NEWS

Controversial trial of cord blood therapy for autism forges ahead

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A trial of umbilical cord blood as a treatment for autism has passed a critical safety test, but many researchers remain skeptical of the approach. Questions about the premise **have dogged the trial** since the start because there is little evidence to support the use of cord blood for autism.

So far, 25 children with autism have received the treatment and have experienced only minor side effects. Parents and clinicians reported behavioral improvements in the children. But the trial was not designed to assess efficacy, as it was small and lacked a control group. The results were published 5 April in *Stem Cells Translational Medicine*[1].

Researchers at Duke University in Durham, North Carolina, launched the trial in 2014 with $26 million in funding from the Marcus Foundation, a philanthropic organization based in Atlanta, Georgia. The researchers plan to enroll 170 young children with autism over the next year in a trial with treatment and placebo arms. In that trial, neither the researchers nor the parents or participants will know whether a participant receives the treatment or placebo; this is considered the best way to conduct such trials.

“I think it’s really important that if we’re going to explore any new treatment for individuals with autism, we do it in a way that is really rigorous,” says **Geraldine Dawson**, director at the Duke Center for Autism and Brain Development, who is leading the trial along with **Joanne Kurtzberg**.

Cord blood is a mixture of all kinds of blood cells, including platelets, plasma and stem cells. Some parents bank their child’s cord blood to preserve the stem cells as potential treatment for deadly diseases such as cancer. In this trial, the treatment required an infusion of cord blood, during which some of the children were sedated.

The researchers said in 2014 that the **rationale for the Duke trial** is based on stem cells. In animals, these cells can stimulate neuron growth and repair, and so might be able to help rewire a

brain that has atypical neuronal connections.

However, they now say the treatment may work because of a type of white blood cells, called monocytes, found in cord blood. These cells release signaling molecules called cytokines that the researchers say may quell inflammation in the brain. Some people with autism show signs of **brain inflammation**.

But evidence supporting this effect of cytokines to treat autism is scant.

“Autism is a very difficult problem to address, especially in the absence of an understanding of the [condition] itself,” says **Arnold Kriegstein**, director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California, San Francisco. “And when that’s coupled to the use of a cell-based therapy whose mechanism of action is equally unclear, it seems very unlikely to succeed.”

Mixed messages:

The idea for the trial emerged in the mid-1990s after Kurtzberg began giving cord blood transplants to children with metabolic diseases. In children with autism, she noticed something striking.

“I observed that their autistic symptoms improved after the transplant,” says Kurtzberg, professor of pediatrics at Duke. “We also learned that cord blood cells engrafted in the brain and repopulated the microglial cells in the brain.”

Since then, brain scans and studies of postmortem brain tissue have hinted that **immune cells called microglia** are unusually active in the brains of some people with autism. Microglia activity typically produces an inflammatory response designed to fight infection or repair tissue damage. In the absence of injury or infection, however, inflammation may harm the brain.

The notion that cytokines in cord blood can alleviate brain inflammation is based on limited data from animals. Cytokines may also stimulate the production of myelin, the protective sheath surrounding nerve fibers. Kurtzberg and her colleagues reported last year that injecting human cord blood into mice with depleted myelin helps repair the myelin sheath[2].

Other work suggests cord blood cytokines lessen the effects of brain injury. A 2015 study showed that infusions of human cord blood eased muscle contractions and other motor difficulties in rabbits with brain injury[3]. The blood cells themselves did not enter the brain, suggesting that cytokines released by the cells led to the improvement.

But whether cytokines from cord blood can temper inflammation or aid repair in the brains of people is unclear. It is “a bit of a leap,” says **Jeremy Veenstra-VanderWeele**, associate professor of psychiatry at Columbia University, who was not involved in the research. “It doesn’t mean that it

isn't possible — almost anything is possible — but it means that the potential mechanisms are quite unclear," he says.

Safety first:

The treatment appears to be safe overall, and the related side effects are relatively minor. Children in the study ranged in age from 2 to 6 years. Immediately after the infusion, two children experienced agitation and four had an allergic reaction. In the year following the procedure, the vast majority of side effects parents reported seemed to be unrelated to the cord blood infusion.

Parents also rated their child's behavior using the Vineland Adaptive Behavior Scales-II before the treatment, and then at 6 and 12 months after. All of the children showed statistically significant behavioral improvement 6 months after the injection, and maintained these improvements at 12 months. These gains were greatest among the 12 children with intelligence quotient scores of 70 or above.

"There is more improvement than you would expect based on [the child's] development itself," says **Antonio Hardan**, director of the Autism and Developmental Disorders Clinic at Stanford University in California, who was not involved in the study.

Clinicians also rated autism features in the children using the Clinical Global Impression Scale, which assesses symptom severity. Of the 22 children for whom results were available, more than half showed minimal improvement or better six months after the injection, and 9 showed no change. The results stayed about the same at 12 months, except two of the children were 'minimally worse.'

Placebo problem:

Autism trials are subject to an enormous placebo effect, however: Hope that the treatment is working may sway behavioral ratings from both parents and clinicians. Parents are particularly **prone to reporting progress** in their children's behavior during a trial. Comparison with a placebo arm would have revealed this effect, but the trial did not include a placebo because the study was designed only to assess safety.

Still, some researchers say they worry the trial's results will encourage parents of children with autism to **seek the unproven therapy**.

In 1998, a small trial showed that the hormone **secretin is safe for children with autism** and hinted at a therapeutic effect. Media reports spread the word about the hormone, and as a result, "tens of thousands of kids received infusions of secretin in the belief that it would do something beneficial," Veenstra-VanderWeele says. "But then abundant randomized controlled studies showed it did nothing whatsoever."

In the placebo-controlled trial, for which enrollment has begun, the researchers plan to give children either their own banked cord blood or donor blood. If donor cells work as well as their own, more children can access the therapy, the researchers say. Results from the trial are not expected for at least two years.

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