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Commentary: Using cardiopulmonary bypass to deliver cellular therapy to the brain

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CENTRAL MESSAGE

The solution for improving neurodevelopmental outcomes after pediatric cardiac surgery may involve bypass circuit-based cellular therapy.

As surgical survival continues to improve in congenital cardiac disease, neurodevelopmental outcomes in infants undergoing cardiac surgery with cardiopulmonary bypass continue to be a growing concern.[1,2] When looking at improving neurologic outcomes in infants with cardiac disease, many have advocated avoiding deep hypothermic circulatory arrest and early complete repair, as well as delaying neonatal cardiopulmonary bypass by utilizing nonpump, palliative, surgical approaches. Most recently, cellular strategies have been promoted, hoping to gain from their anti-inflammatory and neuroprotective qualities.[3]

Maeda and colleagues[4] report supporting data for their current Phase 1 study looking at the safety and feasibility of the delivery of bone marrow-derived mesenchymal stromal cells (BM-MSC) via cardiopulmonary bypass in neonates and infants undergoing congenital cardiac surgery. They conducted a translational study using an ex vivo cardiopulmonary bypass circuit to determine whether administration of BM-MSC in the circuit affects the performance of the oxygenator. In addition, they sought to assess the immune response and changes in cytokine levels after the BM-MSC administration. Their ex vivo study design was sound and resulted in several key findings in this novel report of cellular therapy utilizing cardiopulmonary bypass for cell delivery:

- BM-MSC administration does not influence the performance of the oxygenator,
- There is no evidence of cellular adherence to the oxygenator filter mesh with the majority of cells being viable after filter, and
- The addition of BM-MSC did not result in an increased immune response but significantly increased interleukin 6 levels.

Although the results presented here add to the feasibility question in their current Phase 1 study, it also raises a few issues. First, the heparin dose used in this experiment is much higher than the typical dose for a 3-kg infant undergoing bypass. It would be interesting to assess the oxygenators of the Phase 1 patients to ensure the lower heparin does not influence the BM-MSC-oxygenator interaction. Secondly, given increased vascular permeability in infants undergoing bypass, one has to wonder how long the administered BM-MSC will stay in circulation when studied in vivo. Finally, do the cells have to be dispensed through the cardiopulmonary bypass circuit? The authors themselves previously demonstrated that BM-MSC administration through an arterial cannula during cardiopulmonary bypass run in a piglet model was an effective way of cell delivery to the brain.[3] Questions of route (eg, aortic, intravenous, or cardiopulmonary bypass circuit) and timing (eg, before, during, or after the bypass run) will certainly come into play as more is discovered about this cellular therapy.

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Maeda and colleagues[4] demonstrate the feasibility of BM-MSC delivery through a complete cardiopulmonary bypass circuit without any negative effects on the oxygenator. This is an exciting early step in what will hopefully translate into an effective therapy in the fight to improve neurodevelopmental outcomes in the pediatric cardiac surgical patient.

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