Developing technologies to improve the treatment of craniosynostosis in children

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Georgia Tech/Emory biomedical engineering professor Barbara Boyan (left) and Children's Healthcare at Scottish Rite clinical director of craniofacial plastic surgery Joseph Williams discuss the technologies they are developing to better diagnose and treat children with craniosynostosis. Credit: Georgia Tech/Gary Meek

Engineers and surgeons are working together to improve the treatment of babies born with craniosynostosis, a condition that causes the bone plates in the skull to fuse too soon. Treating this condition typically requires surgery after birth to remove portions of the fused skull bones, and in some cases the bones grow together again too quickly -- requiring additional surgeries.

Researchers in the Atlanta-based Center for Pediatric Healthcare Technology Innovation are developing imaging techniques designed to predict whether a child's skull bones are likely to grow back together too quickly after surgery. They are also developing technologies that may delay a repeat of the premature fusion process.

"Babies are usually only a few months old during the first operation, which lasts more than three hours and requires a unit of blood and a stay in the intensive care unit, so our goal is to develop technologies that will simplify the initial surgery and limit affected babies to this one operation," said center co-director Joseph Williams, clinical director of craniofacial plastic surgery at Children's Healthcare of Atlanta at Scottish Rite and clinical assistant professor in the Department of Plastic and Reconstructive Surgery at Emory University.

Craniosynostosis affects approximately one in every 2,500 babies in the United States. The condition is caused by the premature closure of sutures with bone. Sutures, which are made of tissue that is more flexible than bone, play an important role in brain growth by providing a method for the skull to increase in size. If the sutures close too soon and get replaced with bony tissue, the skull may limit the normal expansion of the brain.

If untreated, craniosynostosis can cause a range of developmental problems. If treated using the standard treatment course, surgeons remove the fused skull bones, break them up, reposition them, and hold them in place with plates and screws. This usually slows bone growth between the bone pieces, allowing room for expansion of the brain. However, studies show that more than six percent of babies need a second operation to separate the bones again and 25 percent of those require a third operation.

"Following the first surgery, there's a clinical need to be able to screen children on a regular basis to predict when their skull bones are going to fuse together again so that the surgeons can determine if additional intervention will be required," said center director Barbara Boyan, the Price Gilbert, Jr. Chair in Tissue Engineering in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University and associate dean for research and innovation in the Georgia Tech College of Engineering.

To address this need, the researchers have developed a non-invasive technique to monitor bone growth with computed tomography images. They created software that identifies bone in the images, quantifies the distance between the bones, the mass of bone in the gap, and the area and volume of the gap. The research team has demonstrated the utility of this "snake" algorithm using a mouse model of cranial development and recently presented their findings at the 2011 Plastic Surgery Education Foundation conference.

"Using our snake algorithm to analyze computed tomography images of developing skulls in mice, we were able to monitor different types and speeds of bone growth on a daily basis for many weeks," said Chris Hermann, an M.D./Ph.D. student in the Coulter Department. "While one suture fused between 12 and 20 days and then significantly increased in mass for the next 20 days, another came closer together and increased in mass but remained largely open."

The research team recently adapted the technology for use in children and began a clinical study to determine the effectiveness of the algorithm to diagnose cases of craniosynostosis. The researchers hope this technology will improve the ability of physicians to diagnose and determine the severity of craniosynostosis.

In addition, the researchers are studying the biological basis of the condition and developing technologies they hope will delay bone growth and eliminate the need for additional operations. In one project, Coulter Department research scientist Rene Olivares-Navarrete and Williams are examining individuals with craniosynostosis to identify genes that influence suture fusion. Determining the genes that control suture closure may help the researchers identify potential therapeutic targets to prevent premature suture fusion.

The research team has also designed a gel to be injected into the gap created between skull bones during the first surgery. The material -- called a hydrogel because it contains a significant amount of water -- would deliver specific proteins to the area to delay, but not prevent, bone growth.

"The hydrogel cross-links spontaneously because of a reaction between a polyethylene-glycol monomer and a cross-linking molecule, allowing for polymerization without the use of chemical initiators or the production of free radicals," explained Hermann.

Preliminary results in a mouse model of cranial development indicate that the gel, developed in collaboration with Coulter Department associate professor Niren Murthy, can be injected into a gap between skull bones, firm up rapidly and not injure underlying soft tissues or impair bone healing. These pre-clinical results were presented at the Society for Biomaterials Annual Meeting in April.

Both Boyan and Williams see promise in using these technologies to improve the treatment of children with craniosynostosis and eliminate additional operations sometimes needed to treat the condition.

"During the initial surgery, injecting the gel may reduce the operation's severity if it eliminates the need for plates and screws to hold the skull bones in place afterward," explained Boyan, who is also a Georgia Research Alliance (GRA) Eminent Scholar. "After the surgery, if the computed tomography images tell us that the skull is closing too quickly, we may be able to inject the gel through the skin overlying the skull without surgery to further delay the bones from fusing."

The researchers are currently improving the protein release kinetics of the hydrogel and conducting pre-clinical experiments to determine which proteins successfully delay bone growth when included in the gel. Approval from the Food and Drug Administration will be required before this system and hydrogel can be used as a treatment for craniosynostosis.

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