The sustaining effect of three polymers on the release of chlorhexidine from a controlled release drug device for root canal disinfection

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ABSTRACT

The aim of this in vitro study was to evaluate the suitability of using chitosan, poly (lactide-co-glycolide) (PLGA), and polymethyl methacrylate (PMMA) to control the release of chlorhexidine digluconate (CHX) from a prototype of controlled release drug device (CRD) for root canal disinfection. Four different prototypes with different formulations were prepared. Group A (n = 12): The device (absorbent paper point) was loaded with CHX as control. Group B (n = 12): same as group A, but the device was coated with chitosan. In Groups C and D, the device was treated in the same way as group A and then coated three times with 5% PMMA (Group C, n = 12), or coated three times with 3% PLGA (Group D, n = 12). The devices were randomly allocated to experimental groups of 12 each.

All CRD prototypes were soaked in 3 mL distilled water. The concentrations of CHX were determined using a UV spectrophotometer. The surface characteristics of each prototype were observed using a scanning electron microscope.

The result showed that release rate of CHX was the greatest in the non-coated group, followed by the chitosan-coated group, the PLGA-coated group, and the PMMA-coated group (P < 0.05). Pores were observed on the surface of the prototypes that were coated with PLGA and PMMA. When the pore size was smaller, the release rate was lower. This data indicate that polymer coating can control the release rate of CHX from the CRD prototypes. (J Kor Acad Cons Dent 29(6): 548-554, 2004

Key words: Controlled release drug device, Chlorhexidine digluconate, Chitosan, Polymethyl methacrylate, Poly (lactide-co-glycolide), Root canal disinfectant

I. Introduction

Complete debridement and effective disinfection of the root canal space are considered essential for predictable long-term success of endodontic treat-
native medicaments should be explored that would maximize microbial eradication when used as intracanal dressings.

Chlorhexidine is effective against a wide variety of Gram-positive and Gram-negative organisms, as well as fungi. Recent studies have shown that the antimicrobial effect of chlorhexidine digluconate (CHX) was equal to that of the conventional irrigants and medicaments. It was also suggested as an effective irrigant to prevent root canal reinfection due to coronal leakage. However, in order to achieve long-term substantive antimicrobial effect, the infected root dentin must be exposed to CHX for a longer time than that afforded by irrigation.

A number of studies have shown that a controlled release drug (CRD) device with water-permeable polymer could effectively sustain the release of CHX from the CRD. However, because of a strong, positive charge of chlorhexidine and its high binding affinity, the development of suitable drug carriers for sustained release of CHX still remains a challenge.

Chitosan, poly (lactide-co-glycolide) (PLGA), and polymethyl methacrylate (PMMA), are well known polymers as controlled drug release carrier. Miyazaki et al. observed the sustaining effect of chitosan on the release of water insoluble indomethacin from granules. A sustained plateau level of indomethacin was obtained for drug/chitosan granules (1:2 mixtures) versus a sharp peak for conventional commercial capsules in a rabbit model. PLGA is one of the best-known biodegradable polymers. It is hydrolyzed without enzymes and metabolized by the body. Moreover, the degradation rate of PLGA can be regulated by changing its molecular weight, chemical composition, and crystal form. PMMA has been used as denture base materials, and one recent study suggested that it could be used as a controlled drug release carrier for antibiotics, for the prevention and treatment of osteomyelitis.

Therefore, all three polymers may be promising controlled drug release carriers.

The aim of this in vitro study was to compare the sustaining effect of chitosan, PLGA, and PMMA on the release of CHX from a prototype of CRD device for root canal disinfection.

II. MATERIALS AND METHODS

1. Standard curve of CHX concentration.

CHX solution (20% wt / wt, 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 experiments.

2. Preparation of the prototype of CRD.

Absorbent paper points (Sure-Endo™, #80, Chungju, Korea) were used as core material. Four different prototypes with different formulations were prepared; group A: absorbent paper points were loaded with 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°C 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 ± 8.43 × 10^-5 g were selected, and they were randomly allocated to experimental groups of 12 each.
3. Measuring release of CHX from a prototype of CRD.

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 7 days). UV absorbance was measured using a UV spectrophotometer (Shimadzu, Tokyo, Japan) to determine the concentration of released CHX from the CRD prototype.

4. Surface observations of CRD devices by SEM.

Each prototype was coated with a thin palladium-gold film, and viewed the surface characteristics under a scanning electron microscope (JEOL, TSM-6320F, Tokyo, Japan) at magnifications of 100× and 5000×.

5. Statistical analysis.

One-way ANOVA test was used to compare the release rates of CHX in each group. The significance was established at 5% level (p = 0.05).

Ⅲ. Results

1. Standard curve of CHX concentration.

The average weight of CHX loaded in the paper points was 0.016g/point. If all the CHX loaded in the paper point was released into 3mL 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.

2. Release rate of CHX from the CRD devices.

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).
3. Surface observations of CRD devices by SEM.

Scanning electron micrographs showed the different surface characteristics of the CRD prototypes. In the non-coated group, the fiber structure of the absorbent paper point was unaffected and no surface pores were observed (Figure 4). In the polymer-coated groups, coated fiber structure was observed in all prototypes. However, the surface pores were only observed in the PMMA- and PLGA-coated groups, and the pore sizes differed between the two groups. The pore size of the PLGA-coated group is about 2 μm and larger than that of the PMMA-coated group which is <1 μm in size (Figures 5 and 6). The chitosan covered absorbent paper points did not show any pores (Figure 7).

Figure 4. SEM images of the non-coated paper point which was loaded with CHX: (a) 100×, (b) 5000×; the fiber structure of the paper point was observed without pores.

Figure 5. SEM images of a prototype of controlled release drug device coated with 5% PMMA three times: (a) 100×, (b) 5000×; surface pores were observed, and all were within 1 μm.

Figure 6. SEM images of a prototype of controlled release drug device coated with 3% PLGA three times: (a) 100×, (b) 5000×; pore sizes larger than those of the PMMA-coated group were observed.

Figure 7. SEM images of a prototype of controlled release drug device coated with chitosan: (a) 100×, (b) 5000×; the fiber structure of paper point was observed without any surface pores.
IV. Discussion

Huang et al.\textsuperscript{22} developed the cylindrical, needle-shaped CRD prototypes with different formulations and demonstrated that the releasing rate of CRD with non-coated formulation was very fast. In contrast, the release rate of CRD with coated formulations was far more controlled.

In this study, similar results were obtained. In the non-coated group, the drug release was very fast, and all loaded CHX was 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 from the chitosan-coated CRD device compared to the PLGA- and PMMA-coated groups. The CHX loaded in the paper point was released through the surface pores on the coated polymer layer. The pore size of PLGA-coated group was larger than that of PMMA-coated group and the release rate of CHX from the latter group was lower than that of the former group. Thus, the surface pore size was very important for the release rate of CHX and various release rates of CHX from CRD devices can be achieved by controlling the pore size of the coated polymer. The ideal CRD device should have the following characteristics. It should not degrade inside the root canal and it should be easily inserted into and removed from the root canal. In addition, the drug should be released continuously for a controlled time period. Heling et al.\textsuperscript{16,17} developed a CRD device containing a biodegradable polymer and demonstrated that it was more effective than calcium hydroxide at disinfecting dentinal tubules. The antimicrobial effect of camphorated paramonochlorophenol, camphorated phenol and calcium hydroxide in the treatment of infected root canals.

References

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Based on the above results, we conclude that the polymer coating can effectively control the release rate of CHX from the CRD prototypes. Further studies are needed to evaluate the antimicrobial effects and the cytotoxicity of these prototypes of CRD device.


제어 방출형 근관 소독제로부터 클로르헥시딘의 방출에 미치는 3 가지 POLYMER 의 제어 효과

복영빈1∙이덕연1∙이찬영1∙김경남2∙금기연1
연세대학교 치과대학 치과보존학교실1, 생체재료학교실2

본 연구는 서방형 근관소독제(CRD)의 prototype 으로부터 chlorhexidine (CHX) 의 방출 속도를 제어하기 위한 3 가지 polymer (chitosan, PMMA, PLGA) 의 제어 효과를 평가하기 위해 이루어졌다. 80번 paper point (Sure-Endo TM, #80) 에 20% CHX를 loading 한 후 각 군당 10 개씩 4 군으로 분류하였다: Group A: Non-polymer coated prototype, Group B: chitosan-coated prototype, Group C: PMMA-coated prototype, Group D: PLGA-coated prototype. 각각의 paper point 에 함유된 CHX 양을 동일하게 하기 위해, CHX loading 후 무게를 측정하여 유사한 무게의 sample을 선택하여 사용하였다. 모든 시편은 3ml 증류수가 담긴 큐벳에 넣은 후 3, 6, 10, 20, 30, 40, 50 분마다 각각 10㎕씩 채취하고, 1주일 후 다시 10㎕을 채취하여 UV 흡광도를 이용하여 CHX 의 방출 속도를 비교하였다. 또한, 각 prototype의 표면 관찰을 위하여 100배와 5000배의 주사전자 현미경을 이용하여 표면 구조를 촬영하였다.

1. CHX 의 방출 속도는 non-coated grupo, chitosan-coated group, PLGA-coated group, PMMA-coated group 순이었으며 각 군간에는 통계학적인 유의차가 있었다 (p < 0.05).
2. PMMA 나 PLGA 를 도포한 CRD 표면에서만 pore가 관찰되었으며 pore size가 커질수록 방출 속도가 빨랐다.

결론적으로 polymer coating 에 의해 제어방출형 근관소독제의 prototype 으로부터 약물 (CHX) 의 방출 속도를 제어 할 수 있었다.

주요단어 : 제어 방출형 근관소독제, 클로르헥시딘, Chitosan, PLGA, PMMA