Local drug delivery: an emerging approach in the treatment of restenosis

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Abstract: Very limited success has been demonstrated with systemic pharmacological treatment to reduce the incidence of restenosis following angioplasty in patients. The lack of success of many of the pharmacotherapeutic agents in reducing the restenosis rates post-angioplasty and following stent implementation is believed to arise from inadequate concentrations of the agents at the lesion site. This has led to the development of various local delivery devices that would ideally deliver and retain adequate amounts of drug to the vessel wall for sufficient periods of time to ensure a therapeutic effect without inducing further injury or compromising blood flow. Local dosing would avoid systemic toxicity, and the use of modified balloon catheters or coated stents might enable percutaneous approaches.

Key words: angioplasty, balloon catheters, stents

Introduction

Enthusiasm for the remarkable success of percutaneous angioplasty1 and arterial manipulation has always been tempered by complications that include early thrombosis and late tissue hyperplasia, and by the inability of most pharmacological approaches to reduce these complications.2,3 This loss of gain in vascular patency, termed restenosis, is multifactorial, and includes processes that involve multiple cell types, with differential effects in different parts of the arterial wall, and at different points in time after the initial intervention. Acute thrombotic and vasospastic phenomena are followed by a range of inflammatory processes that ultimately produce obstructive neointimal hyperplasia from the combined effects of vascular smooth muscle cell proliferation and migration, extracellular matrix deposition, and chronic remodeling of the vessel wall.

Over recent years there has been intensive research effort directed towards identifying pharmacotherapeutic regimens to reduce the neointimal restenotic process. Many of these agents have been found to be effective in preventing restenosis in animal models of vascular injury following systemic administration.4,5 There have been some promising studies using the antioxidant probucol6,7 or a platelet aggregation inhibitor, cilostazol.5,9 However, these drugs must be given at least a month before the patient undergoes angioplasty and for months afterwards. In general, the clinical use of most of the agents has been disappointing.5 The potency and narrow therapeutic window of many of the compounds limits their tolerance when administered systemically. Local drug delivery to the site of injury might achieve greater local concentrations with lower overall dose to maximize effects in the tissue of interest while minimizing undesired systemic toxicity. Many devices have been developed to administer drugs or genetic material locally to the site of injury. The ideal delivery device would deliver and retain adequate amounts of drug to the vessel wall for sufficient periods of time to ensure a therapeutic effect, without injury or compromising blood flow and the delivery device.

Conceptual motivation

The concept of local delivery was first proven to be successful in animal models using perivascular delivery system.10,11 Polymeric matrix heparin-releasing devices were wrapped around rat carotid arteries at the time of balloon injury. These devices continuously released the drug with definable kinetics and for predetermined periods of time,10 diminishing arterial obstruction more effectively than continuous systemic pump-based infusion of heparin or release from drug/polymer matrices placed in a subcutaneous site distant from the injured artery. Polymeric wraps containing endothelial cells as a source of endogenous vasoregulatory agents were even more efficient at reducing neointima formation in rat12 and pig13 models of vascular injury. While such delivery systems are useful in animal models to allow for the identification of suitable agents that inhibit neointimal hyperplasia at sites of local delivery after vascular injury, they require surgery at the site of application. Thus, a number of non-invasive techniques have been presented for local delivery.

Local drug delivery devices

Because vascular restenosis is a localized event, usually limited to the area of intervention, it is an ideal candidate...
for local drug delivery therapy. Access to the site of the pathological process can be facilitated by the nature of the vascular intervention. Many devices have been developed for intravascular local drug delivery, including those designed for intraluminal, intramural, or stent-based delivery. In general, the delivery efficiency of these devices, i.e., the percentage of agent that leaves the catheter and enters the vessel wall, is less than 1%. Yet, even this results in a local concentration several hundred-fold greater than that in systemic circulation.

Balloon catheter-based systems

Diffusion-driven
The earliest approach to percutaneous local drug delivery employed a double-balloon catheter. This device is passed over a guidewire like a conventional angioplasty balloon, and the two balloons are inflated proximal and then distal to the site of injury. The intervening vascular segment is isolated and can then be filled with and bathed in a concentrated drug solution, which if desired can be aspirated away before balloon deflation and systemic exposure. This device has been used to deliver both pharmacologic agents and genetic material in a variety of animal models. Double-balloon catheter delivery of the specific thrombin inhibitor recombinant-hirudin was more effective in reducing platelet deposition and thrombus formation following balloon angioplasty. In patients undergoing percutaneous transluminal angioplasty for superficial femoral artery occlusion, the recanalized segment was isolated with a double-balloon catheter. Recombinant human tissue-type plasminogen activator and heparin were then infused into the enclosed space for 30 min, followed by intravenous heparin for 24 h. At 10 and 30 days, all six patients had evidence of recanalization, re-stenosis following balloon angioplasty significantly better than systemic administration. Low molecular weight heparin delivered with this type of catheter to hypercholesterolemic rabbits with atherosclerotic iliac stenoses reduced restenosis following balloon angioplasty significantly better than systemic administration. In patients undergoing percutaneous transluminal angioplasty for superficial femoral artery occlusion, the recanalized segment was isolated with a double-balloon catheter. Recombinant human tissue-type plasminogen activator and heparin were then infused into the enclosed space for 30 min, followed by intravenous heparin for 24 h. At 10 and 30 days, all six patients had evidence of recanalization, re-stenosis following balloon angioplasty significantly better than systemic administration. In one study, rabbit iliac arteries were balloon-injured followed by local delivery of the low molecular weight heparin, reviparin, with a Dispatch catheter. The Dispatch catheter was shown to be safe and feasible. However, the infusion of highly concentrated reviparin over a short period of time did not result in a reduction of neointimal formation and restenosis. More importantly, the Dispatch catheter has been used successfully clinically in delivering heparin to reduce restenosis and in delivering urokinase to eliminate thrombus formation.

Pressure-driven
Pressure-driven devices have been developed to enable drugs to penetrate further into the vessel wall. The porous balloon works by inflation of a non-compliant balloon that directly delivers the drug through pores into the adjacent arterial wall. The depth of penetration is directly proportional to the perfusion pressure, but this also means that there is the potential for vascular trauma from the fluid jet streaming out of the pores, and acute vascular dissection may be followed by an increased long-term neointimal response. Drugs introduced into the vessel wall by local catheter delivery systems may be rapidly washed away within minutes to hours after administration.

Microparticles are composed of biodegradable polymer impregnated with the drug. They are small enough to be administered percutaneously but large enough to be retained in the vessel wall where the drug is gradually released. Porous balloon catheters have also been used to deliver microspheres into the vessel wall in rodents. A report using the rat carotid balloon-angioplasty model demonstrated that biodegradable microspheres could deliver dexamethasone throughout the arterial wall. The dexamethasone was present in the treated coronary segment for up to 2 weeks following a single 3-min infusion and significantly decreased neointimal formation. In another study, hydrocortisone-loaded microspheres delivered locally via a porous balloon catheter significantly reduced intimal hyperplasia in rabbit iliac arteries 4 weeks after angioplasty.

Although intravenous administration of low molecular weight heparin has been successful in animal models to prevent restenosis, it has failed to be effective clinically. However, the PILOT study demonstrated the clinical safety and feasibility of the local intracoronary delivery of reviparin, an optimized low molecular weight heparin, using a porous balloon following angioplasty, even in...
smaller diameter coronary arteries. The angiographic restenosis rate was 28% (5/18) at the 6-month follow-up.

The microporous balloon is a modification of the porous balloon. It consists of an inner balloon with an array of pores surrounded by an outer membrane with thousands of micropores of less than 1 μm diameter. 28 Although the inflation pressure is similar to that of the porous balloon, the drug gently exudes from the pores in the external membrane, reducing the risk of tissue injury. Paclitaxel, an anti-neoplastic compound that prevents cell proliferation by stabilizing microtubules, has successfully inhibited neointimal formation in balloon-injured rabbit arteries following local delivery using a microporous catheter. 29 Though innovative technologies, the porous and microporous balloon designs have additional limitations. Because both systems rely on hydrostatic pressure to inflate the balloon and infuse the contents of the catheter, significant systemic administration of the drug may occur during balloon inflation or deflation. In addition, the pores can become plugged resulting in an uneven delivery of the drug.

Several delivery catheters have been developed with the aim of disassociating drug infusion pressure from the pressure required to inflate the angioplasty balloon. The Channel catheter (Boston Scientific Scimed) is a central conventional angioplasty balloon covered with longitudinal channels. 30 This allows local low-pressure infusion during high-pressure balloon inflation, with no additional vessel damage beyond that due to angioplasty. Studies have demonstrated safe intracoronary use of the Channel balloon in the porcine model. 31 Local infusion of urokinase with this device resulted in significant intramural drug deposition that persisted for at least 5 h and, in comparison with conventional thrombolytic techniques, resulted in enhanced intravascular thrombolysis. The Channel catheter has successfully delivered adenovirus expressing the gax gene, an anti-proliferative homeobox gene, reducing intimal hyperplasia after balloon injury of the rabbit iliac artery. 32 The Transport catheter (Boston Scientific Scimed) is similar to the Channel, with a semi-compliant central balloon surrounded by an outer porous balloon for drug delivery. 33 Both of the Channel and Transport catheters simplify the procedure of angioplasty and drug delivery by allowing the intervention and subsequent pharmacotherapy to be performed sequentially with the same device. Another variation consists of an infusion sheath (Infusasleeve: Localmed, Inc.), which is advanced over any standard angioplasty catheter and advanced to the lesion after balloon dilation. 34

**Polymeric endoluminal paving via catheter**

In this technique, a catheter, usually a double-balloon or porous catheter, is used to deliver a biodegradable polymer containing the drug to the site of injury following angioplasty. Depending on the nature of the polymer, which is infused as a liquid, it polymerizes upon warming or exposure to light. The latter uses a catheter containing a fiber optic illumination element. 35 Solid or gel paving can be achieved by using an appropriate type of polymer. Solid paving offers the vessel wall support, a physical barrier and a site of local sustained intraluminal drug delivery. The solid polymer takes several months to biodegrade and hence functions as a long-term (3–6 months) drug delivery vehicle. 36 Gel paving coats the wall with a hydrogel which provides a short term non-structural physical barrier that can deliver drugs for days to weeks. 37

**Electrical and mechanical devices**

The iontophoretic balloon uses a gentle electrical current to increase cell permeability and facilitate transport into the vessel wall. The catheter consists of a porous balloon containing the cathode. 38 An anode is placed on the skin. Electrical current drives negatively charged molecules outside of the balloon into the arterial wall. This results in significantly greater delivery efficiency than obtained by passive diffusion, with minimal trauma to the vessel wall. Unfortunately, this device is only useful for applying negatively charged substances by electrical forces into the wall. It has been demonstrated that this device can deposit heparin into the intima and internal elastic lamina, with subsequent rapid diffusion of the drug into the media following balloon injury of porcine coronary arteries. 45 Heparin was found to remain in the wall for at least 24 h. Antisense oligonucleotides were retained in porcine coronary arteries after balloon angioplasty and iontophoresis for over 7 days. 46

The needle injection catheter features circumferential extendable fine needles of 250 μm in diameter that penetrate the media and deliver drug or genetic material to the perivascular tissue, including the adventitia. 37 Despite its invasive nature, this device is reported to cause minimal trauma. 47 This device allows relative high levels of drugs to be deposited into the perivascular space where they can be protected from being washed away owing to blood flow. The transfection of cells in the vessel wall after delivery of plasmid DNA via the needles has been successfully demonstrated in porcine models after balloon injury. 48, 49 However, the transfection did not always result in neointimal reduction. One study looked at the potential uses of the gene for SDI-1 as a therapeutic agent. 49 SDI-1 is normally found in senescent, quiescent vascular smooth muscle cells, and it regulates cell proliferation by inhibiting DNA synthesis. Although plasmids containing the sdi-1 gene were delivered via the needle catheter, only a limited number of adventitial, medial and neointimal cells were transfected and produced SDI-1 for up to 4 months, and there was no reduction in neointima formation. The transfer efficiency was too low to affect overall arterial narrowing. However, transfer of antisense sdi-1 did have a biological effect: there was an increase in neointima thickening after 3 weeks owing to clusters of antisense-transfected cells proliferating as clones. In another study, plasmids encoding an immunoform of cecropin, an antimicrobial peptide with anti-proliferative properties in mammalian cells, were locally delivered to perivascular tissue in a porcine arterial injury model using a needle injection catheter, which resulted in a significant reduction of neointimal formation. 50

The Infiltrator (InterVentional Technology, Inc.) is a balloon catheter that features protruding rows of nipples that penetrate into the internal elastic artery on balloon inflation to deliver the drug or gene into the media and deeper layers of the wall with high efficiency. 51 Percutaneous adenovirus-mediated nitric oxide synthase gene transfer resulted in efficient local overexpression of functional nitric oxide synthase after angioplasty in porcine coronary arteries. Restored nitric oxide production in injured coronary arteries significantly reduced luminal narrowing. 52 The Infiltrator catheter was demonstrated to be safe for

clinical use when it was used to deliver low molecular weight heparin following angioplasty of the coronary artery.\textsuperscript{53}

The optimal local catheter delivery device should be simple to use, and result in the greatest deposition and retention of drugs in the vessel wall without causing local trauma, distal ischemia or systemic administration. The use of drug-impregnated biodegradable microsphere could help with the retention of the drug. The ideal catheter system is still under development.

**Stents**

Stents can minimize elastic recoil after angioplasty and create a large post-procedural lumen diameter, but their use may be limited by acute thrombosis and in the log run by in-stent restenosis. To reduce complications, conventional stents may be coated with polymer materials, which can absorb active substances contained in an eluting or non-eluting form. The amount of drug contained on a stent depends on the substance properties, the structure of the stent and the surface area of the stent. Unfortunately, the presence of the ‘inert’ coatings can induce an extensive inflammatory response,\textsuperscript{54} though several polymers such as poly-L-lactic acid, fibrin, and a polyamine-dextran sulfate trilayer have shown promise.

The Benestent II pilot study demonstrated that implantation of a polyamine-dextran sulfate-coated stent, to which heparin was covalently bound, reduced the overall restenosis rate of patients to 13%.\textsuperscript{55} However, the polymer was non-eluting and the heparin remained attached to the stent. In other studies, metallic stents have been coated with biodegradable drug-impregnated polymers, capable of gradually releasing the therapeutic agent into the vessel wall for up to 28 days in animal models.\textsuperscript{56,57} Using a porcine coronary injury model, a wire coil stent was coated with a layer of dexamethasone suspended within a poly-L-lactic acid polymer. The polymer did not evoke an inflammatory response and the dexamethasone was shown to elute into the vessel over a period of time.\textsuperscript{57} However, it did not inhibit neointimal proliferation. A possible reason for the poor effect of the drug may be that the thin polymer coating could carry only a limited amount of drug and could not therefore maintain a high local drug concentration over the extended period of time. In a recent study in pigs,\textsuperscript{58} heparin-coated stents were shown to be effective in the prevention of late coronary stent restenosis compared with uncoated stents. It was concluded that the eluting heparin reduced restenosis by inhibiting neointimal cell proliferation.

Biodegradable polymer stents that can contain large amounts of drugs have been developed. Biodegradable stents can remain in place for a predicted period of time keeping the vessel wall patent and then degrading to nontoxic substances. During this time drugs can be released from the polymer. A biodegradable poly-L-lactic acid stent containing a tyrosine kinase inhibitor, ST638, reduced neointimal proliferation induced by balloon injury in porcine coronary arteries.\textsuperscript{59}

Coating stents with genetically engineered cells that secrete biological products might make use of novel stent designs and innovations in molecular biology. Although genetically engineered endothelial cells have been successfully grown on stents,\textsuperscript{60} they tend to shear off following expansion under blood flow conditions.\textsuperscript{61} Further work is still required. Successful gene transfer and expression has been demonstrated following implantation of polymer stents impregnated with a recombinant adenovirus carrying a nuclear-localizing beta-galactosidase reporter gene into rabbit carotid arteries. These studies suggest that surface-modified polymer stents may ultimately be useful adjunctive devices for both mechanical support and gene transfer devices.\textsuperscript{62}

Encouraging results in animal models has indicated the potential use of radioactive beta-emitting stents for local irradiation of the lesion site to prevent restenosis.\textsuperscript{63-65} Recent Phase I studies have shown that \textsuperscript{125}P-labeled stents appear to be safe to use clinically during 30-day\textsuperscript{66} or 6-month follow-up studies.\textsuperscript{67} However, their long-term clinical therapeutic effect still needs to be determined.

The use of coated stents has the advantage over catheter-based delivery systems of potentially being able to release drugs over an extend period of time. But there are still issues to resolve, including coating enough drug on the stent.

**Summary**

Restenosis is the net result of a series of complex events, which is slowly being revealed. Consistent failure of systemic pharmacotherapy to reduce the rate of restenosis is, in most part, likely the result of inadequate tissue concentrations of biologically active agents. Local vascular delivery will become a vital component in the prevention of restenosis. As reviewed here, there are various local delivery devices already being tested, which are continuously being improved on. As our understanding of the restenotic process improves, better choices of drugs and genetic material will be developed that in conjunction with the local delivery devices will hopefully help to prevent restenosis.

**References**


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