Advancing Aneurysm Neck Healing: Evidence from Drug-Eluting Stent Technologies

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DOI: https://doi.org/10.56293/IJASR.2025.6401

IJASR 2025
VOLUME 8
ISSUE 2 MARCH - APRIL **ISSN: 2581-7876**

Abstract: Subarachnoid haemorrhage resulting from intracranial aneurysms (IAs) represents the third most prevalent acute cerebrovascular disease with high mortality and disability rates, following ischaemic stroke and hypertensive intracerebral haemorrhage. Cerebral aneurysms pose a significant threat to public health in China, imposing substantial economic burdens on families and society. Current treatment modalities predominantly include surgical clipping and endovascular intervention, with the latter emerging as the primary therapeutic approach. Studies indicate that standalone coil embolisation is associated with a slightly higher postoperative recurrence rate compared to stent-assisted coiling, largely due to incomplete endothelial coverage at the aneurysm neck. To enhance endothelialisation at the aneurysm neck and mitigate risks of rupture and recanalisation, recent research has focused on applying advanced coating materials to bare metal stents, aiming to promote neointimal formation at the diseased arterial segment. This article provides a retrospective analysis of the efficacy of various stent coating materials in facilitating postoperative endothelialisation at the aneurysm neck.

Keywords: Drug-eluting stents, Endothelialisation, Intracranial aneurysm recurrence

1. Background

Intracranial aneurysms (IAs) are localised, pathological dilations of the intracranial arterial wall. Aneurysmal subarachnoid haemorrhage, a consequence of IA rupture, ranks as the third most common acute cerebrovascular disorder with high rates of disability and mortality, following ischaemic stroke and hypertensive intracerebral haemorrhage. In China, the prevalence of unruptured intracranial aneurysms among adults is as high as 7%[1], with an estimated total of 40 million individuals harbouring such aneurysms. This condition poses a significant threat to public health, imposing profound social and familial burdens. The primary treatment modalities for IAs include surgical clipping and endovascular intervention. With advancements in technology and extensive clinical research, endovascular intervention has garnered deeper investigation and broader application. Owing to the evolution of interventional techniques and the continuous innovation of materials, endovascular procedures have become the mainstay of IA treatment. Among these, stent-assisted coil embolisation (SACE) accounts for approximately one-quarter to one-fifth of all interventions[2]. Stent-assisted coil embolisation (SACE) involves the deployment of a stent across the aneurysm neck during coil embolisation to provide vascular support, prevent coil migration, and promote endothelialisation at the aneurysm neck. This technique is particularly indicated for intracranial aneurysms[3] with a dome-to-neck ratio <2 or a neck diameter ≥4 mm, where permanent stent support is often required to prevent coil prolapse or displacement[4]. According to clinical data, SACE demonstrates superior aneurysm neck endothelialisation compared to standalone coil embolisation, resulting in significantly lower postoperative recurrence rates[5]. However, the use of stent-assisted therapy is associated with complications such as neointimal hyperplasia (NIH), which can lead to in-stent restenosis (ISR) and delayed ischaemic events. These complications are closely linked to inadequate or delayed endothelialisation[6].

Re-endothelialisation at the aneurysm neck primarily relies on the migration of vascular endothelial cells (VECs) from adjacent intact endothelium, as well as the mobilisation and adhesion of circulating endothelial cells. Therefore, promoting rapid re-endothelialisation at the aneurysm neck is crucial for preventing in-stent restenosis (ISR) and thrombosis. Endothelial repair involves both the migration of VECs from neighbouring healthy

endothelial tissue and the homing and adhesion of circulating VECs. However, the cellular origins of endothelialisation remain a subject of debate[7]. As endothelial progenitor cells (EPCs) are present in peripheral blood, circulating EPCs are considered a primary cellular source for reconstructing damaged endothelium[8]. On the other hand, an increasing body of evidence suggests that EPCs in the bloodstream (most likely monocytes) do not directly promote endothelial regeneration by forming part of the regenerating endothelium[9]. Hagensen and others[10] pointed out that the recovery of endothelial cells primarily relies on the migration of adjacent normal endothelial cells. Douglas et al. [11] found that the migration of vascular endothelial cells (VECs) and the adhesion of endothelial progenitor cells (EPCs) in circulation both contribute to the endothelial repair of damaged blood vessels. Additionally, studies have shown that re-endothelialization is a complex mechanobiological process, regulated by the proliferation and migration of endothelial cells from the uninjured intima[9,12], as well as the adhesion of circulating endothelial cells[13,14]. Therefore, the mechanisms of endothelialization at the site of injury still require further investigation.

In order to promote rapid endothelialization at the neck of aneurysms and reduce postoperative complications, researchers have developed stent coatings based on inorganic and organic compounds (including drugs, nanoparticles, and biological components such as genes and cells). These coatings are primarily used to control biocompatibility, degradation rate, protein adsorption, and to promote endothelialization, thereby ensuring clinical efficacy after surgery, reducing recurrence, preventing restenosis, and avoiding thrombosis. This paper describes the effects of the following stent coatings on promoting endothelialization:(1)**Inorganic coatings**: nitric oxide donors, various oxides, precious metals, diamond-like carbon, hydroxyapatite, and carbides.(2) **Organic polymer coatings**: polyurethane, phosphorylcholine, etc.(3) **Antiproliferative substance coatings**: argatroban, miRNA-22, mTOR inhibitors (such as sirolimus, zotarolimus, everolimus, biolimus, amphilimus, and tacrolimus), probucol, paclitaxel, and Tyrphostin AGL-2043.(4) Biological coatings: monoclonal antibodies against glycoprotein IIb/IIIa, heparin, anti-CD34 antibodies, vascular endothelial growth factor (VEGF), and extracellular matrix proteins.

2. Inorganic coating

2.1 nitric oxide donor

Nitric oxide (NO) is one of the most critical gaseous signalling molecules in biological systems, playing a pivotal role in both physiological and pathological processes. NO exhibits anti-thrombotic properties by reducing platelet adhesion, inhibits bacterial growth, and suppresses neointimal hyperplasia and smooth muscle cell proliferation[15–17]. Supplementing nitric oxide (NO) exogenously by incorporating NO donors is a highly promising method for biomimetic modification of blood-contacting biomaterial surfaces[18,19]. A variety of devices capable of controlled NO release have been widely developed through physical encapsulation or incorporation of NO donors[18,20,21]. This has led to the development of new therapeutic strategies and novel nitric oxide donors[15,16,22].

Pustovalova et al. investigated the structural characteristics of nitrogen-containing titanium dioxide thin films[23]. The results indicate that nitrogen-containing titanium dioxide thin films, when used as stent coatings, can directly serve as nitric oxide (NO) reservoirs. Their study also predicts that coatings of nitrogen-containing titanium dioxide thin films enhance the corrosion resistance of implants and reduce the risk of inflammation. Additionally, these films inhibit the electron transfer of fibrinogen to the surface, thereby decreasing platelet aggregation and fibrinogen coagulation. The NO released from the coating performs essential biological functions, promoting endothelialization and stimulating the growth of endothelial cells.

In the study by Ma et al. [24], it was found that mimicking the nitric oxide (NO) release and glycocalyx function of natural vascular endothelium on the surface of cardiovascular stents has been proven to effectively reduce in-stent restenosis (ISR). Both in vitro and in vivo experimental results indicated that stents loaded with NO significantly enhanced anti-thrombosis, anti-inflammation, anti-restenosis, and promoted re-endothelialization[25]. The study suggests that this durable endothelium-mimicking coating may be a promising platform for addressing the major clinical complications often associated with blood-contacting devices.

In the TITAX-AMI trial study by Lehtinen et al. [26], it was found that the titanium nitride oxide-coated bioactive stent (BAS) achieved complete endothelialization of the vessel following implantation. In contrast, late incomplete endothelialization after implantation of paclitaxel-eluting stents (PES) is not uncommon. The nitric oxide (NO)-

catalysing bioactive coating provides an endothelium-like microenvironment that facilitates the restoration of endothelium on the stent lumen surface and addresses long-term complications such as restenosis and thrombosis. We believe that this work may have broad implications for the design of vascular devices and promote the development of a new generation of vascular stents.

2.2 A variety of oxides

Among all inorganic materials, titanium dioxide coatings have a promising future in the application of cardiovascular stent coatings. In the study by Hou et al. [27], magnetron sputtering technology was employed to deposit a Ti-O film on the inner surface of a 316L stainless steel stent to promote endothelial cell growth. A novel pressure-resistant polymer drug-eluting stent was fabricated and characterized. On the outer layer of the stent, a Ti-O thin film was first deposited, followed by an ultrasonic spray deposition of a PTMC (polymethyltrimethylene carbonate) coating loaded with rapamycin. This dual-layer coating system facilitated re-endothelialization and inhibited the migration and proliferation of smooth muscle cells (SMCs), thereby reducing the risk of restenosis. In Xu's study[28], three different voltages (20, 40, and 60 V) were employed to prepare three different diameters of titanium dioxide nanotubes via anodization. The results indicated that titanium dioxide nanotubes can induce the polarization of macrophages towards the anti-inflammatory M2 state, increasing the expression of arginase-1, mannose receptor, and interleukin-10. The polarized macrophages release VEGF, which activates the ERK1/2 and PI3K/AKT pathways, as well as the extracellular signal-regulated kinase 1/2 pathway, thereby accelerating endothelialization.

Additionally, the application of titanium oxynitride (TiO_xN_y) as a nitric oxide (NO) donor in stent coatings to promote endothelialization has been validated in various experiments. The idea that TiO_xN_y coatings are relevant to mechanisms of vascular regeneration during the healing process was first proposed by Lehtinen et al. [26] and has since been promoted through experimental studies. In a comparative trial involving 425 patients with acute myocardial infarction, the results showed that bioactive stents (BAS) coated with TiOxNy exhibited better endothelialization compared to paclitaxel-eluting stents (PES). The research by Sarra-Bournet et al. [29] provides insights into the impact of nitrogen content in reactive magnetron plasma discharge on the structure and properties of deposited TiO_xN_y thin films. When the nitrogen content is increased to a $3N_2/O_2$ mass flow ratio, the rutile phase predominantly forms in the deposited film. The presence of nitrogen in the plasma inhibits the growth of the anatase phase of TiO2, resulting in a fourfold reduction in the grain size of the thin film.Moreover, the N_2/O_2 ratio significantly affects the physicochemical properties of the TiO_xN_y-coated stent surface, such as its electrical potential, roughness, wettability, and surface energy. In a clinical study by Karjalainen et al.[30], 201 patients received bioactive stents (BAS) coated with titanium oxynitride (TiO_xN_y), while 204 patients received paclitaxel-eluting stents (PES). The three-year follow-up revealed no stent thrombosis in the BAS group, indicating superior outcomes compared to the PES group.

In previous clinical trials [25,30,31], the new generation of titanium oxynitride (TiOxNy)-coated stents and the TITAX-AMI stent have been proven to be safe and successful in reducing in-stent restenosis (ISR). These stents are already available on the market. The clinical outcomes of these stents are comparable to those of drug-eluting stents (DES), such as the TAXUS-Liberte stent.

Iridium oxide has been investigated as a biocompatible, inert ceramic coating material for stents[32]. Unfortunately, the hydrogen peroxide generated during its corrosion process has been found to be harmful to arteries and to cause inflammatory responses[33].

In the study by Asano et al., the first-in-human trial results of SiO_2-coated bare metal stents (BMS) showed insufficient suppression of neointimal hyperplasia[34].

2.3Precious metals

According to research, gold exhibits excellent corrosion resistance and good biocompatibility[35]. However, the clinical outcomes of gold-coated stainless steel stents are not satisfactory.

2.4 Diamond-like carbon

A review of the properties of diamond-like carbon (DLC) surfaces and their suitability for medical applications has been reported[36]. This material possesses the desired mechanical and surface properties, and exhibits good biocompatibility[37,38], making it a successful coating material for medical implants[39]. In vitro experimental results indicate that diamond-like carbon (DLC) and DLC coatings can prevent thrombosis in vascular applications and exhibit good biocompatibility and hemocompatibility[40,41]. Cobalt-chromium stents coated with nanostructured and uniform diamond-like carbon (DLC) films using physical vapour deposition (PVD) can inhibit fibrin deposition and platelet activation[37]. This property can induce completer and more uniform endothelialization of the vascular endothelium and prevent thrombus formation. The antibacterial properties of DLC (diamond-like carbon) and doped DLC have been documented in the literature[42]. In the study by Kwok et al. [43], calcium- and phosphorus-doped DLC (diamond-like carbon) films were prepared using plasma immersion ion implantation and deposition (PIIID). Doping DLC with calcium or phosphorus enhances the blood compatibility of stent surfaces. Compared to the uncoated material, silicon as a dopant in DLC films can reduce inflammatory activity[44]. In the study by Nagashima et al. [45], diamond-like carbon (DLC) films deposited by radio-frequency plasma-enhanced chemical vapour deposition (RF-PECVD) and treated with oxygen plasma were found to increase thromboresistance. The experiments demonstrated that the properties of DLC films are strongly dependent on the deposition conditions and doping effects[36,46–48]. Results from in vivo trials and medical research on DLC (diamond-like carbon)-coated stents have also been reported[36,49–51]. The application of DLC coatings on stents is believed to have positive outcomes in terms of blood compatibility and anti-thrombogenicity. To confirm these findings, more comparative studies are needed, and the long-term performance of carbon-based materials, including their degradation behaviour in vivo, requires further investigation.

2.5 Hydroxyapatite

Pezzatini et al.[52] synthesised hydroxyapatite (HA) nanocrystals and characterised them on endothelial cells. Microvascular endothelial cells were exposed to HA nanocrystals. Cell morphology and cytoskeletal proteins were analysed using scanning electron microscopy and monitored by immunofluorescence. Endothelial nitric oxide synthase (eNOS) and cyclooxygenase-2 (COX-2) are biochemical markers of endothelial cell physiological and pathological responses, which can be detected by immunofluorescence. Crystalline HA can maintain endothelial cell viability without any cytotoxic effects. Immunohistochemical results of key biochemical signalling pathways in endothelial cells indicate that HA nanocrystals can maintain eNOS expression without increasing COX-2 expression. These results also show that HA nanocrystals can activate endothelial cells, which helps promote vascular endothelialisation. Rajtar et al. analysed hydroxyapatite (HA) deposited by sol-gel (SG) technology as a stent coating material. Nanoporous HA membranes with thicknesses ranging from 0.1 to 1.0 μm were designed for drug encapsulation. The samples exhibited good biocompatibility, but no significant improvement was observed in histological characterisation. A sirolimus layer without polymer deposition on top of the hydroxyapatite membrane, used as a stent coating, showed lower local toxicity and faster healing responses compared to uncoated stainless steel stents.

2.6 Carbide

Amorphous silicon carbide (SiC), which possesses anti-thrombogenic properties, is used as a stent coating to reduce the deposition of platelets, white blood cells, and monocytes on the stent surface[53]. However, further experimental and clinical data are still required to confirm its performance.

3. Organic polymer coating

3.1 Polyurethane

Yang et al. [54] synthesised a series of polyurethanes (PU) with a backbone composed solely of hard segments and side chains consisting of pendant poly(ethylene glycol) (PEG) soft segments (PEGPU). This novel polyurethane with a hard main chain and hydrophilic soft side chains (HMHS) achieves microphase separation in water and a transition between soft and hard phases. Their research found that during the water absorption process, the hydrophilic tertiary amine side chains of PU migrate to the surface, enhancing surface hydrophilicity, inhibiting

platelet adhesion, and activating the intrinsic coagulation pathway, thereby exerting anticoagulant effects in tertiary amine-containing polyurethanes (TAPUs). This is beneficial for preventing thrombosis following vascular stent implantation. Additionally, TAPUs with weak positive charges on the tertiary amine groups support the adhesion and growth of human umbilical vein endothelial cells (HUVECs) well, promoting endothelialisation of vascular stents.

In addition, as found in the research by Laura-Cristina Rusu et al. [55], polyurethanes (PUs) can be successfully used as anti-thrombotic coatings due to their excellent biocompatibility and biological inertness[56], effectively preventing thrombus formation[57]. The current trends in the application of polyurethanes include endothelialisation of cardiac implants and the utilisation of human pluripotent stem cells. Therefore, we can anticipate that polyurethanes will play a role in promoting vascular endothelialisation during the growth of vascular endothelium, thereby accelerating the restoration of normal vascular function.

3.2 Phosphorylcholine

Phosphoryl choline (PC) groups are the hydrophilic end groups of phosphatidylcholines, a fundamental unit of cell membranes. Grafting molecules containing PC onto material surfaces is one of the ways to achieve a chemical composition and morphology similar to that of cell membrane surfaces. Studies have shown that surfaces modified with PC groups and their copolymers can significantly enhance the blood compatibility of materials[58,59]. In the study by Marosfoi et al. [60], 40 New Zealand white rabbits with elastase-induced aneurysms were treated using either the classic Pipeline (C-PED) or the Pipeline Flex with Shield T technology (SPEED). The results showed that flow diverters with phosphorylcholine surface modification effectively prevented in-stent stenosis in small vessels.

3.3 Anti-proliferative coatings

3.3.1 Argatroban

Argatroban is a synthetic derivative of L-arginine piperidine carboxylic acid. It is a small molecule with high selectivity that can reversibly and directly inhibit the activity of thrombin. Argatroban can rapidly bind to both free thrombin in circulation and thrombin within blood clots, producing an anticoagulant effect. In the study by Daisuke Arai et al. [61], stents loaded with Argatroban were implanted into a rabbit aneurysm model. The degree of aneurysm occlusion was examined at one- and two-weeks post-implantation. The results showed significant organic development within the aneurysm in the drug-eluting stent group, with a marked reduction in the incidence of in-stent thrombosis.

3.3.2 miRNA-22

MicroRNAs (miRNAs) are non-coding RNAs approximately 22 nucleotides in length that bind to specific mRNA targets and regulate their translation and degradation. Studies have confirmed that miRNAs act as regulatory factors and play a crucial role in the development of cardiovascular pathophysiological processes[62,63]. Specifically, miRNAs can function as gene regulators, inducing the differentiation and phenotypic transition of vascular smooth muscle cells (VSMCs) in response to vascular disease or injury [62,64]. Jing Wang et al. [65] developed a miR-22-eluting coating on cardiovascular stents and conducted in vivo experiments using a porcine coronary artery injury model to evaluate its phenotypic regulation and anti-restenosis performance. A microRNA-eluting cardiovascular stent was developed using a self-healing encapsulation process. miR-22 was used as a model microRNA to regulate smooth muscle cells (SMCs), achieving uniform and controllable loading of miR-22 with a maximum dosage of up to 133 pmol/cm^2. In vitro cell experiments confirmed that the miR-22-loaded coating significantly inhibited the proliferation of SMCs, thereby promoting the predominant growth of endothelial cells (ECs). In vivo stent implantation experiments in the porcine coronary artery injury model demonstrated that the miR-22-loaded PEC (polyelectrolyte complex) coating enabled competitive growth of ECs over SMCs, which is conducive to endothelialisation at the stent implantation site and provides a new solution for reducing in-stent restenosis after stent implantation.

3.3.3 mTOR inhibitor drugs

First-generation drug-eluting stents (DES) loaded with sirolimus have been shown to reduce the rate of in-stent restenosis. However, these stents are still associated with the risk of late stent thrombosis due to hypersensitivity[66]. The study by Bae et al. [67] demonstrated that in an animal experiment involving iliac artery stent implantation in rabbits, the group with stents loaded with sirolimus exhibited a lower rate of in-stent restenosis compared to the control group. The results indicated that sirolimus released from the stent effectively inhibited the proliferation of smooth muscle cells.

In the second generation, the development of zotarolimus-eluting and everolimus-eluting stents further reduced this risk, demonstrating lower hypersensitivity, higher flexibility, acceptable recoil, and better compliance[66]. In long-term follow-up, everolimus-eluting stents demonstrated minimal neointimal response[68] and a lower incidence of thrombotic complications[69]. In contrast, zotarolimus-eluting stents have shown good antibacterial effects in the treatment of vascular diseases in diabetic patients[70].

Compared with bare-metal stents (BMS), bioabsorbable everolimus-eluting stents (BES) have significantly reduced the likelihood of restenosis following stent implantation[71]. In a randomised comparison of everolimus-eluting stents (EES), zotarolimus-eluting stents (ZES), and bioabsorbable everolimus-eluting stents (BES) in all patients, a study[72] involving 1,911 patients randomised to EES (n=638), BES (n=634), and ZES (n=639) found that, at 24-month follow-up, BES were non-inferior to EES and ZES in terms of device-oriented composite outcomes. Landmark analysis did not indicate any significant differences in efficacy and safety between BES and EES/ZES after one year.

3.3.4 Probucol

Since its discovery, probucol has been regarded as a lipid-lowering drug and also functions as an antioxidant[73], capable of reducing restenosis following angioplasty[74]. It has been identified as a vascular protectant. In the animal experiment by Weon Kim et al. [75], it was found that probucol exerts certain inhibitory effects on the proliferation and migration of smooth muscle cells through antioxidant-mediated vascular remodeling and additional vasodilatory actions.

3.3.5 Paclitaxel

Paclitaxel is a lipophilic antiproliferative drug that can rapidly cross cell membranes and irreversibly bind to microtubules, stabilising their structure. This action blocks cell mitosis and continuously inhibits cell proliferation, thereby preventing or treating restenosis. Studies have shown that low doses of paclitaxel can induce the tumour suppressor genes p53/p21, thereby affecting cell cycle progression at the G0-G1 and G1-S phases[76]. In contrast, high doses of paclitaxel impact the G2-M and M-G1 phases of cell division, leading to cell necrosis or apoptosis. Paclitaxel has been used clinically for an extended period. Although the incidence of in-stent restenosis after stent implantation is significantly reduced compared to bare-metal stents, paclitaxel not only inhibits the proliferation of vascular smooth muscle cells but also suppresses the proliferation, migration, and adhesion of endothelial progenitor cells (EPCs), which are essential for promoting vascular endothelialisation. This results in delayed vascular endothelialisation[77].

3.3.6 Tyrphostin AGL-2043

Tyrphostin AGL-2043 is a potent synthetic tricyclic quinoxaline inhibitor of the platelet-derived growth factor receptor (PDGFR) tyrosine kinase[78], as well as the kinases Kit and Flt3[78,79]. Inhibiting PDGF-BB-induced phosphorylation of the h-receptor can selectively and effectively inhibit the migration and proliferation of smooth muscle cells (SMCs) as well as mitosis, with only minimal inhibitory effects on the growth of endothelial cells. This approach minimises interference with vascular wall healing. AGL-2043 selectively inhibits vascular smooth muscle cells (SMCs) in a dose-dependent manner. In the study by Banai et al. [80], 180 mg of AGL-2043 was implanted in 24 Sinclair minipigs. After 28 days, histomorphological analysis revealed that in animals treated with AGL-2043, the degree of in-stent stenosis was reduced by 50%, the absolute neointimal area decreased by 44%, and the absolute lumen area increased by 57%. The experiments confirmed that Tyrphostins selectively inhibit the PDGF receptor

tyrosine kinase (PTK) and significantly reduce the proliferation and migration of smooth muscle cells (SMCs). This effect was observed in reducing neointimal formation in balloon-injured porcine femoral arteries and in reducing neointimal stenosis in porcine coronary arteries when delivered via biodegradable nanoparticles.These results suggest that local delivery of Tyrphostin AGL-2043 formulated in biodegradable nanoparticles may be suitable for anti-restenosis therapy. Another study by Banai et al. demonstrated that AGL-2043 selectively inhibits vascular smooth muscle cells (SMCs) in a dose-dependent manner. At drug concentrations of 0.5-1.0 mmol, AGL-2043 inhibited the proliferation of rat SMCs, and at 50 mmol of AGL-2043, cell proliferation was almost completely abolished.

4. Biological coating

Special stent coatings based on biomaterials are highly attractive in the fabrication of vascular stents. The primary function of biomaterial coatings is to act on the endothelial cells that cover the stent surface following implantation. The aim is to promote the proliferation and differentiation of endothelial cells, thereby accelerating the process of vascular intimalisation. This, in turn, helps to inhibit thrombus formation and restenosis caused by excessive proliferation of smooth muscle cells within the stent.

4.1 Glycoprotein IIb/IIIa monoclonal antibody

Monoclonal antibodies (mAbs) targeting platelet glycoprotein (GP) IIb/IIIa block the GP IIb/IIIa receptors on platelets, thereby inhibiting the binding of these receptors to endothelial cells. This mechanism can influence vascular patency following arterial reconstruction surgery. Additionally, these antibodies may improve blood perfusion by suppressing the interaction between platelets and platelet aggregates with the microvasculature. When applied to diseased arteries or lesion sites, these mAbs can effectively inhibit platelet deposition. In the study by Yin et al. [81], stents coated with a monoclonal antibody (mAb) targeting platelet glycoprotein (GP) IIb/IIIa and bare-metal stents (BMS) were implanted into the iliac arteries of inbred New Zealand white rabbits. After four weeks, the BMS group exhibited significant neointimal hyperplasia with a marked reduction in lumen area and a stenosis degree of 30%, while the mAb-eluting stent group showed a stenosis degree of less than 10%. After 12 weeks, neointimal hyperplasia continued to increase in the mAb-eluting stent group, with the stenosis degree rising to 15%, whereas there was no significant difference in the intimal thickness in the BMS group compared to the initial findings. These results indicate that mAb-eluting stents can effectively reduce the degree of in-stent restenosis. Additionally, studies have shown that mAb-eluting stents have the potential to prevent thrombus formation due to interactions between the stent and blood. This is achieved by inhibiting neointimal hyperplasia and reducing the stenosis rate[82]. In the study by Neumann et al. [83], it was found that abciximab, an antagonist of the glycoprotein (GP) IIb/IIIa receptor, improved the recovery of coronary vascular function and local vascular wall motion when administered perioperatively during interventional procedures, compared to conventional heparin therapy.

4.2 Heparin

Heparin is a sulfated glycosaminoglycan that exerts its anticoagulant activity by binding to antithrombin III, thereby inhibiting the activation of factor Xa (FXa) and further preventing the activation of factor IIa (thrombin), which plays a crucial role in antithrombotic effects. It can be covalently attached to polymers or adsorbed onto stent surfaces to provide non-thrombogenic surfaces. Additionally, due to its binding domains, surfaces modified with heparin can bind growth factors, slow down their diffusion, and protect them from enzymatic degradation, effectively maintaining their biological functions. This significantly enhances the adhesion and proliferation of vascular endothelial cells (VECs) and promotes endothelialisation at sites of vascular injury.

Heparin that has been applied clinically is mostly based on unfractionated heparin (UFH), low molecular weight heparin (LMWH), and synthetic ultra-low molecular weight heparin (ULMWH) pentasaccharides, such as fondaparinux. Among these, unfractionated heparin (UFH) is a sulfated polysaccharide that has been in use for decades. It has several advantages, including rapid onset of action after intravenous injection, reversibility, wide availability, and low cost. However, UFH is associated with severe complications, such as bleeding, heparin-induced thrombocytopenia, osteoporosis (more common in women), hypoaldosteronism, heparin-induced skin necrosis, and variable dosing responses in different patients, which require careful monitoring.The development of low molecular

weight heparin (LMWH) has provided several advantages over UFH, such as increased half-life and improved bioavailability. Moreover, LMWH does not require additional monitoring after administration[84].

In the future, heparin modification on the surfaces of artificial blood vessels will play a significant role. It will be combined with biological components such as vascular endothelial growth factor (VEGF) to achieve the purpose of modification, instead of simply immobilising heparin[85].

4.3 Anti-CD34 antibody

Anti-CD34 antibodies interact with CD34 on the surface of endothelial progenitor cells (EPCs) to specifically capture EPCs from the bloodstream, thereby accelerating vascular re-endothelialisation after stent implantation. In an in vitro cell experiment, Jialong Chen et al. found that magnetic nanoparticles modified with anti-CD34 antibodies could effectively capture EPCs and promote their adhesion to iron stents for rapid endothelialisation[86]. The in vivo and in vitro experimental data from Guowei Fu et al. show that the efficiency of capturing human umbilical vein endothelial cells (HUVECs) by a novel stent directly conjugated with anti-CD34 antibodies is approximately six times higher than that of conventional metal stents. This significantly enhances endothelialisation of the stent[87]. Chen et al. [88] found that sirolimus-eluting stents (SES), anti-CD34 antibody-coated stents (GS), and a combination of anti-CD34 antibody with sirolimus-eluting stents (hcase) were implanted into normal porcine coronary arteries. Samples were collected at 60, 90, and 120 days for scanning electron microscopy (SEM) and histological analysis. The results confirmed that stents coated with anti-CD34 antibodies significantly enhanced endothelial cell coverage, promoted endothelialisation, and reduced in-stent stenosis. In the study by Lin's team[89], the experimental subjects were male New Zealand white rabbits. They found that anti-CD34 antibodies can accelerate the attachment of vascular cells to stents, thereby achieving rapid endothelialisation. Functionalisation with anti-CD34 antibodies can specifically promote the attachment and growth of endothelial cells. This finding has important implications for achieving rapid endothelialisation within blood vessels and reducing in-stent stenosis caused by excessive proliferation within the stent. It also provides a new direction for research.

4.4 Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is characterised by eight conserved cysteines and functions as a homodimer[90]. It promotes the migration, proliferation, and angiogenesis of human umbilical vein endothelial cells (HUVECs) through the ERK1/2 and PI3K/AKT signalling pathways. VEGF has the potential to enhance the recruitment of endothelial progenitor cells (EPCs) and endothelial cells (ECs), facilitate neovascularisation and tissue regeneration, and maintain physiological levels in various tissues. This accelerates endothelialisation and vascular repair, forming new vessels to overcome ischemic diseases. Among pro-endothelialisation factors, VEGF is the most effective to date[91].

In the study by Liu et al. [92], efforts were dedicated to constructing a biofunctional layer on titanium surfaces using anti-CD34 antibodies, heparin, and VEGF through nanotechnology to create a more biocompatible surface. The results confirmed that the biofunctional titanium surface significantly enhanced endothelialisation and antithrombotic capabilities, induced the differentiation of endothelial progenitor cells into endothelial cells, and suggested that the combination of anti-CD34 antibodies and VEGF can markedly promote re-endothelialisation on titanium surfaces. This finding was also corroborated by Liu et al[93]. In a study on the application of in situ capture technology for circulating endothelial progenitor cells (EPCs) in a porcine coronary artery model[94], the Takabatake team first coated the surface of bare-metal stents with polyethylene glycol (PEG) to form a film. Subsequently, they chemically bound vascular endothelial growth factor (VEGF) and anti-CD34 antibodies to the PEG-coated stents, respectively, and implanted them into porcine coronary arteries. The results showed that in terms of early endothelialisation, VEGF outperformed the anti-CD34 antibody-coated stents. The VEGF-coated stents achieved highly selective capture of endothelial progenitor cells, subsequently accelerating the formation of natural endothelial tissue. In addition to the study by Wen et al. [95], a nickel-titanium alloy sheet co-loaded with VEGF and anti-CD34 antibody biofactors based on polydopamine was constructed. Experiments on HUVEC proliferation, migration, and EPC capture were conducted, and the results confirmed that the alloy sheet could effectively capture EPCs, promote the proliferation and migration of HUVECs, and exhibit superior biocompatibility compared to bare stents. Therefore, it is anticipated that vascular endothelial growth factor (VEGF) can be applied to promote vascular endothelialisation and reduce in-stent restenosis[96].

4.5 Extracellular Matrix Proteins

Extracellular matrix proteins (ECM), such as laminin, fibronectin, bovine serum albumin, and collagen, as well as peptides derived from them, can mimic the natural ECM to influence cell behaviour[97,98]. The most commonly used peptides are the tripeptides RGD (Arg-Gly-Asp), REDV (Arg-Glu-Asp-Val), and YIGSR (Tyr-Ile-Gly-Ser-Arg). The presence of RGD can promote the proliferation of human umbilical vein endothelial cells (HUVECs) [99]. The REDV sequence binds to endothelial cells (ECs) by interacting with the α4β1 integrin subunits, while also inhibiting the adhesion of smooth muscle cells and platelets [100]. The peptide YIGSR, derived from the β1 chain of laminin, has been shown to mediate endothelial cell (EC) behaviour while inhibiting platelet adhesion [101,102]. In the study by Ge Peng's team[103], peptide sequences such as YIGSR, RGD, and REDV were covalently immobilised on the surface of electrospun silk fibroin scaffolds. Compared to scaffolds modified with a single peptide, those modified with YIGSR + RGD significantly enhanced the proliferation of human umbilical vein endothelial cells (HUVECs), while scaffolds modified with YIGSR alone markedly improved the migration of HUVECs. Therefore, loading appropriate ECM components on the surface of scaffolds holds promise for rapid endothelialisation.

5. conclusion

As researchers continue to explore the mechanisms of endothelialisation, there is a growing focus on developing new materials, methods, and solutions to promote endothelialisation of vascular stents. This is aimed at improving the clinical efficacy of existing stents, providing patients with safer and more effective treatments, increasing the success rate of disease treatment, reducing recurrence rates, and minimising postoperative complications. This paper reviews recent research on promoting rapid endothelialisation, covering the current status and applications of various types of vascular stent coatings.

Since the introduction of the first stent, newer categories of stents have been designed and applied in clinical treatments. These stents, coated with various substances, aim to inhibit platelet aggregation and thrombus formation, recruit endothelial progenitor cells and endothelial cells, and promote rapid endothelialisation within the stent, while also ensuring appropriate physical and chemical properties. However, to date, there is still no ideal stent coating for promoting rapid endothelialisation at the neck of aneurysms. We believe that biological coatings hold great promise for promoting rapid vascular endothelialisation and preventing excessive proliferation within the stent.

We hope that in the near future, with further research into stent coatings, the challenges we currently face will be overcome one by one. This will provide better treatment options for patients and advance the development of intracranial aneurysm treatment strategies.

Acknowledgements

This research was supported by No.33122212, the Guangzhou Basic Research Program Jointly Funded by Guangzhou Municipal Science and Technology Bureau and Universities (Institutes) in Guangzhou, China.

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