

10代の先天性心疾患患者が運動耐容能を改善する(Late breaking Science V)

FUEL試験: 経口薬が重症の先天性単心室症の若年患者における運動耐容能を改善する

FUEL: Oral drug improves exercise capacity in adolescents with severe, congenital single-ventricle heart defects

小児心疾患患者に対する薬物療法の中で過去最大の臨床試験の結果、経口薬 **udenafil** が重度の先天性単心室症を有する若年患者の運動耐容能を有意に改善したことが明らかになった。FUEL試験の対象患者は、中等度運動中の酸素摂取量および他の運動耐容能測定値が有意に改善した。また、最大運動時の酸素摂取量においても数値的には改善を認めたが、これは統計学的に有意ではなかった。研究リーダーは、今回の生理学的有益性はFontan手術施行患者の治療における画期的な出来事である、と述べている。この試験結果は American Heart Association's Scientific Sessions 2019で発表され、同時に *Circulation* に掲載された。

Full Text

The largest-ever clinical trial of a medication for pediatric cardiology patients found that an oral drug significantly improved exercise capacity in adolescent patients with severe, congenital single-ventricle heart defects. A study leader says the physiologic benefits represent a milestone in the care of those who have undergone the Fontan procedure, a palliative operation for single-ventricle disease.

"Exercise capacity is a surrogate for morbidity and mortality outcomes in children with single-ventricle congenital heart disease. It is our hope that an improvement in exercise capacity will translate into better long-term outcomes," said pediatric cardiologist David J. Goldberg, MD, of the Cardiac Center at Children's Hospital of Philadelphia (CHOP) and co-principal investigator of the multicenter Fontan Udenafil Exercise Longitudinal Assessment Trial (FUEL). The principal investigator of the trial, also from CHOP's Cardiac Center, was Stephen Paridon, MD.

Goldberg reported the FUEL Trial results at the 2019 Scientific Sessions of the American Heart Association in Philadelphia and was the lead author of an article published concurrently in the journal *Circulation*.

The Phase 3 randomized, double-blind, placebo-controlled clinical trial, sponsored by Mezzion Pharma Co., Ltd., enrolled 400 male and female participants aged 12 to 18 years old from 30 centers in the United States, Canada and South Korea within the Pediatric Heart Network.

"This study of udenafil provides the first evidence of clinical benefit for a medication in this unique population of children with single-ventricle heart disease," said Goldberg.

Patients born with single-ventricle heart defects have a severely underdeveloped pumping chamber in their hearts. A series of complex childhood surgeries culminating in the Fontan procedure has greatly improved survival of patients with single-ventricle disease. However, the surgical corrections do not provide normal blood circulation, and survivors have low cardiac output and long-term complications. Among those complications is exercise intolerance, associated with increased morbidity and mortality.

The researchers reported that participants in the FUEL trial had statistically significant improvements in oxygen consumption and other measures of exercise capacity during moderate levels of activity. There was also a numeric improvement in oxygen consumption at peak exercise, although this did not achieve statistical significance. "These benefits in exercise capacity reflect better circulatory function and should correlate with better long-term circulatory health for patients who have undergone the Fontan procedure," said Goldberg.

The patients who took udenafil tolerated the treatment well, with side effects limited to those previously known from phosphodiesterase type 5 inhibitors, more commonly including headache, facial flushing, abdominal pain, nosebleed and erection.

A related trial, the FUEL Open-Label Extension (FUEL OLE) Trial is currently proceeding, with the goal of measuring treatment tolerability and safety over a longer period for this patient population. In the meantime, added Goldberg, "For the many patients with heart disease worldwide now living with Fontan physiology, these trial results represent a big step in the right direction."

In addition to sponsorship by Mezzion, other support came from the National Heart, Lung and Blood Institute of the National Institutes of Health.

In addition to their CHOP titles, Goldberg and Paridon are on the faculty of Perelman School of Medicine at the University of Pennsylvania. Drs. Goldberg and Paridon both receive grant support from Mezzion and are co-inventors of patent US10137128B2 which is for the use of udenafil in Fontan physiology. CHOP holds these patent rights in conjunction with Mezzion.

AHA 2019 特集

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