A NASA discovery has current applications in orthopaedics

Howard B. Cotler, MD, FACS, FAAOS

ABSTRACT
Low-level laser therapy (LLLT) has been actively used for nearly 40 yr, during which time it has been known to reduce pain, inflammation, and edema. It also has the ability to promote healing of wounds, including deep tissues and nerves, and prevent tissue damage through cell death. Much of the landmark research was done by the National Aeronautics and Space Administration (NASA), and these studies provided a springboard for many additional basic science studies. Few current clinical studies in orthopaedics have been performed, yet only in the past few years have basic science studies outlined the mechanisms of the effect of LLLT on the cell and subsequently the organism. This article reviews the basic science of LLLT, gives a historical perspective, and explains how it works, exposes the controversies and complications, and shows the new immediately applicable information in orthopaedics.

Key Words
Laser, LED, NASA, orthopaedic, injury

BACKGROUND
The pursuit of space travel has opened new areas for study and knowledge. Space medicine has had applications in various subspecialties. Although some think there is little application in orthopaedics, it may be that there has been much discovered but little appreciated. The National Aeronautics and Space Administration (NASA) was established by the United States government in 1958 as a civilian space program for aeronautics and aerospace research. In 1959 the Astronaut Corps was founded. The insertion of humans into space presented many challenges from a biologic standpoint. In 1993, Quantum Devices (Barneveld, WI) developed a light-emitting diode (LED) for NASA to use in their plant growth experiments. The experiments demonstrated that red LED wavelengths could boost plant growth, but coincidentally the scientist's skin lesions began to heal faster as well. NASA subsequently began to study the use of LED to increase the metabolism of human cells and stem the loss of bone and muscle in astronauts.

Dr. Harry T. Whelan, a professor of pediatric neurology at the University of Wisconsin, began the study of LEDs and lasers, receiving grants from NASA and the National Institutes of Health. He determined that astronauts get four problems: immune deficiency, pituitary insufficiency, delayed wound healing, and muscle and bone atrophy. He observed these results in the laboratory.

MECHANISMS OF ACTION
From a historical perspective we now know that light has a biologic effect, but what we need to know is how energy from lasers and LEDs work on a cellular level and what the optimal light parameters are for different uses.

The power plant of cells is located in the mitochondria that are able to produce cellular energy or adenosine triphosphate (ATP) from pyruvate and oxygen. When tissues are stressed or ischemic, mitochondria make their own mitochondrial nitric acid (MtNO), which competes with oxygen. The MtNO bind to cytochrome C oxidase (CcO) that displaces oxygen. This subsequently reduces ATP synthesis and increased oxidative stress, which leads to inflammation. Hypoxic or stressed tissues are affected by LLLT in four stages: (1) light energy is absorbed by cytochrome C oxidase, triggering several downstream effects; (2) nitric oxide is released; (3) ATP is increased; and (4) oxidative stress is reduced. These biochemical intermediates affect components in the cytosol, cell membrane, and nucleus that control gene transcription, cell proliferation, migration necrosis, and inflammation. Cells in blood and lymph, which have been light activated, can travel a distance for systemic effects.

APPLICATIONS
The four common targets for LLLT are:
L – lymph nodes to reduce edema and inflammation.19
I – site of injury to promote healing and reduce inflammation.17,18
N – nerves to induce analgesia.20–22
T – trigger points to reduce muscle spasms.23,24

LLLT is a transcutaneous procedure with no invasive portion. The physician determines the correct synchronizations of continuous or pulsed laser emission. Penetration depth is determined by wavelength and power. The U.S. Navy research determined 810 nm to be optimal for penetration.25 Treatment times are in the range of 30 s to 1 min, but there are many areas treated for comprehensible protocol, which often takes approximately 30 min to perform. For stimulating repair and decreasing inflammation, 2.5 Hz pulse is recommended, while a continuous beam is ideal for analgesia and tender points.

ADMINISTRATION

The Federal Drug Administration (FDA) approved the use of LLLT in 2003. In some states, a prescription is mandatory before treatment. Treatment can be administered by a certified therapist, radiology technologist, or a physician. European sports therapists have used LLLT for over a decade; however, they report only a 50% success rate,26,27 which may be due to inconsistent laser parameters and dose. Recent advances by researchers at Harvard Medical School have clarified the mechanism by which there is biphasic dose response.28,29

Side effects and complications can result from traditional treatments for musculoskeletal pathology. Nonsteroidal antiinflammatories can cause ulcer disease, hypertension, bleeding, and cardiac events. Steroids (oral and/or epidural) can result in infections (including epidural), bleeding, ulcers, avascular necrosis, and tissue fragility. Studies have found LLLT to have no side effects or adverse events beyond those reported for placebo.30

With over 4000 basic science research and clinical studies according to pubmed.gov, and low complication rate, LLLT should be considered as a first-line treatment option for conditions such as acute neck or back pain, tendinitis, plantar fasciitis, mild carpal tunnel syndrome, and ligamentous sprains.30–33 Its safety profile provides a persuasive argument, with the added benefits of accelerated healing, tissue remodeling, pain relief, and decreased inflammation. LLLT subsequently has been accepted by both the British and Canadian health services. Although approved by the FDA, LLLT has not been recognized or accepted by Medicare or insurance companies because it is viewed as investigational treatment.

Clinical practice guidelines of the American Academy of Orthopaedic Surgeons (AAOS) in 2008 on treatment of carpal tunnel syndrome included laser treatment but carried no recommendations for or against its use because there is insufficient evidence.44 The literature on LLLT for the treatment of lymphedema, wound healing, prevention of oral mucositis, or for pain demonstrates inconsistent results and methodological weaknesses as per the Blue Cross Blue Shield of Kansas Medical Policy, March 12, 2013. More up-to-date, prospective studies, using newer treatment guidelines by clinicians, are needed to provide a complete picture of efficacy and cost-effectiveness.

CONCLUSION

LLLT will not replace orthopaedic surgery for structural pathology, but it may be useful as an adjunct therapy for patients seeking noninvasive symptomatic treatment or accelerated wound healing.

REFERENCES

1. Wikipedia. http://www.ask.com/wiki/Nasa?0=2800&qsrc=999.
2. Sheuring RA, Mathers CH, Jones RA, et al. Musculo-skeletal injuries and minor trauma in space: incidence and injury mechanism in U.S. Astronauts. Aviat Space Environ Med. 2009; 80:117–124.
3. NASA Tech Brief. Cold laser and LED therapy provide non-invasive treatment options. Medical Design Briefs. 2009; 1–4.
4. Sommer AP, Pinheiro ALB, Mester AR, et al. Biostimulatory window in low-intensity laser activation: lasers, scanners and NASA's light-emitting diode array system. J Clin Laser Med Surg. 2001; 19:29–33.
5. Whelan HT, Smits RL, Buchman EV, et al. Effect of NASA light-emitting diode irradiation wound healing. J Clin Med Surg. 2001; 19:305–314.
6. Whelan HT, Houle JM, Donohoe DL, et al. Medical applications of space light-emitting diode technology-space station and beyond. CP 458, Space Technology and Applications International. In: El-Genik Mohamed S, ed. Forum. ; 1999:3–15.
7. Wong-Riley MTT, Bai X, Buchmann E, et al. Light-emitting diode treatment reverses the effect of TTX on cytochrome oxidase in neurons. Neurochemistry. 2001; 12:3033–3037.
8. Sutherland JC. Biologic effects of polychromatic light. Photochem Photobiol. 2002; 76:164–170.
9. Karu TI. Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. Photochem Photobiol. 2008; 84:1091–1099.
10. Eilt Jr. Wong-Riley MTT, Nerhaeve J, et al. Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. Mitochondrion. 2004; 4:559–567.
11. Karu T. Mitochondrial mechanism of photobiomodulation in context of new data about multiple roles of DNA. Photomed Laser Surg. 2010; 28:159–160.
12. Ehreigh SJ, Furchat RF. Relaxation of mammalian smooth muscles by visible and ultraviolet radiation. Nature. 1968; 218:682–684.
13. Milka M. 1998 Nobel Prize winners are announced: three discoveries of nitric oxide activity. J Am Med Assoc. 1998; 280: 1648.
14. Palacios-Callender M, Quintero M, Hollis VS, et al. Endogenous NO regulates superoxide production at low oxygen concentrations by modifying the redox states of cytochrome C oxidase. Proc Matl Acad Sci USA. 2004; 101:7630–7365.
15. Sharma SK, Kharkwal GB, Sajo M, et al. Dose response effects of 810 nm laser light on mouse primary cortical neurons. Laser Surg Med. 2011; 43:851–859.
16. Chung H, Dai T, Sharma SK, et al. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng. 2012; 40:516–533.
17. Omar MTA, Shaheen AAM, Zofar H. A systematic review of the effect of low-level laser therapy on the management of breast cancer-related lymphedema. Support Care Cancer. 2012; 20:2977–2984.
18. Stergioulas A. Low level laser treatment can reduce edema in second degree ankle sprain. J Clin Las Med Surg. 2004; 22:125–128.
19. Aimbre F, Albertini R, Pacheco MTT, et al. Low-level laser therapy induces dose-dependent reduction in TNFa levels in acute inflammation. *Photomed Laser Surg.* 2006; 24:33–37.

20. Chow RT, David MA, Armati PJ. 830 nm laser irradiation induces varicosity formation, reduces mitochondrial membrane potential and block fast axonal flow in small and medium diameter rat dorsal root ganglion neurons: implications or analgesia effects of 830 laser. *J Peripher Nerv Syst.* 2007; 12:28–39.

21. Chow RT, Johnson M, Lopes-Martins RAB, et al. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomized placebo or active-treatment controlled trials. *Lancet.* 2009; 374:1987–1908.

22. Konstantinovic LM, Cutovic MR, Milovanovic AN, et al. Low-level laser therapy for acute neck pain with radiculopathy; a double-blind placebo-controlled randomized study. *Pain Med.* 2010; 11:1169–1178.

23. Chen K-H, Hong C-2, Kuo FC, et al. Electrophysiologic effects of a therapeutic laser on myofascial trigger spots of rabbit skeletal muscles. *Am J Phys Med Rehabil.* 2008; 87:1006–1014.

24. Smith K, Heckert R, Gerst H, et al. Light promotes regeneration and functional recovery and alters the immune response after spinal cord injury. *Laser Surg Med.* 2005; 36:171–185.

25. Silveira PC, Do Silva LA, Pinho CA, et al. Effects of low-level laser therapy (Ga As) in an animal model of muscular damage induced by trauma. *Laser Med Sci.* 2013; 28:431–436.

26. Tumility S, Munn J, McDonough S, et al. Low level laser treatment of tendinopathy: a systematic review with meta analysis. *Photomed Laser Surg.* 2010; 28:3–16.

27. Bjordal JM, Lopes-Martins RA, Joensen J, et al. A systematic review with procedural assessments and meta-analysis of low-level laser therapy in lateral elbow tendinopathy (tennis elbow). *BMC Musculoskeletal Discord.* 2008; 9:75.

28. Huang YY, Chen AC, Carroll JD, et al. Biphasic dose response in low-level light therapy. *Dose Response.* 2009; 7:358–383.

29. Huang YY, Sharma SK, Carroll JD, et al. Biphasic dose response in low-level light therapy – an update. *Dose Response.* 2011; 9:607–618.

30. Bjordal JM, Johnson MI, Iversen V, et al. Low-level laser therapy in acute pain: a systematic review of possible mechanism of action and clinical effects in randomized placebo-controlled trials. *Photomed Laser Surg.* 2006; 2:158–168.

31. Stergioulas A, Stergioulas M, Aarkog R, et al. Effects of low level laser therapy and eccentric exercise in the treatment of recreational athletes with chronic Achilles tendinopathy. *Am J Sports Med.* 2008; 36:881–887.

32. Hopkins JT, McLoda TA, Seegmiller JG, et al. Low-level laser therapy facilitates superficial wound healing in humans: a triple blind sham controlled study. *J Athl Train.* 2004; 39:223–229.

33. De Marchi T, Leal Junior E, Bartoli C, et al. Low-level therapy (LLLT) in human progressive-intensity running; effects on exercise performance, skeletal muscle status, and oxidative stress. *Laser Med Sci.* 2012; 27:231–236.

34. American Academy of Orthopaedic Surgeons. Clinical practice guidelines on the treatment of carpal tunnel syndrome. 2008. Available online at: http://www.aaos.org/research/guidelines/CTSTreatmentGuidelines.pdf. Last accessed September 2011.