 Methods of contrast agent application. (a) For barium sulphate (left to right): syringe, drops, spray and sinus wash. (b) For iodine: nasal adaptor for nebulization

application of contrast agents in the upper airway as a method to enhance tissue contrast has not been investigated.

Therefore, the purpose of this pilot study is to explore the topical use of two contrast agents (barium sulphate and iodine) to improve tissue contrast in the upper airway (nasal and pharyngeal parts).

Materials and methods

This pilot study was approved by the Health Research Ethics Board—Biomedical Panel at the University of Alberta, Edmonton, AB, Canada (ID Pro00030422).

Contrast agents

Different concentrations of barium sulphate suspension 105% w/v (Liquid Polibar Plus®; E-Z-EM Inc., Lake Success, NY) were tested. Then, different methods of application, including nasal drops, needle-less syringes,

nasal spray, sinus wash and nebulization, were tested (Figure 1).

Barium sulphate is insoluble and partly cleared by mucociliary transport, expectoration and coughing, with the remainder removed by macrophages, resulting in accumulation in the tracheobronchial lymph nodes and localized opacity for years.¹⁰ Accordingly, barium sulphate was not nebulized. Instead, water-soluble iodine 240 mg I ml⁻¹ [Omnipaque™ (iohexol) 52%; GE Healthcare, Waukesha, WI) was nebulized, using the PARI SinuStar™ (PARI Respiratory Equipment Inc., Midlothian, VA) with a nasal adaptor, because it is water soluble and does not remain in the lungs.

In vitro

An anthropomorphic airway phantom (Figure 2) was used to optimize the concentration of barium sulphate. The airway phantom included the pharyngeal, nasal and paranasal airway from the level of the frontal sinus superiorly to the hypopharynx inferiorly. It was built based

Figure 2 Anthropomorphic airway phantom. (a) Frontal and (b) lateral views

on an MDCT scan of an adult subject by a rapid prototype using acrylic plastic with wax support material. The construction details of the model are described in the study by Storey-Bishoff *et al.*¹¹ Barium sulphate concentrations tested were 50.0%, 25.0% and 12.5% by diluting with sterile water. Diluted barium sulphate (6 ml) was applied through each nasal aperture of the phantom in the supine position using a nasal syringe. Then, the phantom was moved and tilted to ensure distribution of the contrast agent. This was repeated for each concentration. After the application of each concentration of barium sulphate, the phantom was stabilized in a plastic cylinder such that it represented the human seated position and then scanned with the Classic iCAT[®] (Imaging Sciences International, Hatfield, PA) CBCT scan. The CBCT protocol used a medium-large field of view (16 cm width $\times$ 13 cm height), 120 kV, 24 mAs, 20 s scan time and 0.3 mm voxel size. After each contrast application, the airway model was thoroughly washed with water and scanned again to ensure that there was no barium residue. The resultant images were subjectively and visually analysed by two examiners (an oral-maxillofacial radiologist and a medical radiologist). A consensus between both examiners was reached to select the optimum barium sulphate concentration. The criteria for the optimum concentration were the absence of detrimental streak or beam hardening artefacts with complete uniform coating of the airway.

In vivo

Five healthy subjects were invited to volunteer in this pilot study. Each volunteer received one method of contrast application as follows: four subjects received 6 ml of 25.0% barium sulphate per nostril (total 12 ml) using needle-less syringes, Salinex[®] (Sandoz Canada Inc., Boucherville, QC, Canada) nasal drops or spray or NeilMed[®] (NeilMed Pharmaceuticals Inc., Santa Rosa, CA) sinus wash. Each subject was asked to sniff after the

administration of barium sulphate. One subject was asked to normally breathe 8 ml of nebulized water-soluble iodine. After the contrast application, a CBCT scan of the upper airway was completed for each participant using a small field of view (16 cm width $\times$ 8 cm height), 120 kV, 24 mAs, 20 s scan time and 0.3 mm voxel size. The resultant images were subjectively and visually analysed by the same examiners. A consensus between both examiners was reached to select the optimum method of distribution, *i.e.* uniform distribution throughout the nasal cavity (inferior, middle, superior meatuses, anterior naris/nostrils and posterior naris/choana).

Results

In vitro (*barium sulphate concentration*)

CBCT images of 50.0%, 25.0% and 12.5% barium sulphate (6 ml per nostril) are presented in Figure 3. 25.0% barium sulphate presented adequate viscosity and reasonable radiodensity.

In vivo (*methods of application*)

None of the volunteers showed immediate or delayed reaction to the contrast agents used in this pilot study. CBCT images of barium sulphate applied *via* nasal drops, spray, syringe, sinus wash and nebulized iodine are presented in Figures 4–8. Barium sulphate inhomogeneously collected at the nostrils and along the inferior and/or middle nasal meatuses and posterior nasal choana. Nebulized iodine failed to distribute into the nasal cavity and scarcely collected at the nostrils.

Discussion

Barium sulphate was chosen for this pilot study because of its greater radiographic density compared with

Figure 3 Barium sulphate concentrations using the airway phantom. Cone beam CT axial images through the inferior nasal meatus with (a) 50.0%, (b) 25.0% and (c) 12.5% barium sulphate

Figure 4 Cone beam CT images of the nasal cavity using nasal drops. (a) Sagittal image and (b) three-dimensional rendering. Contrast and brightness of all three-dimensional images (Figures 4–8) were adjusted to highlight the contrast agent against the surrounding osseous tissues

water-soluble iodine contrast agents.¹² Owing to its iso-osmolality, barium sulphate can also give better mucosal coating and adherence, as noted in the sites of gastrointestinal leakage.^{12,13}

The ideal barium sulphate–water mixture has yet to be developed. Key factors for this mixture are radio-opacity, concentration and viscosity. Ideally, the contrast agent distributing along the upper airway would be of low–medium viscosity to allow reasonable flow with even coating and medium radio-opacity to avoid detrimental beam-hardening artefact, suggesting that the medium–low concentration is preferred. Using the airway phantom, 50.0% barium sulphate was too radio-opaque with evident beam-hardening artefact (Figure 3a). However, it showed more areas of contrast adherence owing to its higher viscosity. 25.0% and 12.5% barium sulphate (Figure 3b,c) were of acceptable radio-opacity, *i.e.* no streaking or beam hardening; however, there was less coating of the nasal cavity. The 25.0% concentration was chosen owing to larger amounts of contrast retention because most of the 12.5% contrast agent leaked through the phantom's hypopharynx.

In studies similar to this pilot study, the amount of radiographic contrast used varied between 0.3 ml and 40 ml (drops, 1.5 ml per naris;⁹ spray, 0.3–10 ml per naris;^{5,8,9} syringe, 40 ml per naris;^{5,8} and sinus wash, 20 ml per naris).⁴ The smaller end of the spectrum was probably selected to reflect typical volumes used in nasal medications, whereas the larger amounts (*i.e.* 40 ml) were used based on the recommendation that 50 ml could fill the average sinus.⁹ For this pilot study, the authors chose to use 6 ml per naris of the contrast agent to allow reasonable contrast distribution while reducing subject discomfort.

Figure 5 Cone beam CT images of the nasal cavity using nasal spray. (a) Sagittal image and (b) three-dimensional rendering

Using 6 ml per nostril of 25.0% barium sulphate, all methods of application demonstrated non-uniform collection at the nostrils, along the inferior and/or middle nasal meatuses and posterior nasal choana (Figures 4–8). However, syringe and sinus wash showed collection of larger volumes in the naso-oropharynx/dorsum of the soft palate. These findings are in agreement with similar studies using iodine. However, Olson *et al*⁴ and Snidvongs

Figure 6 Cone beam CT images of the nasal cavity using syringe. (a) Sagittal image and (b) three-dimensional rendering

Figure 7 Cone beam CT images of the nasal cavity using sinus wash. (a) Sagittal image, (b) frontal image and (c) three-dimensional rendering

*et al*⁵ tested sinus delivery using iodine. Using spray and syringe or sinus wash and positive pressure irrigation (sniffing contrast from the palm of the hand), it was evident that most of the contrast agent drained through the nose or oropharynx, with few streaks of contrast in the maxillary sinuses or in the inferior and middle meatuses of the nasal cavity.^{4,5} Similarly, Rudman *et al*⁹ found that iodine (*via* nasal spray and drops) variably collected along the anterior nasal vestibule, anterior–inferior meatus and nasopharynx. Senocak *et al*¹⁴ used nasal spray and assessed iodine distribution in the nasal cavity over time by imaging with MDCT three times (3 min apart). Iodine collected in the anterior nasal floor and inferior turbinate, and, with time, it reduced in volume and reached the posterior nose and then the nasopharynx in a few subjects.¹⁴

In these studies, the ultimate goal was local drug delivery to the sinonasal cavity, and the contrast agent was considered even if only a small droplet reached an anatomical area. As such, it was counted and quantified by means of volume or proportion. In this pilot study, however, the aim was for the contrast agent not only to reach the superior anatomical areas of the nose but

Figure 8 Cone beam CT images of the nasal cavity using nebulization. (a) Sagittal image and (b) three-dimensional rendering

also to uniformly coat their surfaces to enhance soft-tissue contrast. Thus, the assessment was qualitative and subjective.

Nebulization delivers drugs to the bronchopulmonary system either through the oral cavity or through the nasal cavity. The PARI SinuStar has a capacity of 6–8 ml with $0.180 \text{ ml min}^{-1}$ output rate. Using the nasal adaptor, the time to nebulize 8 ml of full concentration iodine was around 11 min. Nebulized iodine failed to distribute into the nasal cavity and scarcely collected at the nostrils (Figure 8). This was in agreement with the results of the study by Olson *et al*,⁴ in which 20 ml per naris of iodine was nebulized by delivering 10 ml at low flow and then repeated by filling the chamber with 10 ml at high flow. It was reported that a particle size of less than $5 \mu\text{m}$ had a higher deposition rate to the osteomeatal complex and maxillary sinus.¹⁵ In this pilot study, the quantity and quality (*i.e.* particle size) of iodine particles produced and of those that reached or bypassed the nasal cavity are unclear.

Based on the preliminary results of this pilot, two factors must be considered in delivering the contrast agent to the upper airway: particle size and flow velocity. Computational simulation of particle deposition using validated airway casts or 3D airway models has been used to assess nasal drug delivery.^{16,17} Using these simulations, the optimum method of delivery and its impact on the physical properties of the contrast agent, including radio-opacity, could be identified.

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