Low-level laser therapy may improve treatment of dangerous bleeding disorder

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A low-intensity type of laser treatment may offer a non-invasive, drug-free treatment for thrombocytopenia - a potentially life-threatening shortage of the blood cells called platelets that are essential to blood clotting. In their paper appearing in *Science Translational Medicine*, a research team from the Wellmen Center for Photomedicine at Massachusetts General Hospital (MGH) reports that low-level laser therapy increased the generation of platelets from precursor cells called megakaryocytes (MKs) and had the same effect in several mouse models of the condition. They also identified the probable mechanism underlying this effect.

"Our study reveals for the first time that low-level laser therapy enhances platelet production in animals with thrombocytopenia, but not in normal controls," says Mei X. Wu, PhD, of the Wellman Center at MGH, the senior author of the study. "This result suggests that a safe, drug-free method that does not depend on donated blood products can be developed for treating or preventing thrombocytopenia."

Among the conditions that can lead to thrombocytopenia are certain types of leukemia, an autoimmune disorder that attacks platelets, and side-effects of certain drugs, including some used for chemotherapy. The most established treatment is platelet transfusion, which since it risks complications including infection, allergic reaction and immunosuppression is limited to the most severe cases. Dosage levels of the FDA-approved drugs that increase platelet levels must be precisely controlled to avoid excessive platelet production that raises the risk of

dangerous blood clots.

Low-level lasers (LLL) - sometimes called cold lasers - emit low-powered laser light that does not heat its target tissue. LLL has been used to improve wound healing, relieve pain, and treat conditions including stroke and neurodegenerative disorders. It is known to protect the function of mitochondria - cellular structures that provide cells with energy - and several conditions associated with impaired platelet production are characterized by abnormalities in mitochondria of the bone marrow cells that give rise to platelets.

The body responds to low platelet levels by rapid differentiation of MKs from hematopoietic stem cells and an exponential increase in the number of the cells. MKs expand in size, along with with many rounds of DNA replication without cellular division, which results in giant cells containing multiple copies of each chromosome - a condition called polyploidy - instead of the two copies found in most cells. Each of these giant, polyploid MKs generates many long, branched, small tubular structures called proplatelets that eventually fragment into thousands of platelets.

The MGH/Wellman team conducted a number of experiments to investigate whether LLL's ability to protect mitochondrial function could mitigate several forms of thrombocytopenia. Their results showed the following:

- LLL treatment of MKs increased their size, accelerated the formation of proplatelets and doubled the production of platelets. Infusion of LLL-treated MKs into mice led to greater platelet production than did infusion of MKs treated with normal light.
- One of the keys to determining the number of platelets generated from MKs was mitochondrial production of the energy molecule ATP.

- LLL treatment greatly increased mitochondrial generation in polyploid MKs, but the increase was only slight in less mature MKs with only two copies of each chromosome.
- Whole-body LLL treatment of mice with radiation-induced thrombocytopenia induced the rapid maturation of MKs and restored platelet levels in a light-dose-dependent fashion. Platelets from LLL-treated mice had normal structure and function. LLL treatment of normal mice did not raise levels of either MKs or platelets.
- LLL treatment also restored platelet levels in mice with the autoimmune form of thrombocytopenia or with thrombocytopenia caused by chemotherapy treatment.
- In cultured human MKs. LLL treatment at dosage levels similar to that used in mice increased ATP production and platelet generation.

Wu notes that LLL's lack of an effect in animals without thrombocytopenia indicates it would probably avoid the potential complications of current drug treatments, which act by increasing the production of MKs from their progenitors in the bone marrow. "Directly stimulating the differentiation of MKs the way all current drugs do risks clotting if platelet levels rise too high. LLL appears to enhance MKs' inherent ability to produce platelets most effectively in response to low platelet levels in the circulation, a response that stops when platelet levels are normalized. The fact that treatment only has an effect in polyploid cells, which are very rare, implies that it would not increase production of mitochondrial in cancer cells or other cells. In fact, while LLL has been employed in research and in clinical treatment for decades, this is the first study reporting that it can promote mitochondrial biogenesis."

An associate professor of Dermatology at Harvard Medical School, Wu notes that the current primary obstacle to testing LLL in human patients is the lack of a device large enough to treat either the entire body or

enough bones to stimulate sufficient platelet production by MKs within the bone marrow, something her team plans to address. She also adds that, while LLL will probably be beneficial for treatment of many forms of acquired thrombocytopenia, it may not be effective when the condition is caused by inborn genetic defects."

More information: "Noninvasive low-level laser therapy for thrombocytopenia," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aaf4964

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