A comparison of chlorhexidine release rate from three polymeric controlled release drug prototypes

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ABSTRACT

Intracanal disinfection of infected root canal is one of important treatment procedure. This *in vitro* study aimed to evaluate whether the surface polymers of controlled release drug (CRD) can effectively control the release rate of chlorhexidine for root canal disinfection. Four CRD prototypes were prepared: Group A (n=12); The core device (absorbent paper point) was loaded with 40% CHX solution as control. Group B (n=12); same as group A, but the device was coated with chitosan. Group C (n=12); same as group A and then coated three times with 5% PMMA. Group D (n=12); same as group A and then coated three times with 3% PLGA. All CRD prototypes were soaked in 3 mL distilled water for experimental periods and the concentrations of released CHX from each CRD prototype were determined using a UV spectrophotometer. Results showed that release rate of CHX were the greatest in the non-coated group (control group), followed by the chitosan-coated group, the PLGA-coated group, and the PMMA-coated group ($P < 0.05$). This data indicate that surface polymers can control the release rate of CHX from the CRD prototypes. [J Kor Acad Cons Dent 29(6):548-552, 2004]

Key words : Controlled release drug prototype, chlorhexidine, chitosan, polymethyl methacrylate, poly (lactide-co-glycolide), intracanal disinfection

Ⅰ. Introduction

Complete debridement and thorough disinfection of infected root canals are considered mandatory for the success of root canal treatment[1]. However, canal preparation and irrigation are not always effective in eliminating total microflora from the root canal system[1-3]. Traditionally, calcium hydroxide has proven to be an excellent intracanal medicament for infected root canals[4,5]. However, it is known to be less effective against the therapy-resistant flora such like *Enterococcus facecalis, Actinomyces* and *Candida* that are frequently isolated in persistent root canals[6]. This is because of dilution of calcium hydroxide as time passes or dentin buffering effects[7]. Therefore, alternative medicaments should be explored that would maximize microbial eradication when used as intracanal disinfection.

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Chlorhexidine (CHX) is effective against a wide variety of Gram-positive and Gram-negative organisms, as well as fungi that are known as infected root canal flora. Previous studies have shown that the antimicrobial effect of CHX was almost same to that of sodium hypochlorite and calcium hydroxide[8-11]. In addition, it has a substantive antimicrobial action for certain period in root canal[12-14]. It was also suggested as an effective irrigant to prevent coronal infection[15]. However, in order to achieve substantive antimicrobial effect, the infected root dentin must be contacted to CHX for a longer time (〉 1 week) than that afforded by canal irrigation[16,17].

Previous studies have shown that a controlled release drug (CRD) device with water-permeable polymers could effectively control the release rate of CHX[16,17]. However, because of a strong, positive charge of CHX and its high binding affinity, the development of suitable polymers for controlled release of CHX still remains a challenge. Chitosan, poly (lactide-co-glycolide) (PLGA), and polymethyl methacrylate (PMMA), are well known polymers as drug carrier. Miyazaki *et al.* observed the sustaining effect of chitosan on the release of water insoluble indomethacin from granules in a rabbit model[18]. PLGA is one of the best-known biodegradable polymers. It is hydrolyzed without enzymes and metabolized by the body[19,20]. PMMA also has been shown that it can be used as a drug carrier for antibiotics[21]. Therefore, the aim of this *in vitro* study was to compare whether three polymers (chitosan, PLGA, PMMA) from CRD prototypes can effectively control the release rate of chlorhexidine.

Ⅱ. MATERIALS AND METHODS

Calculation of CHX standard curve

CHX solution (20% w/w, Sigma, St. Louis, MO, USA) was diluted serially in 1:1 ratios, and the UV absorbance was measured for each dilution using a UV spectrophotometer (Shimadzu, Tokyo, Japan). The standard curve of CHX concentration versus UV absorbance was used to determine CHX concentration in the following experiment.

Preparation of CRD prototypes

Absorbent paper points (Sure-Endo™, #80, Chungju, Korea) were used as CRD core. Four different CRD prototypes were prepared: group A; absorbent paper points were loaded with 40% CHX. The paper points were immersed in 40% concentrated CHX solution obtained by drying process for 30 minutes and then dried. The 40% concentrated CHX solution was obtained by evaporating water of 20% CHX solution in an oven at 50℃ until target weight was reached. Group B; after loading with CHX as in group A, the paper points were coated with an acidic aqueous 3% solution of chitosan (Texan MedTech, Kwangju, Korea) and dried. Groups C and D were treated as Group B except that the paper points were coated three times with 5% PMMA (Group C, Aldrich®, Milwaukee, WI, USA) in methylene chloride, or three times with 3% PLGA (Group D, Sigma®, St. Louis, MO, USA) in methylene chloride, respectively. For Group C and D, the CHX-loaded paper points were dip-coated with polymer solutions and dried, and this process was repeated twice. All loaded absorbent paper points were individually weighed before being coated. The ones with the range of $0.033 \pm 8.43 \times 10^{-5}$ g were selected, and they were randomly allocated to experimental groups of 12 each.

Calculation of CHX release rate from CRD prototypes

Each prototype was immersed in 3 ml of distilled water. 10 ㎕ of this solution was then sampled at predetermined times (i.e., at 3, 6, 10, 20, 30, 40 and 50 min and at 1, 2, 3, 4, 5 and 6h, and at 7days). UV absorbance was measured using a UV spectrophotometer (Shimadzu, Tokyo, Japan) to determine the concentration of released CHX from the CRD prototype.

Statistical analysis

One-way ANOVA test was used to compare the release rates of CHX in each group. A P value 〈 0.05 was considered significant.

Ⅲ. Results

Standard curve of CHX release

The average weight of CHX loaded in the paper points was 0.016 g/point. If all the CHX loaded in the paper point was released into 3 mL of distilled water, the concentration would have been about 0.53%. From Figure 1, we calculated that the UV absorbance of 0.53% CHX was about 1.1, which thus represented the maximum UV value.

Release rate of CHX from the CRD prototypes.

Statistically significant differences were found between the groups by One Way ANOVA ($P < 0.05$). The release rate of the CHX was the greatest in the non-coated group, followed by the chitosan-coated group, 3% PLGA-coated group, and 5% PMMA-coated group (Figures 2 and 3).

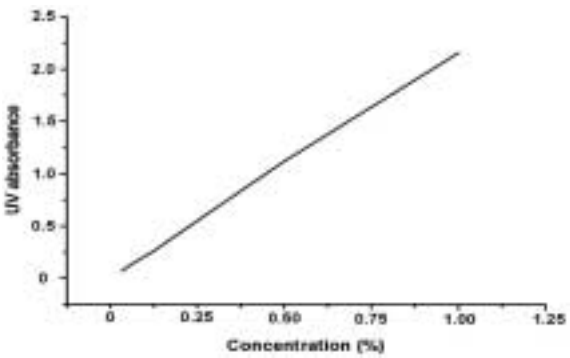

Figure 1. Standard graph of CHX concentration and UV absorbance (Y=1.99X; X axis: concentration of CHX, Y axis: UV absorbance).

Ⅳ. Discussion

This study evaluated the role of three polymers used as CRD drug carrier. One previous study manufactured and tested a needle-shaped CRD prototype used water-permeable polymer as drug carrier. In their study, the releasing rate of the non-coated CRD prototype was very fast, while the release rate of CRD with coated formulations was far more controlled.

In the present study, similar results were obtained. In the non-coated control group, the loaded CHX was totally released within 2h. In contrast, CHX release from the polymer-coated groups was more controlled. Chitosan was more sensitive to water and easily swollen with water and ruptured. This resulted in faster release of CHX compared to the PLGA- and PMMA-coated CRD groups. We speculate that the loaded CHX might be released through the surface pores on the coated polymer layer of CRD prototypes. Further studies are needed to investigate the exact mechanism of CHX release from the CRD prototypes.

The ideal CRD device should have the following characteristics. It should be easily inserted into and removed from the root canal. The use of absorbent paper point as core material can easily be inserted into root canals and they can be easily removed from the root canal after use with the help of locking

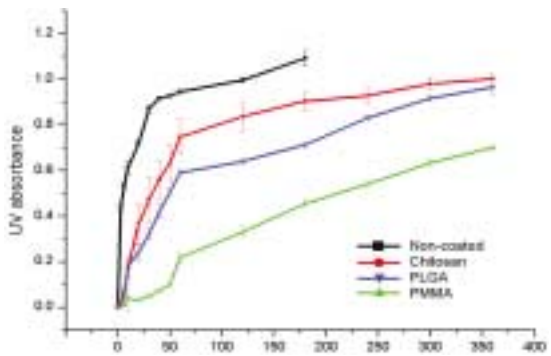

Figure 2. Short-term release pattern of CHX after immersion of 4 CRD prototypes in distilled water.

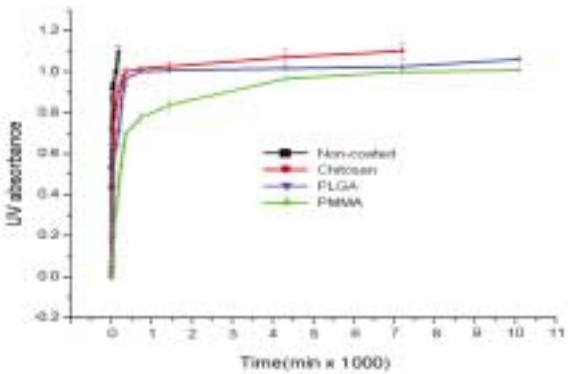

Figure 3. Long-term release pattern of CHX after immersion of 4 CRD prototypes in distilled water.

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In addition, the drug should be released continuously for a certain period (at least 1 week) in root canal. Heling *et al* developed a CRD device containing a biodegradable polymer and demonstrated that it was more effective than calcium hydroxide at disinfecting infected dentinal tubules[16,17]. However, if used for root canal disinfection, it may not be completely degraded at the time for root filling. Any remaining polymer fragments in the root canal system may interfere with the filling quality, and thus result in leakage.

Due to this problem, insoluble polymers were used as CHX carriers in the present study. Chitosan is insoluble at an alkaline or neutral pH[18]. PMMA, which has been used for denture base material, is also an insoluble and non-degradable polymer. PLGA is a biodegradable polymer, but the degradation rate of PLGA can be controlled using the lactide to glycolide mole ratio[19]. Therefore, all three polymers are suitable as drug carriers of CRD prototypes.

In conclusion, our present study demonstrates that three polymer used as drug carrier of CRD can effectively control the release rate of CHX. Further studies, however, are needed to evaluate the antimicrobial effects of the CRD before clinical application.

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국문초록

제어방출형 소독제의 약물전달 체로 사용된 폴리머 유형에 따른 클로르헥시딘 제어 방출속도 비교

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본 연구는 제어방출형 근관소독제(CRD)로 부터 chlorhexidine (CHX)의 방출 속도를 제어하기 위한 3가지 polymer (chitosan, PMMA, PLGA) 의 코팅 효과를 평가하기 위함이다. 80번 paper point (Sure-Endo™)에 20% CHX를 loading 한 후 각 군당 10개씩 4군으로 분류하였다: Group A: 폴리머를 코팅하지 않은 CRD prototype (control), Group B: chitosan-coated prototype, Group C: PMMA-coated prototype, Group D: PLGA-coated prototype. 모든 시편은 3 ml 증류수가 담긴 큐벳에 넣은 후 3, 6, 10, 20, 30, 40, 50분 마다, 1, 2, 3, 4, 5, 6시간 마다 각각 10 μl 씩 채취하고, 1주일 후 다시 10 μl을 채취한 후 UV 흡광도를 이용하여 CHX의 방출 속도를 비교하였다. 실험결과 제어방출형 근관소독제로부터 CHX의 방출속도는 대조군, 키토산, PLGA, PMMA-군 순으로 천천히 일어났으며 PMMA군에서 가장 천천히 일어났다. 결론적으로 제어방출형 근관소독제 표면의 폴리머는 약물 (CHX) 방출 속도를 효과적으로 제어하였다.

주요단어 : 제어방출형 근관소독제, 클로르헥시딘, Chitosan, PLGA, PMMA