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NEW METHOD FOR LOCAL DRUG DELIVERY USING RESORBABLE BASE MATERIAL IN PERIODONTAL THERAPY

BY

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ABSTRACT

A new method for local drug delivery to the subgingival plaque was developed using hydroxypropylcellulose (HPC) as a base material. Using this material prepared in the form of strips containing antimicrobial drugs, the clinical and microbiological effects by this method on the human periodontal disease were studied.

Before the clinical trials, the rate of the drug release from the strips was studied. Both drugs used in this study (CH: chlorhexidine and TC: tetracycline) were released almost within 2 hours from the strips *in vitro*. In the gingival crevicular fluid, however, it was found that the TC was maintained for 24 hours after the local delivery.

Five patients who had deep pockets contralaterally were selected. The CH-containing HPC strips (5%) were applied in one pocket of each patient and the placebo strips were applied in other pocket on day 0, 2 and 4. Plaque Index, Gingival Index, probing depth and the presence or absence of bleeding on probing were recorded on day 0, 2, 4 and 6.

Marked reduction of bleeding on probing was found in the pockets applied the CH-containing HPC strips. There was a significant reduction in the proportion of *Bacteroides asaccharolyticus* in these pockets ($p<0.01$).

Key words: Periodontal Disease, Chemical Plaque Control, Local Drug Delivery, Hydroxypropylcellulose.

INTRODUCTION

Based on the microbiological studies, it is well documented that the subgingival plaque, in which the gram-negative anaerobic rods are predominant, is associated with the destructive periodontal disease (Slots [1]; Listgarten and Helldén [2]; Tanner *et al.* [3]). For the purpose of controlling the subgingival plaque in different ways from the conventional methods, several studies have been made (Goodson *et al.* [4]; Lindhe *et al.* [5]; Addy *et al.* [6]; Yeung *et al.* [7]; Coventry and Newman [8]; Goodson *et al.* [9]; Soskolne *et al.* [10]; Dunn *et al.* [11]). These methods, using hollow fiber devices or acrylic resin strips and monolithic fibers, seem to be effective in changing the microflora in the periodontal pockets and in improving the periodontal inflammation. However, for the routine use of these methods in the treatment of the periodontal disease, all these

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methods require carriers in the drug administration. One of the problems of these methods is to require the removal of the carrier at regular intervals from the pockets after the release of the drugs. The other is the lack of retention of the carrier in periodontal pockets.

To solve these problems, we devised a new method for the access to the subgingival plaque. The base material used in this method is made of hydroxypropylcellulose (HPC). HPC dissolves slowly in contact with the saliva or gingival crevicular fluid and adheres to both the tooth surface and the soft tissue. Using this material containing antimicrobial agents prepared in the form of strips, it is possible to deliver the drugs directly to the periodontal pockets.

The purpose of the present study is to introduce our new method and to investigate both *in vivo* and *in vitro* the drug release from the strips. The microbiological and clinical effects of this method on the human periodontal disease were also studied.

Materials and Methods

Preparation of drug-containing HPC strips

The chemical structure of HPC is as shown in Fig. 1. The drug-containing strips were prepared as follows: Twenty-eight grams of HPC powder were dissolved in 500 g of ethanol (99.5%) and at the same time 0.28 g of tetracycline (1% TC) or 1.4 g of chlorhexidine (5% CH) were added. The solution was poured into the plates (7 mm deep) up to the brim. Under reduced pressure, the solution was dried to form a sheet of 300 μm thickness after 24 hours. The sheet was cut into strips and used for this study.

In vitro release of drugs from strips

A sheet of 300 μm thick was cut into 2.5 cm×5 cm strips. Each strip was weighed, put in a vessel containing 300 m*l* of distilled water and incubated at 37°C, rolling at 100 rpm. Five milliliters of water were pipetted off at each sampling time and replaced with an additional 5 m*l* of distilled water. The sampling time was every 5 minutes for the first 60 minutes and thereafter every 10 minutes between the 60-minutes and 120-minutes period, every 20 minutes between the 120-minutes and 240-minutes period, every 30 minutes between the 4-hours and 6-hours period. For the sets of three test strips of drugs (CH and TC) and placebo strips, the concentration of the drugs in the water dissolved from each strip was determined by measuring the absorption peak at 253 nm for CH and 357 nm for TC on the UV/visible spectrophotometer*[3].

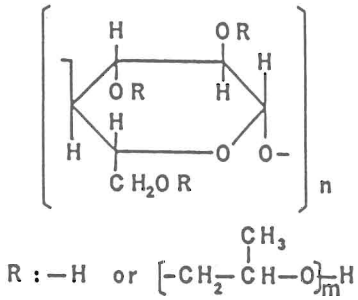

Fig. 1. Chemical Structure of Hydroxypropylcellulose (HPC).

In vitro solubility of base material (HPC) in distilled water

The concentration of HPC in the gingival crevicular fluid was measured using a simulation model *in vitro*. This model was prepared as shown in Fig. 2. The TC- containing HPC strip was placed in the glass tube (b) and the distilled water was added from the the top of the glass tube (a). The flow rate of the distilled water was 1 m*l* per hour, controlled by

*[3] Hitachi Spectrophotometer 124, Hitachi Ltd., Tokyo.

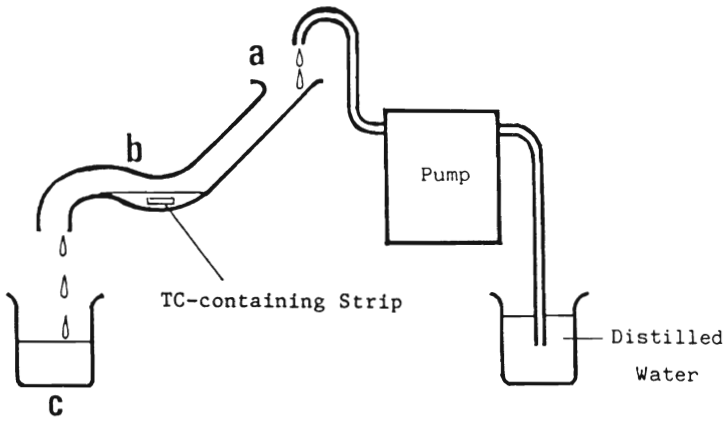

Fig. 2. Simulation Model of GCF Flow.

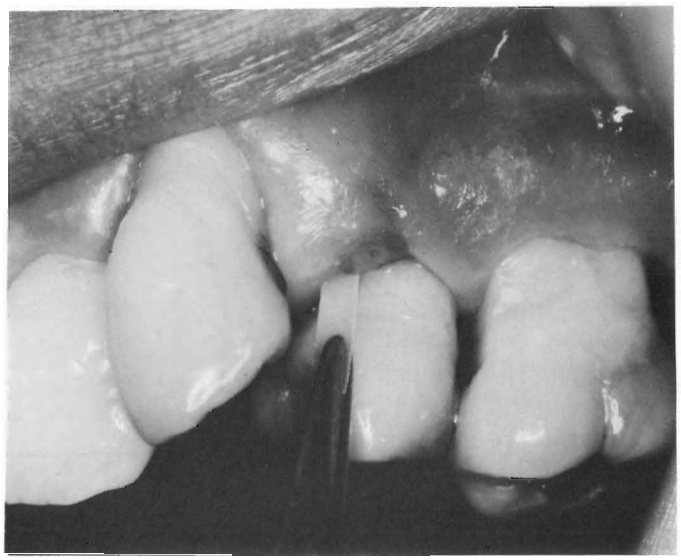

Fig. 3. Insertion of HPC Strip Into Periodontal Pocket.

an electric pump*[4]. The water flowing out of the glass tube was gathered in the beaker (c). One milliliter of water was pipetted off at each sampling time. The concentration of HPC in the water was measured by the phenol-sulfuric acid method. The concentration of TC released in the water was also measured by the UV spectrophotometer.

Accessibility of the HPC strips to the bottom of pockets

Twenty-four deep pockets (≥5 mm) in 12 patients were selected. The single HPC strip was cut into a size of 10 mm in length and 1 mm in width and inserted into each pocket (Fig. 3). The length of the strip inserted into the pocket was compared with the probing depth to ascertain the accessibility of the strips to the bottom of pockets.

In vivo release of drug from strips

Nine patients who had deep pockets of more than 5 mm were selected. The gingival crevicular fluid (GCF) was sampled

*[4] Peristaltic Pump 1200, Varioperpex, LKB, Sweden.

with microcaps*[5], 24 hours after the application of the TC-containing strips. The GCF was transferred into a test tube containing 1 m*l* of distilled water. The concentration of TC in the GCF was measured in the same way as by the *in vitro* determination. The background absorbance was determined by the measurement of the GCF taken from the same pockets before the insertion of the strips.

Clinical and microbiological observations

Five patients, who had deep pockets (more than 5 mm) contralaterally, were selected for the clinical and microbiological investigation. They had not received any antibiotics for 6 months prior to this study and no instruction in oral hygiene was given to these patients. The CH-containing strips (5%) were applied to one pocket of each patient and the placebo strips, which did not contain CH, were applied to the other pocket on day 0, 2 and 4. Plaque Index (PlI) (Silness and Löe [12]), Gingival Index (GI) (Löe and Silness [13]), probing depth and the presence or absence of bleeding on probing were recorded on day 0, 2, 4 and 6.

Microbial samples from the bottom of the pockets were taken by a tuberculin syringe on day 0 and 6. The samples were dispersed under CO_2 gas flush by sonic oscillation (100 W ultrasonic disintegrator*[6]), for 20 seconds at the amplitude of 6 μm. Ten-fold serial dilution was performed. Following the dispersion and dilution, 0.2-m*l* aliquots were spread on the enriched BHI*[7] agar plates. After seven days of anaerobic incubation, a high dilution plate containing 20–50 isolates was chosen for further study. They were immediately cultured anaerobically and were identified by the Minitek system*[8].

Results

The rate of the release of chlorhexidine (CH) and tetracycline (TC) from the strips are shown in Fig. 4 and 5. The vertical axis shows the mean value of the three measurements (%) and the horizontal axis the time (h). For CH, it was found that about 90% of the amount mixed in the material was released after one hour and almost 100% after 2 hours. For TC, it was found that more than 80% of the amount mixed in the material was released within one hour and almost 100% within 2 hours.

The amount of HPC dissolved and TC

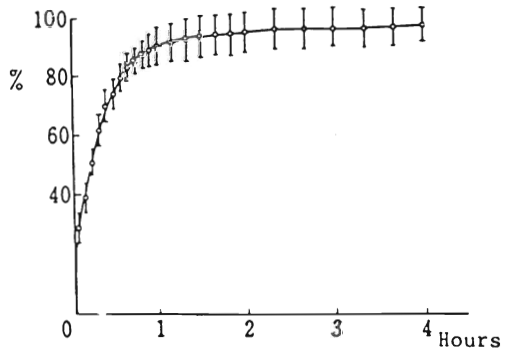

Fig. 4. Rate of Release of Chlorhexidine From Strips. (5%)

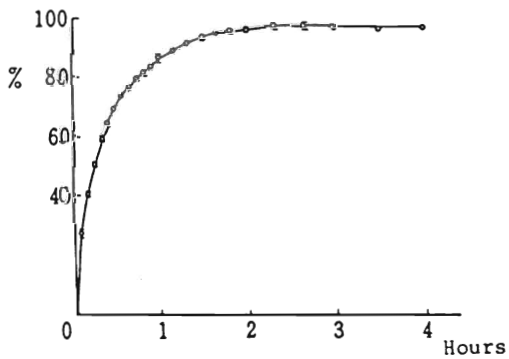

Fig. 5. Rate of Release of Tetracycline From Strips. (1%)

*[5] Drummond Scientific Co., USA.
*[6] Ultrasonic Disintegrator MK2, MSE Incorp., England.
*[7] BBL., USA.
*[8] BBL., USA.

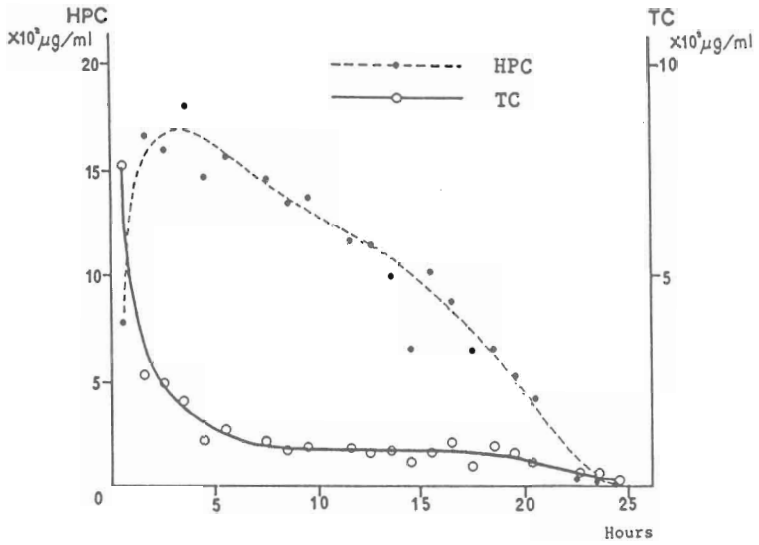

Fig. 6. Amount of HPC Dissolved and TC Released in Water in Simulation Model.

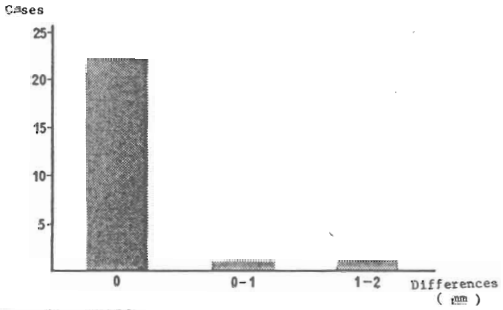

Fig. 7. Differences Between Probing Depth and Length of Strips Inserted.

released in the water is illustrated in Fig. 6. The maximum amount of TC released was at one hour and this decreased rapidly during the next 2 hours, but the rate of decrease was low from 3 hours to 20 hours. On the other hand, the amount of HPC reached the peak at 3 hours and then gradually decreased. After 24 hours, neither HPC nor TC could be detected.

The difference between the probing depth and the length of the strips inserted into the pockets is shown in Fig. 7. From these results, it is clear that the strips can be inserted to the bottom of the

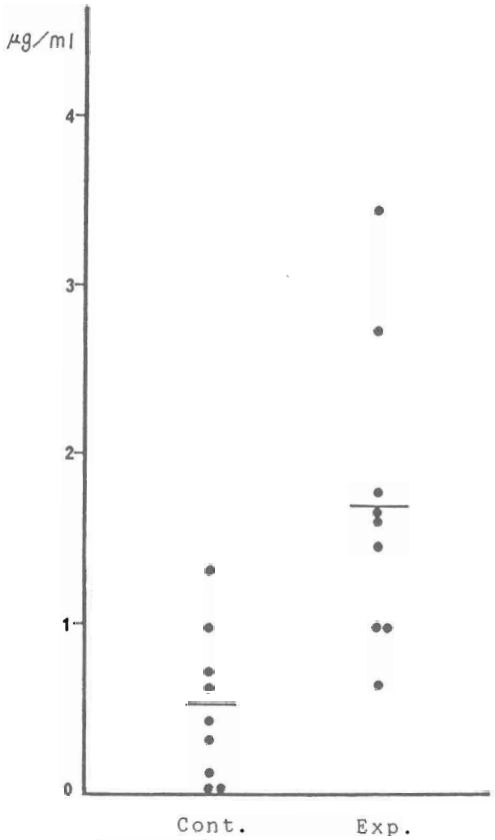

Fig. 8. Amount of TC in GCF After 24 Hours *in vivo*.

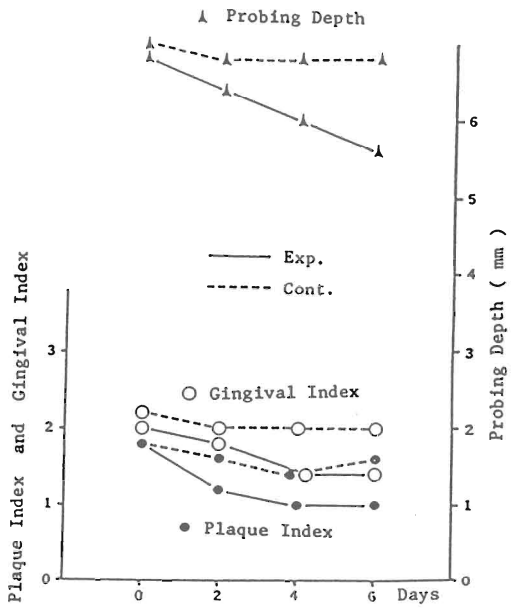

Fig. 9. Changes of PlI, GI and Probing Depth.

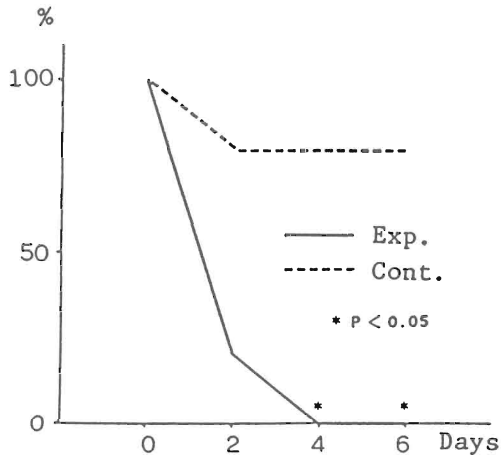

Fig. 10. Rate of Bleeding on Probing.

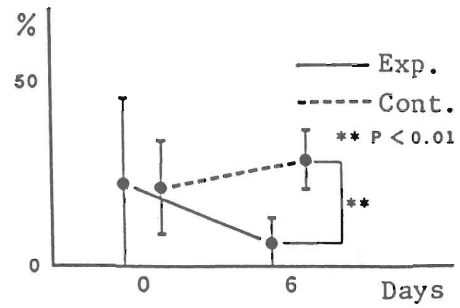

Fig. 11. Proportion of *Bacteroides asaccharolyticus*.

periodontal pockets in most cases.

The amount (%) of TC in the GCF 24 hours after the insertion of the TC-containing strips into the pocket is shown in Fig. 8. As the measurement was performed on the basis of the UV absorbance, the background absorbance at this wave-length for GCF is shown in the same figure (left). A significant difference was found between the control group and the experimental group ($p<0.05$).

In Fig. 9, the change of PlI, GI and probing depth are shown. The straight line shows the results at the experimental sites and the dotted line at the control sites. At the control sites, no significant difference could be found during the experimental time regarding the PlI, GI and probing depth. At the experimental sites, the probing depth, GI and PlI were decreased but there was no significant statistical difference found on experimental day ($p<0.05$). In Fig. 10, the changes in bleeding on probing are shown. A significant reduction of bleeding was found at the experimental sites ($p<0.05$). Fig. 11 shows the results of the microbiological examination. The percentage shown on the vertical axis means the proportion of *Bacteroides asaccharolyticus* to the total cultivable microbial count in the subgingival plaque. A significant difference was found between the experimental sites and the control sites on day 6 ($p<0.01$).

Discussion

Taking into account the limited access of the instruments to the deep periodontal pocket for scaling or root planing, it is very important to attack the subgingival plaque by chemotherapeutic agents. However, the systemic administration of drugs is not practical except in the case

of acute periodontitis or acute gingival infections because of the various side effects such as development of resistant strains and gastrointestinal disturbances.

Thus, methods for the local drug delivery to the subgingival plaque have been studied by several investigators. Goodson *et al.* [4] and Lindhe *et al.* [5] used hollow fibers filled with tetracycline as a device to carry the drug to the subgingival plaque. In order to achieve the same purpose, Addy *et al.* [6] and Yeung *et al.* [7] used acrylic resin strips, Coventry *et al.* [8] dialysis tubes and Soskolne *et al.* [10] ethyl cellulose films. Some changes in the bacterial flora in the pocket and other favorable clinical results have been reported in the patients treated by these methods. However, the lack of adhesion of the devices used in the local drug delivery produces a tendency to be dislodged or lost between the placement time (Yeung *et al.* [7]; Soskolne *et al.* [10]).

On the other hand, some investigators have been trying direct irrigation by the use of a syringe and blunt needle (Hardy *et al.* [14]; Soh *et al.* [15]; Wieder *et al.* [16]). In these cases, aqueous solutions are applied as chemotherapeutic agents but there is no possibility of these agents to penetrate to the apical plaque border (Pitcher *et al.*, [17]).

In this investigation, we used hydroxypropylcellulose (HPC) as the base material and tried to apply the drugs directly to the subgingival plaque. HPC is a nontoxic and water-soluble polymer. Any kind of drugs, for example antibiotics and antiseptics, can be mixed easily with this material without affecting its original property.

The HPC containing 1% tetracycline or 5% chlorhexidine formed solid and elastic strips. These strips were inserted easily into the bottom of the periodontal pocket without patient discomfort (Fig. 4).

The *in vitro* release of the drugs from these strips showed that almost 100% of this material added was released within 2 hours (Fig. 4, 5). It is favorable that the drug is released rapidly at a relatively high concentration and stays for a long time in the pocket. With our method, it was found that the drug was released rapidly from the material at a high concentration, and the concentration of the drug released into the pocket can be controlled by altering the concentration of the drug mixed in the strips.

The assay of the TC level in the gingival crevicular fluid after 24 hours reveals that approximately high levels of TC were still maintained (Fig. 8). The mechanism of the drug release and/or the drug remaining in the pocket are not known. But, the viscous property of the HPC in both the soft tissues and hard tissues and the adsorption of TC to the teeth (Baker *et al.* [18]) may have played a significant role for the TC to remain in the gingival fluid.

It is important to know whether the base material (HPC) itself will be washed away by the gingival fluid or remain in the pocket after the release of the drug.

The study to clarify this point *in vitro* by preparing a simulation model using the TC-containing strips was carried out. According to these results, the TC was released rapidly also in this model at almost the same rate as shown in Fig. 5 and the HPC dissolved more slowly in the water. But after 24 hours HPC could not be detected. It may be suggested from these results that the base material do not remain in the pocket after the drug was released .

From the clinical results obtained in this study, it was found that Plaque Index, Gingival Index, probing depth and

bleeding on probing tended to be less when the CH-containing strips were inserted. A statistically significant improvement was found in bleeding on probing. Lindhe *et al.* [5] reported the same results regarding the GI and bleeding on probing. Coventry *et al.* [8] published the same report on the reduction of bleeding on probing in acute periodontal inflammation.

The results obtained from the microbiological studies showed that the CH-containing HPC altered effectively the microbiological composition of the subgingival plaque. Soskolne *et al.* [10] mentioned that the CH-treated group showed a marked decrease in the relative proportion of motile rods and spirochetes using the dark field microscopy. In our method using the anaerobic culture technique, a significant reduction of *Bacteroides asaccharolyticus* was observed (Fig. 11). In spite of the difference in the microbiological technique between our method and that of Soskolne *et al.* [10], both results are almost similar regarding the significant reduction of the microorganisms found in advanced adult periodontitis.

This new direct drug delivery using the HPC as a base material was found to be effective to control the subgingival plaque and at the same time to produce signs of clinical improvement. However, further studies will be necessary regarding optimal concentration of TC and/or CH contained in the strips and the long term clinical effects of both drugs. And, furthermore, future study would include the establishment of the role of this new method in the entire conventional periodontal therapy.

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