Xtrace: Novel Bioresorbable Device for Patent Foramen Ovale Closure

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Keywords: Patent Foramen Ovale, Cryptogenic Stroke, PFO Closure, Bioabsorbable Occluder.

Abstract: Patent foramen ovale (PFO) is a congenital cardiac lesion, affecting about 25% to 30% of the adult population. It is associated with several serious complications, including cryptogenic strokes, transient ischemic attacks, and migraine. The prevalence of PFO has significantly increased in patients with cryptogenic stroke; up to 40% of ischemic strokes with an unknown cause have a PFO. Recently, technical advancements in medical engineering have made the percutaneous transcatheter closure of PFO a feasible treatment option. However, current PFO closure devices may lead to complications such as the need for replacing the device after several years, sudden migration of the implant, erosion, infection, or arrhythmias. Attempts are needed to produce a safer and more effective closure devices. Here, we propose an innovative medical device called Xtrace. It consists of a biodegradable material that will be partially degraded by the host body while substituted by autologous host tissue. This innovative device will potentially fulfill the essential unmet clinical need, as well as provide a safe and effective delivery of therapy for the general population.

1 INTRODUCTION

The foramen ovale is a compulsory channel between the two atria during fetal development. It provides placental oxygenated blood to reach the arterial circulation of the fetus. Naturally, the hole is completely sealed at birth, as it can be seen in Figure 1. However, closure does not occur for approximately a quarter of the general population (Hagen, 1984). This is due to a defect in the postnatal fusion of the septum primum and secundum, forming tunnel-like gap called patent foramen ovale (PFO). Although the reason behind PFO is unknown, studies suggest that it may be genetic. PFO has been implicated in several serious complications, including cryptogenic strokes, transient ischemic attacks, and migraine. The primary cause of stroke is still unknown in about 40% of patients with a stroke diagnosis (Giblett, 2019). The occurrence of a PFO with either transient or continuous right to left shunt can potentially lead to paradoxical embolism (Belkin, 1990). Over the past three decades, technical advancements in medical engineering have made the percutaneous transcatheter closure of PFO a feasible treatment option. Several percutaneous PFO closure devices have various advantages and are expected to work equally well if placed in their most suitable anatomy (Ko, 2010). However, PFO closure devices may lead to some complications such as the need for replacing the device after several years, sudden migration of the implant, erosion, infection, thrombogenicity, or arrhythmias. Attempts to produce safer and more effective closure devices are underway.

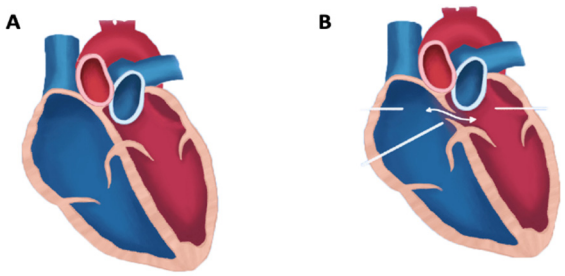

Figure 1: Representation image of a human heart. (A) Normal heart with a closed foramen ovale. (B) Heart with an open foramen ovale.

Ajamieh, S., Mindroc-Filimon, D., Mozo, I. and Rocha, I.
Xtrace: Novel Bioresorbable Device for Patent Foramen Ovale Closure.
DOI: 10.5220/0009374603440349
In *Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2020) - Volume 1: BIODEVICES*, pages 344-349
ISBN: 978-989-758-398-8; ISSN: 2184-4305

2 STATE OF THE ART

Currently, there are different varieties of therapeutic approaches that can be adopted for the treatment of PFO.

2.1 Pharmacological Treatment

Anticoagulant or antiplatelet therapies can be used to treat PFO. However, drug treatment is only symptomatic, and may be contraindicated in some cases and requires life lasting engagement. Cross-sectional multicenter studies have shown that PFO closure is associated with a significant risk reduction when compared with pharmacological treatment (Saver, 2017).

2.2 Implantation of Occluders

Percutaneous PFO closure procedures have been originated from well-established atrial septal defect (ASD) closure techniques. In experienced centers, this is a very low-risk procedure that can be carried out in a short time (Meier, 2005). Therefore, catheterization laboratories worldwide have seen a substantial rise in the number of trans-catheter PFO closures being performed (Opotowsky, 2008). In some practices, a submissive sizing balloon together with periprocedural echocardiographic guidance (either trans-esophageal or intra- cardiac) is used in patients during PFO device closure (Ko, 2010). From the design features perspective, several types of devices can be distinguished:

Self Expanding Double Disk Occluders: These devices consist of commonly used PFO closure devices; they include two metallic opposing discs covered by fabric and attached by a thin waist. A combination of oppositional mechanical forces formed by the 2 opposing discs and fibrous tissue encapsulation seal the PFO. The GORE^{R} CARDIOFORM Septal Occluder and the Abbott Amplatzer^{TM} PFO Occluder, both using a nitinol framework, are the only devices of this nature currently permitted by the US Food and Drug Administration (FDA) for PFO closure in the United States.

Occluders with PFO Tunnel: These devices are placed on the PFO tunnel and stabilized by adjustable atrial anchors. This technique brings the septum primum and secundum in close apposition, reducing the amount of material exposed to blood circulation. The Coherex FlatStent^{TM} occluder (Coherex Medical, Inc) is the most popular device of this family.

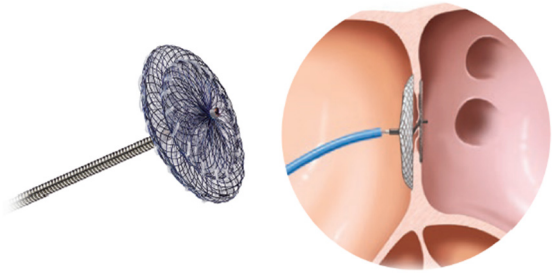

Figure 2: Amplatzer device and respective intervention. (Amplatzer, 2019).

Bioabsorbable PFO Occluders: Bioabsorbable occluders follow the same deploying technique as metallic occluders. However, they substitute the metallic material constituting the disk with resorbable polymers, which are expected to be replaced by native tissue upon reabsorption. The risk of thrombosis is reduced, as well as arrhythmia and device migration. However, bioabsorbable devices are still ongoing clinical evaluation phases

HeartStitch^{R} Occluder (Sutura, Inc): The HeartStitch occluder utilizes complex suture technology to seal the septum primum and secundum. However, this technique requires greater surgeon proficiency and is still not available for clinical use.

The current solutions present a series of disadvantages. The pharmacological treatment represents just a symptomatic solution and does not actually solve the problem. On the other hand, the metallic disk occluders can be refused by the patient's body, cause inflammation, migrate from the foramen ovale or require a replacement after a specific time. Plus, these devices are composed of metallic materials, and can cause long term inflammatory response as well as magnetic resonance artifacts. The bioabsorbable occluders are not available anymore, since a higher risk of shunts was associated to their use. Moreover, the available devices were still leaving a metallic framework behind in the body (Meier, 2005).

3 PROPOSAL OF THE PRODUCT

3.1 Design of the X-trace Device

The proposed device will be composed by two opposed disks of an acellular porcine collagen type I matrix, each of which will be supported by two arms of the biodegradable JDBM-2 Mg alloy (Mao, 2017). Each of the arms will account with 3 interposed spring hinges that will serve to attach the device to the host tissue.

3.1.1 Disks Design

The disks will be composed of porcine collagen type I matrix. This material offers full guarantees as it has already been used in PFO closure procedures (Morgan, 2010). Full growth of autologous tissue has been shown six months after implantation of this type of collagen matrix. This suggests that the material induces a sufficient host tissue response to repair the size of the defect.

3.1.2 Framework Design

The framework will be composed by a Mg alloy, Mg-2.2Nd-0.1Zn-0.4Zr, denoted JDBM-2, that has already shown promising results upon application on vascular stents (Morgan, 2010). Magnesium is one of the most promising metals used on bioabsorbable devices, as the corrosion products of Mg alloys can be absorbed or excreted by the human metabolic system (Staiger, 2006). Mg alloys also show excellent anti-platelet deposition (Gu, 2009) and low thrombogenicity (Staiger, 2006). After being exposed to a double extrusion procedure, the JDBM-2 alloy shows excellent mechanical properties (YS = 66 +- 3 Mpa, UTS = 181 +- 5 MPa, elongation = 10.2 +- 1.3%), which makes it a promising candidate for cardiovascular intervention. Moreover, the treatment applied to the JDBM-2 alloy implies a great improvement of its corrosion properties, which are often a problem in Mg alloys.

Classically, the galvanic corrosion rates of Mg alloys are too high compared with those of other metals, which derives on device failure between the tissue has completely healed. However, the JDBM-2 alloy corrosion properties (0.37 mm/year) make it suitable for this kind of applications, as complete structural and mechanical integrity of stents manufactured with this alloy has been shown after 6 months of implantation (Mao, 2017).

3.2 Delivery System and Deployment of the Device

The delivery and deployment of the device will be done following the same techniques and principles used on metallic devices implantation. As usual, the whole process will be guided through fluoroscopy and intracardiac echocardiography (ICE), and patients will be under general sedation. The delivery system, based on the AMPLATZER Delivery system, will be composed of:

Loader: Used to introduce the device intro the catheter

Hemostasis Valve: This part accounts with an extension tube and stopcock that controls bleeding
Delivery Sheat: Used to deliver the device itself
Dilator: Used to allow tissue penetration
Delivery Cable: This cable is used for delivery of the device, which is screwed to the distal tip of the cable. To hydrate the collagen disks, the device will have to be exposed to a soaked saline solution during approximately 5 minutes. The device will be then collapsed and loaded into the delivery system thanks to the loader cable. The device will be administered together with heparin and antibiotics to prevent coagulation and infections.

3.3 Follow-up

The follow up of the procedure will consist of periodic transthoracic echocardiography and chest RX at 24 hours, three months, six months, and one year after implantation, as done with similar devices. It is also important to perform blood marker control in order to check for any possible complications such as coagulation and infections.

3.4 Benefit and Concerns

The use of 100% bioabsorbable materials translate into multiple potential benefits of our device, X-Trace. Those include decreased long-term thrombogenicity, lower inflammatory response, lower erosion potential and reduced arrhythmogenicity. Plus, as the device will be substituted by fibrous endothelialized tissue, the risks of lifespan and chronic mechanical stress are almost avoided. Moreover, the X-Trace device will increase eligibility for PFO closure treatment: until now, all the devices being used contain metallic materials that have a long life inside the body which are not compatible with the treatment of atrial fibrillation (echocardiographic ablation). The proposed device, which does not leave any metallic residues behind, will enhance a better treatment of comorbidities. The most significant concern is resorption or mechanical failure of the device before its replacement by autologous endocardial tissue, which could lead to a recurrent device over it.

4 RISK ANALYSIS AND ESSENTIAL REQUIREMENTS

According to 21 CFR 860, our product classifies as Class III Medical Product. This translates into a high

Table 1: Risk Assessment.

Hazardous situation	Hazard	Initial risk level	Safety control measures	Final risk level
Wrong insertion of catheter	Bruising, damage to artery	Acceptable	Experienced medical staff, trainings	Acceptable
Forgetting to assembly parts of the intervention set	Incomplete intervention set, necessity of removal and reinsertion	Unacceptable	Trainings, intuitive design of the product, warnings, clear instructions of use	Acceptable
Use of contrast agent for imaging	Allergic reaction	Acceptable	Thorough pre-examination of the patient record	Acceptable
Misplacement of the product in situ	Migration of the device, incomplete closure	Unacceptable	Training, accurate imaging	Acceptable
Device does not open in situ	Tissue harm by removal and reinsertion	Unacceptable	Testing, training, clear instructions of use	Acceptable
Shape of collagen matrix is compromised	Tissue harm by removal and reinsertion	Unacceptable	Testing, training, clear instructions of use	Acceptable
Different absorption rate of the materials	Incomplete closure of the ovale	Unacceptable	Thorough preclinical and clinical trials	Acceptable
Migration of the device	Artery, blockage, tissue harm	Unacceptable	Thorough preclinical and clinical trials	Acceptable

risk medical device, which poses numerous risks and its design requires a thorough risk analysis .Our work follows the requirements from 21 CFR 820 in terms of this risk analysis. Some of the identified risks are presented in Table 1.

5 DEVELOPMENT PLAN

5.1 Timeline

The development plan will include the following steps:

1. Initiation opportunity and risk analysis: During this phase, the minimum requirements in terms of mechanical properties, performance and bioabsorbability for the device will be assessed through literature review and advice from professionals and key opinion leaders (KOL). Moreover, basic financial, regulatory and legal aspects will be evaluated, in conjunction with early risk assessment and regulatory and clinical path. Furthermore, a market and competence analysis will be performed. Funding opportunities will be assessed.
2. Formulation of concept and feasibility: The initial project plan will be elaborated and responsibilities will be allocated to individual team members. Plus, considering the needs and problem specification – mechanical properties, self-deployability, bioabsorbability, etc- and the professional's opinion, an early prototype will be selected. The extended risk analysis will be initiated; all the possible risks, as well as alternatives to avoid and minimize them, will be listed. The preliminary economic, financial and regulatory strategies will be further defined. Pre-clinical studies to prove the non-toxicity and to characterize the mechanical properties of the materials to be used will be also performed. Moreover, basic prototypes to sustain proof of concept will be elaborated.
3. Design and development: At this phase, the product design will be implemented and evaluated, ensuring that the basic essential requirements are satisfied. Moreover, the risk management, in which design, use and process will have to be considered, and regulatory

strategies will be defined and implemented, considering the specific device design. Furthermore, the clinical validation plan will be designed considering the applicable legislation as well as the particularities of the designed device.
4. Final validation and product launch preparation: At this phase, approval from the competent authorities (in this case, FDA) will be required to commercialize the product. Hence, all the applicable documentation (clinical studies, safety, etc) will have to be presented. Moreover, a market launch plan must be prepared: direct contact with professionals and health provider must be made to make them aware of our product.
5. Product launch and post-launch assessment: During this phase, physicians must be trained in the use of our product and sales strategies must be set in practice. Moreover, to ensure safety, post-market surveillance and follow up studies must be done. Follow up is fundamental to identify and correct any potential mistakes appearing on the process.

5.2 Tests and Experiments

During the product development phase, a series of tests and studies is necessary in order to be able to finally access the market. These tests are the recommended endpoints by ISO 10993-1:2009 and FDA. Firstly, cytotoxicity and cytocompatibility in-vitro tests will have to be performed to evaluate the toxic potential of the materials used in our product and their biological acceptance by human tissue. Permanent lineage cells will be used to classify the modifications from non-cytotoxic to severe cytotoxicity, while human differentiated cells will be used to evaluate the cytocompatibility. For both tests, it is afterwards intended to use small animal models as rats for initial in-vivo testing of the bioresorbable materials. A mechanical analysis in silico would be necessary to test the material properties.

Secondly, a large animal model as a sheep is necessary to validate in vivo biocompatibility and the whole intervention process. Preferably, interventional cardiologists would perform PFO closure on created defects in the atrial septum of 10-20 animals. Irritation, acute systemic toxicity, genotoxicity, implantation and hemocompatibility can be evaluated through these experiments. The collected data will be used for further modifications of the device.

After successful experiments on animal models, a pilot clinical study with 5-10 patients would have to be performed to evaluate the device in terms of biological reaction and the intervention process in humans. This study will be a long term study with follow-up of the patients to assess the degradation rate of the materials, potential inflammations or other complications. The collected data will be used for further modifications of the device. The following trials would be clinical trials on a bigger number of patients to collect the necessary data for clinical approval. Inclusion criteria, the choice of the comparator, blinding, the duration of the study and follow-up are all matters which will be taken into consideration when creating the protocol. After successful entry on the market, post-market follow-up studies will have to be performed to collect complaints and mitigate emerging risks.

6 DISCUSSION

Previous studies have tried to develop effective solutions that prevent the adverse side effects and complications of the current FDA approved PFO occluders but without a successful outcome (Giblett, 2019 and Schwerzmann, 2005). The use of metallics materials (mainly nitinol) can lead to late erosion. Moreover, the bioabsorbable occluders are not available in clinic due to higher risk of shunts. Evidence suggests that the closure of PFO using the bioabsorbable device is correlated with a low complication rate and a low recurrence rate of embolic events. Nevertheless, a high percentage of mild or moderate residual shunting is present in the following 6-months after the procedure. We analysed previous clinical studies (Van den Branden, 2010), performed literature review, as well as gained feedback from professionals and key opinion leaders (KOL) on designing the novel medical device in order to solve these complications.

In order not to leave any foreign material behind, the used material must be bioabsorbable, i.e., capable of being absorbed into living tissue. To prevent complete failure of the device before complete tissue replacement, the service lifetime of the device must be between 6 and 12 months. As the material will be in direct contact with living tissue, it must be bio- and hemocompatible. The used material must prevent platelet aggregation and thrombogenesis. Moreover, it must not cause excessive tissue inflammation. Therefore, it is essential to assess the mechanical properties, performance and bio-absorbability of our proposed device to achieve a safe treatment. We find ourselves in the very early stages of the project at the moment of this communication, therefore the majority of the research has been done only at a theoretical level.

7 CONCLUSION

Although our aim is initially to target the adult population who suffer from cryptogenic strokes and other complications, our prospects do include expanding our target audience and tacking pediatric treatment too. Moreover, skills are certainly needed to be learned for the PFO closure procedure with the help of an experienced interventional cardiologist performing interventions with our device. The availability of the product for different categories of patients will fulfill the essential unmet clinical need, as well as provide a safe and effective delivery of therapy for the whole population. On the technical side, there is the possibility to include a bioactive coating capable of releasing anticoagulant drugs directly into the framework of the device, thus removing the necessity of administering the drugs after the intervention separately.

ACKNOWLEDGEMENTS

We want to give a special thanks to the organisers of EIT Health Clinmed 2019 summer school, as well as the mentors for giving us advice and feedback on our project during the workshop days. We also thank the Faculty of Medicine of the University of Lisbon and the Cardiology Imaging Unit at the Santa Maria Hospital (Lisbon, Portugal) for arranging the immersive experience.

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