- Aggarwal V, Singla M, Miglani S, Kohli S. Comparative evaluation of push-out bond strength of ProRoot MTA, Biodentine, and MTA Plus in furcation perforation repair. J Conserv Dent. 2013;16(5):462-5.
- 24. Simsek N, Alan H, Ahmetoglu F, Taslidere E, Bulut ET, Keles A. Assessment of the biocompatibility of mineral trioxide aggregate, bioaggregate, and biodentine in the subcutaneous tissue of rats. Niger J Clin Pract. 2015;18(6):739-43.
- 25. Saberi EA, Karkehabadi H, Mollashahi NF. Cytotoxicity of various endodontic materials on stem cells of human apical papilla. Iran Endod J. 2016;11(1):17-22.
- Margunato S, Tasli PN, Aydin S, Karapinar Kazandag M, Sahin F. In vitro evaluation of ProRoot MTA, Biodentine, and mm-MTA on human alveolar bone marrow stem cells in terms of biocompatibility and mineralization. J Endod. 2015;41(10):1646-52.
- 27. Gomes-Cornélio AL, Rodrigues EM, Salles LP, Mestieri LB, Faria G, Guerreiro-Tanomaru JM, et al. Bioactivity of MTA Plus, Biodentine and an experimental calcium silicate-based cement on human osteoblast-like cells. Int Endod J. 2017;50(1):39-47.
- Rodrigues EM, Gomes-Cornélio AL, Soares-Costa A, Salles LP, Velayutham M, Rossa-Junior C, et al. An assessment of the overexpression of BMP 2 in transfected human osteoblast cells stimulated by mineral trioxide aggregate and Biodentine. Int Endod J. 2017 Dec;50 Suppl 2:e9-18.
- 29. Pace R, Giuliani V, Pagavino G. Mineral trioxide aggregate as repair material for furcal perforation: case series. J Endod. 2008 Sept;34(9):1130-3.
- Rahimi S, Ghasemi N, Shahi S, Lotfi M, Froughreyhani M, Milani AS, et al. Effect of blood contamination on the retention characteristics of two endodontic biomaterials in simulated furcation perforations. J Endod. 2013;39(5):697-700.
- Üstün Y, Topçuoglu HS, Akpek F, Aslan T. The effect of blood contamination on dislocation resistance of different endodontic reparative materials. J Oral Sci. 2015 Sept;57(3):185-90.
- 32. Nagas E, Kucukkaya S, Eymirli A, Uyanik MO, Cehreli ZC. Effect of laser-activated irrigation on the push-out bond strength of ProRoot mineral trioxide aggregate and Biodentine in furcal perforations. Photomed Laser Surg. 2017 Apr;35(4):231-5.
- Al-Zubaidi AK, Al-Azzawi AKJ. The effect of various endodontic irrigants on the sealing ability of Biodentine and other root perforation repair materials: in vitro study. J Bagh Coll Dent. 2014;26(3):1-8.
- Saunders WP. A prospective clinical study of periradicular surgery using mineral trioxide aggregate as a root-end filling. J Endod 2008;34(6):660-5.
- 35. Soundappan S, Sundaramurthy JL, Raghu S, Natanasabapathy V. Biodentine versus mineral trioxide aggregate versus intermediate restorative material for retrograde root end filling: an in vitro study. J Dent (Tehran). 2014;11(2):143-9.
- Mandava P, Bolla N, Thumu J, Vemuri S, Chukka S. Microleakage evaluation around retrograde filling materials prepared using conventional and ultrasonic techniques. J Clin Diagn Res. 2015;9(2):ZC43-6.

- 37. Naikmm, Ataide IN, Fernandes M, Lambor R. Assessment of apical seal obtained after irrigation of root end cavity with MTAD followed by subsequent retrofilling with MTA and Biodentine: an in vitro study. J Conserv Dent. 2015;18(2):132-5.
- Akcay H, Arslan H, Akcay M, Mese M, Sahin NN. Evaluation of the bond strength of root-end placed mineral trioxide aggregate and Biodentine in the absence/presence of blood contamination. Eur J Dent. 2016;10(3):370-5.
- Pawar AM, Kokate SR, Shah RA. Management of a large periapical lesion using Biodentine(T) as retrograde restoration with eighteen months evident follow up. J Conserv Dent. 2013;16(6):573-5.
- Caron G, Azérad J, Faure MO, Machtou P, Boucher Y. Use of a new retrograde filling material (Biodentine) for endodontic surgery: two case reports. Int J Oral Sci. 2014;6(4):250-3.
- Shin SY, Albert JS, Mortman RE. One step pulp revascularization treatment of an immature permanent tooth with chronic apical abscess: a case report. Int Endod J. 2009;42(12):1118-26.
- Kirchhoff AL, Raldi DP, Salles AC, Cunha RS, Mello I. Tooth discolouration and internal bleaching after the use of triple antibiotic paste. Int Endod J. 2015;48(12):1181-7.
- Bezgin T, Sonmez H. Review of current concepts of revascularization/revitalization. Dent Traumatol. 2015;31(4):267-73.
- Kontakiotis EG, Filippatos CG, Tzanetakis GN, Agrafioti A. Regenerative endodontic therapy: a data analysis of clinical protocols. J Endod. 2015;41(2):146-54.
- 45. Nosrat A, Homayounfar N, Oloomi K. Drawbacks and unfavourable outcomes of regenerative endodontic treatments of necrotic immature teeth: a literature review and report of a case. J Endod. 2012;38(10):1428-34.
- 46. Kim JH, Kim Y, Shin SJ, Park JW, Jung IY. Tooth discoloration of immature permanent incisor associated with triple antibiotic therapy: a case report. J Endod. 2010;36(6):1086-91.
- 47. Yoldas SE, Bani M, Atabek D, Bodur H. Comparison of the potential discoloration effect of bioaggregate, Biodentine, and white mineral trioxide aggregate on bovine teeth: in vitro research. J Endod. 2016;42(12):1815-8.
- Kohli MR, Yamaguchi M, Setzer FC, Karabucak B. Spectrophotometric analysis of coronal tooth discoloration induced by various bioceramic cements and other endodontic materials. J Endod. 2015;41(11):1862-6.
- Marconyak LJ Jr, Kirkpatrick TC, Roberts HW, Roberts MD, Aparicio A, Himel VT, et al. A Comparison of coronal tooth discoloration elicited by various endodontic reparative materials. J Endod. 2016;42(3):470-3.
- Nagas E, Cehreli ZC, Uyanik MO, Vallittu PK, Lassila LV. Effect of several intracanal medicaments on the push-out bond strength of ProRoot MTA and Biodentine. Int Endod J. 2016;49(2):184-8.

# Quality of three techniques for root canal filling: an in vitro cross-sectional analysis in mandibular molars

Carla Roberta Souza **RODRIGUES**<sup>1</sup> Tatiany Sanches Leite **PATARA**<sup>1</sup> Victor Eduardo de Souza **BATISTA**<sup>2</sup> Fellippo Ramos **VERRI**<sup>3</sup> Graziela Garrido **MORI**<sup>4</sup>

DOI: https://doi.org/10.14436/2358-2545.9.3.037-043.oar

#### ABSTRACT

**Introduction:** Reciprocating system can prepare the root canal using only one instrument. However, to ensure successful endodontic treatment, it must result in high-quality root canal filling. In this regard, several techniques can be used, and it is important that their efficiency is determined. This study analyzed three different techniques in terms of their ability to fill root canal. **Material and Methods:** The study involved 30 extracted human mandibular molars. Mesial canals of these teeth were instrumented using WaveOne system and then divided into three groups according to the technique used for root canal filling. The single-cone technique, Tagger's hybrid technique, and an experimental technique (single-cone plus gutta-percha condenser) were used

for Groups I, II, and II, respectively. Filled teeth were sectioned transversely into 0.3-mm sections 2, 4, and 6 mm from the root canal apex. The sections were then digitized and analyzed. Data were statistically compared using Kruskal-Wallis and Dunn tests, with p-values < 0.05 indicating significance. **Results:** There was no significant difference among experimental groups in terms of the amount of gutta-percha or sealer used. However, in Groups II and III, there were fewer voids in root canal filling than in Group I (p < 0.05). **Conclusion:** The techniques for root canal filling presented in the current study yielded a low number of empty spaces, and thermoplastification techniques result infewer voids.

**Keywords:** Root Canal Filling. Root Canal Filling Material. Root Canal Preparation.

How to cite: Rodrigues CRS, Patara TSL, Batista VES, Verri FR, Mori GG. Quality of three techniques for root canal filling: an in vitro cross-sectional analysis in mandibular molars. Dental Press Endod. 2019 Sept-Dec;9(3):37-43. DOI: https://doi.org/10.14436/2358-2545.9.3.037-043.oar

<sup>1</sup> Universidade do Oeste Paulista, Faculdade de Odontologia de Presidente Prudente, Curso de Especialização em Endodontia (Presidente Prudente/SP, Brazil).

<sup>2</sup> Universidade do Oeste Paulista, Faculdade de Odontologia de Presidente Prudente, Disciplina de Prótese Dentária (Presidente Prudente/SP, Brazil).

<sup>3</sup> Universidade Estadual Paulista, Departamento de Materiais Dentários e Prótese Dentária (Araçatuba/SP, Brazil).

<sup>4</sup> Universidade do Oeste Paulista, Faculdade de Odontologia de Presidente Prudente, Disciplina de Endodontia (Presidente Prudente/SP, Brazil). » The authors report no commercial, proprietary or financial interest in the products or companies described in this article.

Submitted: June 06, 2017. Revised and accepted: July 26, 2018.

Contact address: Graziela Garrido Mori E-mail: grazielagm@hotmail.com

## Introduction

Cleaning, shaping, and complete sealing of the root canal system are essential to root canal treatment success.<sup>1,2</sup> Recently, several advances have been made in techniques used for root canal preparation and filling, leading to an improved endodontic treatment.<sup>1-7</sup>

Among these techniques, the reciprocating system is particularly promising, once the anatomy of the original root canal is maintained, aside from cleaning and shaping the root canal efficiently. It also minimizes work time, leading to stress and fatigue reduction for both clinician and patient.<sup>3,4,8</sup>

The single-cone technique for root canal filling was introduced simultaneously with the reciprocating instrumentation system. This technique uses a single-cone of gutta-percha and a sealer. The cone has a similar form to the reciprocating instrument used for root canal preparation.<sup>5,6,9</sup> Thus, after biomechanical preparation, the clinician selects the appropriate cone and introduces it into the working length (WL) portion, along with the sealer of choice.<sup>9</sup> This is an easy and fast technique, and its efficiency for root canal filling should be considered, especially in ovoid or flattened root canals and also when there are ramifications and isthmi.<sup>6,8,9</sup>

In addition, adequate filling procedures, such as thermoplastification techniques, must be used to ensure effective sealing between the filling material and the root canal wall,<sup>1</sup> which is indicated by good adaptation and absence of empty spaces or voids.<sup>1,6-10</sup>

Thermoplastification techniques employ specific instruments for gutta-percha heating and allow better adaptation of root canal filling.<sup>1,7</sup> For instance, Tagger's hybrid technique uses a gutta-percha condenser to heat gutta-percha. The gutta-condenser should have a diameter twice the size of the main gutta-percha point, and should be 4 mm shorter than the WL or the straight portions in a curved root canal. These techniques enable adaptation of the main gutta-percha point at the apical region, ramifications, isthmi, and other areas, favoring complete root canal filling both in straight and curved root canals.<sup>11,12</sup>

Considering the ease and agility of root canal filling when using the single-cone technique and the importance of correct filling without voids or empty spaces between gutta-percha cone, sealer, and the wall of the root canal, in this study, we proposed a technique that combines single gutta-percha cone with thermoplastification. However, to allow routine clinical use, it is necessary to determine which technique provides better root canal filling to achieve outcomes.

Therefore, this study used a cross--sectional analysis to evaluate, in vitro, three different filling techniques for performing root canal fillings.

## **Material and methods**

the present study was conducted on 30 extracted human mandibular molars in which instrumentation was performed on mesial root canals (flattened with presence of isthmi). The teeth were obtained from the Tooth Bank of Universidade do Oeste Paulista after approval by the institutional review board (protocol #2037). Soft tissues and calculus adhered to root surfaces were removed using periodontal curettes. Teeth were then stored in saline solution (Darrow Laboratórios S.A, Rio de Janeiro, RJ, Brazil).

## **Preparation of specimens**

The present study followed the methods suggested by Marciano et al,<sup>13</sup> in 2011. Coronal opening was performed using diamond burs with a diameter compatible with that of the pulp chamber (FKG Sorensen, Cotia, SP, Brazil).

Root canal length was measured by introducing a #10 K-file with a rubber stop (Dentsply Maillefer, Ballaigues, Switzerland). When the file tip crossed the apical foramen, the rubber stop was placed at the coronal edge, and the length was recorded. Working length (WL) was determined by subtracting 1 mm from total root canal length.

Root canals were prepared using the primary instrument (25/.08) of the WaveOne system (Dentsply Maillefer, Ballaigues, Switzerland). A reduction handpiece was used with the specific selection of the reciprocating system (X-Smart Plus; Dentsply Maillefer, Ballaigues, Switzerland). The instrumentation technique followed the standards established by the manufacturer, and a single instrument was used to perform biomechanical preparation. Specimens that exceeded the diameter of # 25 K-file after root canal preparation were excluded and replaced. At every change of instrument, root canals were irrigated using 2 ml of 2.5% sodium hypochlorite solution (Fórmula & Ação, São Paulo, SP, Brazil). After instrumentation was complete, root canals were filled with 2 ml of 2.5% sodium hypochlorite solution. This solution was activated for one minute, using passive ultrasonic irrigation (PUI) with irrisonic tip (Helse, Santa Rosa de Viterbo, SP, Brazil) placed 1 mm short the WL. This procedure was repeated three times, as described in a 2007 study by van der Sluis et al.<sup>14</sup>

Thereafter, root canals were irrigated using 2 ml of 17% EDTA solution (Biodinâmica, Lobato, PR, Brazil) for three minutes, washed using 2 ml of distilled water, and then dried with #25 absorbent paper points (Dentsply Maillefer, Ballaigues, Switzerland).

After biomechanical preparation was complete, the teeth were randomly divided into three groups of 10 specimens, according to the technique used for root canal filling. To this end, a random allocation open-source software program (<u>http://www.openepi.</u> <u>com/Menu/OpenEpiMenu.htm</u>) was used. Group I comprised root canals filled using the single-cone technique; the primary gutta-percha point (25/.08) of the WaveOne system was selected. The points were adapted to the WL of the root canal using 0.05 ml of AH Plus endodontic sealer (Dentsply Maillefer, Ballaigues, Switzerland). To complete root canal filling, vertical condensation was performed 1 mm below root canal opening.

Group II consisted of root canals filled by Tagger's hybrid technique; the 25/.02 main point was selected (Dentsply Maillefer, Ballaigues, Switzerland). Thus, the points were adapted at the apical limit of instrumentation using 0.05 ml of AH Plus. Next, three points (15./02) were inserted into the root canal using size B finger spreaders (Dentsply Maillefer, Ballaigues, Switzerland), and a gutta-percha condenser (#35) (Dentsply Maillefer, Ballaigues, Switzerland) was inserted at low speed into the root canal 4 mm short the WL to allow plastification of gutta-percha points. Root canal filling was completed using the vertical condensation technique.

Therefore, in Group III, root canals were filled using the experimental technique; the primary gutta-percha point (25/.08) of the WaveOne system was selected. The points were adapted to the root canal at the WL using 0.05 ml of AH Plus. A gutta-percha condenser (#50) was then inserted 4 mm short the WL into the root canal for plastification of gutta-percha points.

After completion of root canal filling, all teeth were sealed using glass ionomer cement (Maxxion R; FGM, Joinville, SC, Brazil), placed in flasks according to the study group, and kept in an oven at 37°C with 100% humidity for seven days.

# Analysis of specimens

Filled teeth were transversely sectioned in an Isomet machine (Buehler, Lake Bluff, IL, USA). Sections of 0.3-mm thickness were obtained 2, 4, and 6 mm from the root apex. Sectioning was performed at 200 rpm under abundant and constant irrigation to avoid heating the gutta-percha. Surfaces of sections were polished under irrigation to eliminate possible irregularities. Sections were digitized, and images were analyzed using Image J software (Wayne Rasband; Research Services Branch, National Institute of Mental Health, Bethesda, Maryland, USA).

# Data collection and analysis

Areas of root canals, isthmi, gutta-percha-filled area, and sealer-filled area were measured individually by a blinded examiner. To identify empty spaces or voids, the examiner subtracted the total filled area (gutta-percha and sealer) from the total area of the root canals and isthmi. Data were organized into tables according to the experimental group, and Shapiro Wilk test was performed to determine the normality of results (p < 0.05). On this basis, a non-parametric analysis was carried out, and Kruskal-Wallis test followed by Dunn post-hoc analysis was applied at a significance level of 5% (p < 0.05) to analyze differences within and between groups.

# **Results**

Results of the present study were described in terms of the amount of gutta-percha, sealer and empty spaces or voids. Absence of voids indicated successful filling of the root canal.

Root canals filled using the single-cone technique (Group I) showed no statistical difference among the 2-mm, 4-mm, and 6-mm sections in terms of quantity of gutta-percha, sealer, and absence of voids (p > 0.05) (Table 1). Filling remained homogeneous independently of the analyzed section using this technique.

In root canals filled using Tagger's hybrid technique (Group II), there was a difference between the 2-mm and 4-mm sections compared to the 6-mm sections in terms of the amount of gutta-percha and sealer (p < 0.05) (Table 2). Despite these differences, the number of voids was small and it did not differ significantly among all sections (p > 0.05) (Table 2).

Root canal filled using the experimental technique (Group III) demonstrated a difference between the 2-mm and 6-mm sections in terms of the amount of gutta-percha (p < 0.05). The 2-mm sections differed from both the 4-mm and 6-mm sections in terms of

quantity of sealer (p < 0.05). Despite these differences, the number of voids was small and did not differ significantly among the sections analyzed (p > 0.05) (Table 3).

There was no difference among experimental groups in terms of the amount of gutta-percha or sealer, regardless of which sections were analyzed (p > 0.05) (Table 4). With regards to the occurrence of voids, there was statistically significant difference between Group I and the other Groups (p < 0.05) (Table 4), indicating the use of gutta-percha condenser resulted in better root canal filling.

Table 1. Median (%) of gutta-percha, sealer, and voids in Group I (single-cone technique).

	2 mm from the root apex	4 mm from the root apex	6 mm from the root apex	р
gutta-percha	67.195ª	75.025ª	72.620ª	0.3668
sealer	22.295ª	15.765ª	17.550ª	0.4121
voids	7.835ª	6.895ª	8.570ª	0.7545

Different letters in the same line indicate statistically significant difference (p < 0.05)

Table 2. Median (%) of gutta-percha, sealer, and voids in Group II (Tagger's hybrid technique).

	2 mm from the root apex	4 mm from the root apex	6 mm from the root apex	р
gutta-percha	54.325ª	67.925ª	92.585 <sup>b</sup>	0.0018
sealer	38.100ª	28.200ª	7.215 <sup>b</sup>	0.0043
voids	4.755ª	0.745ª	Oa	0.1690

Different letters in the same line indicate statistically significant difference (p < 0.05).

Table 3. Median (%) of gutta-percha, sealer, and voids in Group III (experimental technique).

	2 mm from the root apex	4 mm from the root apex	6 mm from the root apex	р
gutta-percha	57.950ª	79.685 <sup>a.b</sup>	99.405 <sup>b</sup>	0.0024
sealer	42.050ª	15.805 <sup>b</sup>	0.595 <sup>b</sup>	0.0015
voids	O <sup>a</sup>	1.800ª	Oª	0.1191

Different letters in the same line indicate statistically significant difference (p < 0.05)

Table 4. Median (%) of gutta-percha, sealer, and voids in root canal system among experimental groups.

	Group I	Group II	Group III	valor de p
gutta-percha	73.330ª	75.405ª	79.535ª	0.3252
sealer	17.550ª	17.025ª	18.335ª	0.7820
voids	8.205ª	0.900 <sup>b</sup>	Ob	p < 0.0001

Different letters in the same line indicate statistically significant difference (p < 0.05)

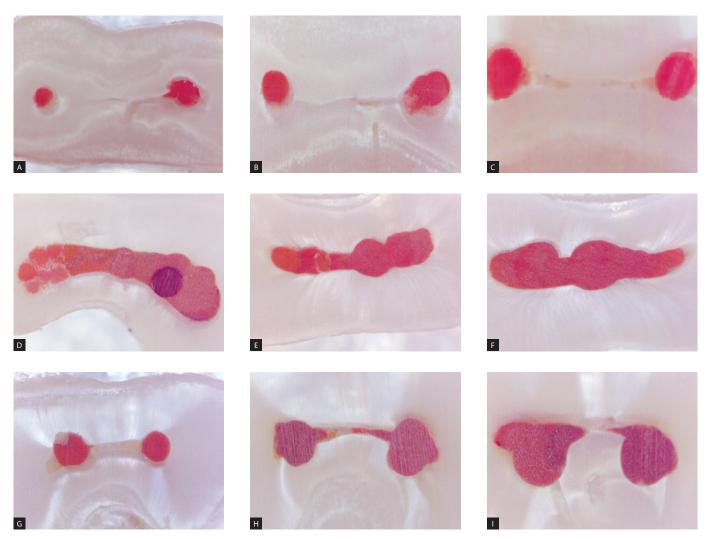


Figure 1. Different sections of the experimental groups. Group 1: A-C) represent the sections at 2, 4 and 6 mm from the apex, respectively, Group I; in these sections, no filling material can be seen in the isthmus area, indicating void spaces. Group II: D-F) represent sections at 2, 4 and 6-mm from the apex, respectively, in Group II; in these sections, filling material can be seen in the isthmus area, yielding fewer empty spaces. Group III: G-I) represent the sections at 2, 4 and 6-mm from the apex, respectively, in Group II; in these sections, filling material can be seen in the isthmus area, yielding fewer empty spaces. Group III: G-I) represent the sections at 2, 4 and 6-mm from the apex, respectively, in Group III; the results and the analyses are similar of those of Group II.

## **Discussion**

This study presented a new technique for the root canal system filling, which combined the ease and flexibility of the single-cone technique with thermoplastification of gutta-percha, as used in Tagger's hybrid technique. However, prior to clinical use of the new method, initial analyses must be carried out in vitro to confirm whether there is adequate root canal filling to achieve endodontic success.<sup>12,13,15</sup> This can be determined by the absence of voids inside the filling mass and root canal walls.<sup>9,12,13,15,15</sup> Voids or empty spaces allow microbial growth and subsequent clinical failure.<sup>2,17,18</sup>

Several methods can be used to analyze the quality of root canal fillings, such as an analysis of voids using micro-computed tomography,<sup>9,19</sup> the fluid filtration method,<sup>20</sup> or the glucose leakage test.<sup>21</sup> In the present study, in order to analyze the quality of root canal fillings, we measured the amount of gutta-percha, sealer, and voids or empty spaces in dentin slices of filled root canal, as described in several published works.<sup>12,13</sup>

In addition, we analyzed complex root canal systems with flattened canals and isthmi, such as the mesial root canal of the mandibular molars, which represents a clinical reality commonly found in End-odontics.<sup>16,22</sup>

Root canal cleaning, shaping, disinfection, and complete sealing are essential to root canal treatment success.<sup>1,2</sup> Adequate sealing between filling material and the root canal wall requires effective root canal filling.<sup>1</sup> To this end, different techniques may be used for root canal filling, and many have shown good results in terms of the amount of gutta-percha, adaptation, and absence of voids in the filling.<sup>1,6,7,10</sup> In this regard, the present study analyzed three different root filling techniques, the experimental technique, the single-cone technique, and Tagger's hybrid technique. The study discovered the techniques analyzed were effective for filling root canal systems, since there were few voids in each of the experimental groups (Table 4).

The thermoplastification techniques used in Groups II and III were more efficient than the methods used in Group I: they resulted in fewer voids and they used similar quantities of gutta-percha and sealer. Marciano et al<sup>13</sup> also found that thermoplastification techniques, (System B and Thermafil) resulted in fewer voids than the single-cone technique using the Pro Taper system. Other authors have related similar results when comparing the single-cone technique with gutta-percha thermoplastification technique.<sup>23,24</sup> Küçükkaya et al23 demonstrated that the warm vertical compaction technique, thermoplastification technique presented better filling quality than the cold lateral compaction and single-cone techniques. Robberecht et al<sup>24</sup> observed better quality in root canal fillings using the thermoplastification technique than when using the single-cone technique. They posited that gutta-percha adjustment influenced root canal morphology.

The heat generated using gutta-percha condenser plasticizes the material and confers homogeneity in

the filling mass, allowing better adaptation to root canal walls.<sup>12,13,17</sup> The present work confirms this explanation, demonstrating similar amounts of gutta-percha and sealer in all groups, except for Groups II and III, in which the condenser was used, revealing significantly fewer voids than Group I (p < 0.05) (Table 4). This indicated that the thermoplastification technique heats gutta-percha and promotes homogeneous filling of the root canal system.<sup>12,13,23</sup>. Filling mass homogeneity and the consequent better adaptation to root canal walls in Groups II and III yielded better quality root canal filling in these groups than in Group I. In this regard, the gutta-percha condenser used in the present work was compatible with the anatomy of the gutta-percha cone. According to Tagger's hybrid technique, the gutta-percha condenser must be two or three sizes larger than the main point,<sup>11</sup> justifying the use of #35 gutta-percha condenser in Group II. However, in Group III, the gutta-percha condenser was larger (#50), due to the single-cone having a greater taper than the main point used in Group II, and because more gutta-percha has to be plasticized using this technique.

# Conclusion

Considering the results and under the limited conditions of this study, the three root canal filling techniques evaluated revealed a low occurrence of voids. However, the thermoplastification gutta-percha techniques (Tagger's hybrid technique and the experimental technique) resulted in fewer voids in the root canal system than the single-cone technique. For a more precise evaluation of the experimental technique and to determine factors affecting its efficacy and security before clinical use, randomized clinical trials are necessary.