

Study on the application of degradable occluder in the interventional treatment of congenital heart disease

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Keywords: Degradable occluder; congenital heart disease; interventional therapy

Abstract: This paper discusses the application characteristics of biodegradable materials in blocking devices related to congenital heart disease, and details the characteristics of levo-poly-lactic acid (PLLA), polyglycolic acid (PGA, PGA), polycaprolactone (PCL), poly-dioxycyclohexanone (PDO) and other materials and their application in the treatment of congenital heart disease. These materials have good biocompatibility and degradability, suitable for the production of congenital heart disease related device. Through animal experiments and clinical observation, the degradable occluder shows good safety and efficacy in the interventional treatment of congenital heart disease. For example, studies of PLL and PDO devices showed that these occluder effectively performed endothelialization after implantation and showed good biocompatibility and degradability. However, some occluder materials such as PCL have limitations in flexibility and require further improvement. Therefore, as a new option for heart disease, but more research is still needed to improve its performance and application.

1. Introduction

In the interventional treatment of congenital heart disease, the occluder is widely used in the treatment of closed heart defects. However, Traditional occluders are mainly made of non degradable materials such as metals, which have the problem of lifelong retention in the body, long-term follow-up after implantation, and foreign body reaction, which affect the treatment effect and quality of life of patients. Therefore, the occluder of degradable materials has attracted much attention as a new therapeutic method. The purpose of this study is to investigate the application of degradable occluder in the interventional treatment of congenital heart disease, evaluate its clinical efficacy and safety, and provide a reliable basis for clinical practice. Through the development of this study, it may provide more safe and effective interventional treatment means for patients with congenital heart disease, and improve their prognosis and quality of life.

2. Application characteristics of degradable materials in the occluder related to congenital heart disease

The selection and application of medical materials depends on their specific use and need to meet specific requirements. For temporary implantation materials with biodegradation ability, in

addition to excellent tissue compatibility, non-toxicity, non-heat source, no carcinogenic and teratogenic risk, they should also be able to decompose into non-toxic molecules or fragments that can be absorbed or metabolized by the human body within a given time^[1]. This material needs to have stable physical and chemical characteristics, easy to process, economical, and resistant to disinfection and sterilization. With the development of materials science, more and more biodegradable biomedical polymer materials are widely used in the medical field. At present, the materials that have been used in the treatment of congenital heart disease mainly include: levo-poly-lactic acid (PLLA), polyglycolic acid (PGA), polycaprolactone (PCL), poly-p-dioxyclohexanone (PDO) and other polymer materials. These materials were selected for their good biocompatibility and the harmless of their degradation products to tissue, some of which have been licensed by the Food and Drug Administration (FDA)^[2]. The following specific description of the characteristics of each material:

2.1 Levine poly-lactic acid (PLLA)

PLLA, the left-handed isomer of PLA, is of high strength and takes more than two years for complete degradation. Both PLA and PLLA are well biocompatible, and their degradation products are carbon dioxide and water.

2.2 Polyglycolic Acid (PGA)

PGA, also known as polyethylene fat, has strong mechanical strength and moderate elongation properties, and is well compatible with biological tissues. However, it has difficulty in the spinning process, poor flexibility, weak antibacterial performance, easy to degrade due to hygroscopic, the preservation condition requirements are high, so its degradation process needs to be improved^[3].

2.3 Polycaprolactone (PCL)

The PCL will soften and melt at temperatures below 60 degrees Celsius. The melting point can be increased by α -ray irradiation or mixing with other polymer materials. PCL is both biocompatible and biodegradable, with a degradation cycle of more than two years, and some studies have begun to explore its use to make vascular stents.

2.4 Cyclohexanone (PDO)

PDO is a material synthesized by ethylene glycol, metal sodium, and chloroacetic acid. It has good physical strength and elasticity, and is easy to be formed by thermal pressure. The PDO can be woven into a self-expanding stent structure that is both safe and biocompatible, and can be fully decomposed into carbon dioxide and water. It is particularly suitable for the production of congenital heart disease (CHD) related occluder, and there has been active research on the PDO woven esophageal stent treatment with esophageal stenosis.

2.5 Polyhydroxybutyrate (PHB)

Polyhydroxybutyrate (PHB) has a mechanical tensile strength equivalent to polypropylene and has a long degradation cycle, and the final decomposition products include hydroxybutyrate, carbon dioxide and water. Studies have shown that PHB is an ideal material, suitable for the manufacture of an occluder related to congenital heart disease.

2.6 Lactate-glycolic acid copolymer (PLGA)

Lactate-glycolate copolymer (PLGA) is a material obtained from copolymerization of ethyl and propylene esters in different proportions with adjustable mechanical strength, elastic modulus and thermoformation. PGA degrades faster, but its mechanical strength decreases quickly, while PLA is less hydrophilic and slowly degraded; by adjusting their ratio, better medical degradable materials can be obtained. The mechanical properties and degradation speed of PLGA can be improved by adjusting the molecular weight, structure and composition. The final degradation products are carbon dioxide and water, while the intermediate product lactic acid is the product of normal metabolism in the body and does not accumulate on any important organ. Many studies have shown that PLGA has superior mechanical strength, flexibility and degradation speed control, as well as good biocompatibility and processing convenience, and has been applied in bone tissue engineering, heart valve manufacturing and vascular tissue engineering^[4].

The degradation time and other physical properties of PLGA can be altered by regulating the ratio of lactate to glyoxylic acid. The PDO degradation cycle is roughly between 6 and 9 months, providing effective support for more than 5 weeks. PGA, however, degrades rapidly in only about 2 weeks. Animal experiments show that the endothelialization inside the occluder takes 1 to 3 months after implantation. Therefore, bioabsorbent materials require slow degradation and provide long-term effective support. Materials such as PLGA and PDO are very suitable for making occlusions related to congenital heart disease.

3. The application of degradable occluder in the interventional treatment of congenital heart disease

3.1 The PLLA occluder

Li^[5]And others developed a fully biodegradable atrial septal sealing device called "Absnow", which consists of support nets, sealing end, plug head, connecting sutures, flow resistance film, observation marks, and locking components. It uses the PII. A double disc structure with waist diameter designed to match the size of the heart defect. The double disc and lumbar sites were sutured through the PLLA line with the PLLA flow membrane. Both ends of the sealing device, namely the sealing end and the plug head are made by PII. A is made of material and the sealing ends contain a connection locking device at the other end with threaded holes for the control wire attached to the control cable.

In Li^[6]In the same study, the "Absnow" fully biodegradable atrial septal occlusion system was used for animal experiments. A total of 45 animals were implanted, divided into 27 animals in the degradable plugging group and 18 animals in the control group. The results showed that the success rate of the operation was 100% (45 / 45), and the effective closure rate was 100% (45 / 45). Of the surgical success rate, 25 were once successful, and three others had successful occlusion after adjustment. Immediately after the procedure, none of the animals had residual shunt or mitral or tricuspid regurgitation. Follow-up echocardiograms at 7 days, 1,3,6, and 12 months after surgery also showed no residual shunting, thrombosis, pericardial effusion, mitral insufficiency or tricuspid valve closure, and no arrhythmia was observed. Anatomic examination records showed that the occluder began to cover the new endothelial tissue 1 month after implantation and completely at 3 months.

In contrast, the conventional nitinol occluder in the control group did not begin to have a thin partial coverage of the new endothelial tissue until 3 months later, and the metal material was still visible at 12 months. Therefore, the biodegradable occluder is significantly better than the nitinol occluder in terms of endothelial cell growth. No thrombus or vegetation formation was seen in all

the follow-up time points. Histopathological examination also indicated that at 3,6, and 12 months after implantation, the occluder was surrounded by large numbers of collagen fibers and fibroblasts, while moderate numbers of inflammatory cells such as neutrophils, lymphocytes, plasma cells, and multinucleated giant cells were observed, but no necrotic tissue was found. Hematoxylin-eosin (HE) staining of important organs such as lung, liver, pancreas and kidney also did not show infarction or other abnormal conditions. Specifically, the experiment confirmed the safety and effectiveness of the degradable occluder.

3.2 The PDO occluder

Zhu^[7]The atrial septal sealing device developed by et al. is composed of a frame woven from PDO (polyterephthalate), PLA (polylactic acid) non-woven fabric and PGA (polyglycolic acid) suture forming a flow resistance membrane. The device is decorated with metal tantalum particles at the symmetrical position of the left and right discs, and is used as a marker for X-ray imaging . Zhu et al used this device to seal on the atrial septum of 16 dogs, 14 were successful and 2 failed. During the subsequent half-year monitoring period, no blocking device shedding or residual shunt was observed, and no animal behavior abnormalities or hemiplegia symptoms occurred. Within four weeks, the occluder began to fuse with the endocardium; after 24 weeks, the surface was covered with a porcelain white endothelial tissue and the PDO wire had become illegible. Pathological examination revealed that local inflammatory reactions occurred around the device at 8 weeks, but by 12 weeks, the inflammation disappeared, the device surface had completed endothelialized and new angiogenesis, and most of the PDO filaments were degraded. No abnormalities were found in the tissues of the lung, liver, spleen, and kidney.

Dai Ke^[8]The atrial septal sealing device designed by et al. also uses PDO wire to weave the frame and uses polylactic acid nonwoven membrane as the flow resistance membrane. This device enables effective sealing of the septal defect through a double-dilatation structure. Using ultrasound guidance, Dai Ke et al. successfully used this blocking device on atrial septal defects in 10 pigs for 6 months. No residual, displacement or shedding of the occluder was observed. On the 30th postoperative day, the edge of the device began to be gradually covered by neointimal tissue; by day 90, the device was almost completely coated by neointimal tissue; and on postoperative day 180, the occluder was completely covered by smooth and dense endothelial tissue.

3.3 The PCL occluder

Research team from the Singapore University of Technology^[9]An ASD / PFO (atrial deficiency and atrial septal defect / patent foramen ovale) closure device named "Double Umbrella" was developed. The device consists of the umbrella disk of the left and right atria and a rod connecting them. The plate is made of PCL (polycaprolactone) material with support rods and flow resistance film made of the same material. The two umbrella discs are connected by an inelastic connecting rod. Once the occluder is successfully positioned, it can self-expand and unfold into a double-disc structure to seal the defect of the heart chamber. The experiment showed that one month after the occlusion device implantation, X-ray and echocardiography showed that the device could be stably positioned in the target position without shunt phenomenon, showing good structural integrity and mechanical strength, and show good endothelialization characteristics. However, a limitation of the occluder is its poor flexibility. Once the defect is not successfully blocked after self-expansion formation, the structure may be destroyed when trying to withdraw the plugging device, so a new occluder needs to be reimplanted in this case. More studies are needed to demonstrate the safety and efficacy of the "Double Umbrella" occlusion device after implantation.

3.4 Absorbable occluder for PFO

The foramen ovale is usually closed in the first year after birth. If the foramen ovale is still not closed in children over 3 years old, it is called patent foramen ovale. In adults, 20% to 25% of the foramen ovale are not fully closed. Patent foramen ovale is the most common congenital heart anomaly in adults, and it can be detected in approximately 1 out of 4 normal individuals. For a long time, people have believed that patent foramen ovale generally does not cause shunting between two rooms and has no impact on the hemodynamics of the heart, so it is considered "irrelevant". In recent years, many studies have shown a close relationship between patent foramen ovale and patients with unexplained stroke. This is because through the patent foramen ovale, the following emboli can enter the left heart system and cause corresponding clinical symptoms: ① thrombosis in the deep or pelvic veins of the lower limbs; ② Air embolism caused by diving or decompression sickness; ③ Fat emboli formed after surgery or trauma. Moreover, for patients with patent foramen ovale who have experienced thrombotic events, the risk of recurrence remains high. Therefore, targeting etiological treatment and sealing the open foramen ovale in high-risk populations is expected to reduce the incidence of patients. Additionally, it has been found that patent foramen ovale is associated with the onset of decompression sickness, migraines, and other conditions. Closing the patent foramen ovale may be beneficial for these patients.

The application of absorbable occluders in PFO intervention therapy is expected to reduce the long-term complications that traditional occluders may bring. This material of equipment can be absorbed by the human body after completing its structural support role, reducing the probability of sustained stimulation and infection of heart tissue. In addition, they may not leave foreign objects after use, making them safer for patients undergoing magnetic resonance imaging (MRI) after implantation. However, absorbable occluders also face some challenges, such as how to ensure their structural stability and functionality during the absorption process, and how to evaluate their long-term sealing effect and safety. At present, research on the use of absorbable occluders in PFO intervention therapy is still in its early stages. Initial clinical trials are necessary to evaluate its safety and efficacy. Researchers need to compare the differences between absorbable occluders and traditional permanent occluders through randomized controlled trials and long-term follow-up, and determine their optimal application in specific patient populations.

4. Conclusion

This paper provides a detailed study and comparison of several different types of atrial septal closure systems, including their materials, structures, properties, and applications. These sealing systems show good results in both animal experiments and clinical applications, providing an effective means for the treatment of atrial septal defects. However, further studies and clinical validation are still needed for the long-term safety and efficacy of the occluder. With the continuous progress and innovation of technology, it is believed that more efficient, safe and degradable blocking systems will be applied in clinical practice in the future to bring better treatment effects for patients.

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