이학석사학위논문

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The reducing effect of neointimal hyperplasia by paclitaxel coating on the terminal part of ePTFE vascular grafts for hemodialysis

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A Thesis for the M.S Degree in Biochemistry

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Abstract

Stenosis associated with neointimal hyperplasia plays a key role in the failure of synthetic hemodialysis vascular grafts. It was demonstrated that the local delivery of paclitaxel coated on the graft effectively prevented this stenosis. Because more than half of stenosis cases arise within 3 cm of the venous anastomosis, we coated the terminal part of the expanded polytetrafluoroethylene (ePTFE) grafts with paclitaxel to minimize the drug dose and systemic toxicity. We evaluated the effectiveness of this new design in a pig model. The terminal part of the ePTFE graft was dip-coated with paclitaxel at a dose of 0.58 μg/mm^2, the total amount of paclitaxel loaded on the graft was 0.66 mg.

A 15 cm-long ePTFE graft was surgically implanted between the common carotid artery and external jugular vein in 8 female Landrace pigs. Animals received grafts coated with paclitaxel and were sacrificed 6 weeks after graft placement**.** Histomorphometric analysis was performed to compare the neointimal areas and the percentages of luminal stenosis between the coated group and the control group.

Paclitaxel-coated vascular grafts significantly suppressed neointimal hyperplasia compared with the control group (P = 0.026). Whereas 7 of

8 paclitaxel-coated grafts were patent, only 1 of the 6 control grafts was patent. The mean ± standard error values of the percentage of luminal stenosis were 26.9 ± 5.1 % (coated group) and 75.7 ± 12.7 % (control). The values for the neointimal area were 3.99 ± 1.01 mm^2 (coated group) and 8.77 ± 1.66 mm^2 (control).

Despite the lower amount of drug loading used in the present study, paclitaxel coating on the terminal part of ePTFE hemodialysis grafts effectively reduced neointimal hyperplasia at the venous anastomosis.

Key Words: Hemodialysis; Vascular graft; Stenosis; Neointimal hyperplasia; Paclitaxel

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Contents

1. Introduction

Millions of patients with end-stage renal disease must receive chronic hemodialysis treatments throughout their lives. Hemodialysis vascular graft implantation is a vital procedure for securing vascular access in these patients; this is particularly true in patients such as the elderly and diabetic patients in whom a native arteriovenous (AV) fistula cannot be sufficiently developed. However, the prevalence of synthetic grafts made of expanded polytetrafluoroethylene (ePTFE) has decreased because of hemodialysis vascular access dysfunction with venous stenosis due to the aggressive development of neointimal hyperplasia at the graft-vein anastomosis, which subsequently results in thrombosis. Synthetic vascular grafts exhibit low patency: 50 % at 1 year and 25 % at 2 years [1]. Despite various attempts to prevent stenosis in vascular grafts, none of these attempts has been successful in clinical trials [2].

The bio-incompatibility of ePTFE graft material, vascular injury through a surgical incision and hemodynamic shear stress at the vein-graft anastomosis were shown to induce an inflammatory response and to play a role in the process of stenosis and thrombosis [3, 4].

Histologically, neointimal hyperplasia arising from a vascular graft is

characterized by the presence of smooth muscle cells and myofibroblasts, angiogenesis, and matrix deposition [5, 6]. Unlike neoplastic cells, these cells do not metastasize and mostly proliferate at the venous and arterial anastmosis only. Accordingly, suppressing the proliferation and migration of smooth muscle cells/myofibroblasts might be a logical approach to improving vascular graft outcome. Since systemically delivered drugs have shown little effect on graft failure [7], the approach of using antiproliferative agents such as paclitaxel and sirolimus locally deserves consideration for the reduction of neointimal hyperplasia.

Paclitaxel is a potent anti-proliferative agent that interferes with the disassembly of microtubules in cell division, effectively inhibits the proliferation of vascular smooth muscle cells, and prevents neointimal hyperplasia in both hemodialysis vascular grafts and stents [8-10].

We have previously demonstrated that the paclitaxel coating on an ePTFE graft reduced venous neointimal hyperplasia in a pig model [11, 12]. Because more than half of vascular stenosis cases occur within 3 cm of the venous anastomosis, we have developed a new design in this study in which both ends of the ePTFE graft were coated with paclitaxel and can therefore be directly applied at each of the anastomosis sites. After coating paclitaxel only on the terminal part of

the ePTFE graft, we evaluated the suppressing effect on stenosis.

2. Materials and methods

Materials and graft preparation

Paclitaxel was purchased from Samyang Genex Co. (Seoul, South Korea) and the ePTFE grafts were supplied by Bard peripheral Vascular, Inc. (Arizona, USA). All other chemicals and reagents were of analytical grade.

Paclitaxel easily dissolves in *tert*-butanol to a concentration of 1 mg/mL in a polypropylene tube. The terminal part of the ePTFE vascular graft was dipped gradually into the paclitaxel solution and was held to the surface in the vertical direction for 1 minute. The coating solution rapidly permeated but slowly diffused into the ePTFE grafts. Hence, only 3 cm of the ePTFE graft was paclitaxel-coated and drying occurred immediately after the graft was removed from the solution. The opposite end of the ePTFE graft was coated with paclitaxel in the same way. The paclitaxel-coated graft was dried under vacuum overnight to completely remove the coating solution.

The concentration of paclitaxel at both 3 cm ends of an ePTFE graft was 0.58 $\mu g/mm^2$ and the total loading amount of drug in a graft was 0.66 mg. All grafts were sterilized in ethylene oxide before implantation.

Surface morphology

The surface morphologies on the inside and outside of the ePTFE graft were analyzed by a scanning electron microscope, JEOL (Tokyo, Japan). We compared the surfaces of each ePTFE graft before and after paclitaxel coating.

in vitro release test

For the *in vitro* release test, we used release medium composed of phosphate-buffered saline (PBS, pH 7.4) and 0.05 % (w/v) Tween 20. Paclitaxel-coated ePTFE grafts of 3 cm length were soaked in conical tubes with 10 mL release medium and incubated in a 37 °C/20 rpm hybridization incubator, FINEPCR (Seoul, South Korea). At each designated time over 28 days, grafts were moved into new conical tubes containing fresh release medium and the existing solution was analyzed by high-performance liquid chromatography (HPLC), Agilent (California, USA) using a 4.6 × 150-mm C18 reverse phase column. The mobile phase used was acetonitrile/water (50/50, v/v) under isocratic conditions at a flow rate of 0.8 mL/min. The UV detector was set at 227 nm and the retention time of paclitaxel was 9.5 min.

Experimental animals and surgical procedure

This procedure which shows below was performed basically via the procedure of my previous study in the same way [13].

Eight female Landrace pigs weighing 50 kg ± 7 received paclitaxel-coated grafts. Hemodialysis ePTFE grafts were placed between the common carotid artery and the external jugular vein in the lateral side of the neck along the sternocleidomastoid muscle. We performed the animal experiments according to the pig model proposed by Rotmans et al [14].

Animals were given ketamine HCl (20 mg/kg) and xylazine HCl (2 mg/kg) for genenal anesthesia. The endotracheal anesthesia was maintained with isoflurane (2 %), and vecuronium bromide (0.1 mg/kg) was injected into an ear vein. Heparin (100 IU/kg) was injected before vessel manipulation. The common carotid artery was clamped using vessel loops and an end-to-side anastomosis was made at ~45° using 6-0 polypropylene sutures. Venous anastomosis was created in a similar manner. Clopidogrel (75 mg/day) and aspirin (100 mg/day) were given to animals from day 0 until the day of euthanasia.

Animals were euthanized 6 weeks after surgery. Until then, the animals were maintained in standard animal care facilities at Samsung Biomedical Research Institute (SBRI) and all procedures regarding the

surgery were performed according to the ‘Guidelines of the Care and Use of Laboratory Animals (National Institutes of Health Publication. No 85-23, revised 2001).

At 6 weeks after surgery, the implanted grafts and adjacent vessels were excised and were immediately placed in heparin-containing PBS (10,000 IU/L) to prevent blood clots in the vessels. Subsequently, grafts were immersed and fixed in 10 % neutral-buffered formalin (NBF) for at least 24 hours.

Tissue preparation and histomorphometric analysis

This analysis methods are same with my previous study [13].

Paraffin-embedded tissue specimens were prepared and sections were cut perpendicular to the direction of blood flow and obtained serially into 5-micron thick slices at the 3 parts of the anastomosis (Figure 1). Masson’s trichrome stain was used for histomorphometric analysis. The neointima stained as pale blue inside of the vascular media, which was visualized as a layer of thick red fibers.

We analyzed the neointimal areas and the percentage of luminal stenosis on each slide to compare the progress of stenosis between the coated group and control group which comes from the reference 13. The neointimal and the entire luminal areas were measured at 3 cross-

sections around the center of the venous anastomosis using captured images obtained with an Aperio ImageScope, Aperio (California, USA). The percentage of luminal stenosis was calculated using the following formula (1.1). The mean values of the neointimal areas and the percentages of luminal stenosis were obtained from 3 cross-sections of each graft.

$$\%\ of\ luminal\ stenosis = \frac{\text{the neointimal area}}{\text{the neointimal area} + \text{the entire luminal area}} \times 100 \quad (1.1)$$

Statistical analysis

The neointimal areas and the percentage of luminal stenosis are expressed as means ± standard errors. Continuous data of the *in vitro* release test are presented as means ± standard deviations. We used repeated measures analysis of variance (ANOVA) to compare the *in vitro* release of paclitaxel from the 2 kinds of paclitaxel-coated grafts. The patency rates of the paclitaxel coated group and the control group were compared using Fisher's exact test. Unpaired Student t-tests were used to compare the percentages of luminal stenosis and neointimal

areas between the 2 groups. P-values < 0.05 were considered statically significant. We used SPSS 18.0 for Windows (SPSS Inc., USA) for all statistical analysis.

3. Results

Characterization of paclitaxel-coated ePTFE grafts

We developed the drug coating method in order to coat both ends of the ePTFE graft selectively. Acetone, in which the paclitaxel easily dissolves, permeates and diffuses quickly to the ePTFE graft. Thus, it is difficult to control the selective coating of the drug on the terminal part of the ePTFE graft using acetone. Although dimethyl sulfoxide (DMSO) is also a good solvent for paclitaxel, it cannot penetrate the wall of the ePTFE graft. In contrast, paclitaxel is well dissolved in *tert*-butanol, which is rapidly absorbed in the ePTFE graft and slowly diffuses to the other part of the ePTFE graft. Therefore, *tert*-butanol was chosen to coat paclitaxel selectively on the terminal parts of the ePTFE grafts.

The surface morphology of the ePTFE grafts was compared to verify whether graft degenerated from the solvent. We confirmed that the surface of the ePTFE graft was not affected by contact with *tert*-butanol (Figure 2).

in vitro release profiles of paclitaxel

Figure 3 shows the *in vitro* release profiles of paclitaxel-coated grafts.

To confirm the differences in the *in vitro* drug release patterns according to the coating method, 2 types of paclitaxel-coated grafts with similar drug loading properties were prepared. The first type of graft was made by the gradual dipping method using *tert*-butanol as described above, and the other type of graft was made by the dipping method in acetone used in previous experiments [11]. For selective paclitaxel coating on the terminal region of the graft, 3 cm of the ePTFE graft was gradually immersed in the paclitaxel-dissolved *tert*-butanol for 1 min. On the other hand, the total ePTFE graft was dipped and incubated in the paclitaxel-dissolved acetone for 30 min.

When gradual dipping method with *tert*-butanol was used, the initial burst of paclitaxel was greater than 50 % of the loading amount. The released amount gradually increased afterward and the cumulative drug release for 28 days was close to 70 %. On the other hand, the cumulative drug release amount from the paclitaxel-coated grafts made by acetone dipping was less than 25 % of the initial loading.

Animal experiments and histomorphometric analysis

All animals survived until they were sacrificed without any evidence of necrosis, edema, or infection around the implanted grafts. Furthermore, all grafts incorporated into the surrounding tissue. Cross-

sections of the venous anastomosis 6 weeks after surgery from the 8 paclitaxel-coated grafts and the 6 uncoated grafts were stained with Masson's Trichrome for identifying neointimal hyperplasia.

Seven of the 8 paclitaxel-coated grafts were patent, even though some degree of neointimal hyperplasia was observed on the luminal surface of the graft wall (Figure 5). In contrast, according to the control results [13], only 1 of the 6 control grafts was patent and the lumen of the 5 grafts was nearly occluded by neointimal growth (Figure 4). Therefore, the patency of the paclitaxel-coated grafts was higher than that of the uncoated grafts ($P = 0.026$, Fisher's exact test).

Of the 8 grafts in the coated group, 4 showed several neointima on the graft wall and 3 exhibited some degree of neointima on the graft wall. Only 1 graft was entirely occluded by thrombosis; those blood clots were probably due to excessive bleeding just after surgery (Figure 5G).

For quantitative analysis of neointimal hyperplasia, the percentages of luminal stenosis and neointimal areas at the cross-section of the graft-venous anastomosis site were measured in both groups (Figure 6). The mean ± standard error values for the percentages of luminal stenosis were 75.7 ± 12.7 % in the control group and 26.9 ± 5.1 % in the paclitaxel-coated group. The percentages of luminal stenosis were

significantly lower in the paclitaxel-coated group than in the control group ($P = 0.004$, unpaired Student t-test). Similarly, the mean ± standard error values of neointimal areas were 8.77 ± 1.66 mm^2 in the control group and 3.99 ± 1.01 mm^2 in the coated group. Despite the variation in vessel thickness between the experimental animals, the neointimal areas of the coated group were significantly decreased compared to the control group ($P = 0.027$, unpaired Student t-test).

4. Discussion

Paclitaxel coating of ePTFE grafts is reportedly effective in suppressing neointimal hyperplasia and stenosis, as shown in our previous studies [11, 12]. However, the appropriate coating amount of the drug and the suitable coating area for effective prevention of vessel narrowing has not been studied. If possible, decreasing the loading amount of the drug is desirable to avoid overdose. We achieved local delivery of paclitaxel on both ends of the ePTFE grafts using the gradual dipping method in the present study, proving that the paclitaxel coating on the terminal region of vascular grafts effectively suppresses neointimal hyperplasia in the venous anastomosis site in an animal model.

The variables that affect the loading amount of drug include the coating length and the coating dose per unit area of the ePTFE graft. In this study, the dose of paclitaxel in the unit area was 0.58 $\mu g/mm^2$ and the total amount of coated paclitaxel in an ePTFE graft was 0.66 mg, which is similar or lower than the doses used in other perivascular studies [10, 15-16]. Because this amount is less than 1 % of the amount used for chemotherapy, local side effects or systemic toxicity from paclitaxel is not expected to occur.

Given that the high blood flow and manipulation during surgery can cause thickening of the venous wall at the graft-venous anastomosis site, some neointima may appear at the venous region of the cross-section (Figure 5 A, E). In contrast, the paclitaxel coating on the graft suppressed the neointimal growth on the graft wall. As a results, a few neointima were found on the graft wall in 4 of 8 samples (Figure 5 A, B, C, E) and 3 of these had neointimal growth on the graft wall (Figure 5 D, F, H), even though these grafts were patent. Therefore, the loading amount of paclitaxel on the ePTFE graft was presumably lower than the sufficient dose for suppression of neointimal hyperplasia on the graft wall.

Among the 8 paclitaxel-coated grafts, only 1 graft was occluded by thrombosis (Figure 5G). More than 90 % of thrombosed arteriovenous grafts were caused by stenosis due to neointimal hyperplasia either at the venous anastomosis site or in the proximal vein. However, if the region of the anastomosis site was occluded by thrombosis, stenosis also occurred in another part of the implanted graft. Therefore, the patency rate was calculated by including the thrombosed graft, whereas the percentages of luminal stenosis and neointimal areas were analyzed by excluding the thrombosed graft.

We compared the *in vitro* release profiles of 2 types of paclitaxel-

coated ePTFE grafts (Figure 3). Because paclitaxel-dissolved acetone permeated into the ePTFE graft wall easily and evaporated very fast and the coating process lasted for 30 min, paclitaxel was thought to be coated in the graft wall homogeneously. However, gradually dipping a 3-cm length of vascular graft into the paclitaxel-dissolved *tert*-butanol resulted in adequate permeation into ePTFE graft wall but evaporation was slower than acetone because the boiling point of *tert*-butanol is 82~83 °C. In addition, the coating process was terminated at 1 min and the graft was immediately dried; thus the coating solution may had not enough time to seep inside the graft wall and the drug may not have coated the outer surface of the graft wall uniformly. As a result, a greater initial burst release of paclitaxel was observed in the grafts made by the gradual dipping method compared to the grafts coated by acetone dipping. In the case of the arteriovenous graft, whether the initially released paclitaxel is more efficient for suppression of neointimal hyperplasia at the early tissue response or whether the long-term release of the drug provides better results for stenosis has not been validated clinically. The results of long-term animal experiments are required to clarify this. However, the weight of pigs, which is proportional to the thickness of their vein, can change greatly over a period of several weeks. This may distort the experimental results for

paclitaxel coating and is a limitation of this animal model.

The results of these animal experiments are comparable to other studies regarding the local delivery of paclitaxel or sirolimus. Unlike other perivascular experiments [10, 15-16], paclitaxel coating on the terminal part of the ePTFE graft does not require additional materials or care during surgery. Therefore, paclitaxel-coated vascular grafts on the terminal part of the ePTFE might reduce the risk of infection and unwanted tissue responses compared with other perivascular methods.

The determination of the coating dose and the release rate of the drug are very important for suppression of neointimal hyperplasia in the venous anastomosis site. Therefore, further experiments that involve increasing the loading amount of paclitaxel on the ePTFE graft by extending the coating length of the terminal region or by increasing the coating dose per unit area of the vascular graft are necessary. In addition, extending the drug release period using polymer coating is worth considering.

5. Conclusions

Paclitaxel coating on the terminal part of ePTFE vascular grafts significantly suppressed stenosis caused by neointimal hyperplasia, suggesting that drug delivery onto the terminal part of grafts is an ideal approach. This concept can easily be applied to clinical trial because reducing the coating amount of the drug is associated with improved safety and it is not require additional care during surgery.

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7. Figures

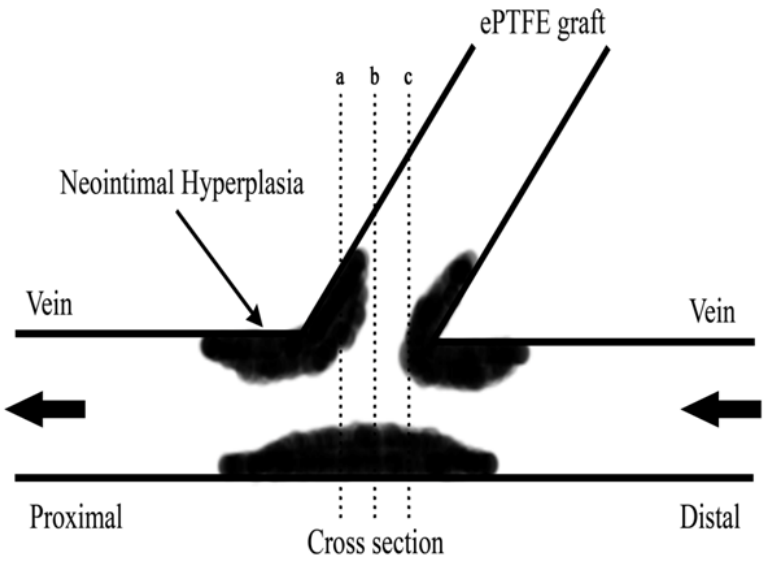

Figure 1. Diagram of a graft-venous anastomosis. The 3 cross-sections were obtained to measure the progress of neointimal hyperplasia. One section was obtained at the center of the anastomosis (b); the others were obtained 2 mm to the proximal side (a) and 2 mm to the distal side (c) of the center of the anastomosis. The mean values of 3 cross-sections were calculated and used to compare the progress of neointimal hyperplasia between the paclitaxel-coated group and the control group.

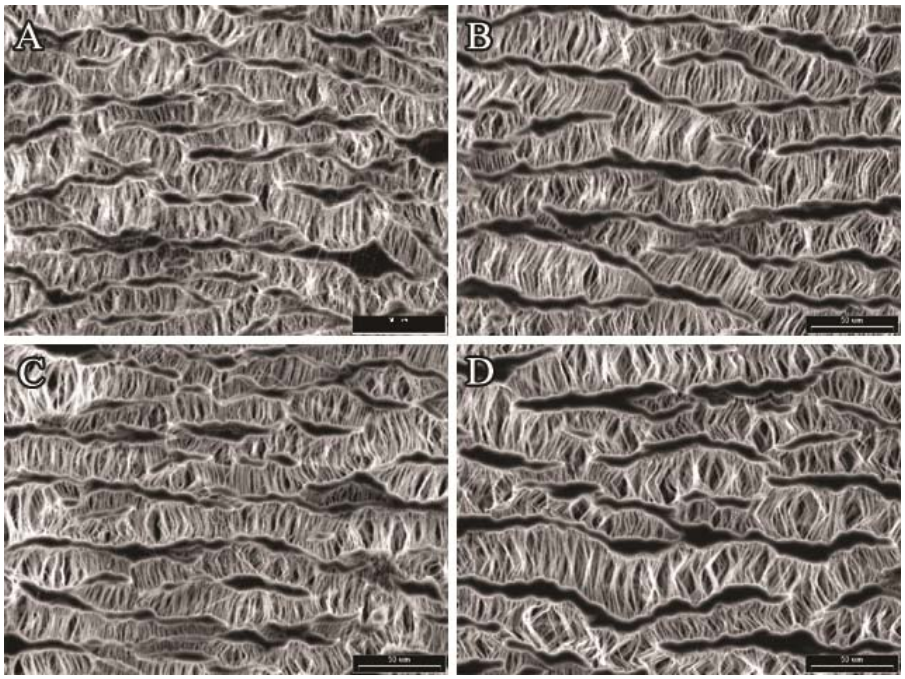

Figure2. Scanning electron microscope images of the uncoated ePTFE graft (A- inside, B- outside) and the paclitaxel-coated ePTFE graft (C- inside, D- outside) (×500). (The scale bar on all images is 50μm).

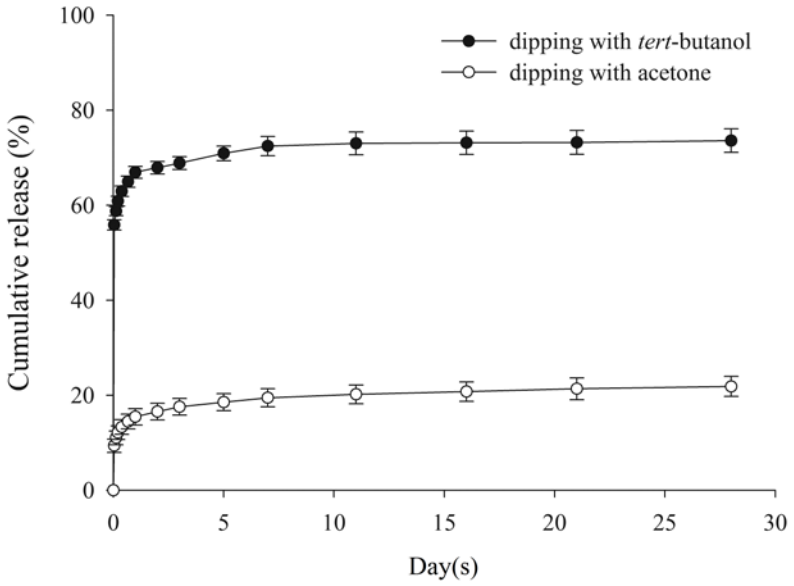

Figure 3. Cumulative in vitro release profiles from 2 kinds of paclitaxel-coated grafts made by the dipping method using acetone and by the terminal coating method using *tert*-butanol ($P < 0.001$ by repeated measures analysis of variance). Data represent the means of 5 experiments, and the bars represent standard deviations.

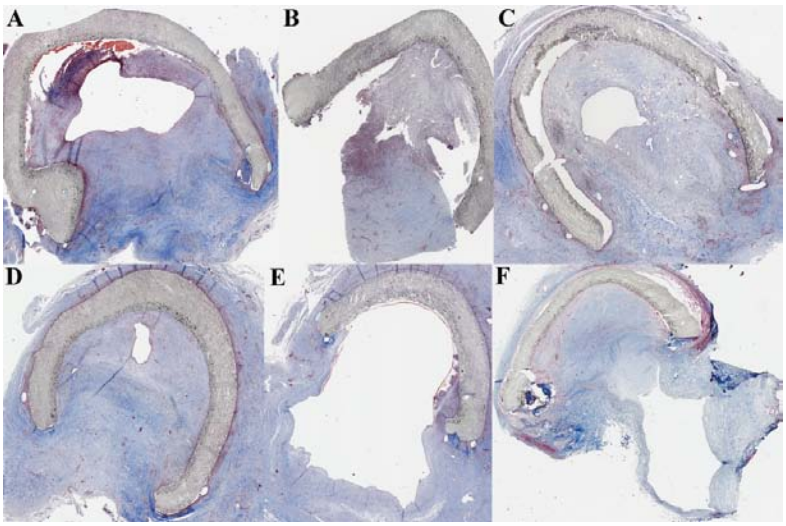

Figure 4. Cross-sections of a venous anastomosis 6 weeks after placing grafts in the control group (Masson trichrome stain) from my previous study in 2012 [13]. The intima was detected as a pale blue area by staining.

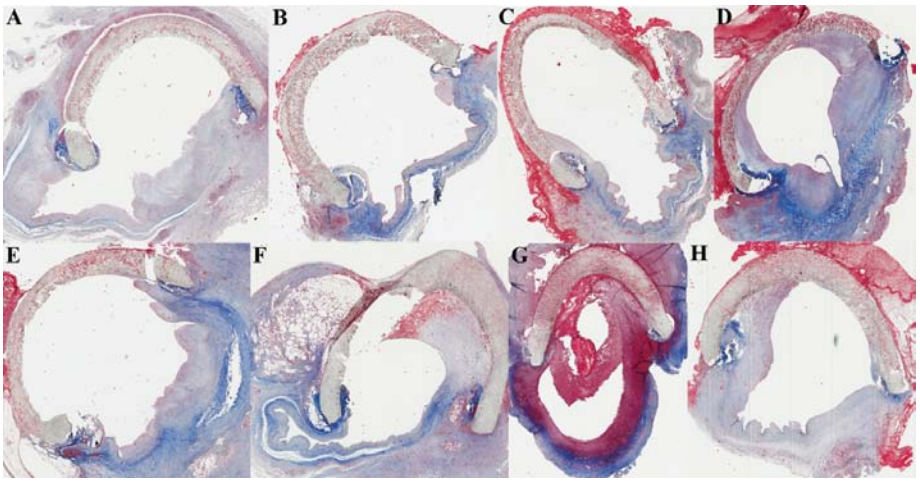

Figure 5. Cross-sections of a venous anastomosis 6 weeks after placing grafts in the coated group (Masson trichrome stain). The development of neointimal hyperplasia in the coated grafts was significantly lower than in the uncoated grafts (Figure 4).

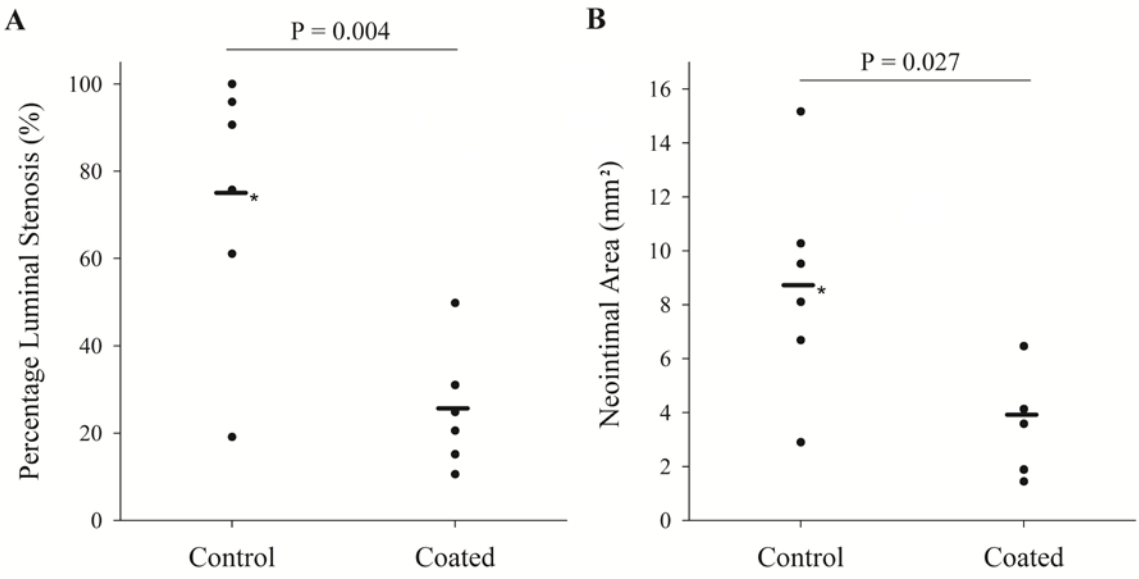

Figure 6. Comparisons of the percentages of luminal stenosis (A) and the neointimal areas (B) in the coated group of this study and the control from the reference 13. Two parameters between the coated and uncoated groups were significantly different ($P < 0.05$, unpaired Student t-test).

8. Abstract in Korean (국문초록)

신장말기 환자들이 혈액투석을 하기 위해서는 안정적인 혈관 접근로가 필요하다. 자가 혈관을 이용한 접근 방법이 가장 선호되는 방법이나, 고령의 환자들이나 당뇨병 환자들처럼 혈관이 좁은 환자들에게는 주로 인공혈관을 이용한 접근법이 시행된다.

그러나, 주로 expanded polytetrafluoroethylene (ePTFE)재질로 만들어지는 인공혈관은 1년에 50 %, 2년에 25 %의 낮은 개존률을 나타낸다. 인공혈관을 이용한 접근로는 주로 정맥 문합 부위의 협착으로 인하여 사용이 중단된다. 협착은 주로 평활근 세포와 근섬유아세포로 이루어진 신내막 과증식에 의하여 발생하며, 후에 혈전이 생성되는 단계로 이어져 혈액의 흐름을 차단한다.

이번 연구에서, 인공혈관의 문합부위에서 발생하는 협착 및 신내막 과증식을 막기 위한 약물 전달 시스템을 개발하였다. 세포 증식을 억제하는 약물인 파클리탁셀을 인공혈관의 말단 부위에 국소적으로 코팅하였다.

파클리탁셀이 코팅된 인공혈관의 신내막 증식의 억제 효과를 확인하기 위하여, 돼지 모델을 이용한 동물실험을 진행하였다. 6 주간의 실험에서, 약물이 코팅된 인공혈관의 개존률은 대조군에 비해 증가하였다. 문합 부분의 신내막 면적과 협착률 역시 대조군(75.0 ±

10.5 %, 7.5 ± 1.7 mm^2) 에 비해 약물이 코팅된 인공혈관(26.8 ± 6.6 %, 3.4 ± 1.0 mm^2)에서 현저하게 줄어들었다.

이번 실험에서, 적은 양의 약물을 사용하였음에도 불구하고, 인공혈관 말단 3 cm의 약물 코팅은 신내막 과증식을 억제하는데 효과가 있음을 확인하였다.

표제어: 혈액투석, 인공혈관, 협착, 신내막 과증식, 파클리탁셀

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