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Original Article

Effects of Liposomal Prostaglandin E1 on Coronary Stenosis and Restenosis after Percutaneous Coronary Intervention: A Prospective Clinical Trial

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Abstract

Background and objectives: Restenosis is a serious complication after percutaneous coronary intervention (PCI) for patients with coronary heart disease (CHD). This prospective clinical study was designed to investigate the effects of liposomal prostaglandin E1 (lipo-PGE1) on coronary stenosis and restenosis.

Methods: Sixty patients diagnosed with CHD and scheduled for PCI surgery in Guangdong Hospital of Traditional Chinese Medicine were enrolled in this study. The patients were divided into either the Control group (n = 30) or lipo-PGE1 treatment group (PGE group) (n = 30). Restenosis after PCI was the primary outcome, and newly increased stenosis was the secondary outcome.

Results: In total, 54 patients finished the follow-up and were included in the final analysis (n = 30 in the Control group and n = 24 in the PGE group). Baseline comparisons of stenosis location, stenosis degree, and the number of vessels in stenosis before PCI were comparable ($P > 0.05$). Comparisons of implanted stents showed similar features in stent diameter and stent length during PCI between the two groups ($P > 0.05$). For the primary outcome, there was no obvious difference in restenosis percentage ($\chi^2 = 1.520$, $P = 0.615$) nor number of vessels in restenosis ($\chi^2 = 0.070$, $P = 0.791$) in three arteries between groups. For the secondary outcome, although there was no significant difference in the number of non-culprit vessels in increased stenosis after PCI between groups ($\chi^2 = 3.902$, $P = 0.272$), the percentage of increased stenosis was much lower in the right coronary artery in the PGE group than the Control group ($U = 263.0$, $P = 0.048$).

Conclusions: This study demonstrated the lipo-PGE1 did not affect restenosis after PCI, but it may be effective in ameliorating newly increased stenosis in arteries.

Keywords: Coronary heart disease; Percutaneous coronary intervention; Nano liposomal prostaglandin E1; Restenosis; Newly increased stenosis.

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; CHD, coronary heart disease; DCB, drug-coated balloon; DES, drug-eluting stents; DM, diabetes mellitus; ISR, in-stent restenosis; lipo-PGE1, liposomal Prostaglandin E1; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

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Introduction

Patients with severe coronary heart disease (CHD) are commonly treated with percutaneous coronary intervention (PCI).[1] However, a loss in vessel lumen area of stented arteries is indicative of in-stent restenosis (ISR), which is a serious complication after PCI.[2] Although drug-eluting stents (DES) have dramatically decreased the incidence of ISR, the occurrence of ISR is still approximately 5–10% among CHD patients after PCI.[3,4] Therefore, there is a need to explore novel medications that can be administered in the peri-operative period of PCI to decrease the occurrence of restenosis or prevent ISR.

Liposomal prostaglandin E1 (lipo-PGE1) is a kind of nanolipid microsphere (liposome)-based PGE1. Previous studies showed

that lipo-PGE1 can decrease coronary restenosis in a canine thrombolysis model[5] and reduce the incidence of periprocedural myocardial injury both in patients[6] and porcrine.[7] Lipo-PGE1 was also found to be effective for improving microcirculation.[8] The nanoliposome delivery system is also a popular method for targeted drug delivery,[9] and reviews have indicated that targeted nanoparticle-mediated delivery of multifunctional drugs could be a promising approach to prevent or treat restenosis.[10] Thus, this prospective clinical study was designed to investigate the effects of lipo-PGE1 on coronary stenosis and restenosis after PCI in CHD patients.

Methods

Ethical approval and informed consent

This study was approved by the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine (approval registration number BF2020-283). All samples were collected with appropriate participant informed consent in compliance with the Helsinki Declaration.

Patient source

Patients were enrolled into groups according to the diagnostic inclusion and exclusion criteria. Initially, 60 patients diagnosed with CHD scheduled for PCI surgery in Guangdong Hospital of Traditional Chinese Medicine from 2020 to Decemebr 2022 were enrolled and divided into two groups: basic medication for prevention and treatment of CHD (Control group, n = 30) and basic medication combined with lipo-PGE1 treatment (PGE group, n = 30).

Group treatments

For the Control group, basic medication normally included drugs for anti-platelet therapy, lipid lowering, controling ventricular rate, and controling hypertension or hyperglycemia. For the PGE group, nanolipid microspheres-based PGE (10 μg) (Penglai Nuokang Pharmaceutical Co., LTD) was added to 0.9% normal saline (NS) (250 ml) for intravenous injection, 20 gtt/min, once a day for 3 days during the peri-operative period of PCI. Basic medications were maintained in the two groups after discharge.

Diagnostic criteria

CHD diagnoses and the criteria for PCI followed the Guidelines for Percutaneous Coronary Intervention (2019) in China.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) The diagnosis fulfilled the criteria of CHD. (2) The condition conformed to the criteria for PCI. (3) The patients were able to complete the follow-up interview. (4) The patients voluntarily participated and signed informed consent.

Exclusion criteria included

(1) Patients with abnormal mental consciousness who could not cooperate, or patients with unstable vital signs. (2) Patients with related drug contraindications or allergies. (3) Those who participated in other clinical trials within 1 month. (4) Older than 80 years of age, pregnant or ready to be pregnant, lactating women, or infants.

Abscission criteria

(1) Patients who withdrew from the trial without adverse reactions or poor efficacy. (2) Those who lost connection during follow-up.

Termination criteria

(1) The researchers considered it medically necessary for the patients to terminate the trial. (2) Patients withdrew from the trial autonomously. (3) Those who suffered severe adverse reactions and could not insist on continuous treatments.

Primary and secondary outcomes

The rate of restenosis after PCI was the primary outcome, and the rate of newly increased stenosis was the secondary outcome. The measurement for restenosis and increased stenosis was performed using angiography or coronary computed tomography (CT), with or without transthoracic coronary doppler ultrasound. All outcomes were observed within 1.5 years after PCI.

Safety index monitoring

Adverse reactions were closely monitored when treatments were administered to all patients. All adverse reactions were observed, treated when necessary, and recorded.

Statistical analysis

A dataset was constructed and analyzed using SPSS (v26.0, Inc. USA) and R (v3.6.2, http://www.r-project.org) software. Continuous data are expressed as mean ± standard deviation, and the Kolmogorov-Smirnov test was used for normally distributed data. If the continuous data fit a normal distribution, comparisons between the two groups were performed using two independent sample Student's t-tests. Otherwise, the Mann-Whitney U test was used. Categorical variables are expressed in frequency and proportions (%). Chi-square (χ^2) tests with or without continuous correction or Fisher's exact test were used for comparisons between groups. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of patients

In total, 60 patients were enrolled based on the criteria, and 6 patients were lost during follow-up. Finally, 54 patients (Control group, n = 30; PGE group, n = 24) finished the follow-up and were included in the final analysis. There were no significant differences in sex, age, diagnosis subsets, comorbidities, and basic treatments between the Control and PGE groups (Table 1).

Baseline of vessel features in stenosis before PCI

We first compared the baseline of vessel features in stenosis before PCI between the Control and PGE groups. Stenosis location was defined as proximal, middle, and distant. We observed no significant difference in stenosis vessel features between the two groups ($P > 0.05$). The stenosis degree was also calculated by the area percent of occlusion and distinguished by total occlusion or not. The results showed no obvious differences between the two groups ($P > 0.05$) (Table 2). Comparisons of the number of vessels in stenosis before PCI were not statistically different ($\chi^2 = 5.982$, $P = 0.050$) (Table 3).

Characteristics of implanted stent features during PCI

As the characteristics of implanted stent features during PCI may affect the prognosis of restenosis,[11] we collected and compared the stent features. There were no statistical differences in the stent diameter and stent length between the two groups ($P > 0.05$) (Table 2). Comparisons of the number of stents implanted during PCI also

Table 1. Comparison of baseline characteristics between groups, [n(%)]

Variables	Control (n = 30)	PGE (n = 24)	*P*
Sex			0.210
female	5 (16.7%)	1 (4.17%)	
male	25 (83.3%)	23 (95.8%)	
Age	61.2 (11.0)	61.2 (9.21)	0.986
Diagnosis			0.063
ACS	7 (23.3%)	1 (4.17%)	
CCS	23 (76.7%)	23 (95.8%)	
Comorbidity			
hypertension	18 (60.0%)	14 (58.3%)	1.000
hyperlipidemia	9 (30.0%)	6 (25.0%)	0.919
DM	10 (33.3%)	10 (41.7%)	0.729
Other	0 (0.00%)	2 (0.08%)	0.193
Basic treatments			
anti-platelet	23 (76.7%)	23 (95.8%)	0.113
lipid-lowering	9 (30.0%)	6 (25.0%)	0.919
Number of comorbidities			0.261
0	2 (6.67%)	5 (20.8%)	
1	15 (50.0%)	8 (33.3%)	
2	8 (26.7%)	6 (25.0%)	
3	5 (16.7%)	3 (12.5%)	
4	0 (0.00%)	2 (8.33%)	

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DM, diabetes mellitus

demonstrated no significant differences between the two groups ($\chi^2 = 1.520$, $P = 0.615$) (Table 4). These results showed that vessel features in stenosis before PCI and implanted stent features during PCI were similar between the Control and PGE groups. This, combined with the demographic characteristics of the patients, indicates that the two groups were comparable at baseline.

Effects of PGE on restenosis in culprit vessels after PCI

The percentage of restenosis was generally divided into less or more than 50% of the artery lumen area, and the number of restenosis in each vessel was calculated.[12,13] We found that restenosis in the LCX was the least severe, and the percentage of restenosis in the LCX was less than 50%. Statistical analysis showed no obvious difference in restenosis percentage of each of these three arteries between the Control and PGE groups ($\chi^2 = 1.520$, $P = 0.615$) (Table 5). Analysis of the restenosis type[14] of each vessel showed similar results, with no significant difference in each artery between the two groups ($P > 0.05$) (Table 6). Comparisons of the number of vessels in restenosis showed no statistical differences ($\chi^2 = 0.070$, $P = 0.791$) (Table 7). These data suggest that lipo-PGE1 has no significant effects on ameliorating restenosis after PCI.

Effects of PGE on newly increased stenosis in non-culprit vessels after PCI

As there was no obvious effect of lipo-PGE1 on restenosis, we further investigated the effect of PGE on newly increased stenosis after PCI, which was calculated by comparing the baseline of vessel stenosis and the stenosis in non-culprit vessels after PCI. The Kolmogorov-Smirnov test indicated abnormal distribution and the Mann-Whitney U test was used for comparison. Results showed that the percentage of increased stenosis of the RCA in non-culprit vessels was much lower after PCI in the PGE group compared to the Control group ($U = 263.0$, $P = 0.048$), while no significant differencew were observed in the LAD and LCX arteries (Table 8). The number of non-culprit vessels in increased stenosis after PCI was also calculated; we found no significant differences between the Control and PGE groups ($\chi^2 = 3.902$, $P = 0.272$) (Table 9). These data suggest that lipo-PGE1 treatment may be effective in decreasing newly increased stenosis in non-culprit vessels after PCI.

Adverse reactions

The most frequently observed adverse reactions of lipo-PGE1 were phlebitis and anaphylaxis, and most of these adverse reactions disappeared after discontinuation of medication (Table 10). No severe adverse reactions were found with lipo-PGE1 treatment.

Discussion

This study examined the effects of nanolipid microspheres (liposome)-based PGE1 on coronary stenosis and restenosis after PCI using a prospective clinical trial design. We found that lipo-PGE1 treatment may be effective in decreasing newly increased

Table 2. Characteristics of vessels in stenosis and stents between groups, [n(%)] or [M(IQR)]

Variables	Control (n = 30)	PGE (n = 24)	*P*
Location of stenosis			
LAD			1.000
proximal	17 (56.7%)	15 (62.5%)	
middle	8 (26.7%)	6 (25.0%)	
distant	1 (3.33%)	0 (0.00%)	
none	4 (13.3%)	3 (12.5%)	
LCX			0.184
proximal	3 (10.0%)	5 (20.8%)	
middle	11 (36.7%)	11 (45.8%)	
distant	3 (10.0%)	4 (16.7%)	
none	13 (43.3%)	4 (16.7%)	
RCA			0.225
proximal	10 (33.3%)	7 (29.2%)	
middle	3 (10.0%)	7 (29.2%)	
distant	5 (16.7%)	5 (20.8%)	
none	12 (40.0%)	5 (20.8%)	
Stenosis in vessels (%)			
LAD	80.0 [50.0;90.0]	75.0 [57.5;86.2]	0.512
LCX	32.5 [0.00;72.5]	80.0 [37.5;90.0]	0.050
RCA	43.5 [0.00;90.0]	85.0 [36.2;90.0]	0.275
Total occlusion	12 (40.0%)	8 (33.3%)	0.825
Stent diameter (mm)			
LAD	2.75 [0.00;3.00]	2.00 [0.00;2.78]	0.130
LCX	0.00 [0.00;0.00]	0.00 [0.00;2.12]	0.572
RCA	0.00 [0.00;1.88]	0.00 [0.00;2.75]	0.921
Stent length (mm)			
LAD	16.5 [0.00;29.0]	22.5 [0.00;29.0]	0.843
LCX	0.00 [0.00;0.00]	0.00 [0.00;4.75]	0.747
RCA	0.00 [0.00;18.0]	0.00 [0.00;29.2]	0.499

stenosis in non-culprit vessels after PCI.

Nanolipid microspheres (e.g. liposome) are a novel drug delivery system. It was reported that drug-loaded liposomes applied on a multilayer-coated balloon catheter improved the limitations of drug-eluting balloons (DEB) for the treatment of coronary artery disease.[15] A double-blind, randomized clinical trial (BLAST study) used liposomal Alendronate as a single intravenous bolus and showed that treatment with liposomal Alendronate could significantly decrease in-stent late loss in patients with baseline monocyte counts higher than the median value.[16] These data sug-

Table 3. Comparisons of the number of vessels in stenosis before PCI between groups, [n(expected)]

Groups	Number of vessels in stenosis			Total	χ^2	*P*
	1	2	3			
Control	9 (7.2)	11 (8.3)	10 (14.4)	30 (30.0)	5.982	0.050
PGE	4 (5.8)	4 (6.7)	16 (11.6)	24 (24.0)	5.982	0.050
Total	13 (13.0)	15 (15.0)	26 (26.0)	54 (54.0)		

Pearson χ^2 test.

Table 4. Comparisons of the number of stents in PCI between groups, [n(expected)]

Groups	Number of stents			Total	χ^2	*P*
	1	2	3			
Control	24 (22.8)	6 (6.7)	0 (0.6)	30 (30.0)	1.520	0.615
PGE	17 (18.2)	6 (5.3)	1 (0.4)	24 (24.0)	1.520	0.615
Total	41 (41.0)	12 (12.0)	1 (1.0)	54 (54.0)		

The minimum expected count was 0.44, used fisher's exact test.

Table 5. Characteristics of vessels in restenosis after PCI between groups, [n(%)]

Variables	Control (n = 30)	PGE (n = 24)	*P*
LAD			0.684
0	27 (90.0%)	21 (87.5%)	
−50	1 (3.33%)	2 (8.33%)	
50−	2 (6.67%)	1 (4.17%)	
LCX			1.000
0	29 (96.7%)	24 (100%)	
−50	1 (3.33%)	0 (0.00%)	
RCA			1.000
0	27 (90.0%)	23 (95.8%)	
-50	2 (6.67%)	0 (0.00%)	
50−	1 (3.33%)	1 (4.17%)	

−50; percentage of restenosis less than 50%, 50−; percentage of restenosis no less than 50%. Pearson χ^2 test or fisher's exact test.

gested that nanolipid microspheres could be a potential method for improving restenosis treatment.

Restenosis in coronary arteries after PCI has several underlying pathogenic causes, such as activation of the clotting system by injured endothelial cells and healing facilitated by vascular smooth muscle cell migration, proliferation, and synthetic activities.[4,14] The average time from restenosis occurance after PCI has been reported to be within 12 months with drug-eluting stents (DES), and typically presents as recurrent angina.[17] Evaluation of staged, target lesions, and other unplanned revascularization procedures during the first year after PCI showed that target lesion revascularization (TLR) occurred with higher hazard rates between 2 to 9 months after PCI.[18] The commonly used technologies for restenosis treatment include bare metal stents, DES, conventional and cutting balloon angioplasty, drug-coated balloons (DCB), and atherectomy devices.[14,19] However, there is still a population of patients who suffer restenosis more than once even with suitable treatments. Thus, adjuvant medication becmomes more important in the peri-operative period of PCI.

PGE1 (also named Alprostadil) has been used to treat chronic arterial obliterans (thromboangiitis obliterans, obliterans arteriosclerosis, etc.) and improve cardiovascular and cerebrovascular microcirculation disorders. A prospective, single-blind, randomized trial of 30 patients administered intravenous PGE-1 by hemodynamically based titration at a mean dosage of 10–20 ng/

Table 6. Characteristics of restenosis types after PCI between groups, [n(%)]

Variables	Control (n = 30)	PGE (n = 24)	*P*
LAD			0.805
none	27 (90.0%)	21 (87.5%)	
type1	2 (6.67%)	3 (12.5%)	
type2	1 (3.33%)	0 (0.00%)	
LCX			1.000
none	29 (96.7%)	23 (95.8%)	
type1	1 (3.33%)	1 (4.17%)	
RCA			0.747
none	27 (90.0%)	23 (95.8%)	
type1	2 (6.67%)	0 (0.00%)	
type3	1 (3.33%)	1 (4.17%)	

Pearson χ^2 test or fisher's exact test.

Table 7. Comparisons of the number of vessels in restenosis after PCI between groups, [n(expected)]

Groups	Number of vessels in restenosis		Total	χ^2	*P*
	0	1			
Control	23 (23.9)	7 (6.1)	30 (30.0)	0.070	0.791
PGE	20 (19.1)	4 (4.9)	24 (24.0)	0.070	0.791
Total	43 (43.0)	11 (11.0)	54 (54.0)		

Note The minimum expected count was 4.89, used continuous corrections χ^2 test.

Table 8. Characteristics of the percentage of increased stenosis after PCI between groups, [M(IQR)]

Variables	Control (n = 30)	PGE (n = 24)	Mann-Whitney U	*P*
LAD	0.00 [0.00;17.5]	0.00 [0.00;0.00]	313.0	0.288
LCX	0.00 [0.00;0.00]	0.00 [0.00;10.5]	340.5	0.659
RCA	0.00 [0.00;28.8]	0.00 [0.00;0.00]	263.0	0.048*

Kolmogorov-Smirnov test and Mann-Whitney U test. *$P < 0.05$ between groups.

Table 9. Comparisons of the number of vessels in increased stenosis after PCI between groups, [n(expected)]

Groups	Number of vessels in increased stenosis				Total	χ^2	*P*
	0	1	2	3			
Control	10 (12.8)	10 (9.4)	8 (5.6)	2 (2.2)	30 (30.0)	3.902	0.272
PGE	13 (10.2)	7 (7.6)	2 (4.4)	2 (1.8)	24 (24.0)	3.902	0.272
Total	23 (23.0)	17 (17.0)	10 (10.0)	4 (4.0)	54 (54.0)		

The minimum expected count was 1.78, used continuous corrections χ^2 test.

kg/min at 2 hours before angiography. The 6-month follow-up showed that restenosis occurrence was 17% in the PGE-1 treated group, compared with 33–50% in the control group which only received basic medication ($P < 0.05$). These data indicated that PGE-1 was effective in decreasing coronary restenosis at 6 months after percutaneous transluminal coronary angioplasty.[20] Since restenosis usually occurrs during the first year after PCI,[17] we examined the effect of PGE-1 at 1.5 years after PCI initially to obtain a more comprehensive understanding of the role of PGE-1 in preventing restenosis occurrence. However, we did not find positive results. The reason may lie in the time point for outcome observation and relatively small sample size.

Although our data did not show significant effects of lipo-PGE1 treatment for restenosis after PCI, we did observe a decrease in restenosis percentages in each of the three arteries examined. Furthermore, the newly increased stenosis in vessels was affected by lipo-PGE1 treatment, and a significant difference was observed in the RCA artery. A previous randomized controlled trial indicated that intracoronary administration of Nicorandil and PGE1 was more effective in improving myocardial perfusion than Nitroglycerin.[21] Another randomized-controlled study administered lipo-PGE1 at 20 μg/day diluted in 10 ml of NS through an intravenous injection over 5 min, starting at 3 days before PCI and continuing for 4 days after PCI. The results suggested that the cardioprotective effects of lipo-PGE1 were associated with its anti-inflammatory properties and its ability to improve microvascular perfusion.[6] Another clinical study suggested a relationship between the microcirculation and restenosis, evidenced by the finiding that lower coronary blood flow responsed to an endothelium-dependent vasodilator stimulus and was associated with long-term recurrence of restenosis.[22] Thus, the anti-inflammatory and microvascular improvement effects of lipo-PGE1 may udnerlie the reduction of newly increased stenosis in arteries.

Future directions

The main limitation of this study was the relatively small sample size. Further studies with more subjects are needed to validate our conclusions. New studies can be designed to evaluate the treatment effect of lipo-PGE1 on restenosis, which can be assessed by quantifying the degree of restenosis before and after lipo-PGE1 treatment. Moreover, the underlying mechanisms of lipo-PGE1's cardioprotective effects should be done by examining endogenous plasma PGE1 levels from CHD patients before and after PCI.

Conclusions

The current study was designed to evaluate the protective effects of lipo-PGE1 on coronary stenosis and restenosis after PCI. Our study showed the lipo-PGE1 did not affect restenosis after PCI, but it may be effective in ameliorating newly increased stenosis in arteries.

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Table 10. Comparisons of the number of adverse reactions between groups, [n(expected)]

Groups	Number of adverse reaction		Total	χ^2	*P*
	No	Yes			
Control	30 (28.3)	0 (1.7)	30 (30.0)	1.946	0.163
PGE	21 (22.7)	3 (1.3)	24 (24.0)	1.946	0.163
Total	51 (51.0)	3 (3.0)	54 (54.0)		

The minimum expected count was 1.33, used continuous corrections χ^2 test.

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Conflict of interest

The authors declare that there is no conflict of interest in the authorship and publication of this contribution.

Author contributions

QL designed the study and finalized the manuscript. AZ, JQ, CW, PL, and CL collected patient information and constructed the dataset. RY and QL completed the first version of manuscript. QL finished manuscript corrections. QL, CW, and GL contributed to manuscript revision. All authors read, revised, and approved the final manuscript.

Ethical statement

This study was approved by the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine, with the approval registration number of BF2020-283.

Data sharing statement

The authors confirm that the data supporting the findings of this study are available within the article, and these data are also available from the corresponding author upon reasonable request.

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