Progress of Surface Modified Materials in Cerebrovascular Interventional Stent

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Abstract

Cerebrovascular intervention has become an important diagnosis and treatment of cerebrovascular diseases, and the updating and development of materials is an important support for this technological progress. Stent is an important device for cerebrovascular intervention, which can open up stenosis and reshape blood flow. Compared with surgery, interventional therapy has less trauma and shorter operation time. However, complications such as restenosis, delayed endothelialization and thrombosis may also occur after stent implantation. Surface modification to improve the biological behavior and function of stents is a reliable way to improve efficacy and safety. In this paper, the application of surface modification in cerebrovascular interventional stent is reviewed.

Keywords: Surface modification; Stent; Cerebrovascular disease; Progress

Introduction

In China, the number of deaths due to cerebrovascular diseases is increasing year by year. According to an analysis published in the Lancet, stroke is now the leading cause of death among Chinese [1]. Cerebrovascular diseases can be divided into ischemic stroke (transient ischemic attack, cerebral embolism, cerebral infarction) and hemorrhagic stroke (cerebral hemorrhage, subarachnoid hemorrhage) according to the nature of the lesions. In recent years, with the development of endovascular interventional therapy technology, interventional technology has been widely applied in the diagnosis and treatment of cerebrovascular diseases [2]. For the diagnosis and treatment of cerebrovascular diseases through endovascular intervention technology, in addition to angiography to show vascular lesions, stents can also be placed to expand the stenosis [3]. At present, most of the world’s clinical centers use cerebrovascular intervention technology to treat symptomatic intracranial and extracranial arterial stenosis, cerebral aneurysms and a variety of other stroke. However, stent, an important material used for cerebrovascular intervention, may present problems such as delayed endothelialization, thrombosis events and restenosis after implantation into the vascular lumen [4]. In order to solve these problems, surface modification materials have been developed rapidly in recent years to improve the efficacy and safety of stents. In this paper, the application progress of various surface modified materials in cerebrovascular interventional stent is reviewed.

Cerebrovascular interventional therapy

Cerebrovascular intervention, including selective angiography, embolization, angioplasty, mechanical clearance, drug delivery and other intravascular treatment for cerebrovascular diseases (intracranial and extracranial vascular stenosis, cerebral aneurysm, arteriovenous fistula, venous stenosis, etc). The most important device is the stent. The success of interventional therapy depends to a great extent on the equipment used, and any defect in the equipment will have serious clinical consequences. Compared with peripheral vascular stent, the development and application of cerebrovascular intervention devices is difficult, it has the following unique requirements:

1. Materials used must be approved for intravascular implantation and should not cause any biological toxicity to nerve cells;

2. Devices should have good flexibility and mechanical properties to avoid any bleeding or ischemic complications [5].

In cerebrovascular intervention, stents are usually introduced from the femoral artery and re-entered the brain through the aorta. Therefore, the flexibility of the device is very important.
In addition, the intracranial arteries are only a few millimeters in diameter, and these arteries often pass through the intracranial extremely tortuous orifices. All of these put forward high requirements for the research and development and application of devices.

Interventional therapy has the advantages of small trauma, wide indications and short operation time, and has gradually become the preferred treatment for cerebrovascular disease. However, compared with the surgical procedure, the implanted stent is also associated with restenosis, thrombotic events and delayed endothelialization. These problems have become the bottleneck of cerebrovascular interventional therapy and need to be broken through urgently [6]. The partial reason for restenosis, thrombotic events and delayed endothelialization lies in the metal materials themselves. By adding various surface modification materials to metal stents, the biological behavior and function of these metal stents can be improved, and the probability of these complications can be reduced, thus providing a reliable way to improve clinical efficacy and safety.

**Application of surface modified stent in cerebrovascular intervention**

Surface modification of biomedical materials, also known as surface modification, is to give new surface properties without changing the bulk properties of the material. Its purpose is to improve the performance of original materials, promote the healing of lesions, and reduce the incidence of perioperative and delayed adverse events [7]. The current surface modifications of metallic materials for endovascular intervention include cellular adhesion, coated proteins, polymeric compounds and their loading drugs, surface coatings and thin films. After the surface modification, the problems of delayed endothelialization and restenosis can be improved.

**Drug releasing stent**

Drug Releasing Stent (DRS), also known as the Drug Eluting Stent (DES), is composed of bare metal stent, polymer, and drug. Drug release stent is an improved product of surface modification of the original metal stent. After stent implantation to the diseased vessels, drugs are spontaneously released from the polymer coating in a controlled manner to exert the effect of drugs [8]. The original drug-release stents used a polymer such as polyethylene glycol or poly lactic acid. Nowadays, new clinical drug release stents often use the mixture of two polymers as drug carriers for controlled drug release, such as poly lactide-hydroxy acetic acid copolymer and polyyl-dextrolactic acid [5]. Drug-release stents are mainly used for the treatment of intracranial stenosis. In view of the restenosis of vascular diseases, drugs are mainly designed for anti-intimal hyperplasia to avoid restenosis of stents, and commonly used drugs include rapamycin and paclitaxel [9]. Drug-release stents were originally developed for coronary heart disease to prevent endometrial hyperplasia and restenosis after stent implantation.

Representative first-generation drug-release stents include Cypher [10] and Taxus [11], whose bare metal stents are stainless steel and composed of non-degradable polymers loaded with rapamycin or paclitaxel, can significantly reduce endometrial hyperplasia functionally. However, due to the thick stent and non-degradable polymer, local inflammatory reaction is triggered and long-term thrombosis and restenosis are still caused in the stent. The second generation of drug-release stents replaces bare metal stents with cobalt-chromium alloy or platinum-chromium alloy [12]. The polymers are more biocompatible, with reduced thickness and improved structure. The drugs are rapamycin derivatives, etc. Compared with first-generation stents, the incidence of in-stent thrombosis and restenosis was reduced. Although the polymer still exists for a long time, its clinical efficacy and safety have been improved. On the basis of the previous two generations, the third-generation drug-release stent was used to replace the polymer with degradable poly (lactic acid) or the mixed poly (lactic acid) -glycolic acid copolymer, which significantly improved the clinical efficacy and safety. After 5-year follow-up test, the incidence of delayed stent thrombosis was less than 0.4% [13].

A meta-analysis involving 5 studies compared the efficacy of drug-release stents and bare metal stents for patients with extracranial vertebral artery stenosis, and the results showed that the rate of stent restenosis, clinical symptom recurrence and vascular remodeling in drug-release stents group were significantly improved compared with those in bare metal stents group [14]. Another meta-analysis of drug-release stents for symptomatic intracranial arterial stenosis included 13 studies, and the results showed that the perioperative complication rate was 6%, long-term complication rate was 2.2%, restenosis rate was 4.1%, and the perioperative complication rate of patients with severe stenosis was significantly higher than that of patients with moderate stenosis [15]. Although these results indicate the effectiveness of drug-release stents, their safety remains a primary concern. Rapamycin and other drugs may cause damage to nerve cells while preventing endothelial cell proliferation [16]. However, polymer degradation may cause occlusion of distal blood vessels and secondary cerebral infarction. In addition, drug anti-endothelial cell proliferation leads to delayed endothelialization. Due to the lack of anticoagulant and anti-platelet effects of endothelial cells in the stent, delayed thrombosis in the stent can happen. Drug-release stents have not been widely used in intracranial vessels, so there is still a lot of room for targeted improvement.

**Coated stents**

The structure of coated stents is simpler than drug-eluting stents, and only consists of bare metal stents and covered film. The coated film can also be divided into non-degradable material and degradable material. Coated stents are used to treat aneurysms or other vascular lesions by isolating them from the target vessels.

Willis balloon Extension coated stent is made in China, based on the coronary artery coated stent, the stent structure, coating and transmission system is improved, more suitable for distal internal carotid artery aneurysms. Reports have shown that the treatment of intracranial pseudoaneurysms, recurrent aneurysms, giant aneurysms, hematoid aneurysms, and traumatic internal carotid artery cavernous sinus aneurysm with Willis dome covered stent has achieved good therapeutic effects, and the incidence of postoperative rebleeding is low [17,18]. However, Willis spherical coated stent also has some defects. Thicker stents and smaller interstitial spaces lead to delayed vascular endothelialization and an obvious inflammatory response, leading to predispositions of intimal hyperplasia and restenosis.

Aiming at these problems of Wills balloon coated stent, adding drugs to the stent to repair the lost endothelium to accelerate endothelium has become a new research direction. At present, such research is mainly carried out in animal models and has not been applied to human beings. Wang et al. [19], added heparin and Vascular Endothelial Growth Factor (VEGF) to the covered stent to treat the rabbit model of cervical aneurysms 3 months after the operation, the aneurysms were completely occluded and the arteries were unobliterated, indicating that after loading heparin and VEGF,
endothelialization could be promoted and improved. Liu et al. [20], placed heparin and rosuvastatin on a coated stent. The results showed that the stent had better anticoagulation and endothelialization in vitro and in vivo, and the higher the concentration of rosuvastatin, the more complete the endothelialization was. The mechanism of this action is through vascular endothelial growth factor. A. Zhang et al. [21], applied similar techniques to add vascular endothelial growth factor and paclitaxel to the coated stent, and cell experiments confirmed that the stent could rapidly release drugs. The application of the stent to the canine cervical aneurysm model significantly improved the aneurysm occlusion rate, promoted the endothelialization process, and achieved a lower restenosis rate. However, these studies have been carried out in animal models, and their effects in human body are still to be studied.

Flow diverter

Flow Diverter (FD) was a blood flow remodeling device developed on the basis of hemodynamic research of intracranial aneurysms. It changed the concept of endovascular treatment for intracranial aneurysms and transferred the former intra capsular embolization to the reconstruction of parent artery. Compared with ordinary intracranial stents, these stents have finer mesh and stronger blood flow guiding ability, so they are more conducive to the migration growth of arterial endothelial cells and the closure of tumor neck cover [22]. Flow diverter of high metal coverage and high rate of mesh design can restore the local blood flow, blood flow to the impact within the parent artery aneurysm to guide the distal normal blood vessels, thus reducing the impact of the local blood flow to the aneurysm, to improve the blood flow dynamics within the aneurysm, and ultimately thrombosis within the aneurysm, occlude the aneurysm [23]. The current commonly used FD include Pipeline flow direction embolization device (Pipeline embolization device, PED), Tubridge vascular remodeling device, SFD, FRED and latest reports p64, BRAVO, Surpass, etc. Currently, the second-generation Pipeline Flex flow-guided embolization device and Tubridge blood vessel reconstruction device are mainly used in domestic market. Multiple center clinical trials proved the good effect of FD in large or giant aneurysms, ruptured aneurysms, small and medium-sized aneurysm, posterior circulation aneurysms, Willis distal aneurysm, but there are also complications of ruptured late-onset aneurysm, branch artery occlusion, stent stenosis and spontaneous parenchymal hemorrhage [24-27]. Whether intimal hyperplasia or inflammatory responses increase the incidence of vascular occlusion or stenosis has not been determined.

The third-generation Pipeline Shield, the most widely used PED in clinical practice, is a surface modification based on the second-generation PED Flex. It covalently binds phosphate choline polymer to the stent surface to reduce thrombosis and postoperative anti-platelet drug use. Studies have found that pipeline shield significantly reduces the incidence of thrombosis in the in vitro human circulation model compared with the PED Flex and FRED stent [29]. A prospective multicenter clinical study showed that none of the patients with intracranial aneurysms treated by pipeline shield had severe stroke after 1 year of follow-up, and the rates of aneurysm occlusion and in-stent stenosis were comparable to PED embolization [30]. A retrospective multicenter study of data from three Neuro Interventional Centers in Australia has shown that the PED of Derivo Embolization Device is a new type of Derivo flow-guided stent, and it shows high surgical safety and effectiveness in the treatment of complex unruptured intracranial aneurysms [32]. It improves X-ray visibility and flexibility over other FDS, enabling more accurate navigation and positioning. It adds a surface modification material that reduces the probability of device thrombosis. A retrospective multi-center study analyzed the safety and effectiveness of Derivo therapy in patients with unruptured intracranial aneurysms. Among the 42 patients, 3 thrombi and 1 aneurysm rupture occurred, and the prevalence of Derivo was 2.4%. In 33 cases of angiography follow-up, 87.9% of them were successfully occluded, demonstrating Derivo’s good safety and effectiveness in the treatment of unruptured aneurysms [33]. But for patients with ruptured intracranial aneurysms, a multicenter preliminary study has shown that Derivo has reached 90% of the aneurysm complete occlusion rate during the follow-up, suggesting that Derivo is feasible to treat ruptured intracranial aneurysms, and it is not related to the incidence of rebleeding [34].

Biodegradable stents

The current stents are basically permanent, and long-term presence in blood vessels in vivo cannot completely avoid inflammation, thrombosis and in-stent restenosis, and long-term postoperative antiplatelet drugs are required. In view of these problems caused by the long-term existence of stents, biodegradable stents have become a new research hotspot. Research of biodegradable stents have magnesium alloy at present, in the animal model of rabbit posterior circulation aneurysms as in vivo experiment, confirmed by angiography and cavity ultrasound, magnesium alloy stents compared with coated stents, shows good curative effect, short term and long term problems of degradation too fast but, clinical requires sustained in the body for at least 3 to 4 months [35]. On this basis, it has become a promising new direction to increase the degradation time of magnesium alloy stents by adding surface modification materials, such as poly lactic acid, poly caprolactone and poly lactic acid-hydroxy acetic acid. Studies have found that poly (lactic acid) and poly (lactic acid-glycolic acid) can better enhance the corrosion resistance of stents, among which poly (lactic acid) shows the best biological compatibility [36]. However, the surface modified biodegradable stents still need to be verified by further animal experiments and clinical trials.

Challenges and Prospects of Surface Modification Materials for use in Cerebrovascular Intervention Stents

Surface modification plays an important role in the development of cerebrovascular intervention stents. The purpose of the surface modification materials is to address the problems associated with previous metal stent implantation, such as delayed endothelialization, stent thrombosis, and restenosis. Different surface modification materials play their respective function mechanism according to different needs, improve the performance of metal stent, and promote the development of cerebrovascular interventional technology.

Although surface modification materials solve the problem of metal supports to a certain extent, it should be noted that surface modification materials themselves may also bring problems. Take DES as an example, polymer release may lead to blockage of distal blood vessels; the drug should be paid more attention to whether it will bring toxicity to neurons, and the side effects of the drug must be carefully considered. In addition, most of the current studies on
cerebrovascular drug-release stents are still in the stage of animal test and in vitro simulation, and there is no toxicological study on local drug release, and the observation time is not long enough, so more in-depth studies are still needed.

In the modern era of multidisciplinary cross and medical-industrial combination, surface modification materials provide a new broad prospect for the application of materials in medicine. The application of surface-modified stents will promote the rapid development of cerebrovascular interventional technology. The development of stents decorated with surface modified materials should be closely related to the purpose of reducing the complications of metal stents, increasing clinical efficacy and safety, and relying on the verification support of more in-depth pharmacology, toxicology, in vitro and in vivo and even human model data, so as to promote their early technical maturity and apply them to the clinic.

References


