Association of single nucleotide polymorphism in the drug tranporter gene with in-stent restenosis after paclitaxel-eluting stent implantation

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The Master's thesis submitted to the

Department of Medicine,

the Graduate School of Yonsei University in partial

fulfillment of the requirements for the degree of

Master of Medical Science

Ahn, Chul Min

June 2006

This certifies that the Master's Thesis

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June 2006

Acknowledgements

I would like to thank professor Yangsoo Jang who gave me the opportunity to participate in such a great project and always provided me with good and thorough ments with deep sincerity. I am in debt to professor Min Goo Lee and Young-Guk Ko who gave me many great advices during this study. In addition, I am especially thanks to Sungha Park who was one of the most important mentors from beginning to end and Ji Hyun Lee who was an excellent helper about the pharmacogenetics. I express my greatest love to my wise and beautiful wife who always prays for me, parents and parents-in-law who supported me with deep love and faith. Finally I dedicate this master's thesis to my shepherd, the LORD almighty.

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ABSTRACT

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Although recent development of drug eluting stents, such as the paclitaxel-eluting stent, has dramatically reduced restenosis, angiographic restenosis still occurs around 10% of the time. Because paclitaxel can be transported by the product of the multidrug resistance 1 gene (MDR1, ABCB1), neointimal hyperplasia after paclitaxel-eluting stent insertion may be affected by polymorphisms in the MDR1 gene. Quantitative coronary angiographic analysis was performed in 96 patients with symptomatic coronary artery diseases who underwent paclitaxel-eluting stent insertion. Genotyping of

MDR1 polymorphisms at 9 loci was performed by a conventional PCR-based assay. A total of 102 stents were implanted in 96 patients with 6 patients undergoing multiple stenting. Among the MDR1 polymorphisms analyzed, G2677T and C3435T were significantly associated with in-stent restenosis of paclitaxel-eluting stents. Interestingly, the CC homozygous allele in C3435T showed a protective effect against in-stent restenosis. Further angiographic analyses revealed that the presence of T alleles at the G2677T and C3435T loci was associated with higher rate of restenosis. Lastly, multivariate logistic regression analysis identified the presence of T alleles as strong risk factors for restenosis consistent with the well known risk factor of diabetes mellitus. MDR1 polymorphisms are significantly associated with in-stent restenosis of paclitaxel-eluting stents. Accordingly, MDR1 gene polymorphisms may be a useful marker for predicting response to paclitaxel-eluting stents.

Key words : In-stent restenosis, Paclitaxel-eluting stent, Drug transporter gene polymorphism

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I. INTRODUCTION

The multiple drug resistance gene-1 (MDR1, also known as P-glycoprotein) is an ATP-binding cassette membrane transporter (designated ABCB1), and is involved in the acquisition of resistance to multiple drugs in both cancer cells and normal tissues.[1,2] The substrate specificity of MDR1 is broad, allowing the MDR1 protein to be a major determinant of drug disposition.[3] The MDR1 gene is a 100 Kb gene on chromosome 7 that consists of 28 exons spliced into a 4.5-Kb mRNA.[3] Recent studies have shown that genetic polymorphisms of MDR1 are associated with functional P-glycoprotein changes, mainly for their

effect on protein expression levels. This mechanism of action may be important in determining different drug responses according to MDR1 genotypes.[3-8]

Recent development of drug-eluting stents, such as the paclitaxel-eluting stent, has dramatically reduced the rate of in-stent restenosis.[9] However, paclitaxel-eluting stents are still associated with an angiographic restenosis rate of 11.7-13.1%.[9-11] Previous studies have shown that the presence of diabetes, ostial lesions, lesion length, and vessel diameter are significant predictors of in-segment restenosis in patients undergoing drug-eluting stent implantation.[12,13] However, genetic factors that may modulate the response to drug-eluting stents are not known. Theoretically, certain genetic factors that affect the pharmacodynamic and pharmacokinetic properties of antiproliferative drugs may have a significant influence on the development of in-stent restenosis. Since paclitaxel is a drug known to be transported by MDR1, neointimal hyperplasia after paclitaxel-eluting stent insertion may be affected by MDR1 genotypes. Therefore, in this study, we investigated the possibility of an association of ABCB1 gene polymorphisms with in-stent restenosis in Korean subjects undergoing paclitaxel-eluting stent insertion.

II. MATERIALS AND METHODS

1. Patient population

The study was approved in advance by the Institutional Review Board of Yonsei University Severance Hospital and procedures were in accordance with institutional guidelines. Patients were enrolled after giving informed consent. The present study included 96 patients with symptomatic coronary artery disease (CAD) who underwent paclitaxel-eluting stent (Taxus; Boston Scientific co; Natick, MA, USA) insertion and 9 month follow-up coronary angiography at Yonsei Cardiovascular Hospital between August 2003 and June 2005. Patients with stable angina or acute coronary syndrome were enrolled in this study if there was at least one lesion of more than 50% diameter stenosis with reference diameters between 2.5 mm to 4.0 mm. There were 30mm limits to the lesion length. Chronic total occlusions, in-stent restenosis, branch vessels of bifurcation lesions and os lesions were excluded from analysis. At the time of initial enrollment, patients underwent a complete physical examination, a baseline electrocardiogram, and laboratory assessment. Ninety-six healthy control subjects were randomly selected, and their health was evaluated by routine physical examinations, laboratory tests, and radiologic examinations.

2. Coronary angiography

Coronary angiographies were performed via the femoral artery. All angiographies were interpreted by the consensus of two independent observers. Significant coronary artery disease was defined as ≥ 50% luminal stenosis of vessels more than 1.5 mm in diameter. CAD patients were classified as one vessel, two vessels, and three vessels disease according to the number of epicardial coronary arteries involved. All patients had undergone successful coronary angioplasty with paclitaxel-eluting stents. Follow-up angiography was performed in all the patients for 9 months after the intervention.

3. Quantitative angiographic analysis

Data were analyzed with the quantitative coronary angiography system (Inturis DICOM Recorder, ModuleInfo; Philips Co., Amsterdam, Netherlands). Matched views were selected for angiograms recorded before and immediately after the intervention and at follow-up. The parameters measured were lesion length, reference diameter, minimal lumen diameter and percent diameter stenosis. Acute luminal gain was calculated as the difference between the final post-stenting minimal lumen diameter and the minimal lumen diameter present before stenting. Late lumen loss was calculated as the

difference between final post-stenting minimal lumen diameter and minimal lumen diameter measured at follow-up angiography. Loss index was calculated as the ratio of late lumen loss and acute lumen gain. Operators who performed the quantitative assessment were unaware of the genotyping data.

4. Genotyping

Whole blood was obtained from each subject and genomic DNA extracted by the use of the QIAmp DNA blood Mini kit (QIAGEN, Hilden, Germany) as described previously.[14] Genotyping was done by single base primer extension assay using the SNaPShot assay kit, according to manufacturer's protocols (ABI, Foster City, CA). Briefly, the genomic DNA region containing both of the single nucleotide polymorphisms (SNPs) was amplified by PCR. Each PCR reaction contained 10.0 ng of DNA, 1X PCR Buffer, 0.125 units of *AmpliTaq Gold* DNA polymerase (ABI), 3.0 mM $MgCl_2$, 0.25 mM of each dNTP, and 0.5 pmole of each primer in a 10 μL reaction volume. Reaction conditions were 95℃ for 10 min, followed by 30 cycles of 95℃ for 30 s, 60℃ for 1 min, and 72℃ for 1 min, followed by a final extension at 72℃ for 5 min. Primer sequences used in this study are shown in Table 1.

Table 1. Oligonucleotide primers for the genotyping of MDR1 polymorphisms

Variant	Primer
G-1459A	Forward: 5’-GGAGCAAAGAAATGGAATACAATA-3’
	Reverse: 5’-TTCTCCCGTGAAGACCAAGTTC-3’
	Genotyping: 5’-GTTTTGCTTTGTTGCTTTAT-3’
A-935G	Forward: 5’-CAGGAAACAGCTATGACCGCATGCTGAAGAAAGACCA-3’
	Reverse: 5’-TGTAAAACGACGGCCAGTCCTTCTCCCGTGAAGACC-3’
	Genotyping: 5’-CGCGCATCAGCTGAATCA-3’
C-709G	Forward: 5’-CAGGAAACAGCTATGACCGCATGCTGAAGAAAGACCA-3’
	Reverse: 5’-TGTAAAACGACGGCCAGTCCTTCTCCCGTGAAGACC-3’
	Genotyping: 5’-CGCTCTCTTTGCCACAGGAAG-3’
T-693C	Forward: 5’-GGAGCAAAGAAATGGAATACAATA-3’
	Reverse: 5’-TTCTCCCGTGAAGACCAAGTTC-3’
	Genotyping: 5’-GAGCTTGGAAGAGCCGCT-3’
A61G	Forward: 5’-GACCGCAATGGAGGAGCA-3’
(exon2)	Reverse: 5’-ACTATGTAAACTATGAAAATGAAACAAGC-3’
	Genotyping: 5’-ATGAAACAAGCTAGTTACCTTTTAT-3’
C1236T	Forward: 5’-CAGGGAAACAGCTATGACCTATTCGAAGAGTGGGCACAA-3’
(exon12,	Reverse: 5’-TGTAAAACGACGGCCAGTTCCATCAACACTGACCTGGA-3’
G412)	Genotyping: 5’-GCCCACTCTGCACCTTCAGGTTCAG-3’
G2677T/A	Forward: 5’-CAGGAAACAGCTATGACCTATTCGAAGAGTGGGCACAA-3’
(exon21,	Reverse: 5’-TGTAAAACGACGGCCAGTTCCAAGAACTGGCTTTGCT-3’
A893S/T)	Genotyping: 5’-TATTTAGTTTGACTCACCTTCCCAG-3’
C3435T	Forward: 5’-TGTTTGACTGCAGCATTGC-3’
(exon26,	Reverse: 5’-TTTATTTGAAGAGAGACTTACATTAGGC-3’
I1145)	Genotyping: 5’-TGTTGGCCTCCTTTGCTGCCCTCAC-3’
G3751A	Forward: 5’-ACCTGCATTGTGATTGCTC-3’
(exon28)	Reverse: 5’-ACTGACCATTGAAAAATAGATGC-3’
	Genotyping: 5’-AGTGGTGTTTCAGAATGGCAGA-3’

After amplification, the PCR products were treated with 1 unit each of shrimp alkaline phosphatase (SAP) (Roche) and exonuclease I (USB Corporation) at 37℃ for 60 min and 72℃ for 15 min to purify the amplified products. One microliter of the purified amplification product was added to a SNaPshot Multiplex Ready reaction mixture containing 0.15 pmoles of genotyping primer. The primer extension reaction was carried out for 25 cycles of 96℃ for 10 s, 50℃ for 5 s, and 60℃ for 30 s. The reaction products were treated with 1 unit of SAP at 37℃ for 1 h and 72℃ for 15 min to remove excess fluorescent dye terminators. One microliter of the final reaction samples containing the extension products was added to 9 μL of Hi-Di formamide (ABI). The mixture was incubated at 95 ℃ for 5 min, followed by 5 min on ice and then analyzed by electrophoresis in an ABI Prism 3730 DNA analyzer. Results were analyzed using Gene Mapper software (ABI).

5. Statistical Analysis

Values were expressed as mean ± SD. χ^2 test for goodness of fit was used to verify agreement with Hardy-Weinberg equilibrium using Fisher's exact test.[14] Comparison of discrete variables was performed using the Chi-square analysis. The haplotype frequency was determined using the Expectation-Maximization algorithm as described previously.[15] Comparison of continuous variables

between the two study groups was performed using the Student's t-test. Multivariate logistic regression analysis was performed to determine the independent association of MDR gene polymorphism with the development of in-segment restenosis. Statistical analysis was performed with SPSS 13.0 (SPSS Inc, Chicago, Il., USA).

III. RESULTS

1. Baseline characteristics

MDR1 genotypes and angiographic findings of 96 CAD patients with paclitaxel-eluting stent insertion (male: female = 73:23) were analyzed in this study. A total of 102 stents were implanted in 96 patients with 6 patients undergoing multiple stenting. The average age of enrolled patients was 58.8±9.0 years.

2. Genotyping

MDR1 polymorphisms at 9 sites (G-1459A, A-935G, C-709G, T-693C, A61G, C1236T, G2677T/A, C3435T and G3751A) with over 1% allele frequency in the database of the Korea Pharmacogenomics Research Network (http://www.pharmacogenomics.or.kr/), were chosen and genotyped in this study (Table 2).

Table 2. Genotype distribution of MDR1 variants in control and coronary artery disease (CAD) patients

Variant		Control	CAD patients		*P*-value
			ISR[b] (no)	ISR (yes)	
G-1459A	+/+[a]	61	42	6	0.709
	+/-	41	34	4	
	-/-	8	10	0	
A-935G	+/+	91	70	7	0.650
	+/-	17	16	3	
	-/-	2	0	0	
C-709G	+/+	107	84	10	0.626
	+/-	3	2	0	
	-/-	0	0	0	
T-693C	+/+	99	74	8	0.779
	+/-	11	12	2	
	-/-	0	0	0	
A61G (exon2)	+/+	109	86	10	-
	+/-	1	0	0	
	-/-	0	0	0	
C1236T	+/+	13	12	1	0.942
(exon12, G412)	+/-	55	41	5	
	-/-	42	33	4	
G2677T/A[c]	+/+	42	39	1	0.032*
(exon21,	+/-	49	36	8	
A893S/T)	-/-	19	11	1	
C3435T	+/+	44	33	1	0.045*
(exon26, I1145)	+/-	47	43	8	
	-/-	19	10	1	

G3751A	+/+	107	84	10	0.626
(exon28)	+/-	3	2	0	
	-/-	0	0	0	

[a] +: major allele, -: minor allele, [b] ISR: in-stent restenosis, [c] G and A alleles are presumed to have an equal functional significance (16). *P* values were obtained by comparisons between ISR positive and negative groups using the chi-square or Fisher's exact test (expected cell value <5). *$P<0.05$.

3. Association of in-stent restenosis and MDR polymorphism

Initially, we undertook to examine associations between MDR1 polymorphisms and in-stent restenosis of paclitaxel-eluting stents, defined as a greater than 50% diameter decrease from the reference diameter in at least in one lesion. Genotype distribution and restenosis rates are shown in Table 2. G and A alleles at the triallelic 2677 locus are presumed to have an equal functional significance according to the results of a recent in vivo human pharmacokinetic analysis performed in the Korean population.[16] Of note, one sites, namely G2677T/A and C3435T, showed a significant association with in-stent restenosis of paclitaxel-eluting stents. It has been demonstrated that G2677T/A and the C3435T loci are in linkage disequilibrium.[14] Therefore, a haplotype-based analysis was done for the G2677T/A and C3435T loci and restenosis rate but no significant association was observed among these haplotypes. (Table 3).

Further analysis was done regarding patient characteristics and the findings of specific angiographic data for these two polymorphisms. There were no significant differences in baseline patient characteristics based on G2677T/A and C3435T genotypes except frequency of hypertension (Table 4). Subsequently, lesion characteristics of pre- and post-procedural coronary angiographic data were compared according to the G2677T/A and C3435T

genotypes (Table 4). There were no significant differences in lesion location, pre-interventional reference diameter, or lesion length according to the genotypes. However, the presence of T alleles at C3435T loci was associated with a significantly higher rate of late lumen loss and loss index in addition to both in-stent and in-segment restenosis (Table 4). Lastly, multiple logistic regression analysis controlling for patient and lesion characteristics including diabetes mellitus, smoking, hypertension, lesion length, lesion complexity, and lesion reference diameter, was performed with the MDR1 haplotypes (Table 5). The odds ratio of the C3435T for in-stent restenosis of paclitaxel-eluting stents was 0.09 (P=0.043) which means significant protective effect of these allele discrimination regards to in-stenosis in contrast to diabetes mellitus, a well-known risk factor, which showed only a marginal significance in the present analysis (Odds ratio 2.82, P=0.164).

Table 3. Haplotype analysis of G2677T/A[a] and C3435T loci

Allele	Control	CAD patients		*P*-value
		ISR (no)	ISR (yes)	
GC	128 (58.1%)	107 (61.4%)	9 (49.9%)	0.343
TT	80 (36.3%)	57 (32.6%)	9 (49.9%)	0.142
TC	7 (3.3%)	3 (1.9%)	0 (0.1%)	0.585
GT	5 (2.3%)	7 (4.1%)	0 (0.1%)	0.393
Total	220	174	18	

[a] G and A alleles are presumed to have an equal functional significance (16).

ISR: in-stent restenosis, CAD: Coronary artery disease.

Table 4. Clinical and Lesion characteristics of pre- and post-procedural quantitative coronary angiographic data

	C3435T		*P*-value*
	CC (34)	CT/TT (62)	
Age	59.2 ±9.4	58.7±8.9	0.796
Sex (M:F)	29:8	47:15	0.942
Diabetes (%)	13(38.2%)	16(25.8%)	0.205
Hypertension (%)	21(61.7%)	29(46.8%)	0.160
Smoking (%)	10(29.4%)	21(33.9%)	0.655
MI (%)	9(26.4%)	9(14.5%)	0.151
Type C lesions (%)	22(64.7%)	44(70.9%)	0.345
Pre average RD (mm)	2.82±0.46	2.98±0.41	0.090
Pre average MLD (mm)	0.67±0.46	0.79±0.51	0.225
Pre lesion length (mm)	17.4±6.95	17.1±5.65	0.780
Acute gain (mm)	2.06±0.55	2.09±0.43	0.825
In-stent restenosis (%)	1 (2.9%)	9 (14.5%)	0.043*
Focal restenosis	1 (2.9%)	6 (9.7%)	
Diffuse restenosis	0 (0.0%)	3 (4.8%)	
FU average RD (mm)	2.89±0.48	2.96±0.43	0.544
FU average MLD (mm)	2.47±0.54	2.37±0.81	0.447
Late loss (mm)	0.25±0.9	0.51±0.77	0.050*
Loss index	0.11±0.23	0.24±0.39	0.038*

	G2677T/A[a]		*P*-value
	GG/AA/GA (40)	GT/TT(56)	
Age	59.4±9.3	58.6±8.9	0.653
Sex (M:F)	30:10	43:13	0.840
Diabetes (%)	14(35.0%)	15(26.8%)	0.388
Hypertension (%)	26(65.0%)	24(42.9%)	0.032*
Smoking (%)	14(35.0%)	17(30.3%)	0.631
MI (%)	11(27.5%)	7(12.5%)	0.063
Type C lesions (%)	26 (65.0%)	40 (71.4%)	0.473
Pre average RD (mm)	2.83±0.47	2.99±0.39	0.081
Pre average MLD (mm)	0.69±0.45	0.79±0.52	0.388
Pre lesion length (mm)	16.7±5.4	17.9±7.0	0.400
Acute gain (mm)	2.08±0.45	2.07±0.50	0.940
In-stent restenosis (%)	1 (2.5%)	9(16.1%)	0.032*
Focal restenosis	1 (2.5%)	6 (10.7%)	
Diffuse restenosis	0 (0%)	3 (5.4%)	
FU average RD (mm)	2.91±0.49	2.95±0.42	0.680
FU average MLD (mm)	2.48±0.58	2.35±0.81	0.402
Late loss (mm)	0.29±0.51	0.51±0.08	0.096
Loss index	0.13±0.25	0.25±0.40	0.079

[a] G and A alleles are presumed to have an equal functional significance (23).

RD: Reference diameter, MLD: Minimal lesion diameter

* P< 0.05

Table 5. Multiple logistic regression analysis for the determinants of in-stent restenosis

Variables	Odds ratio (95% CI)	*P*-value
C3435T(CC allele)	0.09 (0.008-0.91)	0.043*
G2677T(GG/AA/GA allele)	0.14 (0.015-1.19)	0.071
DM	2.82 (0.88-11.98)	0.164
Type C lesion	5.02 (0.74-33.25)	0.099
Smoking	2.07 (0.53-8.11)	0.298
Hypertension	0.81 (0.23-2.89)	0.742
Lesion Reference Diameter	0.43 (0.09-2.13)	0.426

* P< 0.05

IV. DISCUSSION

The antitumor activity of taxane depends upon drug binding to the beta subunits of tubulin, which causes stabilization of tubulin polymerization and subsequent cell cycle arrest at the G2/M phase.[17] The most important mechanism of drug resistance to taxane depends on the expression of P-glycoprotein 170, which is mediated by the expression of the MDR 1 gene.[18,19] It has been reported that MDR 1 gene polymorphisms affect the expression of membrane transporter proteins and the pharmacokinetics of various substrate drugs.[6,20,21] Therefore, it is anticipated that MDR1 polymorphisms may affect intracellular concentrations of paclitaxel in patients implanted with paclitaxel-eluting stents. We hypothesized that differing intracellular levels of paclitaxel in the coronary arteries of patients implanted with paclitaxel-eluting stents may influence the rate of in-stent restenosis. We found that the presence of the T allele at the G2677T/A and C3435T loci was significantly associated with a higher rate of in-stent restenosis and other adverse angiographic indices at follow-up (Table 5).

The underlying molecular mechanisms responsible for associations between MDR1 genotypes and clinical outcomes of paclitaxel-eluting stents are the subjects of future investigations. Although the C3435T polymorphism at exon 26 is a synonymous single nucleotide polymorphism (SNP) that does not

result in an amino acid change, several studies have demonstrated a significant association of the polymorphism with differing pharmacokinetics of various drugs such as digoxin, fexofenadine, nelfinavir and anti-epileptic drugs.[4,6,8,20] However, the differing expression of MDR1 protein and the different pharmacokinetics associated with the C3435T polymorphism have shown contradictory results, especially among different ethnicities. For example, Caucasians with the T allele have been reported to show decreased MDR 1 protein expression,[20] whereas Japanese subjects with the T allele are reportedly associated with increased MDR1 expression.[6,22] This may be due to the linkage disequilibrium of SNPs with unidentified functional polymorphisms in the MDR1 gene according to the different ethnicities (14).

Assuming that MDR1 expression in Koreans is similar to that in Japanese because of shared East Asian ethnicity, increased MDR1 expression in patients with the T allele could induce subsequent lower concentrations of intracellular paclitaxel and the proliferation of vascular smooth muscle cells, which might explain the higher rate of in-stent and in-segment restenosis. However, a pharmacokinetic study performed in Korean subjects has reported a higher plasma fexofenadine concentration for individuals with the homozygote 3435T than with 3435C, suggesting a decreased MDR1 expression in individuals with the T allele.[16] In this case, the more plausible

explanation for the higher restenosis rate in the T allele would be a mechanism of increased cytotoxicity and vascular inflammation resulting from excessive intracellular accumulation of paclitaxel in the vascular smooth muscle cells of patients expressing the T alleles.

It has been suggested that the functionality of the non-synonymous C3435T variation is due to an association with the triallelic G2677T/A (Ala893Ser/Thr) locus.[16,23] As observed in the present study, more than 95% alleles in these loci are either in GC or TT linkage disequilibrium (Table 3). An *in vivo* pharmacokinetic study of humans revealed that MDR1 proteins with 2677G or A have a higher drug disposition ability that those with the T allele in Korean subjects.[16] In addition, a previous study demonstrated a trend of higher duodenal MDR1 content and a lower talinolol bioavailability in Caucasian subjects with the 2677GG or GA genotype versus those with the 2677GT or 2677TT genotype.[23]

Previous studies have found diabetes mellitus, lesion length and lesion diameter to be important determinants of restenosis after drug-eluting stent implantation.[12,13] The regression analysis in this study demonstrated that the presence of T alleles at G2677T and C3435T was associated with a stronger risk of in-stent restenosis when compared to diabetes, which showed only a marginal significance. These results indicate that genetic factors that modulate

the cellular transport of paclitaxel may be important in the development of in-stent restenosis independent of other known clinical variables.

In conclusion, large differences in the clinical outcomes of paclitaxel-eluting stents according to MDR1 genotypes were observed in the present study. These results suggest that MDR1 genotype assessment may help select patients who will benefit most from implantation of paclitaxel-eluting stents.

V. CONCLUSION

Significant differences in the clinical outcomes of paclitaxel-eluting stents according to MDR1 genotyping especially G2677T and C3435T loci were observed in the present study. These results suggest that MDR1 genotype assessment may help select patients who will benefit most from implantation of paclitaxel-eluting stents.

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ABSTRACT (IN KOREAN)

탁솔 방출 스텐트 삽입 후 스텐트내 재협착과 약물 운반 단백 유전자 단일 염기 다형성과의 연관성

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스텐트내 신생내막 조직의 축적은 약 6개월에 최고조에 달하여 이후 3년까지 신생내막은 섬유성 성숙에 의해 얇아지고 최소내강지름(minimal lumen diameter)이 증가한다는 것이 추적검사를 통해 알려져 있다. 약물 방출 스텐트의 도입 이후에 현저한 신생내막증식의 감소를 보였고 특이 두개의 약물 방출 스텐트 즉 Sirolimus eluting stent와 paclitaxel eluting stent에 대한 비교 분석 자료는 최근까지 지속적으로 보고되고 있다. Sirolimus-Eluting stent와 Paclitaxel-Eluting stent 스텐트간 비교에서 스텐트 삽입 후 9개월 후 주요 심장 사건은 각각 6.2%와

10.8%, 목표병변 재개통률은 4.8%와 8.3%였고 혈관촬영으로 확인된 스텐트내 재협착은 6.6%와 11.7%로 통계적으로 유의한 차이를 보였으나 그 기전에 대한 추가적인 연구는 아직 보고되지 않고 있다. Paclitaxel 은 polymerased microtubules을 안정화하고 microtubular assembly을 증가시키면서 세포질에서 unorganized, desensitized microtubule 을 형성한다. 세포복제는 주로 세포주기의 G0/G1과 G2/M phase에서 억제된다. Paclitaxel은 지용성이고 비수용성 세포막을 통해 빨리 흡수되어 전신적인 소실을 최소화하므로 polymer-based delivery에 적합하며 한 번 도포로 오랜 항증식 효과를 가지고 durable simple coating으로 금속에 바로 적용될 수 있다. 세포내 약물은 drug transporter protein에 의해 그 농도의 변화를 가져오고 active transporter인 ABC(ATP binding cassette) protein은 매우 큰 gene family로서 광범위한 물질- 영양분, 아미노산, 당분, 각종 이온물 및 대사산물-의 결정적인 역할을 하는 것으로 알려져 있다. 현재 49개의 subfamily가 알려져 있으며 Multidrug resistance(MDR) gene protein인 p-glycoprotein과 multidrug resistance-associated protein(MRP)가 대표적으로 연구되고 있다. 본 연구에서는 탁솔 방출 스텐트 삽입한 환자에서 약물 운반 단백 유전자의 단일 염기다형성에 의한 세포내 농도의 차이로 인한

신생내막증식의 차이가 스텐트 내 재협착에 미치는 영향을 알아보고 그 스텐트내 재협착의 예측인자로서의 가능성을 알아보고 유전약물학적 임상적용을 목표로 하였고. 신촌 세브란스 병원에 협심증 및 심근경색증으로 입원 후 탁솔 방출 스텐트를 삽입하고 추적관찰 후 관상동맥 조영술을 시행한 환자 96명을 대상으로 MDR gene polymorphism과 스텐트내 재협착과의 관련성을 보았다. ABCB1 C3435T gene 의 Genotype의 분포는 CC:CT:TT이 34(35.4%):51(53.1%):11(11.5%) 이었으며 구간내 재협착 (in-segment restenosis) 및 스텐트내 재협착(in-stent restenosis)는 모두 CC:1/34(2.9%), CT 와 TT:9/62 (14.5%)(p-value =0.043)로 보였으며 homozygous C allele와 CT,TT allele의 유의한 차이를 보였다. 후기 손실(late loss) 역시 각각 0.25±0.9mm와 0.51±0.77mm (P-value: 0.05)로 군간 유의한 차이를 보여 MDR gene protein의 polymorphism에 따른 스텐트 삽입 후 결과예측에 대한 유전적 소인의 관련성을 보여주었고 맞춤형 스텐트 삽입술의 계기를 마련할 것으로 사료된다.

핵심 되는 말: 탁솔 방출 스텐트, 스텐트내 재협착, 약물 운반 단백 유전자 단일 염기 다형성