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Glass ionomer cements functionalised with a concentrated paste of chlorhexidine hexametaphosphate provides dose-dependent chlorhexidine release over at least 14 months

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ABSTRACT

Objectives: The aim of this study was to create prototype glass ionomer cements (GICs) incorporating a concentrated paste of chlorhexidine–hexametaphosphate (CHX–HMP), and to investigate the long-term release of soluble chlorhexidine and the mechanical properties of the cements. The purpose is the design of a glass ionomer with sustained anticaries efficacy.
Methods: CHX–HMP paste was prepared by mixing equimolar solutions of chlorhexidine digluconate and sodium hexametaphosphate, adjusting ionic strength, decanting and centrifuging. CHX–HMP paste was incorporated into a commercial GIC in substitution for glass powder at 0.00, 0.17, 0.34, 0.85 and 1.70% by mass CHX–HMP. Soluble chlorhexidine release into artificial saliva was observed over 436 days using absorbance at 255 nm. Diametral tensile and compressive strength were measured after 7 days' setting (37 °C, 100% humidity) and tensile strength after 436 days' aging in artificial saliva. 0.34% CHX–HMP GICs were tested for their ability to inhibit growth of *Streptococcus mutans in vitro.*
Results: GICs supplemented with CHX–HMP exhibited a sustained dose-dependent release of soluble chlorhexidine. Diametral tensile strength of new specimens was unaffected up to and including 0.85% CHX–HMP, and individual values of tensile strength were unaffected by aging, but the proportion of CHX–HMP required to adversely affect tensile strength was lower after aging, at 0.34%. Compressive strength was adversely affected by CHX–HMP at substitutions of 0.85% CHX–HMP and above.
Conclusions: Supplementing a GIC with CHX–HMP paste resulted in a cement which released soluble chlorhexidine for over 14 months in a dose dependent manner. 0.17% and 0.34% CHX–HMP did not adversely affect strength at baseline, and 0.17% CHX–HMP did not affect strength after aging. 0.34% CHX–HMP GICs inhibited growth of *S. mutans* at a mean distance of 2.34 mm from the specimen, whereas control (0%) GICs did not inhibit bacterial growth.
Clinical Significance: Although GICs release fluoride *in vivo,* there is inconclusive evidence regarding any clinical anticaries effect. In this study, GICs supplemented with a paste of chlorhexidine-hexametaphosphate (CHX–HMP) exhibited a sustained release of chlorhexidine over at least 14 months, and small additions of CHX–HMP did not adversely affect strength.

1. Introduction

Glass ionomer cements (GICs) are used for a number of purposes, including as direct restorative materials, lining and luting materials, adhesives, and in atraumatic restorative therapy. GIC restorations typically have shorter lifetimes than composites or amalgams [1–3], although the reasons for this are complex and, of course, the materials are not selected at random but are chosen by the clinician according to clinical need. When a GIC does fail, there are a number of potential reasons, one of which is secondary caries; this is responsible for 25% of failures of GIC-lined restorations after 18 years of clinical service [4] and around 18% of GIC failures over a range of 0.1–23 years [5].

GICs leach fluoride into the oral environment. This results in elevated fluoride concentrations close to the restoration, and thus there is an hypothesis that this may reduce dental caries in the

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local area owing to the interaction of the fluoride ion with the hydroxyapatite in the enamel and dentine. This hypothesis is broadly supported by *in vitro* data, but *in situ* and clinical studies of caries incidence in the vicinity of fluoride-releasing restoratives do not show consistent results [6]. At the current time it is not possible to conclude whether fluoride release from GICs provides lasting protection against dental caries [6,7].

Chlorhexidine (CHX) is a biocide with broad spectrum efficacy against a wide range of microbes. Its main application in dentistry is as a topical agent, usually in oral care products, products for treatment of periodontal disease, and varnishes. CHX is efficacious against the microbes implicated in dental caries, and is used in a number of products designed to protect the dentition against decay. However, the CHX salts in currently available commercial form have poor retention *in situ*, providing typically a few hours of antimicrobial function. One commercial material used for treatment of periodontal disease provides some sustained CHX release, but this is a short-term effect with 80% of the CHX released within the first 2 days, and a very slow release over the following 3–4 weeks [8].

There have been a number of attempts to incorporate CHX into GICs, with the aim of creating a restorative material that offers lasting protection against caries. GICs doped with CHX diacetate and CHX digluconate have been reported, and these inhibited growth of *Streptococcus mutans* and *Lactobacillus acidophilus*, but there was also some deterioration of mechanical properties and the antimicrobial effects were limited to the first 40–90 days of the study, with no bactericidal effect observed after this time [9]. There are also reports of an increase in porosity and setting time and a reduction in hardness and tensile bond strength when GICs are doped with CHX digluconate [10,11]. CHX diacetate and CHX hydrochloride have also been incorporated into GICs, and these too inhibited growth of caries-causing organisms, but CHX release was only observed for 24 h so it is not clear how long this effect would be sustained [12]. CHX diacetate doped resin modified GICs exhibited some sustained release of CHX, although this reached completion in 14–21 days [13]. The release profiles of soluble CHX from GICs doped with these conventional salts of CHX exhibit a high initial release followed by little or no sustained release, and this perhaps explains the cytotoxic effects observed against fibroblasts when GICs were doped with 1% CHX diacetate [14]. However, supplementation of a resin-modified GIC with CHX digluconate at modest concentrations (1.25%) had no adverse effects on osteoblasts *in vitro* and resulted in an elimination of *S. mutans* populations following indirect pulp treatment *in vivo* [15], suggesting a potential clinical benefit of a CHX-functionalised restorative material.

We have previously reported the use of a novel salt of CHX: CHX–hexametaphosphate (CHX–HMP) [16]. CHX–HMP has a lower solubility than CHX digluconate or CHX diacetate and, when used as a coating or dopant, can confer a sustained release of CHX that persists for at least three months [17]. We have described the use of CHX–HMP as a filler for GICs [18]. In that study, large clusters of CHX–HMP particles were used, and the size of these large particles, which were formed due to the production process, is likely to account for the adverse effects on the mechanical properties observed. The aim of the study described here was to investigate the use of CHX–HMP particles as GIC fillers but using a new preparation method which omits the drying process which creates the large aggregates and instead uses a process of ionic strength adjustment and centrifugation to sequester the particles. CHX release was probed over a clinically relevant timescale of over one year, and both compressive and tensile strength were investigated; the latter was measured also after 14 months' aging to determine if the modification of the cement adversely affects long-term mechanical properties.

The hypothesis was that the prototype cements incorporating a concentrated paste of CHX–HMP particles would confer a more sustained CHX release, sufficient to inhibit growth of cariogenic microbes, coupled with less adverse effects on mechanical properties in comparison to large, dry aggregates of CHX–HMP or conventional salts of CHX such as digluconate or diacetate.

2. Methods

2.1. Preparation of CHX–HMP paste

Aqueous 10 mM solutions of CHX digluconate and sodium HMP were prepared. 100 mL of each solution were combined in a glass beaker under ambient laboratory conditions. The suspension created was stirred vigorously for approximately 1 min, then 30 mL 1 M potassium chloride was added. Stirring continued for a further 1 min before the preparation was allowed to settle for 24 h. The precipitate settled at the bottom of the flask and the supernatant was gently discarded leaving a concentrated suspension of the precipitate. This suspension was then centrifuged at 4760 × *g* for 30 min. The supernatant was again discarded and the pellet of paste was removed from the centrifuge tubes using a spatula and used immediately.

2.2. Preparation of specimens

A commercially available GIC, Diamond Carve™ (Kemdent Ltd., Purton, UK), was used as the base material to create the experimental cements. This GIC comprises a powder, consisting of alumina–silica based glass filler particles which contain calcium fluoride and other minor salt components and freeze dried poly (vinyl) phosphonic acid, and a liquid, which contains polyacrylic and tartaric acids. The manufacturers' instructions indicate that the powder and liquid should be mixed in a 4:1 ratio by mass to create the finished cement.

The water content of the paste was established to allow the concentration of the liquid component of the GIC to be adjusted to account for the additional water in the CHX–HMP paste. CHX–HMP paste was weighed as freshly prepared, then stored at 37 °C and weighed periodically until the mass of the powder was constant, indicating that the available water had evaporated (24 h). This revealed a composition of 83% water and 17% CHX–HMP particles. The GIC liquid component was thus prepared at a concentration that resulted in the standard final concentration when diluted by the paste. The paste was substituted for the overall mass at 0, 0.17, 0.34, 0.85 and 1.70% by mass of CHX–HMP (0, 1, 2, 5 and 10% by mass of the paste). The paste was mixed into the liquid first and then the powder was added to the paste–liquid combination. Mixing of the specimens was completed in 40–50 s and packing into the moulds took a further 10 s, such that all manipulation of the cement was completed within 1 min.

GICs were packed, using a stainless steel spatula, into stainless steel moulds with dimensions of 6 mm height and 4 mm diameter (for compressive strength determination) or 4 mm height and 6 mm diameter (for measurement of diametral tensile strength and elution of CHX). The moulds were lined with a thin layer of petroleum jelly to aid removal of the set cement. Immediately after packing, the moulds were placed between two sheets of acetate and a 2 kg weight placed on top of the specimens on a flat surface in order to ensure even distribution of the cement. After 5 min the specimens were sanded using a P120 grit sanding disc (Hermes, Hamburg, Germany) to remove excess material and were then placed into small, sealed plastic vessels containing wet tissue paper packed into the lid to achieve 100% humidity without direct contact with water. Specimens were stored at 37 °C for 7 days prior