

# Efficacy of prosthodontic dental materials in reduction of metallic artifacts in the presence and absence of MAR tool

Hala M. Elkamash<sup>1\*</sup> *BDs*, Yousria S. Gaweesh<sup>2</sup> *PhD*, Lobna M. Elsaadawy<sup>3</sup> *PhD*

## ABSTRACT

**BACKGROUND:** Artifacts produced in cone-beam computed tomography (CBCT) images by metallic restorations might lead to inaccurate diagnosis.

**OBJECTIVES:** This study assesses the efficacy of Blu-mousse and medium-body polyvinyl siloxane (PVS) in reducing CBCT artifacts produced by metallic restorations and orthodontic brackets in the presence or absence of the metal artifact reduction (MAR) tool.

**MATERIALS AND METHODS:** Four extracted teeth with multi-surface amalgam, full-coverage metal crown, zirconium inlay, and metal orthodontic bracket were used. The teeth were set in a dental stone model and an impression was taken as a replication template for Blu-mousse and PVS. The teeth were covered by each dental material and scanned using CBCT with or without the MAR. CBCT images were exported and analyzed quantitatively by assessing the mean of gray values, and their standard deviations (std dev) and ranges. Moreover, CBCT images were scored qualitatively by two radiologists.

**RESULTS:** The MAR tool enhanced image quality and reduced the artifacts as per the quantitative and qualitative analysis. Both Blu-mousse and PVS increased the mean gray values in the presence or absence of the MAR tool. Dental materials' effects on std dev and range of gray values were site-specific. Likewise, qualitative scoring demonstrated that CBCT artifacts were reduced by impression materials, particularly Blu-mousse in the absence of MAR tool. Furthermore, Blu-mousse had better effects in decreasing CBCT artifacts than PVS.

**CONCLUSION:** This study evidenced that prosthodontic materials (Blu-mousse and PVS) have artifact-reduction properties or might act separately as an artifact-reduction strategy in the absence of MAR tool.

**KEYWORDS:** Beam hardening artifacts; CBCT; Blu-mousse; MAR; medium body PVS

**RUNNING TITLE:** Prosthodontic dental materials overcome CBCT artifacts.

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1- MSc candidate, Department of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology, Faculty of Dentistry, Alexandria University, Alexandria, Egypt

2- Professor of Oral Medicine, Department of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology, Faculty of Dentistry, Alexandria University, Alexandria, Egypt

3- Lecturer of Oral Radiology, Department of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology, Faculty of Dentistry, Alexandria University, Alexandria, Egypt

*\*Corresponding author:*

[hala.hassan.dent@alexu.edu.eg](mailto:hala.hassan.dent@alexu.edu.eg)

## INTRODUCTION

Cone-beam computed tomography (CBCT) is a three-dimensional(3D) imaging modality used extensively nowadays in the dental field (1). It is beneficial in diagnosing and formulating a correct treatment plan in various dental situations (2, 3). CBCT has recently grown to be one of the most popular imaging method in dental radiography for viewing the dentition and the maxillofacial skeleton (4). The ability to view intraoral structures in 3D using CBCT has resolved the issue of anatomical superimposition that is encountered frequently with conventional two-dimensions (2D) imaging modalities (5). Although CBCT has made huge progress in the dental field, it is liable to some

limitations owing to "cone-beam" projection geometry, detector sensitivity, and spatial resolution, which sometimes results in unclear images leading to missing clinical data (6). CBCT images are also prone to artifacts like noise, scatter, and beam hardening artifacts (7). Artifacts may hinder the image analysis process as it causes some alterations in the image contrast and quality (8).

Image artifact is a term used to describe discrepancies on the radiographic picture that are not present in the evaluated object. Due to technical aspects including the X-ray beam's geometry and image generation processes, many artifacts are created (9). One of the most encountered artifacts is beam

hardening (10, 11). Beam hardening is the process whereby low-energy photons are absorbed more readily than high-energy photons as the x-ray beam passes through a high-density item resulting in inaccuracies in the 3D reconstructed images in the form of dark bands and streaks (12).

Different methods have been proposed to eliminate CBCT artifacts and enhance image quality such as choosing the best scanning parameters during image capture or using certain reconstruction techniques. According to certain reports, some CBCT devices may produce fewer artifacts when using greater kilovolt peak (kVp) and higher milliamperage (mA) (13, 14). Others restricted the field of view (FOV) as much as possible with the target item in the center (15). Additionally, those artifacts may be reduced by using the metal artifact reduction (MAR) tool, which is present in various CBCT equipment and appears to be one of the most useful and simple tool without affecting radiation dose (16). MAR is used during the reconstruction of the basis images to reduce gray value variability and improve the contrast-to-noise ratio (16).

A recent and novel metal artifacts reduction method was suggested by the Hinchy et al (17). In their study, covering the source of the metal artifacts such as dental amalgam and metallic crown with seven different types of common dental lab materials including alginate, baseplate wax, Aluwax™, pink wax, Blu-Mousse® (vinyl polysiloxane (VPS) bite registration material), polyvinyl siloxane (PVS) medium body, and red beading wax influenced the metal artifacts and helped in producing better image quality as indicated by the image analysis quantification method. Blu-Mousse and PVS, in particular, showed the most favorable CBCT artifact attenuation effects, which could be attributed to their chemical natures. Both prosthetic impression materials involve lead dioxide, which could be responsible for their radiopacity and X-ray beam attenuation owing to its high atomic number (18). To the best of our knowledge, Hinchy et al (17) recent study is the only attempt to introduce the use of dental impression materials as an effective method to decrease CBCT-associated artifacts. Nevertheless, the role of MAR tool and its impact on these prosthetic materials was not considered in their study. Furthermore, important sources of metal artifacts such as zirconium and orthodontic bracket were not evaluated in their study.

Therefore, our study aimed to explore the effects of two dental lab materials (Blu-mousse bite registration material and medium body PVS) on CBCT-associated image artifacts produced by different metallic restorations such as multi-surface amalgam, full-coverage metal crown, and zirconium inlay as

well as metal orthodontic bracket. Furthermore, our study evaluated whether the presence or absence of the MAR tool might influence the impact of these dental lab materials on CBCT metal artifacts.

## MATERIALS AND METHODS

### *Ethical approval:*

This study followed the ethical principles outlined in the World Medical Association Declaration of Helsinki of 1975, as revised in 2000, and was approved by the Research Ethics Board of Alexandria University's Faculty of Dentistry (IRB No. 0728-07/2023). Patients who donated their extracted teeth to the faculty of dentistry were all informed of their use for research purposes.

### *Sample size calculations:*

Sample size was calculated assuming 80% study power and 5% alpha error. Hinchy et al (17) reported mean ( $\pm$  standard deviation) overall variance =  $134.7 \pm 83.42$  and  $44.3 \pm 16.3$  for Blu-Mousse and PVS materials, respectively. The sample size was calculated to be 9 scans per group, increased to 10 to make up for laboratory processing errors. The total required sample size = number of groups  $\times$  number per group =  $6 \times 10 = 60$  scans (19). The sample size was calculated using Software G\*Power Version 3.1.9.7 sample size calculator.

### *Study design:*

The study was conducted on four teeth (three molars and one canine), which were extracted for periodontal purposes. These teeth were prepared and covered by different dental restorations. The first molar was prepared and covered with a full metal crown. The second molar received a zirconium inlay. As for the third molar, multi-surface amalgam restorations (MOD) were prepared. The canine had a metal orthodontic bracket on the buccal surface (Figure 1-A). These teeth were set in a dental stone model (Type III dental gypsum) consisting of calcium sulfate dehydrate ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ) at the level of the cemento-enamel junction (CEJ). The anatomic crowns of the teeth had a wax overlay made of red beading wax molded over them at a constant thickness of 3 mm in the three planes (buccal, occlusal, and lingual) to act as a spacer. An impression was made using Sci Dental PVS Putty Impression Material as a replication template for each of the two chosen dental lab materials; Blu-Mousse® (vinyl polysiloxane) bite registration material (Parkell, New York, USA) or polyvinyl siloxane (PVS) medium body (Mydent international, New York, USA) (Figure 1-B). The replication guide was used to mold these two materials so that they completely and uniformly encircled the coronal sections (17).

### *Image acquisition:*

The Green X: PHT-75CHS machine (Vatech, E-WOO Technology Co, Ltd. Hwaseong, Republic of Korea) was used to obtain the CBCT volumes for the teeth without coverage (teeth only without the prosthetic materials) as a control (Model) and for them covered with the selected two materials (Blumousse and PVS). To ensure the reproducibility of each image, the model was fitted in a putty material that was placed in an acrylic box. Additionally, marker lines and points were made on the acrylic box (Figure 1-C). The specified exposure parameters provided by the manufacturer for a person of average height and weight were used to produce the CBCT volumes. The following exposure standards were used: 90 kVp, 8.0 mA, and a voxel of 0.08 mm (20). Ten separate consecutive volumes were acquired for the control (Model) group and each dental material type (Blumousse and PVS) without MAR. Then another 10 volumes were acquired for each group with MAR.

A total of 60 digital imaging and communications in medicine (DICOM)-formatted volumes were imported into OnDemand3D™ (2015) version 1.0.10.4304 software (Cybermed International, Seoul, Republic of Korea). After the initial volume examination in the control (Model) group, one slice was selected along the axial plane for the region that best depicted the metal artifact without adjusting contrast or brightness. Next, the representative axial slice of each volume was captured and saved as a portable network graphics (PNG). All CBCT acquired images were standardized on the same control slice using hash line option to ensure reproducibility.

#### *Analysis of CBCT volumes:*

##### *Quantitative:*

An ImageJ 1.37b image analysis system (National Institutes of Health, Bethesda, MD, USA) was used to analyze the individual PNG files. For each image, five regions of interest (ROI) were selected (four buccal and one lingual) that included dark and white streaks (Figure 1-D). A 20 mm × 40 mm rectangle was drawn for each ROI. ROI-1 represents the metal artifact zone for the metal crown, while ROI-2 represents the metal artifact zone for zirconium inlay from the buccal surface. ROI-3 represents the metal artifact zone for multi-surface amalgam restoration, while ROI-4 represents the metal artifact zone for orthodontic bracket. ROI-5 represents the metal artifact zone for zirconium inlay from the lingual surface. ROIs were set in 8 bit-scale within the 256 available grayscale values of the image. ImageJ analyses calculated the mean gray value, maximum gray value, minimum gray value, and standard deviation of gray values (std dev) of gray values of each (21). The range gray value was calculated by subtracting the minimum gray value from the maximum gray value. Results were then

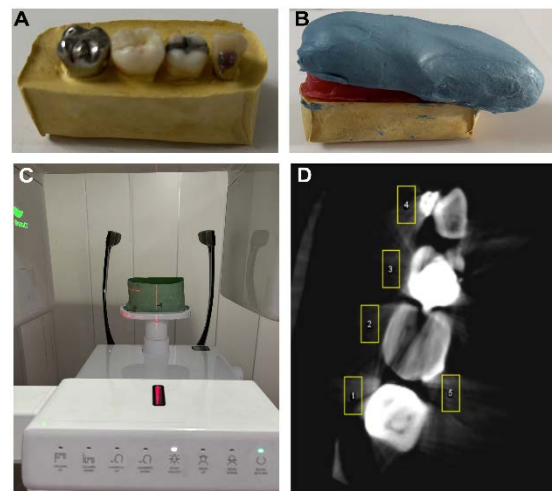
imported on an Excel sheet and final measurements were calculated.

##### *Qualitative:*

To assess the artifact patterns in the CBCT images, two skilled and calibrated oral and maxillofacial radiologists qualitatively analyzed the images. The observers received two digital video discs (DVDs) (DVD-R 4.7 GB, Sony, Zaventem, Belgium) containing 60 acquisitions in a blind random sequence. 15 acquisitions were randomly re-evaluated after 14 days. Images were viewed on OnDemand3D™ (2015) version 1.0.10.4304 software (Cybermed International, Seoul, Republic of Korea). An adaption of Sutare et al (22) methodology was employed as follows: Score 0 = absence of artifacts. Score 1 = very few artifacts (Hypodense halo limited to the source of artifact). Score 2 = few artifacts (Hypodense halo and few amount of white streaks). Score 3 = more artifacts surrounding (Extensive amount of white streaks). Score 4 = more artifacts image distortion (cupping artifacts and distortion of tooth).

##### *Statistical analysis:*

The numerical data of the quantitative and qualitative analysis were expressed as Mean ± standard deviation of the mean (SD). The statistical analysis was performed using two-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test to compare the variabilities between different dental materials in the absence and presence of MAR. Significances were considered when *P* values were less than 0.05. All statistical analysis and graphing were carried out using Graph Pad Prism (version 5) software (GraphPad Software, Inc., La Jolla, CA, USA). All CBCT scans were evaluated by two skilled oral radiologists. Inter- and intra-examiner reliability was checked between the two evaluators and by re-evaluating 25% of the scans after 14 days. The inter- and intra-class correlation coefficient (ICC) was computed to be 0.82 and 0.96; respectively.



**Figure 1:** (A) A set of four teeth placed in a dental stone at the level of CEJ with different dental restorations (metal crown in 1<sup>st</sup> molar, zirconium inlay in 2<sup>nd</sup> molar, and multi-surface amalgam in 3<sup>rd</sup> molar) and a canine with a metal orthodontic bracket. (B) A waxy overlay covering the teeth with clinical restorations and bracket to allow space for the materials to be molded with an impression made over it. (C) Markers were made to grant the experimental model a fixed allocation in the same site with each volume. (D) CBCT image highlighting all ROIs that were quantitatively and qualitatively analyzed.

## RESULTS

Generally, CBCT images of all ROIs demonstrated the impact of Blu-mousse and PVS materials on the artifacts in the presence or absence of MAR. Figure 2 shows CBCT images from different groups that were evaluated quantitatively and qualitatively.

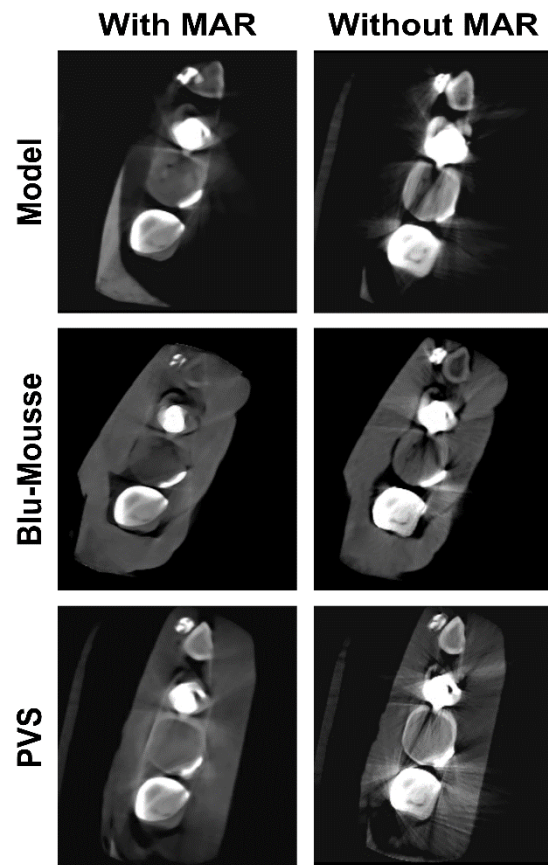
In the absence of the MAR tool, the mean gray value of the model was significantly lower than Blu-mousse and PVS ( $P<0.05$ ) at all ROIs. The std dev of the model was significantly higher than that of Blu-mousse and PVS in almost all ROIs ( $P<0.05$ ), except for the metallic crown in ROI-1, where no significant difference was reported between the model and PVS groups. Considering the range, the model was significantly wider than Blu-mousse in ROI-1, ROI-3, and ROI-4 ( $P<0.05$ ) as well as ROI-3 in the PVS group (Figure 3, 4, and 5).

In the presence of the MAR tool, the mean gray value in the model group was significantly lower than the two dental materials ( $P<0.05$ ) at all ROIs. Meanwhile, the std dev was significantly high in the model group as compared to the Blu-mousse group in ROI-2, ROI-3, and ROI-5 ( $P<0.05$ ) and the PVS group at ROI 3 and ROI-5 ( $P<0.05$ ). Considering the range, the model was not significantly different from Blu-mousse and PVS groups (Figure 3, 4, and 5).

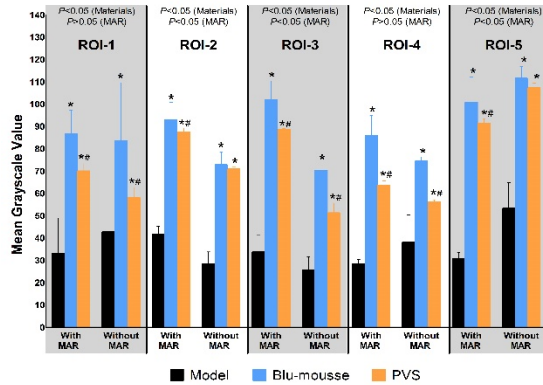
Comparing the Blu-mousse with PVS in the absence of the MAR tool, Blu-mousse had a significantly higher mean gray value than PVS at ROI-1, ROI-3, and ROI-4 ( $P<0.05$ ). Concerning std dev, Blu-mousse had significantly lower std dev than PVS in ROI-1 and ROI-3 ( $P<0.05$ ). Considering the range, Blu-mousse had no significantly different range of mean gray values than PVS in all ROIs (Figure 3, 4, and 5).

Comparing the Blu-mousse with PVS in the presence of the MAR tool, Blu-mousse had significantly higher mean gray values than PVS in all ROIs ( $P<0.05$ ). Concerning std dev, Blu-mousse had significantly lower std dev than PVS only at ROI-2 ( $P<0.05$ ). Regarding the range, there were no significant differences between Blu-mousse and PVS groups at all ROIs (Figure 3, 4, and 5).

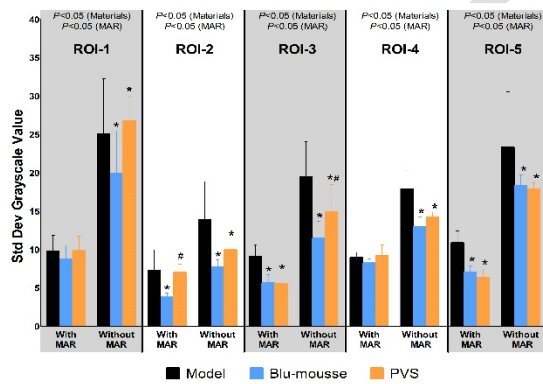
The qualitative analysis scoring revealed that the CBCT artifacts scores were significantly ( $P<0.05$ ) lower in the presence of the MAR tool at all ROIs. In the absence of the MAR tool, CBCT artifacts were lowered by the Blu-mousse as compared to the model group at all ROIs ( $P<0.05$ ) except ROI-3. Whereas PVS effects were documented only at ROI-4 ( $P<0.05$ ) as compared to the model group. The qualitative score was not significantly different in Blu-mousse and PVS groups at all ROIs. In the presence of the MAR tool, Blu-mousse significantly ( $P<0.05$ ) decreased the artifacts at all ROIs as compared to the model group, except ROI-4. Whereas PVS effects were documented only at ROI-5 ( $P<0.05$ ) as compared to the model group. The qualitative score was lower in Blu-mousse at ROI-1 and ROI-2 as compared to the PVS group ( $P<0.05$ ) (Figure 6).



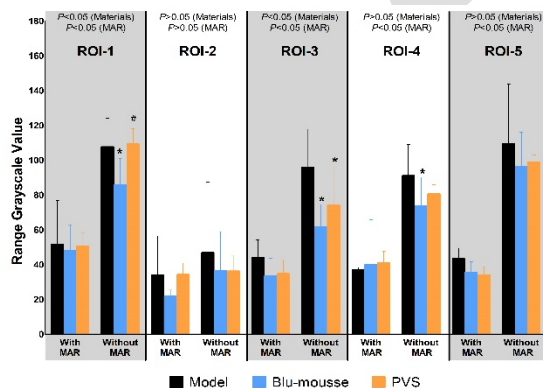
**Figure 2:** CBCT images from different groups that were quantitatively and qualitatively analyzed. The left panel represents the effects of Blu-mousse and PVS on CBCT artifacts compared to the model in the presence of MAR. The right panel represents the effects of Blu-mousse and PVS on CBCT artifacts as compared to the model in the absence of MAR.



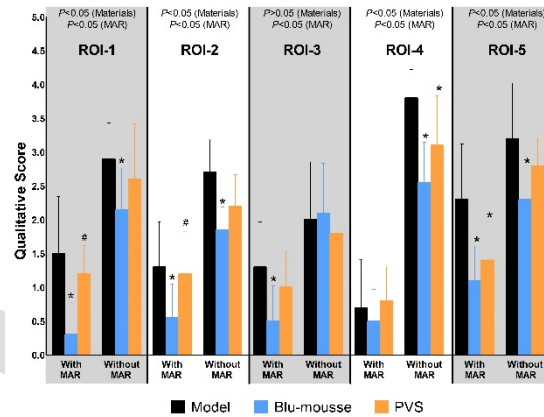
**Figure 3:** Quantitative analysis of the effects of different dental materials on CBCT artifacts in presence or absence of MAR at all ROIs as indicated by the mean gray values. Data is presented as Mean±SD and statistically analyzed using two-way ANOVA followed by the Bonferroni post hoc test. \*P≤0.05 significant (Blu-mousse or PVS vs Model). #P≤0.05 significant (Blu-mousse vs PVS).



**Figure 4:** Quantitative analysis of the effects of different dental materials on CBCT artifacts in presence or absence of MAR at all ROIs as indicated by the std dev of the mean gray values. Data is presented as Mean±SD and statistically analyzed using two-way ANOVA followed by the Bonferroni post hoc test. \*P≤0.05 significant (Blu-mousse or PVS vs Model). #P≤0.05 significant (Blu-mousse vs PVS).



**Figure 5:** Quantitative analysis of the effects of different dental materials on CBCT artifacts in presence or absence of MAR at all ROIs as indicated by the range of the mean gray values. Data is presented as Mean±SD and statistically analyzed using two-way ANOVA followed by the Bonferroni post hoc test. \*P≤0.05 significant (Blu-mousse or PVS vs Model). #P≤0.05 significant (Blu-mousse vs PVS).



**Figure 6:** Qualitative analysis of the effects of different dental materials on CBCT artifacts in presence or absence of MAR at all ROIs. Data is presented as Mean±SD and statistically analyzed using two-way ANOVA followed by the Bonferroni post hoc test. \*P≤0.05 significant (Blu-mousse or PVS vs Model). #P≤0.05 significant (Blu-mousse vs PVS).

**DISCUSSION**

The present study compares the impact of using dental lab materials on the reduction of metal artifacts of CBCT in the absence and presence of the MAR tool. The quality of CBCT images can be significantly declined by metal artifacts, which are displayed as dark and white bands on the reconstructed images (4, 23, 24). Our study is an attempt to introduce a novel method for metal artifacts reduction, which could improve the quality CBCT images and enhance the diagnostic capabilities of the well-known imaging method. Several solutions, with varying degrees of effectiveness, have been previously proposed to reduce CBCT artifacts. However, none of these solutions were fully successful in eliminating metal artifacts (25, 26). Here, we suggested that capping the sources of metal artifacts by either of the two dental impression materials could decrease the white streaks and improve the quality of CBCT images. Moreover, our study considered comparing the impact of these dental impression materials with the MAR algorithm, which was designed to decrease the effects of beam hardening and improve the quality of CBCT images (27). This technique serves as a tool for image post-processing during image reconstruction (28).

In the present study, we compared prosthetic dental materials with or without using the MAR tool to detect the best method for metal artifact reduction. The qualitative results of this study generally revealed that CBCT artifact's scores are significantly higher in the absence of MAR. Likewise, the quantitative analysis confirmed the marked role of MAR in reducing CBCT artifacts as indicated by its significant impact on mean, std dev, and range of grayscale values. Various research has been conducted to evaluate the MAR approach. However, the accuracy of the MAR algorithm on the reduction of metal artifacts is not fully known and is considered material specific (7, 27, 29). In an *in vitro* study, Bechara et al (27) found that activating the MAR tool improves the contrast-to-noise ratio (CNR) along with less gray scale level variation. On the other hand, the *in vitro* study by Madian et al (30), which evaluated the fracture endodontic instruments in filled and unfilled canals, demonstrated much better detection of the broken endodontic files using the periapical radiographs as compared to CBCT with MAR tool. Another study by Queiroz et al (7) suggested that the MAR tool would be beneficial in the case of CBCT scans of metallic materials like amalgam, aluminum, and copper alloy. Yet, it is not preferable in the case of gutta-percha as it didn't improve the quality of the image.

A novel method to reduce CBCT metal artifacts was proposed by the Hinchy et al (17) study, which assumed that some prosthetic materials may reduce metallic artifacts. In their study, covering artifact sources (dental amalgam and metallic crown ) by the impression materials, especially the Blu-mousse and the medium body PVS, decreased the image artifacts and improved the image quality, particularly at lower resolutions. However, the role of MAR tool and its impact on the prosthetic materials were not considered in Hinchy et al study (17). Here, our study evaluated for the first time the impact of MAR algorithm and its possible synergistic role with the prosthetic materials (Blu-mousse and PVS). Furthermore, important sources of metal artifacts such as zirconium and orthodontic bracket were included in our study that were not previously evaluated. Notably, the findings of Hinchy et al (17) study were merely built upon image analysis methodology, which considered drawing a general profile line in front of all metal artifacts sources. In our study, we used similar image analysis methodology in the quantitative analysis of the artifacts and considered five standardized rectangle ROIs in front of each metal artifacts sources. Additionally, we used a standardized clinical evaluation scoring methodology in the qualitative analysis of the artifacts by two radiologists for better simulation of the clinical scenarios. In the

present study, we used two-way ANOVA to analyze the two independent variables (impression materials and MAR), which helped in recognizing the effect of each variable and their statistical interaction.

In the quantitative analysis, we measured the mean, std dev, and range of grayscale values to analyze the effect of Blu-mousse and PVS on the existence of metal artifacts, which appeared as bright and dark patches and linear streaks. This quantification method is considered reliable and reproducible in numerical assessing the magnitude of artifacts. The positive correlation between the grayscale values and photons intensity in the CBCT detector is the foundation of this method, which could be manifested as higher photon intensity in relation to greater the gray values and image quality (17). As for the qualitative analysis, the artifact patterns in the CBCT images were scored by two skilled examiners using a calibrated and reported scoring system, which often employed in previous studies owing to its clinical relevance (22, 31). The higher the score, the more intensity and spreading of the streak artifacts. The perfect agreements between the examiners, as indicated by the high ICC values, assured the validity of the qualitative method.

From a theoretical point of view, Blu-mousse and PVS should increase the beam hardening effect as they attenuate more x-ray beams due to their natural composition, which includes lead with a very high atomic number ( $Z=82$ ) (18). Nevertheless, these dental materials have a heterogenous nature (32), which makes them more likely to cause Compton scattering interaction leading to more noise in the resultant image. This noise will favor the quality of the image by masking the produced artifacts (18). The present study reported that the qualitative scores of CBCT artifacts were decreased by Blu-mousse at almost all ROIs in the absence of MAR. Yet, the effect of the PVS was statistically noticed only at ROI-4. This comes in agreement with Hinchy et al study (17), which reported the effectiveness of Blu-mousse in reducing amalgam-associated CBCT artifacts without MAR tool.

Meanwhile, the presence of the MAR tool synergistically enhanced the demolishing impact of the dental materials, particularly the Blu-mousse, against the CBCT artifacts. These findings suggest the maximizing effect of combining both methods to eliminate these artifacts. The same results were assured by the quantitative measurements. Our study demonstrated that the std dev of grayscale values was significantly lower in the Blu-Mousse group in the presence of MAR. Std dev estimates the overall degree of metal-induced darkening and brightness. The higher the std dev, the more artifacts on the image (4). When the MAR tool was switched off, the Blu-mousse group demonstrated the lowest std dev in all ROIs. This

means that Blu-mousse may mask the extremes of black-and-white artifacts and enhance the quality of the image. Accordingly, the lack of the MAR tool in some CBCT machines could be overcome with the Blu-mousse for initial diagnosis as per our quantitative analysis results. Considering PVS, the std dev was smaller than that of the model in the presence of MAR. However, in the absence of the MAR tool, the results were not significant about the efficacy of PVS in the reduction of metal artifacts compared to the model group.

Notably, ROI-2 demonstrated the lowest number of artifacts as the source of artifacts was placed lingually and the region of interest was placed buccally. In addition, switching off the MAR tool is characterized by a narrower range of grayscale values in the Blu-Mousse group compared to the model group in all ROIs, except ROI-2. This indicates that Blu-mousse masks the extremes of gray values caused by artifacts. When artifacts were not prevalent as in ROI-2, the effect of Blu-mousse was questionable. The presence of extreme grayscale values at each end of the 256-grayscale spectrum represents the emergence of artifacts, which is denoted by white when the number approaches 256 and black when it approaches zero. A smaller numerical difference between the highest and minimum grayscale values represents a reduction in metal artifacts (17).

## CONCLUSION

The findings of this study introduced clear evidence that prosthodontic materials, particularly Blu-mousse, could augment the artifacts reduction properties of the MAR tool. Moreover, Blu-mousse might be suggested as an artifact counteracting technique in CBCT machines that lack the MAR tool.

The alignment between the employed qualitative and quantitative assessment methods assured the validity and credibility of research findings as well as balancing the limitations of one type by the strengths of the other, which could result in better understanding and integration of the study results. Meanwhile, possible limitation of the current study includes the unavailability of a phantom to detect the effect of Blu-mousse and PVS on each restorative material used separately. Within the limitation of this study, we suggest conducting further studies to evaluate the abilities of Blu-mousse and PVS to reduce metallic artifacts in the presence of other clinical modules such as broken files, missed canals, and root fractures for fully assessing their diagnostic capabilities. Additionally, the present study was conducted on a selected field of view. It did not show the effect of the Blu-mousse and PVS in case the parameters were changed.

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**AUTHOR CONTRIBUTIONS:** H.M.E. was responsible for collection, analysis, and interpretation of data (first radiologist), handling the used software, application of methodology and writing the original manuscript. L.M.E. was responsible for interpretation of data (second radiologist), supervision of handling the used software, application of methodology, validation of the study as well as editing and reviewing manuscript. Y.S.G. was responsible for conceptualization, final editing, and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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