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Ballon perfusion novel bi-layer nanoparticles to inhibition restenosis in animal models

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Introduction: At present, percutaneous transluminal coronary angioplasty (PTCA) and stent implantation is the most effective treatment for coronary atherosclerotic heart disease. However, the incidence of restenosis within 6 months after the operation is as high as 30% to 50%, becoming a main cause for the restricted long-term clinical efficacy and the increased medical expenses. Recent studies show that the difficult healing of blood vessel endothelium and the neointimal proliferation arising from excess migration and proliferation of vascular smooth muscle cell are two main causes for the formation of restenosis. Prevention and treatment of restenosis using systematic administration is often restricted by systematic toxic and side effect as a result of overdose and such factors as low efficiency of drug distribution and metabolizing in blood vessel, resulting in hardly effective local concentration of drug in blood vessel and short lasting of effective local concentration of drug. Local administration can directly deliver the high concentration therapeutic agent to the target tissue, improving the efficiency of administration and avoiding the above-mentioned defects of systematic administration. Nanotechnology can be used in manufacturing pharmacy to improve infiltration and redistribution of drug in tissues and increase local retention of drug. In our study, we designed a novel kind of VEGF/ PTX nanoparticles (VEGF/PTX NPs) which can release VEGF and PTX step by step, to healing of endothelium and inhibiting smooth muscle cells proliferation. By local infusing VEGF/PTX NPs in atherosclerotic animal models, we detected the effective of VEGF/PTX NPs to inhibit restenosis.

Materials and Methods: VEGF/PTX NPs were prepared by double emulsion evaporation methods. Detection of VEGF/PTX NPs diameter and morphology by SEM, TEM and dynamic laser light scattering were done. Gene and PTX release sequently in vitro be checked, the function of gene which release from VEGF/PTX NPs were detected by ELISA. The cell activity was tested by MTT. The effective of VEGF/PTX NPs to inhibit restenosis be tested in atherosclerotic rabbit models, saline, PTX NPS, VEGF NPS be using in control groups.

Results and Discussion: VEGF/PTX NPs were successfully prepared, with a mean particle diameter of 78.82 nm and mean Zeta electric potential measurement of -12.2. The PTX entrapment rate was 92%, the PTX load was 28.58%, the gene entrapment rate was 98%, and the gene load was 4.67%. Protein expression can be detected by ELISA in cells medium which transfected gene, and after protein expression two days, inhibition of proliferation can be observed by the result of MTT. After in vivo perfusion into rabbits, the vascular restenosis in both the VEGF NPs group and the VEGF/PTX NPs groups was inhibited. Particularly, good healing was observed in VEGF NPs group by OCT. Immunohistochemical results indicated that the VEGF/PTX NPs group had lower PCNA positive cell expression rate and MMP-2 & TIMP-2 protein positive expression volume than the physiological saline control group and the blank NPs control group.

Conclusions: Novel VEGF/PTX NPs which release gene and PTX sequentially, it is effective to controlled restenosis in atherosclerotic animal models than control groups. By this way, we can see the sunshine of restenosis therapy.

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