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Study proposes new protocol for treatment of thalassemia

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Iron accumulation in myocardial cells, potentially resulting in heart failure or fatal arrhythmia, is one of the complications most feared by patients with thalassemia major, a hereditary disease also known as Mediterranean anemia.

An article by Brazilian researchers published in the journal *Blood* reports that a daily dose of amlodipine combined with chelation resulted in more effective reduction of cardiac iron in a clinical trial involving 62 patients. Amlodipine is an inexpensive drug with few side effects and is already available for the treatment of hypertension.

"The drug has been used clinically for decades and is considered safe for adults and children. As an adjunct to standard treatment, it can be greatly beneficial to patients and has few side effects," said Juliano de Lara Fernandes, a researcher at José Michel Kalaf Research Institute in Campinas, São Paulo State, Brazil, and principal investigator for the project.

The trial was conducted in partnership with researchers at the University of Campinas Blood Center (Hemocentro UNICAMP), Boldrini Child Cancer Center, and São Paulo Blood Center (CHSP), among others.

Thalassemia major, Fernandes explained, is an inherited blood disorder in which the body makes an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen. The disorder results in a low red cell count, which leads to chronic anemia, so patients require blood

transfusions every three to four weeks. The downside of this treatment is a buildup of iron in the organism.

"The iron in red blood cells is normally reused when new red cells are produced, but transfusions introduce a lot of extra iron into the patient. The concentration of iron can double after ten transfusions," Fernandes said.

The body lacks mechanisms to excrete the excess iron, which builds up in the cells of several organs, especially the heart and liver. This accumulation is usually treated with chelating drugs, which bind with the excess iron to produce compounds that can be excreted in urine or feces.

"Chelation therapy works well in peripheral organs, but it's hard to remove iron from the heart," Fernandes said. "Myocardial dysfunctions are currently the main cause of death among patients with thalassemia and can emerge in children from the age of ten."

The most serious problem of all, he added, is caused by an accumulation of non-transferrin bound iron (NTBI) in myocardial cells. NTBI is toxic and can cause cell death. Normally scarce in the bloodstream, it can increase significantly as a result of successive transfusions.

NTBI enters and leaves the liver without causing much damage to the organ, but it enters the heart via a channel whose main role is to carry calcium into cells.

"It occurred to us that drugs capable of blocking the calcium channel could also prevent NTBI from entering the heart and therefore increase the efficacy of chelation therapy," Fernandes said. "Calcium-channel blockers are widely used to treat problems such as high blood pressure and irregular heart beat."

The hypothesis was tested in 62 patients with thalassemia major. This number was considered sufficiently representative because the disease is rare. The volunteers were divided into two groups. Both were given conventional chelation therapy, but amlodipine was administered to only one. The other received oral placebo.

Before the clinical trial began, peripheral venous blood samples were collected for chemistry and hematology analyses, and MRI scans were performed on patients who had not had one within 30 days before enrollment. Depending on the iron concentrations found in their organs, each group was subdivided into those with and without initial cardiac iron overload. MRI scans were repeated a year later.

"Myocardial iron concentration fell 21% in patients with initial iron overload who were treated with chelation plus amlodipine, whereas it increased by 2% in those with initial overload who were treated with chelation plus placebo," Fernandes said.

A comparison of results for the subgroups without initial iron overload showed no significant difference between those who received amlodipine and those who received placebo.

"Perhaps we would have needed to monitor these patients for a longer period to see the benefits of preventive therapy with amlodipine for people who don't have excess iron in their organs," Fernandes said. "For those who do, however, the results show it's worth using amlodipine. There's no need to change the existing therapy. It's enough to administer the anti-hypertensive orally every day."

More information: J. L. Fernandes et al. A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major, *Blood* (2016). DOI: 10.1182/blood-2016-06-721183

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