Effectiveness of MI VarnishTM and PreviDentâ Varnish in Non-cavitated Interproximal Lesions: A Randomized Clinical Trial.

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Research Article

Keywords: Fluoride varnish, Remineralization, Non-cavitated interproximal

Posted Date: March 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-228093/v1

Abstract

Background: the clinical investigations regarding the efficacy of different fluoride products are limited. Aim: to compare the effectiveness of Colgateâ PreviDentâ and MI™ varnishes to the standard (1.23%) acidulated phosphate fluoride gel in the remineralization of non-cavitated proximal incipient lesions.

Design: this randomized clinical trial included 91 lesions which were assigned to three groups. We performed an initial examination, and 3- and 6-month follow-ups.

Result: teeth treated with both MI™ and Colgateâ PreviDentâ varnishes showed statistically significant improvements in caries progression. In the Colgateâ PreviDentâ group, nine surfaces with white spots with dryness remained unchanged, one surface changed to a white spot without dryness, and one surface improved to a sound surface. In the MI™ group, nine surfaces with white spots with dryness remained unchanged, and one surface changed to a white spot without dryness. Only teeth treated with MI varnish™ showed significant improvements radiographically. Teeth affected by outer enamel caries remained the same or improved to sound surfaces. Additionally, teeth with inner enamel caries remained the same. **Conclusion**: both MI™ and Colgateâ PreviDentâ varnishes are effective therapies to remineralize non-cavitated incipient lesions. However, there were no significant differences in the radiographic outcomes among the three types of varnish applications.

Trial registration

This clinical trial was registered at ClinicalTrials.gov (no. NCT03925740), and the first registration date was on 24/04/2019. Ethical approval was obtained from the institutional ethical committee at King Abdulaziz University (REC-013-01019).All methods were carried out in accordance to the ethical committee at King Abdulaziz University guidelines and regulations.

Background

Dental caries is the most prevalent chronic disease that affects all populations and has become a pandemic.[1] In Saudi Arabia, the prevalence of dental caries is approximately 80% in primary teeth and 70% in permanent teeth.[2] Tooth decay is a multifactorial disease; the primary etiological factors are the presence of fermentable carbohydrates, acid-producing bacteria, a susceptible tooth surface, and time.[3] The principal causative bacteria associated with dental caries are *Streptococcus sp.* (*Streptococcus mutans* and *Streptococcus sobrinus*).[3] Dental caries is the result of variations in pH caused by bacterial organisms in the biofilm, leading to demineralization of the dental hard tissues.[4,5] Caries can profoundly affect children's quality of life due to pain that could progress to acute and chronic infections, altered sleeping and eating habits, as well as high treatment cost and loss of school days. Caries management should focus on minimum intervention and maximum prevention.[6] Incipient carious lesions are areas showing early features of tooth decay. Indeed, they can reverse, be arrested, or progress to cavitation. Such early lesions can remineralize if diagnosed early and treated at the appropriate time.[6,7] Therefore,

an adequate home-care regimen and accurate clinical intervention are essential to initiate the remineralization process. Fluoride treatment has been the foundation of non-invasive dental treatment for incipient caries.[5] Low levels of fluoride inhibit the demineralization of sound enamel and initiate the remineralization of demineralized enamel. Additionally, fluoride affects bacterial metabolism and decreases the ability of cariogenic bacteria to produce acid.[8–10] When the oral pH drops, high levels of fluoride result in the temporary formation of a calcium-fluoride-like material on the tooth surface that enhances the uptake of calcium and fluoride by the hydroxyapatite crystals, forming fluorapatite.[10] Fluorapatite is more acid resistant than hydroxyapatite.[8,9] Different types of fluoride treatments are used in various applications, concentrations, durations, and frequencies. Newer products are continuously evolving, but the evidence for their efficacy is insufficient. MI varnish™ with RECALDENT, which consists of casein phosphopeptide-amorphous calcium phosphate (CCP-ACP), is recommended for the treatment of white-spot lesions in orthodontic patients. The active ingredients are CCP-ACP and 5% NaF (22,600-ppm fluoride), which show a synergistic effect and a deeper remineralization capability. Colgate→ PreviDent varnish is another product with 5% NaF (22,600-ppm fluoride) and xylitol as active ingredients. Most of these new products have not been sufficiently studied to recommend their use to the general public. Our objective was to compare the effectiveness of Colgate PreviDentand MI varnish™ with the standard 1.23% acidulated phosphate fluoride (APF) gel in the remineralization of non-cavitated proximal incipient lesions.

Materials And Methods

Ethical considerations and registrations

This clinical trial was registered at ClinicalTrials.gov (no. NCT03925740), and and the first registration date was on 24/04/2019. Ethical approval was obtained from the institutional ethical committee at King Abdulaziz University (REC-013-01019). The study started in January 2019 at King Abdulaziz University Dental Hospital (KAUDH) in Jeddah. Informed consents were signed by the parents or guardians of all patients. All methods were carried out in accordance to the ethical committee at King Abdulaziz University guidelines and regulations.

Study design

This double-blind, randomized-clinical trial was conducted in three arms. The patients were allocated to one of the three groups to compare the efficacy of two different fluoride varnishes with a standard fluoride gel. The examiners were blinded during the clinical and radiographic assessment, and the patients and their parents were not aware of the patient's allocation group. However, blinding of the clinicians during the application of the material was not possible due to the different packaging of the materials.

Sample size calculation

The minimum sample size was calculated at www.openepi.com. Ninety-one incipient carious lesionswere considered sufficient for this study. Patients were recruited from the postgraduate and undergraduate clinics of XXX.

Random allocation and blinding

The three arms were defined as the Colgateâ PreviDentâ, MI varnish™, and control (APF gel) groups. Patients were randomly allocated to the Colgateâ PreviDentâ and MI varnish™ groups by a coin toss. After obtaining the consents and answers to the questionnaire, the examiners assessed the lesions clinically and radiographically using the International Caries Detection and Assessment System (ICDAS) criteria, and each lesion was scored before random allocation. Randomization was performed separately after the assessment of each lesion.[11] A two-digit code was allotted to each patient; the first digit represented the patient's serial number, and the second digit represented the group. At the 6-month follow-up, radiographic re-assessment with bitewing and periapical radiographs was performed. We identified each radiograph with the patient's two-digit code along with the medical record number. After the radiographs of all patients were obtained, they were mixed together before interpretation to ensure blindness. Two trained and calibrated general dentists performed the randomization and assessment. Inter- and intra-examiner reliability were assessed at two different time points with 90% agreement and a kappa score of 0.613 (substantial).

Patient selection:

A total of 18 children (6 to 15 years old) who sought dental treatment inKAUDH were evaluated for inclusion in the study according to the inclusion/exclusion criteria.

Inclusion criteria:

The inclusion criteria were as follows: anterior or posterior, primary or permanent teeth with proximal incipient caries; clinical and radiographic ICDAS score of 1 or 2; and lesions detected by visual and tactile examination with the aid of ample light and mouth mirrors and probes, as well as by bitewing radiographs for posterior teeth and periapical for anterior teeth.[11]

Exclusion criteria:

The exclusion criteria were as follows: presence of active initial carious lesions (ICDAS scores ≥ 3) or deep caries crossing the dentinoenamel junction on bitewing radiographs[11]; and chronic medical

conditions and negative dental behavior. Children who presented with other needs for dental treatment were referred to complete their treatment. After excluding patients according to the inclusion and exclusion criteria, 18 patients (91 lesions) were included in the study (Fig. 1).

5% NaF MI varnish™ and 5% NaF Colgateâ PreviDentâ groups

Patients were randomly assigned to two groups (MI varnish™ or Colgateâ PreviDentâ) by a coin toss after we obtained the consent of their parents/guardians. We assigned three patients with 30 lesions to the MI varnish™ group and five patients with 33 lesions to the Colgateâ PreviDentâ group. Oral hygiene assessment was performed using the Greene and Vermillion oral hygiene index.[12] The decay-missing-filled-by surface (DMFS) index was recorded. Oral prophylaxis was performed with plaque removal using a polishing brush attached to a low-speed handpiece and dental floss. Orthodontic separators or wedges were placed between the teeth with incipient lesions on X-rays, and the patient was asked to return the next day. The teeth were dried, and the material (according to the group of the particular patient) was directly applied in the interproximal areas with the incipient lesions and then to the rest of the teeth. Patients were instructed to not rinse or drink water for 30 minutes and to avoid hard and sticky foods and eat only soft foods for the next 2 hours, according to the manufacturer's instructions. Detailed oral hygiene instructions, including brushing twice with a fluoridated toothpaste (1100 ppm) and flossing the site of the lesion with waxed dental floss, and an oral hygiene checklist were provided. The next follow-up visit was scheduled after 3 months.

1.23% APF gel (control) group

Ten patients (28 lesions) were recruited by scanning dental records, including radiographs of patients who were treated in the undergraduate clinics. APF application was performed using the tray technique as follows: The patient was seated in an upright position. After plaque removal with a polishing brush attached to a low-speed handpiece, an APF gel was dispensed on a disposable foam tray no more than 1/3 full, according to the manufacturer's instructions. The patient was instructed to not swallow the gel and exert slight pressure using the checks and tongue, as well as light biting force to allow the gel to flow interproximally for 4 minutes. A saliva ejector was used for salivary isolation and removal of excess gel. The patient was instructed to not eat, drink, or rinse for at least 30 minutes.

Follow-up visits for the Colgateâ PreviDentâ and MI varnish™ groups

The first follow-up visit was scheduled after 3 months (T1) and the second follow-up visit after 6 months (T2), according to the Caries Management by Risk Assessment criteria (CAMBRA).[13] At T1, scores for the

oral hygiene index were determined, oral prophylaxis, including plaque removal, was performed, and orthodontic wedges or separators were placed interproximally. The patients were recalled the next day. Thereafter, orthodontic wedges or separators were removed, teeth were dried, and the material was applied interproximally to the selected lesion and then to the rest of the teeth. The same instructions as T0 were provided to the patients and their parents. Oral hygiene instructions were reinforced, and another follow-up visit was scheduled after 3 months. At T1, no loss to follow-up was recorded for either group. We had two discontinued interventions in the Colgateâ PreviDentâ group because of a misdiagnosis by the physician (they had been restored by composite restoration) (Fig. 1).

At the 6-month visit, the same procedure was performed. Additionally, bitewing and periapical radiographs were obtained to assess the lesions. At T2, no loss to follow-up or discontinued intervention was recorded for either group (Fig. 1).

Follow-up visit for the APF gel (control) group

At the 6-month visit, the same procedure was performed as for the other two groups. No T1 visit was scheduled for patients in this group, since this was the protocol followed at the undergraduate dental clinics. At T2, no loss to follow-up or discontinued intervention was recorded for this group (Fig. 1).

Outcome assessment criteria:

The primary outcome was to evaluate the caries lesion progression clinically and radiographically using direct visual examination and ICDAS scores at baseline and comparing them after 6 months. Clinical and radiographic success was considered as maintenance of the caries score after 6 months or decreased to sound surfaces free of caries.

Statistical analysis:

Statistical analysis was performed using the SPSS version 20 software (Armonk, NY: IBM Crop). Descriptive statistics were displayed as frequencies and percentages for categorical variables and mean and standard deviation (±) for continuous variables. The chi-square test was performed, with statistical significance at $p<0.05$, and the post-hoc Bonferroni correction was applied. The Fischer's exact test was used when cells consisted of fewer than five cells.

Results

Of the total children participating in the study, 8 (44.4%) were boys. The mean age of the children was 9.3 ± 2.38 years, mean oral hygiene score was 1.67 ± 0.91, and mean DMFS score was 24.39 ± 11.15 (Table 1). Of the included patients, 29 (32.6%) had primary dentition, 78 (89%) primary molars were assessed, and 52 (58.4%) lesions were mesial (Table 2).

After 6 months of follow-up, both MI varnish™ and Colgate→ PreviDent groups showed statistically significant improvements in ICDAS scores for incipient caries. In the PreviDent group, five surfaces of teeth changed to from carious to sound. One of them was a white spot with dryness confined to the outer enamel radiographically, while the rest were white spots without dryness confined to the inner enamel radiographically. After we performed the Bonferroni correction to adjust the *p*-value for results of the chi-square test, nine surfaces (81.8%) with white spots accompanied by dryness remained unchanged, one surface changed to a white spot without dryness, and one surface changed to sound (Table 3). In the MI varnish™ group, four surfaces changed to sound. One of them was a white spot without dryness and confined in the inner enamel radiographically, while the rest were white spots with dryness in the outer enamel radiographically. After the Bonferroni correction was performed, nine (81.8%) surfaces with white spots accompanied by dryness remained unchanged, and one surface changed to white spot without dryness.

Radiographically, only teeth in the MI varnish™ group showed statistically significant improvements. Among the 16 surfaces that were originally affected by caries of the outer enamel surface, eight remained on the outer enamel surface (8/16 [50%]), five improved to sound surface (5/16 [31.3%]), and three progressed to the inner enamel surface (3/16 [18.7%]) ($p < 0.05$) after the Bonferroni correction. Furthermore, of the 14 surfaces that were diagnosed with caries on the inner enamel surface, one changed to outer enamel caries (1 [7.1%]) and one changed to sound surface (1 [7.1%]). None of the surface caries progressed to outer dentinal caries (Table 4).

Table 5 shows statistically significant differences in the clinical outcomes among the three groups of varnishes ($p = 0.004$). After the Bonferroni correction, teeth in the control group showed statistically significantly increased frequency of failures compared to teeth in the experimental groups ($p < 0.05$). However, there were no statistically significant differences in the radiographic outcomes among the three groups of varnishes.

Table 1
Demographic characteristics of patients (n = 18).

Variable		Frequency (%)
Age, years	**Mean ± SD**	9.3 ± 2.38
Sex	Male	8 (44.4)
	Female	10 (55.6)
Socio-economic status	Low	4 (22.2)
	Moderate	3 (16.6)
	High	11 (61.1)
Maternal education	≤High school	8 (44.4)
	≥University	10 (55.6)
Paternal education	≤High school	5 (27.8)
	≥University	13 (72.2)

SD: standard deviation

Table 2
Characteristics of patient's dentition surfaces (n = 89).

Variable		Mean ± SD or Frequency (%)
Oral hygiene score *		1.67 ± 0.91
DMFS		24.39 ± 11.15
Dentition	Primary	29 (32.6)
	Permanent	60 (67.4)
Site of lesion	Mesial	52 (58.4)
	Distal	37 (41.6)
Location		
Right vs. left	Right	47 (52.8)
	Left	42 (47.2)
Anterior vs. Posterior	Anterior	11 (12.4)
	Posterior	78 (89)
Upper vs. Lower	Upper	45 (50)
	Lower	44 (49.4)
Oral hygiene score	Poor	41 (46.1)
	Fair	16 (18)
	Good	19 (14.6)

*Green and Vermillion oral hygiene index

SD: standard deviation; DMFS: D: decayed, M: missing, F: filled, S: surface

Table 3
Progression of caries on tooth surfaces in the three varnish groups after 6 months according to the clinical ICDAS scores

	Varnish groups	Surfaces	Clinical ICDAS scores after 6 months, frequency (%)				Total	*p*-value
			Sound (A)	**White spot with dryness (B)**	**White spot without dryness (C)**	**Shadow without catch (D)**		
Baseline clinical ICDAS scores	**Colgate→ PreviDent**	White spot with dryness	1 (9.1)	9 (81.8) **(A, C)**	1 (9.1)	0	11 (100)	< 0.001*
		White spot without dryness	4 (20) **(B)**	1 (5)	12 (60)	3 (15)	20 (100)	
	MI varnish™	White spot with dryness	3 (15)	16 (80) **(C)**	1 (5)	-	20 (100)	0.019*
		White spot without dryness	1 (10)	4 (40)	5 (50) **(B)**	-	10 (100)	
	APF gel	White spot with dryness	0	3 (42.9)	4 (57.1)	0	7 (100)	0.12
		White spot without dryness	2 (25)	1 (12.5)	2 (25)	3 (37.5)	8 (100)	

Results are based on two-sided tests with a significance level of 0.05, using the Bonferroni correction. For each significant pair, the key of the category (A, B, or C).

**The frequency is significantly higher than the number under the category that appears next to it.

**p*-value significant at 0.05

ICDAS, International Caries Detection and Assessment System; APF, acidulated phosphate fluoride

Table 4
Progression of caries on tooth surfaces in the three varnish groups after 6 months according to radiographic ICDAS scores

	Varnish groups	Surfaces	Radiographic ICDAS scores after 6 months, frequency (%)				Total	*p*-value
			Sound (A)	Outer Enamel (B)	Inner Enamel (C)	Outer Dentin (D)		
Baseline radiographic ICDAS scores	**Colgate→ PreviDent**	Outer enamel	4 (28.6)	7(50)	2 (14.3)	1(7.1)	14 (100)	0.17
		Inner enamel	4 (23.5)	3 (17.6)	7 (41.2)	3 (17.6)	17 (100)	
	MI varnish™	Outer enamel	5 (31.2) **(C)**	8 (50) **(C)**	3 (18.8)		16 (100)	0.001*
		Inner enamel	1 (7.1)	1 (7.1)	12 (85.7) **(A, B)**		14 (100)	
	APF	Outer enamel	2 (12.5)	10 (62.5)	3 (18.8)	1 (6.2)	16 (100)	0.086
		Inner enamel	2(16.7)	2 (16.7)	4(33.3)	4 (33.3)	12 (100)	

Results are based on two-sided tests with a significance level of 0.05, using the Bonferroni correction. For each significant pair, the key of the category (A, B, or C).

**The frequency is significantly higher than the number under the category that appears next to it.

**p*-value is significant at 0.05

ICDAS, International Caries Detection and Assessment System; APF, acidulated phosphate fluoride

Table 5
Clinical and radiographic outcomes after 6-month follow-up for the three varnish groups.

Outcome		Colgate→ PreviDent	MI varnish™	APF	*p*-value
Clinical outcome	Decreased (A)	6 (19.4)	8 (26.7)	3 (20)	*p* = 0.004*
	Same (B)	21 (67.7)	21 (70)	5 (33.3)	
	Increased (C)	4 (12.9)	1 (3.3)	7 (46.7) **(A)**	
	Total	31 (100)	30 (100)	28 (100)	
Radiographic outcome	Decreased	11 (35.5)	7 (23.3)	6 (21.4)	*p* = 0.261
	Same	14 (45.2)	20 (66.7)	14 (50)	
	Increased	6 (19.4)	3 (10)	8 (28.6)	
	Total	31 (100)	30 (100)	28 (100)	
Results are based on two-sided tests with a significance level of 0.05, using the Bonferroni correction. For each significant pair, the key of the category (A, B, or C).					
**The frequency is significantly higher than the number under the category that appears next to it.					
* *p*-value significant at 0.05					
APF, acidulated phosphate fluoride					

Discussion

The aim of this clinical trial was to validate a potential cost-effective treatment modality for incipient proximal carious lesions in children. Using dental floss to remove the biofilm from proximal areas is the simplest and most effective way to control caries progression.[14] Indeed, the method and frequency of flossing by the patients affects the outcome of caries management.[15] Furthermore, children's poor compliance to flossing renders the proximal areas difficult to clean.[16] Thus, early interventions for incipient carious lesions are essential to prevent cavitations. Fluoride treatments can remineralize incipient carious lesions, and fluoride products containing CCP-ACP and xylitol may have an impact on the clinical and radiographic outcomes of incipient caries. In recent studies, CCP-ACP has shown promising outcomes in the treatment of incipient caries.[17–22] The addition of CCP-ACP to fluoride has a synergistic effect.[22] However, some studies have found that the addition of CCP-ACP to fluoride has no clinical benefit over fluoride alone.[23–27] This notable discrepancy in the studies regarding the clinical relevance of CCP-ACP can be attributed to the study design, duration of use, differences in the severity

and activity of the lesions, and the possible variations between orthodontic and non-orthodontic incipient carious lesions.

A previous systematic review showed that fluorides, combined with CCP-ACP, have a clinical advantage over fluoride monotherapy on the occlusal surface.
In contrast, fluoride monotherapy may have the same effect on smooth surface lesions.[28] Our study showed that both MI varnish™ and Colgate→ PreviDent significantly improved the clinical ICDAS scores of incipient carious lesions. However, radiographically, only lesions treated with MI varnish™ showed significant improvements. Nonetheless, there were no significant differences in the radiographic outcomes among the three types of varnishes used. The results of this study support the previous systematic review,[28] since we also analyzed smooth surface lesions (proximal). Although there were no significant differences in the radiographic outcomes among the three types of varnishes, further long-term studies may be required to validate the results of this study. A study that evaluated the efficacy of a 3-month CCP-ACP application regime with a follow-up duration of 12 months showed that CCP-ACP is effective.[29]

There are several limitations to this study. This randomized clinical trial included patients with incipient carious lesions and compared three fluoride products. Hence, this evidence is not relevant to the population free of carious lesions. A major limitation was the control group, which we recruited from undergraduate clinics. Therefore, the initial clinical caries assessment was not performed by the same research examiners. Another limitation was the use of visual-tactile rather than instrumental diagnostic methods such as laser fluorescence and quantitative light-induced fluorescence. However, the use of these technologies in our multisite trial was not possible due to economic constraints.

Nonetheless, this randomized clinical trial has several strengths. The outcome is a parameter that is crucial to dentists and patients. Moreover, all groups were comparable at recruitment by randomization, and the results were consistent when adjusted for sex, age, and initial severity. Regarding assessment, a 6-month follow-up duration was chosen to include the time required to visualize significant radiographic improvements while minimizing loss of follow-up. A period of at least 6 months is required to show evident changes in caries regression.[30] All examiners and patients were blinded during the assessment. Additionally, the patient compliance was high. No patient dropped out of the trial due to adverse effects such as allergy, inflammation of the gingiva, or plaque accumulation. We recommend a longer follow-up period and the use of quantitative light-induced fluorescence in future studies to substantiate the results of this study.

Conclusions

Prevention of dental caries is vital to preserve natural teeth in dental practice. Incipient carious lesions treated with both MI varnish™ and Colgateâ PreviDentâ showed statistically significant improvements in clinical ICDAS scores. However, radiographically, only teeth treated with MI varnish™ showed significant improvements. Nonetheless, there were no significant differences in the radiographic outcomes among

the three types of varnishes used. Previous studies have reported that CPP-ACP has a synergistic effect when added to fluoride, and this randomized controlled trial validated this finding. This ongoing registered trial has many future prospects, including longer follow-up periods and larger sample sizes. This study provides preliminary evidence to support the paradigm shift in pediatric dentistry from standard restorative treatment to disease prevention and conservation of tooth structure.

List Of Abbreviations

Casein phosphopeptide-amorphous calcium phosphate (CCP-ACP)

Acidulated phosphate fluoride (APF)

King Abdulaziz University Dental Hospital (KAUDH)

International Caries Detection and Assessment System (ICDAS)

The decay-missing-filled-by surface (DMFS) index

First follow-up visit after 3 months (T1)

Second follow-up visit after 6 months (T2)

Caries Management by Risk Assessment criteria (CAMBRA)

Declarations

Ethical Approval and Consent to Participate

Ethical approval was obtained from the institutional ethical committee at King Abdulaziz University (REC-013-01019)and the first registration date was on 24/04/2019. Informed consents were signed by the parents or guardians of all patients. All methods were carried out in accordance to the ethical committee at King Abdulaziz University guidelines and regulations.

Consent for Publication

Not applicable.

Availability of Data and Material

The data used to support the findings of this study are restricted by the Institutional ethical committee at King Abdul-Aziz University in order to protect patient privacy. Data are available from the Pediatric

Dentistry Department at King Abdul-Aziz University for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

This trial is self funded.

Author Contribution

N.H. and H.S. conceived the ideas and sponsored the materials.

G.A. and L.A. collected the data, led the writing and participated in the editing.

H.S. Analyzed the data and wrote the result.

N.H. and H.S. revised the manuscript and did the major editing.

Acknowledgements

We would like to thank Editage (www.editage.com) for editing.

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Figures

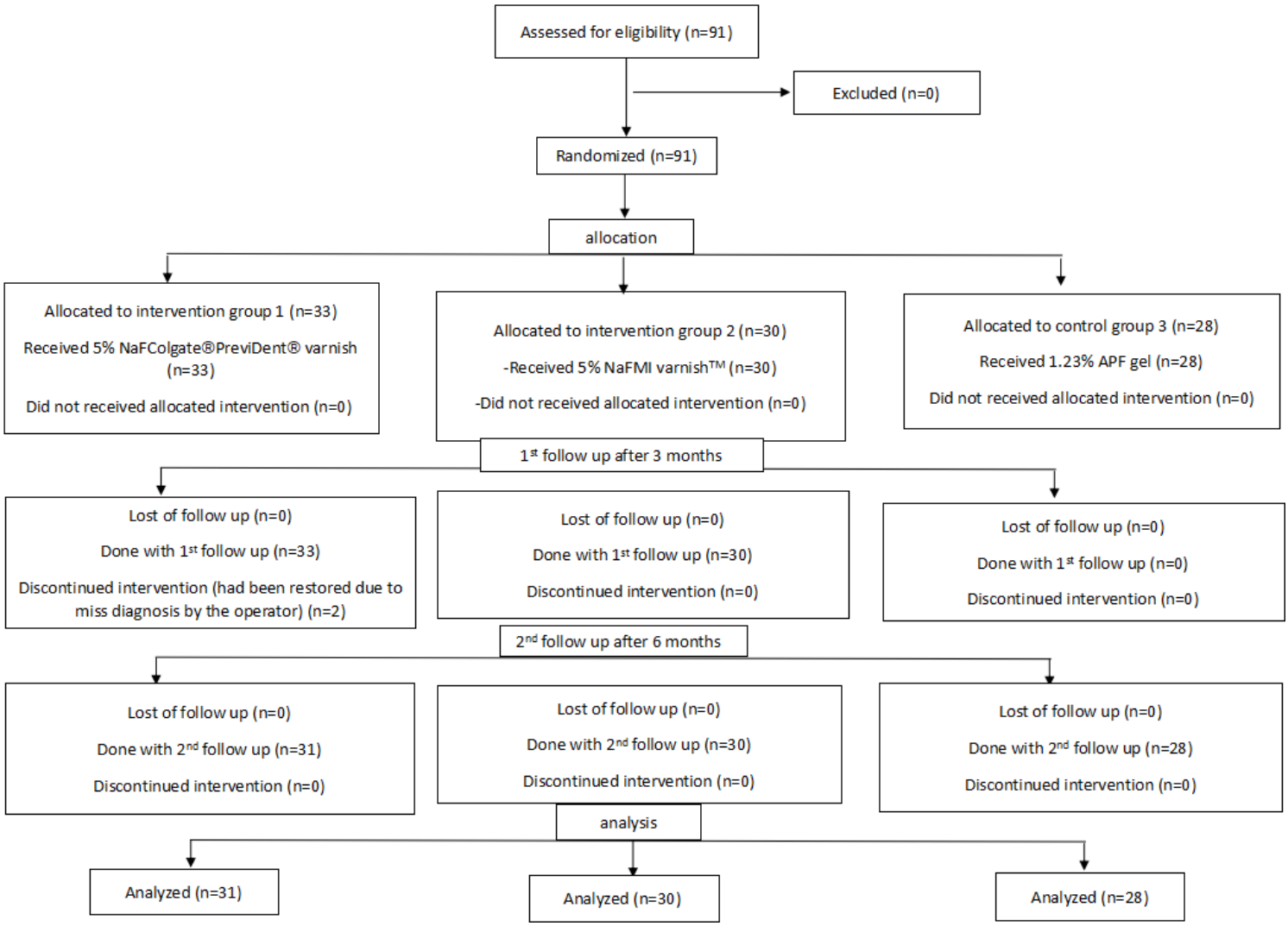

Figure 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients' randomization