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TiO_2 nanotube-containing glass ionomer cements display reduced aluminum release rates

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Abstract: Titanium dioxide nanotubes (TiO_2-nts) were incorporated into a glass ionomer cement (GIC) with improved mechanical properties and antibacterial activity. The aims of the present *in vitro* study were to define the elemental characterization, aluminum (Al) release rate, and initial working time for GIC reinforced with TiO_2-nts, in an experimental caries model. TiO_2-nts were incorporated into GIC powder components at 5% by weight, and compared with unblended GIC. Experimental approaches used energy-dispersive spectrometry (EDS), atomic absorption spectrophotometry (AAS), and brightness loss to define surface element properties, Al release rates, and initial working time, respectively. Statistical analysis was performed by 2-way ANOVA, Tukey's test, generalized linear models, and Student's t test ($a = 0.05$). EDS data analysis revealed that TiO_2-nts incorporated into GIC had no significant impact on the typical elemental composition of GICs in an *in vitro* caries model. Regarding the demineralizing solution, GIC with TiO_2-nt significantly decreased the Al release rate, compared with the control group ($p < 0.0001$). Moreover, TiO_2-nt incorporated into GIC did not alter the initial working time of the material ($p > 0.05$). These findings add information to our scientific body of knowledge concerning the potential impact of TiO_2-nt on the performance of conventional GICs.

Keywords: Glass Ionomer Cements; Titanium; Nanotubes; Aluminum.

Introduction

Glass ionomer cements (GICs) are extensively used in different clinical situations, because their linear expansion coefficient is similar to that of the tooth, and because of their biocompatibility, adhesion to dental structure, and fluoride-release anticariogenic activity.[1,2] On the downside, GICs have limitations, such as high sensitivity to humidity, leading to dimensional instability in the first 24 h of the setting reaction, decreased wear resistance, and formation of cracks and gaps.[2,3] These limitations may affect their survival rate by approximately 50%, in atraumatic restorations involving multiple surfaces in areas of high masticatory effort in children at high risk of caries activity.[4]

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Nanodentistry-based strategies have currently been proposed to address the above-mentioned clinical limitations of GICs. Nanodentistry is an emerging field and uses nanostructured materials to diagnose, treat and prevent oral and dental disease, relive pain, and preserve and improve dental health.[5] In general, nanostructures have the potential to improve the physicomechanical properties of dental materials.[6-11] Titanium (Ti) stands out in particular, because it is a chemically stable, non-toxic, inorganic additive, with potential antimicrobial effects[7]. A number of strategies have been used to incorporate nanostructures into GICs, with promising results regarding GIC antibacterial activity, surface hardness, attrition wear, and flexural and compressive strength.[6,9,12-14] Interestingly, titanium dioxide nanotubes (TiO_2-nts) have been found to significantly improve GIC fluoride release rates at different concentrations, without affecting their adhesion to dentin substrates or fibroblast morphology.[6,9] Based on the potential effect of TiO_2-nt on fluoride release, a similar impact can be expected on other GIC elements, such as aluminum, silicon, lanthanum, calcium, sodium, and phosphorus. Although, aluminum release rates have been shown to be similar to fluoride release rates,[15,16] most studies have assessed only fluoride release rates from GIC, without taking into consideration that aluminum may form stable compounds with fluoride ions to boost the antimicrobial properties of dental materials.[17] In overall terms, the release rates of aluminum and other elements from GIC blended with nanoparticles, and their potential effects, have not been fully established.[9-22]

Therefore, the goal of the present study was to determine the effect of TiO_2-nt (at 5% by weight), incorporated into a conventional GIC, on surface element characteristics, initial setting reaction, and aluminum release rates after exposure to de- and remineralizing solutions. The null hypotheses herein were: a) GICs containing TiO_2-nts do not differ from conventional GICs in terms of initial working time and surface characterization, assessed using EDS, and b) the incorporation of 5% TiO_2-nt into a conventional GIC does not affect aluminum release rates under exposure to de- and remineralizing solutions.

Methodology

Experimental design

The following factors were under study: a) incorporation of 5% TiO_2-nt concentration by weight (/wt) into a conventional GIC (Ketac Molar EasyMix®, 3M ESPE, Maplewood, MN, USA); b) pH-cycling (de- and remineralization solutions); and c) aluminum release rates at 1, 2, 3, 5 and 7 days. The two groups under study were: Ketac Molar (KM=control) alone and Ketac Molar added to 5% n-TiO_2 (KM+5%TiO_2-nt). The parameters evaluated included initial working time analysis by GIC brightness loss (in seconds, n = 12/group), surface element characterization by energy-dispersive spectrometry (at a percentage [%] of Al, n = 6/group), and the aluminum release rate by atomic absorption spectrometry (in µg/mL, n = 6/group).

Sample size

In the current study, a pilot experiment was performed (n = 3) to determine the sample size (n). The level of significance and statistical power were considered at 0.05 and 0.8, respectively, and the effect size was stipulated at 2.08 (initial working time), 0.9 (EDS, % of Al), and 1.99 (total of Al release after 7 days). The values considered for standard deviation were 3.5, 2.2, and 0.08, respectively. The sample size calculation indicated a minimum of 5 samples for the initial working time, yielding experiments with n = 12, and a minimum of 5 samples for % of Al, and 2 for Al release, yielding experiments with n = 6.

Specimen preparation

Nanotubes (20 nm in length and 10 nm in diameter) were synthesized using the alkaline method to form a single sheet of the material curled into a spiral[23]. Briefly, TiO_2-nts were prepared by mixing 12 g anatase TiO_2 (Aldrich, 99%) with 200 mL of 10 M NaOH. This mixture was kept in an open Teflon container placed in a glycerin bath and heated with a mantle heater at 120°C for 24 h. Syntheses were carried out at ambient pressure, at which only precursor reagents were submitted to alkaline treatment. Following the treatment, the mixture was washed repeatedly with 0.1 M hydrochloric acid and deionized water to remove the sodium ions. Next, the pH of the solution was adjusted to 7. Lastly, the materials obtained were dried in a conventional incubator at 200°C for 24 h in air atmosphere[23]. The resulting TiO_2-nts at 5%/wt were weighed on a precision scale accurate to 0.0001 g (Adventurer Oshaus, Parsippany, USA), and added to the GIC component powder (Ketac Molar Easy Mix® - color A3; Powder: aluminum-calcium-lanthanum fluorosilicate glass, 5% polycarbonate acid [15 g]; Liquid: polycarbonic acid and tartaric acid [10 g]; 3M/ESPE, Maplewood, USA, batch # 4238523 and 642344). Next, TiO_2-nts were homogenized using a QL-901 vortex (Biomixer, Taft, USA) for 2 minutes.[6,9] This concentration was determined by preliminary studies that demonstrated improved physicomechanical properties of GIC with 5% TiO_2-nt.[6,9] Material agglutination was performed for the powder/liquid ratio (1:1), using a metal spatula and a pad of waterproof paper.[1] The specimens were prepared at room temperature (23 ± 1°C and 50 ± 5% relative humidity) as recommended by the manufacturer. KM with or without TiO_2-nts was placed in bipartite molds (4 mm thick x 6 mm diameter), inserted in a single increment using a Centrix syringe (Centrix Inc., Shelton, USA), and pressed between polyester strips (Proben, Catanduva, Brazil) under a glass slide with a static load of approximately 200 g for 6 min. After the initial setting of the material, the specimens were removed from the mold, covered with a thin layer of petroleum jelly (Bioquímica, São José do Rio Preto, Brazil), identified, and stored in an conventional incubator at relative humidity for 24 h at 37°C.[6,9]

Initial working time analysis by brightness loss analysis (n = 12/group)

The experiments were performed by a single experienced operator to ensure a standard mixing protocol. Briefly, GIC powder was measured with a spoon provided by the manufacturer, and weighed on a precision scale. Measurements were repeated 5 times for each group to establish and confirm the amount of powder used in the mixture: KM (0.147 ± 0.003 g) and KM + 5%TiO_2-nt (0.172 ± 0.004 g). Likewise, the same protocol was used to calibrate the amount of liquid dispensed with each drop (0.085 ± 0.005 g). By following this methodology, a uniform 1:1 ratio was achieved across the experimental groups, as recommended by the manufacturer. GIC brightness loss was analyzed by a blinded and calibrated examiner who manipulated the material and timed the experiment from the beginning of the agglutination of the first half of the powder up to the appearance of the matte effect on the material surface at the specified parameters of temperature and controlled relative humidity (37 ±1 °C and 90% relative humidity). The time elapsed from the initial agglutination up to brightness loss was recorded with a digital TIMEX in seconds.[24]

pH-cycling (n = 6/group)

A 7-day pH-cycling model was used to simulate cariogenic conditions in patients at risk of caries, by monitoring the elemental alteration on the surface of the materials, and the Al release rates.[25,26] The specimens were immersed individually, and each cycle consisted of a 6-hour immersion in demineralizing (DE-) solution, followed by an 18-hour immersion in remineralizing (RE-) solution (artificial saliva = 1.5 mmol/L calcium, 0.9 mmol/L phosphate, 150 mmol/L potassium chloride, 20 mmol/L buffer cacodylate, pH 7.0, area/volume ratio of 1.02 mm^2/mL). The specimens were washed in deionized water for 30 s, dried on absorbent paper, and immersed individually in 7.5 mL of DE- solution (2.0 mmol/L calcium, 2.0 mmol/L phosphate, 0.075 mol/L acetate, pH = 4.3, area/volume ratio 0.51 mm^2/mL). Both solutions contained thymol crystals to prevent microbial growth. DE- and RE- solutions were replenished at each cycle. The specimens were subjected to constant agitation at 120 rpm, 1.7 Hz, 25 ± 1°C (Shaking Table, Dragonlab Laboratory Instruments Limited, Beijing, China) during pH-cycling.

Energy dispersive spectroscopy (EDS) analysis (n = 6/group)

Analysis of the % of atoms on the GIC surfaces was performed using EDS (SEM - JEOL-JSM 5600LV, Tokyo, Japan) equipped with an X radiation EDS detector (Voyager, Noran Instruments, Middleton, USA), operated at low vacuum and in backscattered electron mode. The specimen surfaces were carbon-coated by evaporation of high-purity carbon rods (Denton

Vacuum Desk II, Moorestown, USA). The whole area of the specimen surface was observed by scanning electron microscope set at 100X magnification, with a working distance of 20 mm, and operated at an acceleration voltage of 15 kV. Measurements were performed on five standard areas of each specimen to quantify the elements on the surface. The results were expressed as a % of atoms by the Easy Macro software program (Noran Instruments, mod. Vantage v.1.2, Middleton, USA), and the average of each specimen was used in the statistical analysis.

Atomic absorption spectrophotometry (AAS) analysis (n = 6/group)

Aluminum release rates were determined on days 1, 2, 3, 5 and 7 of pH-cycling by Atomic Absorption Spectrophotometry (AAS), using nitrous oxide, an acetylene flame and a hollow cathode lamp at 309.3 nm. The spectrophotometer (VARIAN - AA-50) was calibrated with five standard solutions ranging from 0.5 to 25 µg Al/mL, and the target solutions were analyzed without any pretreatment, and with a device sensitivity limit of 0.1 µg Al/mL. Sample values below the standard curve were considered as zero.[15,27]

Statistical analysis

The original data were analyzed using the Shapiro-Wilk normality and the Levene homoscedasticity tests. Initial working time data analysis was performed by Student's t test. EDS data (% of Al) were subjected to two-way ANOVA and Tukey´s test. Chlorine and magnesium were submitted to Student's t test, since they were detected in only two groups. Al release data were evaluated by generalized linear models. Analyses were performed using the SAS System (SAS Institute, SAS System version 9.3; Cary, USA, 2012) ($\alpha = 0.05$).

Results

In overall terms, the data analysis revealed that TiO_2-nts did not significantly affect either the GIC initial working time (brightness loss) or its surface composition. An average of 321.4 (+ 3.4) and 319.9 (+ 7.1) seconds was obtained for KM and KM+5% TiO_2-nt, respectively ($p > 0.05$ – Table 1). In addition, EDS analysis revealed an overall similarity between the experimental groups, insofar as KM+5% TiO_2-nt showed that levels of the assessed compounds were comparable to the KM group with and without pH-cycling. Further analysis showed that sodium was the only compound among those investigated that was affected by TiO_2-nt at the baseline ($p < 0.05$ – Table 2). Lastly, AAS analysis showed that the Al release rates were significantly decreased by using

Table 1. Mean (standard deviation) working time (in seconds) of the experimental group.

Experimental group (n = 12/group)	Working time (in seconds)
KM (control)	321.4 (3.4) ^{a}
KM + 5% TiO_2-nt	319.9 (7.1) ^{a}

Similar letters indicate no statistical difference ($p > 0.05$);
KM = Ketac Molar EasyMix; TiO2-nt: titanium dioxide nanotube.

Table 2. Mean (standard deviation) values of EDS analysis (% at) of glass ionomer cements with or without of 5% TiO_2-nt, and with or without pH-cycling.

Experimental group (n = 6/group)	KM (control) (% at)		KM + 5%TiO_2-nt (% at)	
pH-cycling	Without	With	Without	With
Aluminum	25.3 (3.5) A	26.8 (2.1) A	24.1(4.8) A	27.8 (2.8) A
Silicon	41.0 (7.9) A	36.8 (5.3) A	37.4 (2.6) A	34.3 (4.1) A
Lanthanum	5.3 (0.8) B	7.8 (1.8) A	5.2 (1.2) B	7.9 (1.0) A
Calcium	18.0 (2.9) A	17.4 (1.7) A	18.1 (2.6) A	18.0 (2.8) A
Sodium	2.0 (1.8) B	1.0 (0.2) B	5.1 (0.9) A	1.2 (0.3) B
Magnesium	3.5 (2.2) A	0.2 (0.1) B	*n.q.*	*n.q.*
Chlorine	*n.q.*	*n.q.*	0.7 (0.3) A	0.2 (0.1) B
Phosphorus	4.8 (1.0) B	10.0 (1.7) A	3.9 (2.1) B	10.5 (1.9) A

Different letters in the same line indicate statistical difference based on two-way ANOVA and Tukey´s test. Chlorine and magnesium were submitted to Student's t test, since they were detected in only 2 groups. ($p < 0.05$). KM: Ketac Molar EasyMix; TiO2-nt: titanium dioxide nanotube; n.q: not quantified.

TiO_2-nt in all the experimental periods in which the samples were submitted to the DE- solution, with a reduction of about 60% through days 1 to 5, and 100% at day 7 ($p < 0.05$). Al levels were below the detection levels for KM and KM+5% TiO_2-nt samples submitted to the RE- solution. Table 3 illustrates the AAS findings.

Discussion

The goal of the current investigation was to further understand the potential impact of TiO_2-nts on the underlying chemical processes of a high-viscosity conventional GIC (Ketac molar – KM). In the current study, the initial working time was defined by the brightness loss of the material during the chemical processes occurring after mixing the powder and liquid components of KM. This was indicated by the absence of free residual acid, or an interference in the reaction kinetics (a critical component for the material to adhere to the tooth).[1] In line with previous studies,[9] we noticed that TiO_2-nt (at 5%/weight) did not affect GIC adhesion to the dentin substrate. In contrast, incorporation of ytterbium fluoride and barium sulphate nanoparticles or germanium into the GIC have been reported to affect the GIC setting characteristics.[28,29]

In the present study, the effect of TiO_2-nt on the elemental composition of a conventional GIC (KM) was determined by using the EDS approach. In general, the test and experimental groups showed comparable levels of the assessed compounds with and without pH-cycling. Interestingly, Ti was not detected by EDS analysis in the experimental group containing TiO_2-nt. Since EDS is highly sensitive to the characteristics of the specimen, and to the equipment setup, we suggest that technical optimization be required to assure Ti detection in this substrate. These observations have been reported in the literature in cases when TiO_2-nts were added to a conventional GIC at 3, 5 and 7% by weight.[6] As previously reported, the EDS analysis for both groups showed an increase in the amount of phosphorous with pH-cycling,[25,26] caused by the presence of phosphate in the treatment solutions. Future studies should consider determining how phosphate concentrations in treatment solutions impact EDS findings.

The Al release rate adopted in the present study was assessed in the DE- and RE- solutions by AAS analysis. Although Al release was reported for GICs,[30] few studies have suggested that Al release may decrease with time, considering that Al may remain trapped inside the GIC matrix.[15-17,31] The intergroup comparisons made herein showed that the addition of TiO_2-nts to a conventional GIC significantly reduced the amount of Al released in the DE- solution, whereas no significant intragroup differences were detected over time (Table 3). Al is a substantial component of GICs, and has been reported as an element critical to securing the stability of the set cement.[30] Additional studies have suggested a positive correlation between the Al and the fluorides release by GICs.[15,16] Previous literature has reported that conventional GICs added to TiO_2-nt increased fluoride release,[6] hence, we hypothesized that the Al release rates from a conventional GIC added to TiO_2-nt would be similar to the increased rate of fluoride release. However, we actually found that the Al release rates were reduced by adding TiO_2-nt to a conventional GIC. Since TiO_2-nt has been reported to improve other properties of GICs,[6,9] it can

Table 3. Mean (standard deviation) values for aluminum release rates (in µg/mL) of KM and KM+5% TiO_2-nt submitted to pH-cycling (de- and remineralizing solutions), over the experimental periods.

Experimental group (n = 6/group)	1st day	2nd day	3rd day	5th day	7th day
DE					
KM	0.296 (0.11)^{a}	0.24 (0.13)^{a}	0.249 (0.14)^{a}	0.22 (0.11)^{a}	0.240 (0.13)^{a}
KM + 5% TiO_2-nt	0.117 (0.10)^{b}	0.117 (0.10)^{b}	0.107 (0.11)^{b}	0.107 (0.11)^{b}	0 (0)^{b}
RE					
KM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
KM + 5% TiO_2-nt	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Different letters indicate a statistically significant intergroup difference ($p < 0.0001$, KM versus KM+5% TiO2); KM: Ketac Molar EasyMix (control); TiO2-nt: titanium dioxide nanotube; DE: demineralizing solution; RE: remineralizing solution.

be suggested that this effect may explain the dynamic of Al and fluoride release from GIC added to TiO_2-nt.

Moreover, the GIC setting reaction involves a number of stages. Initially, the acid reacts with the surface of glass particles, followed by a loss of ions, whose movement in the matrix is indicative of their reaction with the polyacid molecules.[17,18,32] The Al ions leach into the cement across the surface layers, thus acting as crosslinkers in the cement matrix.[17,18,33] However, part of these ions may be diffused or may leach out of the conventional GICs. GIC properties can be improved by adding TiO_2-nt. This may promote a stronger matrix of the material,[9] rich in cross-links obtained from more reactive Al, which decreases the release of Al cations over time, as shown in Table 3. Further analysis showed that the Al release was not detected when the experimental samples from both KM and KM+5% TiO_2-nt were submitted to the RE- solution (artificial saliva), thus confirming previous findings that have reported increased Al release rates in acidic environments.[18,31] Thus, in the RE- solution, the longer step (ion release) involves diffusion, whereas the DE- solution involves erosion. These patterns influence the bioactivity of the material.[18]

Regarding the impact of Al release on cellular toxicity, the findings of the present study have shown that the amount of Al detected by AAS in the DE- solutions was low, and below the tolerable weekly intake value established by the Food Additives Expert Committee (Covance Laboratories, 2010). In line with our findings, Cibim et al.[6] detected no significant impact of TiO_2-nt addition on the fibroblast cell cultures grown on GIC discs. The range of findings of the present study sheds light on the potential of GICs added to TiO_2-nt. Basically, this addition does not alter the initial working time of the GIC, or increase Al release in the pH-cycling model. However, the use of TiO_2-nt to improve the clinical performance of GICs is a relatively new concept, and the current investigation was limited to an *in vitro* experimental design that cannot fully mimic the "real" clinical setup. This being the case, additional studies should be designed to further define the potential impact of TiO_2-nt on other GIC properties, including syneresis and imbibition processes, material aging on affected teeth, and longitudinal randomized clinical studies.

Conclusions

The incorporation of TiO_2-nts into GICs did not change the initial working time or typical elemental composition of conventional GICs, nor did it affect the aluminum release rate in an *in vitro* model. These findings add information to our current body of scientific knowledge regarding the potential impact of TiO_2-nt on the performance of conventional GICs.

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