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AUTHOR(S)

Aamir Hameed, Garry P. Duffy, Babar Hasan, Saulat Husnain Fatimi

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Tissue Engineered Solutions for Intracardiac Septal Defects: A Large Step Forward in an Unmet Clinical Need

Aamir Hameed¹ M.B., B.S, Garry P. Duffy^{1, 2, 3} PhD, Babar Hasan⁴ MD, FAAP, Saulat Husnain Fatimi⁵ MD

¹ Tissue Engineering Research Group, Department of Anatomy, Royal College of Surgeons in Ireland (RCSI), 123 St. Stephens Green, Dublin 2, Ireland

² Trinity Centre for Bioengineering, Trinity College Dublin (TCD), College Green, Dublin 2, Ireland

³ Advanced Materials and Bioengineering Research (AMBER) Centre, RCSI & TCD, Dublin 2, Ireland

⁴ Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan

⁵ Section of Cardiothoracic Surgery, Department of Surgery, Aga Khan University, Karachi, Pakistan

Corresponding author and for reprints: Aamir Hameed, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland, Mobile no. 00353861084397, email: aamirhameed@hotmail.com

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Congenital heart disease (CHD) is the occurrence of an anomaly in the heart structure during fetal development. The incidence of CHD is estimated to be 8 per 1000 live births in US, 6.9 per 1000 live births in Europe and 9.3 per 1000 live births in Asia. ¹ CHD vary in severity and timing of emergence of symptoms, hence they differ in ways of management.

CHD constitutes the most commonly diagnosed congenital diseases in new-borns. Despite significant advancements in surgical techniques over the years, the complex or severe forms of CHD are still the leading cause of mortality among congenital abnormalities. ² According to a report from the American Heart Association, of all the infants who died of a birth defect in 2011, 23.8% were attributed to CHD. ¹ Intracardiac septal defects i.e. atrial septal defects (ASD) or ventricular septal defects (VSD) are the most common CHD types diagnosed in children and young adults. The current gold standard for tackling these defects, especially VSD, is surgical closure with a patch which is sutured over the defect in the septum by open heart surgery. Despite of shorter cardiopulmonary bypass (CPB) and cross clamp time in cases of ASD and VSD closure, the deleterious effect of CPB on neurodevelopmental outcome is of concern in children. A recently published multicentre study documented neuropsychological impairments in children who underwent corrective open heart surgeries for ASD and VSD. ³ Neuroprotection, improved cosmesis, less post-procedural pain and reduction in rehabilitation time are the envisioned targets for the evolution of minimally invasive and catheter based approach towards managing CHD. ⁴ Although transcatheter occluding devices have the advantage of being a minimally invasive alternative to CPB, there are risks associated with blocking the conduction system, cardiac erosion and thrombus formation, which all limit their use. ⁵ For this reason, clinicians and scientists have been looking for a suture-less and minimally invasive solution to address these defects in order to reduce the postoperative complications and shorten the hospital stay.

Tissue engineered biodegradable patches with adhesive characteristics in a wet environment could be an answer to the long quest for a feasible suture less and atraumatic closure of intracardiac septal defects. Recently, Lang and colleagues engineered biocompatible surgical glue. They combined a biodegradable and biocompatible prepolymer of poly (glycerol sebacate acrylate) (PGSA) with a photoinitiator and named it hydrophobic light-activated adhesive (HLAA). ⁶ It is a thick gel that crosslinks within seconds by ultraviolet (UV) light. It was shown to infiltrate the epicardium forming crosslinks with collagen. The PGSA components; glycerol and sebacic acid are readily metabolised and hence are not toxic. Furthermore, the hydrophobic nature of the sealant resists its washout from the heart. ⁶ The study also revealed successful attachment of the PGSA patch coated

with HLAA to an intracardiac septum defect in small and large animal model studies.⁶ Poly (glycerol sebacate urethane) (PGSU) was selected because of its superior UV light transparency. However, for minimally invasive application it requires a specific delivery system with a UV light source. In order to translate it into clinical reality, a group of scientists and engineers have recently come up with a compatible delivery system for deployment of the patch with HLAA. The novel delivery system consists of a reflective distal balloon on an inner shaft for unfolding the patch and a proximal stabilising balloon. The stabilising balloon provides ample compression force for adhesive activation with the endocardial surface. The UV fibre optic can be advanced through the inner shaft to the distal reflective balloon in order to disperse light onto the precoated patch with photocurable adhesive. The pre-clinical results of occluding the intracardiac septal defect with tissue engineered biodegradable PGSU patch with HLAA using this novel multifunctional catheter in rat and porcine models was recently published.⁵ It took approximately 2 minutes to activate adhesion with this biodegradable patch system using echocardiographic guidance. One of the biggest advantages of this suture less system has over other mechanical occluders is that it does not require mechanical anchorage and hence is atraumatic to the friable myocardium of the children.⁵

After achieving initial feasibility in preclinical studies, the next step would be the modification and optimisation of this system for use in a clinical setting. It may require further evaluation in order to get satisfactory safety data as issues of patch embolization and dislodgement of an immediate patch release device were reported recently.⁷ The developers of this device system are hopeful for its scalability and potential for its wider application including closure of patent foramen ovale (PFO) and iatrogenic injuries caused by various transcatheter procedures such as transapical and transseptal valve replacements. This is important in terms of cost effectiveness of the system as cost benefit ratio for simple lesions (ASD or VSD) may not be that great compared to its use in more complex scenario like accidental perforations. Given the potential of HLAA to secure patches in highly dynamic environment like heart and coupled with minimally invasive delivery system, this is definitely an exciting step forward in the area of biomaterial development and cardiovascular research. However, it might be worth evaluating the potential limitations associated with this technology. Proximity of aortic valve and conduction system to perimembranous VSDs warrants special care while using transcatheter closure devices.⁸ Inability to retrieve or reposition the wrongly placed patch once hydrophobic light-activated adhesive is activated may consequently lead to emergency open heart surgery. Thus precision is the key in avoiding damage to the adjacent structures. The cellular composition of the tissue replacing the patch and its long term stability also needs to be assessed.

Tissue engineered biomaterials coupled with minimally invasive delivery system could contribute in structural improvement and function of repaired hearts and hence may provide revolutionary therapeutic opportunities. Therefore, there is an urgent need to expedite both the research and the efforts to bring the tissue engineered materials and their delivery systems to the clinic. It requires a close interaction between scientists, clinicians, people at the helm of regulatory affairs and marketers. Speedy entry of innovative biomaterials and medical devices to the clinic and market will not only serve the unmet clinical need but will also foster future innovative research for paediatric surgery.

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