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ORIGINAL ARTICLE

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Efficacy evaluation of pepsin enzyme-based gel in chemo-mechanical caries removal on primary anterior teeth: a randomized controlled clinical study

Avaliação da eficácia do gel à base de enzima pepsina na remoção químico-mecânica da cárie em dentes anteriores decíduos: um estudo clínico controlado randomizado

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ABSTRACT

Objective: To evaluate the efficacy of a new pepsin enzyme-based gel compared with Carisolv as a CMCR agent. Clinical and radiographical evaluations of recurrent caries were made 3 and 6 months after treatment. **Material and Methods:** A split-mouth designed randomized controlled clinical study was carried out on 40 primary anterior teeth of children aged between 4-7 years. Pepsin enzyme-based gel and Carisolv solution were applied to carious lesions until complete removal of caries. The efficacy of both agents was evaluated by the number of application times to remove all caries. Recurrent caries were evaluated clinically and radiographically after 3 and 6 months of treatment. **Results:** Results showed no statistically significant differences in the efficacy of caries removal by the number of application times ($P = 0.919$). Concerning recurrent caries, clinical and radiographical evaluation after three and six months showed no statistically significant differences between the two groups ($P = 0.574$, $P = 0.547$, respectively). **Conclusion:** Pepsin enzyme-based gel can be considered similar to Carisolv gel regarding its efficacy as a CMCR agent for small carious lesions on primary anterior teeth in children aged 4-7 years old.

KEYWORDS

Carisolv; Chemo-mechanical caries removal; Pepsin enzyme; Caries; Minimally invasive dentistry.

RESUMO

Objetivo: avaliar a eficácia de um novo gel a base de enzima pepsina comparada com o Carisolv como um agente na remoção químico-mecânica da cárie. Avaliações clínicas e radiográficas de cárie recorrente foram feitas em 3 e 6 meses apos o tratamento. **Material e Métodos:** um estudo clínico controlado randomizado de boca-dividida foi realizado em 40 dentes deciduos anteriores de crianças com idade entre 4-7 anos. Gel à base de enzima pepsina e a soluçao de Carisolv foram aplicados sobre a lesão cariosa até a completa remoção da carie. A eficácia de ambos agentes foi avaliada pelo número de tempo de aplicações para a remoção de todo tecido cariado. Cárie recorrente foi avaliada clinicamente e radiograficamente após 3 e 6 meses de tratamento. **Resultados:** Não houve diferença significativa na eficácia de remoção de cárie pelo número de tempo de aplicação ($P = 0.919$). Em relação à cárie recorrente, avaliação clínica e radiográfica apos 3 e 6 meses mostraram que não houve diferença estatisticamente significante entre os 2 grupos ($P = 0.574$, $P = 0.547$, respectivamente). **Conclusão:** o gel à base de enzima pepsina pode ser considerado similar ao gel Carisolv em relação a sua eficácia como um agente químico-mecânico na remoção da cárie para lesões cariosas pequenas em dentes anteriores decíduos em crianças entre 4-7 anos de idade.

PALAVRAS-CHAVE

Carisolv; Remoção químico-mecânica da carie; Pepsina; Cárie; Odontologia Minimamente Invasiva.

INTRODUCTION

The traditional caries removal method typically engages digging and drilling using a rotational handpiece to remove decayed structures [1]. Nonetheless, it is efficient in removing bacterial dentine, yet is seen as uncomfortable, apprehensive, and painful to young patients. The conventional caries removal method regularly trespasses into the intact dentin in the inner layer compromising many dentinal tubules to be opened, thus yielding abundant pain and tension. Therefore, using local anesthesia is considered necessary during treatment [2].

These days, easy treatment and "minimal intervention" are essential standards in pediatric dentistry [2]. The logic of minimally invasive caries removal is one of the utmost imperative applications of the minimal intervention dentistry concept built up amid the final decade [3]. The use of laser ablation, air abrasion, sono-abrasion, or chemo-mechanical agents to eradicate infected dental tissue has prominently endorsed other existing minimally invasive caries-removal practices [3].

The Chemo-mechanical method per se is one of the most dominantly documented as a substitute to the traditional drilling method [2]. This approach, extensively known as the CMCR, has been found throughout the literature to be consisted of proteolytic substance application. The material itself moderates dentin tissues infected with caries and enables its removal using manual tools [4].

Chemo-mechanical caries removal agents are normally classified into two sub-categories: sodium hypochlorite (NaOCl) or enzyme-based agents [3]. The 5% concentration version of NaOCl has been used as a chemo-mechanical caries removal agent since the seventies, but still, it has proven unstable [3]. The subsequent improvement was known as the GK-101 solution, introduced by Goldman and Kronman in 1976 [4]. GK-101 was further modified to GK-101E (Caridex) [5].

In 1998, Carisolv (Medi Team Dental AB, Goteborg, Sweden) was announced as the latest version of the NaOCl-based chemo-mechanical agents [3].

Even though Carisolv was an unprecedented success in dental medicine cycles, definite downsides have also been traced in its usage, which incorporates the requirement of customized instruments, excessive application time, and noticeably increased cost. These factors rendered it available to the fewest able-to-afford dentists [6].

Contrastively, proteolytic enzymes have the ability to cleave collagen fibers that become exposed in carious areas after the adjoining hydroxy-apatite is dissolved by the organic acids formed by the microorganisms. This very action is bound to their specific substrate, and this property perhaps proves a clear advantage of enzymes in contrast to unspecific agents like sodium hypochlorite, making them self-limiting. Moreover, enzymes get only active when their optimal pH level is preserved. Therefore, they are prone to inactivation the moment their local pH changes [7].

The activity of collagenase, pronase, and pepsin on dentin degradation have been previously studied [7]. It was found that enzymes were capable of removing denatured dentin, leaving demineralized tissue, which has the potential to remineralize [7].

The new enzymatic products commercially available such as Papacarie®, Carie-Care™, and Brix 3000®, contain in its composition the papain enzyme, similarly to the pepsin enzyme [8, 9].

Biosolv ™ (SFC-V gel, 3M-ESPE AG, Seefeld, Germany) is a moderately acidic buffered solution of an enzyme (pepsin) with the ability to specifically disintegrate carious dentin [7].

Additional components in the formulation yield a sufficient viscosity, stabilize enzymatic activity, and ensure storage stability [7]. The information about Biosolv has been detected through this current study as very limited and is based mainly on the manufacturer's claims, which remains an experimental material [3,9].

However, these enzyme-based agents are somewhat less economical than others due to cost, limited shelf life, and wastage during the application, in addition to the unpleasant smell and taste produced by most of these agents, which cause discomfort to the patient [10].

The pepsin enzyme has been studied as a chemical-mechanical caries removal agent in several in-vitro studies, which found that the pepsin enzyme can remove the denatured superficial dentin while retaining the partially

demineralized dentin, considering it to be less aggressive than NaOCl [7,11,12].

Therefore, this study was conducted as the first clinical study in dental literature to evaluate the efficacy of the Pepsin enzyme-based gel in an attempt to find an alternative agent that overcomes the disadvantages of the previous agents in terms of smell, ease of application, and limited shelf life. And can be easy to manufacture, with low cost.

This randomized controlled trial aimed to compare the efficacy of the pepsin enzyme-based gel with Carisolv solution in chemo-mechanical caries removal in small lesions of primary anterior teeth by comparing the number of applications required of each chemical agent for complete caries removal. And to check clinically and radiographically the presence of secondary caries after 3 and 6 months of follow-up.

MATERIALS AND METHODS

Study design

This study was designed as a split-mouth randomized controlled trial (RCT). Every child included in the sample represents the experimental and control sample at the same time. Consequently, two treatment methods are compared on the same subject. Upon obtaining the approval of the Ethics Scientific Committee at the study institution, the trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) with the trial ID: ACTRN12621001759886.

Sample size calculation

G*Power software version 3.1.9 (University Kiel, Germany) was used to calculate the sample size using the following criteria: the effect size was 0.581, according to Pathivada et al. [5]. The power of 90%, an alpha level of 0.05, and paired-samples t-test as a statistical test was chosen. The required sample size was 17 primary anterior teeth per group. The sample size was increased to 40 primary anterior teeth to compensate for drop-outs during follow-up or due to other causes such as attrition. (Figure 1)

Study groups

The sample included 40 primary anterior teeth in 20 patients whose ages ranged between 4–7 years and were recurrent patients at the Pediatric Dentistry Department, Damascus University. Information sheets were distributed to all parents or legal guardians of all participants, and informed consent was obtained. Each patient in the sample was given a coded number from 1 to 20 and was randomly assigned to one of two groups using the following website: http://www.randomization.com. After randomization, the sample was allocated as follows: Group A stands for the group in which the right side will be treated using the pepsin

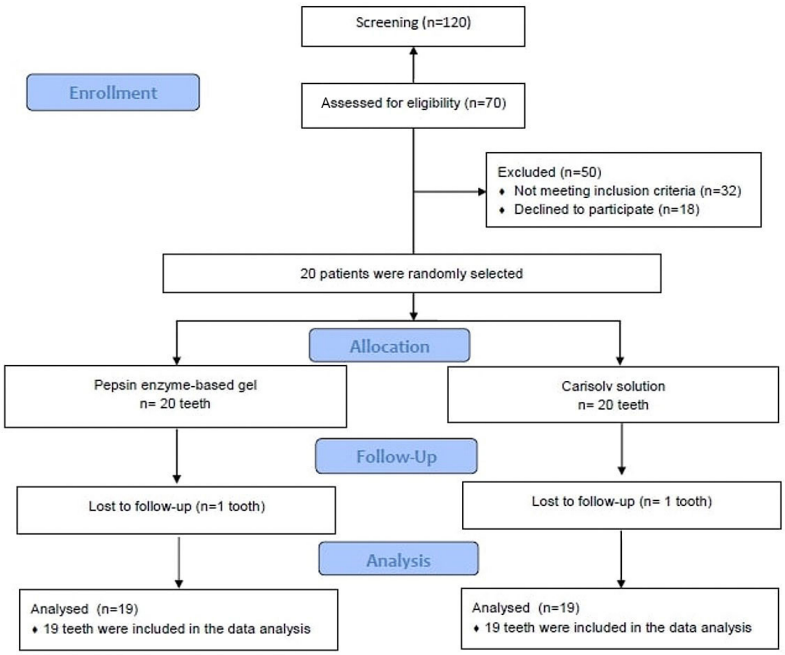

Figure 1 - CONSORT flow diagram of patients' recruitment, assignment, and follow-up.

enzyme-based gel, whereas group B inculcates the group in which the right side will be treated with Carisolv. Blinding of the researcher was not applicable. Therefore, blinding was applied only to participants and the outcomes assessor.

Inclusion criteria

Healthy Children (who do not have any systemic diseases such as diabetes, chronic respiratory disease, or cancer) exhibiting definitely positive or positive behavior according to Frankl's behavior rating scale [13], and who have at least two primary anterior teeth with similar open buccal carious lesions that need aesthetic restorations, where the DIAGNOdent digital values were between 25-35, referring to an early dentinal enamel lesion [14]. And that don't show any clinical and/or radiographical signs or symptoms of pulpal and periapical lesions or developmental defects [13].

Preparation of the pepsin enzyme-based gel

The pepsin enzyme (Sigma Aldrich, Germany) 5 g was dissolved in 100 ml distilled water. Then 0.1 g chloramine, 0.1 g sodium benzoate, and 2 g glycerin were added accordingly. The mixture was then filtered under reduced pressure. After completing the filtration process, 2 g sodium alginate was added extremely slowly. It is a prerequisite that allows a solution to take the formula of a gel.

Later, the pH of the solution was adjusted to a level of pH = 2 by adding phosphoric acid. Finally, drops of green apple flavor were added to improve the product's smell. The final gel product was packaged in sealed dark plastic containers and stored in a refrigerator at about 4° C.

Before conducting the present study, an in-vitro pilot study was conducted on ten carious extracted primary teeth to determine the efficacy and the convenient time of application. The ability of the gel to make a carious dentin tissue soft – easily marked to be removed using unsharpened hand excavators – was noted. The evaluated optimal application time was 40 seconds for each one.

Intervention

All interventions in this study were performed at the Pediatric Dentistry Department, Damascus University. After clinical examination, Digital X-ray periapical radiographs were taken, and a DIAGNOdent (KAVO, Dental Gmbh, Jena, Germany) examination was performed for each tooth to determine the depth of the carious lesion. Upon achieving the inclusion criteria, children received treatment for corresponding teeth in the same session of examination to maintain the same conditions surrounding the treatment and the psychological status of the child in both treatment methods. Isolation was performed using rubber dam, and either pepsin enzyme-based gel for 40 seconds or Carisolv solution (Medi Team Dental AB, Goteborg, Sweden) for 30 seconds was applied. Consequently, the softened carious dentin was removed by rapid and rotational scraping movements via a hand excavator without applying any pressure, under the stipulation that the lesion remains covered with gel as much as possible throughout the removal process [15]. The procedure was repeated until a clear colored gel was observed when applied in the cavity. When the cavity seemed caries-free, the gel was removed, and the region was cleaned with a damp cotton pellet. Another blinded researcher evaluated the cavities to ensure that all carious tissues had been removed using visual and tactile assessment, followed by using a caries detector. If remaining carious tissues were observed, caries removal agents were reapplied until a free caries cavity is reached. Finally, cavities were restored using glass ionomer cement (GC Fuji IX GP, GC Corporation, Tokyo, Japan). (Figures 2 and 3)

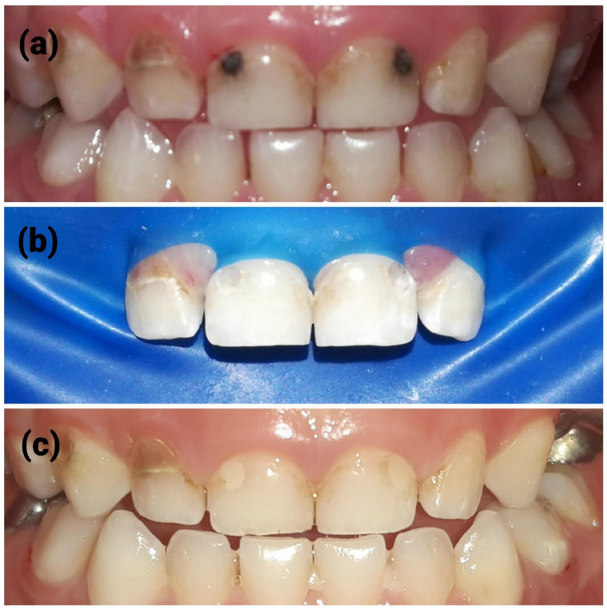

Figure 2 - A case illustrating work stages on Upper incisors; a: Diagnostic image, b: Rubber dam isolation and caries removal, c: Final restoration with GIC.

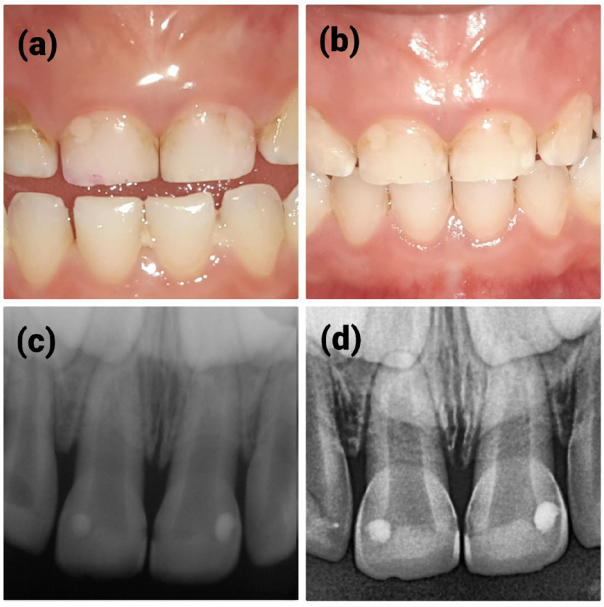

Figure 3 - Clinical and Radiographic follow-up: a: Clinical follow-up after 3 months, b: Clinical follow-up after 6 months, c: Radiographic follow-up after 3 months, d: Radiographic follow-up after 6 months.

The clinical and radiographic assessment were conducted by two researchers without informing them of the applied caries removal method. Cohen's kappa test was utilized to calculate the intra-examiner reproducibility and inter-examiner reliability. The kappa for intra-examiner agreement and inter-examiner reliability reached 0.86.

Outcome measures

The number of application times to remove all of caries lesion

The number of application times for each caries removal agent was calculated from the first application until the caries is completely removed (1 - 2 - 3 - 4 – 5 …).

Post-treatment evaluation – 3 and 6 months

1- *Clinical examination:* The clinical examination was carried out by two researchers with the absence of diagnostic case sheets in order to blind the researchers about the type of treatment applied.

- Caries recurrence was evaluated using a caries detector. Results were recorded as follows:

1- there is no caries, 2- marginal caries, and 3- transverse caries [15].

2- *Radiographic examination:* The radiographic examination was conducted to assess caries recurrence. It was accomplished by the same two researchers blinding them over the applied caries removal method. Their assessment was given for the presence or absence of caries recurrence.

Statistical analysis

Data were analyzed using the SPSS 13.0 software for Windows (SPSS Inc., Chicago, Ill., USA). The Mann-Whitney U test was used to study the differences in the number of application times and the clinical recurrent caries, whereas the chi-square test was used to study the differences in the radiographic assessment of caries recurrence between two groups at the 95% confidence level and $P < 0.05$.

RESULTS

The sample consisted of 40 anterior primary teeth in 20 young patients – 11 males and 9 females – whose ages ranged between 4-7 years (mean age = 5.8 years ± 1.1). The primary teeth in the sample were randomly divided into two equal groups according to the treatment medium, pepsin-based gel or Carisolv. (Table I)

The Mann-Whitney U test was utilized to examine the significant differences in the number of application times between the pepsin enzyme-based gel group and the Carisolv group. Furthermore, it was noted that at a 95% confidence level there were no statistically significant differences in the number of application times between the two study groups. It holds true if the two sets of obtained values traced by readers of this current research, as the *p*-value reached 0.919. (Table II).

Nevertheless, one patient dropped this study and didn't show up for follow-up after treatment due to personal reasons. Therefore, only 19 patients were enrolled in the statistical analysis, three months and six months post-treatment.

The Mann-Whitney U test was utilized to study the significant differences in the degree of clinical caries recurrence between the pepsin enzyme-based gel group and the Carisolv group. According to the time periods studied, it was noted that at a 95% confidence level, there were no statistically significant differences in the degree of clinical caries recurrence after three months and six months of follow-up between

Table I - The distribution of the sample according to the type of treated tooth and the treatment method used

Method of treatment	Number of primary teeth					Percentage%				
	Upper incisor	Upper lateral incisor	Upper canine	Lower canine	Total	Upper incisor	Upper lateral incisor	Upper canine	Lower canine	Total
Pepsin enzyme-based gel	4	3	3	10	20	20.0	15.0	15.0	50.0	100
Carisolv solution	4	3	3	10	20	20.0	15.0	15.0	50.0	100

Table II - Number of application times in the sample according to the treatment method used

Method of treatment	Number of teeth					Percentage%				
	One application	Two application	Three times application	Four times application	Total	One application	Two application	Three times application	Four times application	Total
Pepsin enzyme-based gel	2	10	5	3	20	10.0	50.0	25.0	15.0	100
Carisolv solution	2	9	7	2	20	10.0	45.0	35.0	10.0	100

Table III - The results of the clinical Caries recurrence in the sample according to the treatment method used and the time periods studied

Time period	Method of treatment	Number of teeth				Percentage%			
		No caries	Marginal caries	Transverse caries	Total	No caries	Marginal caries	Transverse caries	Total
After 3 months	Pepsin enzyme-based gel	19	0	0	19	100	0	0	100
	Carisolv solution	19	0	0	19	100	0	0	100
After 6 months	Pepsin enzyme-based gel	17	1	1	19	89.5	5.3	5.3	100
	Carisolv solution	18	0	1	19	94.7	0	5.3	100

Table IV - The results of the radiological caries recurrence assessment in the sample according to the treatment method used and the time periods studied

Time period	Method of treatment	Number of teeth			Percentage%		
		No caries	Caries teeth	Total	No caries	Caries teeth	Total
After 3 months	Pepsin enzyme-based gel	19	0	19	100	0	100
	Carisolv solution	19	0	19	100	0	100
After 6 months	Pepsin enzyme-based gel	17	2	19	89.5	10.5	100
	Carisolv solution	18	1	19	94.7	5.3	100

the two studied groups. The probability values reached 1.000 and 0.574, respectively. (Table III)

The chi-square test was also utilized to study the differences between the two groups concerning radiographic caries recurrence. Building to the time periods studied, it was evident that there were no statistically significant differences three and six months post-treatment between the two groups, the *p*-values took the result of 0.547. (Tables IV)

No statistically significant differences were detected in caries relapse, clinically or radiographically, between the two time periods studied at a 95% confidence level, regardless of the treatment method used.

DISCUSSION

This trial compared a new Pepsin enzyme-based gel with Carisolv solution (NaOCl based) in terms of efficacy of caries removal by counting the number of application times to remove all caries, and Clinical and radiographic assessment of caries recurrence three and six months after treatment.

Since this is the first clinical study to be carried out using locally formulated pepsin enzyme-based gel, the comparisons were made with other enzymatic products that have the same mechanism of action to that of the pepsin enzyme.

In this study one researcher has removed caries for all teeth to standardize the caries removal procedure for all the sample. Taking into account the use of the same excavators with both materials, as Carisolv excavators (Medi Team Dental AB, Goteborg, Sweden) were used.

The investigator could not be blinded during the application process as a result of the different odor and texture of both materials.

No statistically significant differences were witnessed in the number of application times for both caries removal agents to remove caries completely. This could be credited to the selection of symmetrically sized carious lesions in the study sample. The results of this study diverge from Hegde et al. [16], who concluded that removing caries using Papacarie requires fewer application times compared with Carisolv, and therefore it takes less time. This difference might be attributed to the dissimilarity in the teeth sample included in the study, where they operated on primary molars. No Caries recurrence was distinguished after three months of clinical and radiographic follow-up. However, only one tooth, re-hit by caries after six months, was detected in the pepsin gel group and two teeth in the Carisolv group. An outcome like this is probably related to the survival of some microorganisms after caries removal or marginal leakage occurrence around the restoration. Another reason is probably due to poor oral health during follow-up periods and the high caries susceptibility of those patients.

No statistically significant differences were spotted for caries recurrence both clinically and radiographically between the two treatment methods used, as well as between the two post-treatment follow-ups, three and six months. This result is somehow consistent with Motta et al. [17] on primary molars, who did not perceive any caries recurrence at follow-ups after 6 and 12 months in the chemo-mechanical caries removal group, using Papacarie followed by restoration using glass ionomer. Accordingly, Hegde et al. [18] underpinned that the primary and permanent molars treated with caries-care were clinically sound and asymptomatic after 1 month, 6 months and 12 months. The reason for no detection of caries recurrence can be ascribed to the basic rules for obtaining a good restoration in terms of good isolation when using a rubber dam. It could also relate to the use of appropriate restorative materials, such as glass ionomer cement, which is characterized by ease of use, adhesion to dental tissues, biocompatibility and fluorine-ions release [17,19].

Throughout the literature on the topic, plenty of studies reveal that chemo-mechanically treated dentin has more surface energy, superior attraction for adhesives material, and better bonding than conventionally treated dentin. Besides, more irregular and rougher surface is found with the absence of smear layer, which possibly improves the bonding between the restoration and the tooth [17,18,20].

Although this is the first study in the literature that evaluated the clinical efficacy of low-cost pepsin enzyme in the removal of caries in a smooth and atraumatic way, and showed a good efficacy in removing caries and similar to that of carisolv solution. This study was limited to small buccal caries on primary anterior teeth, with a relatively short follow-up period of six months. Additionally, the investigator could not be blinded during the application process as a result of the different odor and texture of both materials. Another limitation of this study is the impossibility of measuring the pressure exerted during caries removal by a researcher, which may considered a confounding factor. Therefore, it is necessary to carry out more studies with longer follow-up periods before generalizing the results of this study to all carious lesions.

CONCLUSIONS

Pepsin enzyme-based gel can be considered similar to Carisolv gel in efficacy and thus can be considered as a CMCR agent for small carious lesions on primary anterior teeth in children aged 4-7 years old. However, Long-term studies are needed to evaluate this product prior to recommending it for routine use in clinical practice.

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Author's Contributions

DAA: Investigation, writing original draft and is the corresponding author. AR: Writing – review & editing. rashad shaadouh: formal analysis and data curation. IK, NT: Writing – review & editing. EAA: Conceptualization, methodology, supervision and manuscript review.

Conflict of Interest

The authors declare that they have no competing interests.

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Regulatory Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee of the study institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards." Informed consent was obtained from all individual participants included in the study.

The approval of the Ethics Scientific Committee from Damascus University, Faculty of Dentistry, was obtained (Protocol No. 2360)

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