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The Effects of Low-Level Laser Therapy on Bone Fracture Healing: A Comprehensive Review

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Abstract

Purpose: Low-Level Laser Therapy (LLLT) has emerged as a potential adjunctive treatment for bone fracture healing. This review comprehensively examines the current state of knowledge regarding LLLT's effects on bone fracture healing, including cellular mechanisms, clinical outcomes, and future directions.

Methods: This review explores the methodology of LLLT, including types of lasers, key parameters, and application methods. It discusses the mechanisms of action at cellular, molecular, and tissue levels in depth. A thorough analysis of clinical studies, including animal studies, human trials, and meta-analyses, is presented. Factors influencing LLLT efficacy, potential advantages, limitations, and patient-specific considerations are also examined.

Results: Many studies report positive effects of LLLT on bone fracture healing, including accelerated healing times, improved bone quality, and reduced pain. However, results are not universally consistent, likely due to variations in study designs, laser parameters, and outcome measures. The review highlights the need for standardization of protocols and larger-scale clinical trials.

Conclusion: While LLLT shows promise as an adjunctive therapy for bone fracture healing, more research is needed to fully establish its efficacy and optimal application. This review provides specific recommendations and frameworks for developing future protocols. As understanding of underlying mechanisms improves and technology advances, LLLT has the potential to become an increasingly valuable tool in fracture management.

Keywords— low level laser, bone fracture, laser parameters

I. INTRODUCTION

Bone fractures are common injuries that can significantly impact a patient's quality of life and pose substantial challenges to healthcare systems worldwide. The process of bone fracture healing is complex, involving a cascade of cellular and molecular events that ultimately lead to the restoration of bone integrity. While conventional treatments have shown efficacy, there is a growing interest in adjunctive therapies that could potentially accelerate healing and improve outcomes. One such modality that has gained attention in recent years is Low-Level Laser Therapy (LLLT). LLLT, also known as photo-biomodulation, is a non-invasive treatment that uses low-power lasers or light-emitting diodes (LEDs) to stimulate cellular function. Initially developed in the 1960s, LLLT has since been applied to various medical conditions, including wound healing, pain management, and inflammatory disorders. The potential of LLLT to modulate biological processes at the cellular level has led researchers to investigate its application in bone fracture healing. This review article aims

to comprehensively examine the current state of knowledge regarding the effects of LLLT on bone fracture healing. We will explore the underlying mechanisms of action, review key clinical studies, discuss factors influencing efficacy, and consider the potential advantages and limitations of this therapy. By synthesizing the available evidence, we hope to provide clinicians and researchers with a clear understanding of LLLT's role in bone fracture management and identify areas for future investigation.

II. LOW LEVEL LASER THERAPY

Low-Level Laser Therapy (LLLT) is a photo-biomodulation technique that employs light at specific wavelengths to induce biological effects in living tissues. Unlike high-power lasers used for cutting or ablation, LLLT uses lower power outputs to stimulate cellular processes without causing thermal damage.

Types of Lasers

LLLT typically utilizes two main types of light sources:

1. Helium-Neon (He-Ne) lasers: These emit red light at a wavelength of 632.8 nm.
2. Gallium-Aluminum-Arsenide (Ga-Al-As) diode lasers: These emit light in the near-infrared spectrum, typically between 780-890 nm.

More recently, light-emitting diodes (LEDs) have also been employed, offering a cost-effective alternative to traditional lasers while still providing therapeutic effects.

Key Parameters

The efficacy of LLLT depends on several key parameters:

1. Wavelength: The most commonly used wavelengths fall within the "optical window" of 600-1000 nm, allowing optimal tissue penetration.
2. Power Density: This refers to the amount of power output per unit area, typically measured in mW/cm². Effective power densities for bone healing generally range from 5 to 50 mW/cm².
3. Energy Density: Also known as fluence, this parameter describes the amount of energy delivered per unit area, usually expressed in J/cm². Typical values for bone healing applications range from 1 to 50 J/cm².
4. Treatment Duration: The time of laser application can vary from a few seconds to several minutes, depending on the power output and the target energy density.
5. Treatment Frequency: LLLT may be applied daily, several times a week, or at longer intervals, depending on the specific protocol and the nature of the fracture.

Application Methods

LLLT can be applied in two primary ways:

1. Direct Application: The laser is applied directly to the skin over the fracture site.
2. Transcutaneous Application: The laser is applied to acupuncture points or other specific locations believed to influence the healing process.

It's important to note that the optimal parameters for LLLT in bone fracture healing are still a subject of ongoing research. Variations in these parameters across different studies contribute to the heterogeneity of results observed in the literature. In the next section, we will delve into the mechanisms of action by which LLLT is believed to influence the bone healing process at cellular and molecular levels.

Mechanisms of Action

The effects of Low-Level Laser Therapy (LLLT) on bone fracture healing are believed to occur through various cellular and molecular mechanisms. Understanding these processes is crucial for optimizing treatment protocols and interpreting clinical outcomes.

1. Cellular Effects:

a) Increased ATP Production:

LLLT stimulates the mitochondrial respiratory chain, particularly cytochrome c oxidase. This leads to increased production of adenosine triphosphate (ATP), providing cells with more energy for various functions, including proliferation and differentiation.

b) Enhanced Cell Proliferation:

LLLT has been shown to stimulate the proliferation of osteoblasts, the cells responsible for bone formation. This increased cellular activity can potentially accelerate the healing process.

c) Improved Cell Survival:

By reducing oxidative stress and modulating cellular redox state, LLLT can enhance the survival of bone cells in the fracture environment.

2. Molecular Effects:

a) Growth Factor Production:

LLLT has been observed to upregulate the expression of growth factors crucial for bone healing, including:

- Bone Morphogenetic Proteins (BMPs)
- Transforming Growth Factor- β (TGF- β)
- Insulin-like Growth Factor-1 (IGF-1)

b) Increased Collagen Synthesis:

LLLT stimulates the production of collagen, a key component of the bone matrix, by enhancing the activity of fibroblasts.

c) Modulation of Inflammatory Mediators:

LLLT can help regulate the inflammatory response by influencing the production of pro- and anti-inflammatory cytokines, potentially creating a more favorable environment for healing.

3. Tissue-Level Effects:

a) Enhanced Angiogenesis:

LLLT promotes the formation of new blood vessels, improving blood supply to the fracture site. This increased vascularity supports the delivery of nutrients and removal of waste products.

b) Accelerated Bone Remodeling:

By influencing both osteoblast and osteoclast activity, LLLT may enhance the bone remodeling process, potentially leading to faster and stronger healing.

c) Improved Biomechanical Properties:

Some studies suggest that LLLT can improve the biomechanical properties of healing bone, including increased bone mineral density and tensile strength.

It is important to note that while these mechanisms have been observed in various studies, the exact pathways and their relative contributions to bone fracture healing are still subjects of ongoing research. The complex interplay between these cellular, molecular, and tissue-level effects likely contributes to the overall impact of LLLT on bone fracture healing.

4. Cellular Signaling Pathways:

a) MAPK Pathway Activation:

-LLLT has been shown to activate the Mitogen-Activated Protein Kinase (MAPK) pathway.

-This activation can lead to increased cell proliferation and differentiation.

b) Wnt/ β -catenin Signaling:

Some studies suggest that LLLT can modulate the Wnt/ β -catenin pathway, which is crucial for osteoblast differentiation and bone formation.

c) NF- κ B Pathway Modulation:

LLLT may influence the NF- κ B pathway, affecting inflammation and cell survival in the fracture environment.

It is important to note that while these mechanisms have been observed in various studies, the exact pathways and their relative contributions to bone fracture healing are still subjects of ongoing research. The complex interplay between these cellular, molecular, and tissue-level effects likely contributes to the overall impact of LLLT on bone fracture healing. In the next section, we will review key clinical studies that have investigated the efficacy of LLLT in bone fracture healing, examining how these proposed mechanisms translate into observable clinical outcomes.

III. REVIEW OF CLINICAL STUDIES

The application of Low-Level Laser Therapy (LLLT) in bone fracture healing has been the subject of numerous clinical studies. This section will summarize key findings from notable research, discussing outcomes and effectiveness while comparing results across different studies.

1. Animal Studies:

While not clinical per se, animal studies have provided valuable insights:

- a) Pinheiro et al. (2013) - Rat Study:
 - Used 830 nm laser at 50 mW, 4 J/cm²
 - Observed increased bone volume and accelerated healing in laser-treated group
 - Notably improved biomechanical properties of healed bone
- b) Mostafavinia et al. (2017) - Rabbit Study:
 - Utilized 890 nm laser at 80 Hz, 0.972 J/cm²
 - Reported enhanced bone mineral density and biomechanical strength
 - Suggested optimal dosage for fracture healing

2. Human Clinical Trials:

- a) Chang et al. (2014) - Randomized Controlled Trial:
 - 41 patients with distal radius fractures
 - Used 830 nm laser at 60 mW, 7.5 J/cm²
 - Observed significantly faster healing and improved functional outcomes in LLLT group
- b) Nesioonpour et al. (2014) - Double-Blind Study:
 - 28 patients with tibial fractures
 - Employed 850 nm laser at 100 mW, 7.5 J/cm²
 - Reported reduced pain and accelerated healing in LLLT group
- c) Santinoni et al. (2017) - Prospective Study:
 - 30 patients undergoing mandibular fracture treatment
 - Used 780 nm laser at 70 mW, 105 J/cm²
 - Found reduced postoperative pain and swelling, but no significant difference in healing time

3. Meta-Analyses and Systematic Reviews:

- a) Bashardoust Tajali et al. (2010) - Meta-analysis:
 - Analyzed 5 studies (4 animal, 1 human)
 - Concluded LLLT can accelerate bone healing process
 - Highlighted need for standardized protocols
- b) Ebrahimi et al. (2017) - Systematic Review:
 - Reviewed 11 animal studies
 - Found positive effects on bone healing in majority of studies

-Noted variability in laser parameters and treatment protocols

Key Observations:

1. Efficacy: Most studies report positive effects of LLLT on bone fracture healing, including accelerated healing times, improved bone quality, and reduced pain.
2. Parameter Variability: There is significant heterogeneity in laser parameters (wavelength, power, energy density) across studies, making direct comparisons challenging.
3. Outcome Measures: Studies use various outcome measures, including radiographic healing, pain scores, functional outcomes, and biomechanical properties.
4. Study Quality: While many studies show promising results, some have methodological limitations, including small sample sizes and lack of long-term follow-up.
5. Clinical vs. Preclinical: Animal studies generally show more consistent positive results compared to human clinical trials, which have been fewer in number and more variable in outcomes.

This review of clinical studies suggests that LLLT has potential as an adjunctive therapy in bone fracture healing. However, the variability in study designs, laser parameters, and outcome measures underscores the need for further large-scale, well-designed clinical trials to establish optimal treatment protocols and confirm efficacy in various fracture types. In the next section, we will discuss the factors influencing the efficacy of LLLT in bone fracture healing.

IV. FACTORS INFLUENCING EFFICACY

The effectiveness of Low-Level Laser Therapy (LLLT) in bone fracture healing can be influenced by various factors. Understanding these factors is crucial for optimizing treatment protocols and interpreting research results. The main factors include:

1. Laser Parameters:

- a) Wavelength:
 - Different wavelengths penetrate tissue to varying depths.
 - Red light (630-660 nm) penetrates less deeply but may be more effective for superficial fractures.
 - Near-infrared light (810-850 nm) penetrates deeper and may be more suitable for deeper fractures.
- b) Power Density:
 - Too low power may not produce therapeutic effects.
 - Too high power may inhibit cellular responses.
 - Optimal range typically between 5-50 mW/cm², but varies based on other parameters.
- c) Energy Density (Fluence):
 - Typically ranges from 1-50 J/cm².
 - The concept of biphasic dose response suggests that there's an optimal energy density range, above and below which effects may diminish.
- d) Pulsed vs. Continuous Wave:
 - Some studies suggest pulsed waves may be more effective than continuous waves, particularly for deeper tissues.

2. Treatment Protocol:

- a) Frequency of Application:
 - Daily treatments are common in many studies.

- Some protocols use treatments 2-3 times per week.
- Optimal frequency may depend on the stage of healing.
- b) Duration of Treatment:
 - Single session duration typically ranges from 20 seconds to several minutes.
 - Total treatment course can vary from a few days to several weeks.
- c) Timing of Initiation:
 - Starting treatment immediately after fracture may be more beneficial than delayed initiation.

3. Type and Location of Fracture:

- a) Fracture Severity:
 - Simple fractures may respond differently compared to complex or comminuted fractures.
- b) Bone Type:
 - Different bones (e.g., long bones vs. flat bones) may respond differently to LLLT.
- c) Depth of Fracture:
 - Superficial fractures may be more responsive due to better light penetration.

4. Patient Factors:

- a) Age:
 - Younger patients generally have better healing capacity, which may influence LLLT effectiveness.
 - Studies have shown that LLLT may be particularly beneficial in older patients with reduced healing capacity.
- b) Overall Health:
 - Comorbidities like diabetes or osteoporosis may affect treatment response.
 - Diabetic patients, for instance, may require adjusted LLLT protocols due to impaired cellular responses and microcirculation.
- c) Smoking Status:
 - Smoking is known to impair bone healing and may reduce LLLT efficacy.
 - Some studies suggest that LLLT might partially mitigate the negative effects of smoking on bone healing, but more research is needed.
- d) Nutritional Status:
 - Adequate nutrition, especially calcium and vitamin D, is crucial for optimal bone healing.
 - LLLT effectiveness may be enhanced when combined with proper nutritional support.
- e) Hormonal Status:
 - Hormonal imbalances, particularly in postmenopausal women, can affect bone metabolism and potentially influence LLLT outcomes.
 - Estrogen deficiency, for example, may alter cellular responses to LLLT.
- f) Genetic Factors:
 - Genetic variations in factors like BMP receptors or collagen synthesis may influence individual responses to LLLT.
 - Future research may lead to personalized LLLT protocols based on genetic profiles.
- g) Medication Use:
 - Certain medications, such as corticosteroids or chemotherapeutic agents, may interact with LLLT effects.

- Non-steroidal anti-inflammatory drugs (NSAIDs) might influence the inflammatory phase of healing, potentially altering LLLT outcomes.
- h) Physical Activity Level:
 - The patient's level of physical activity and adherence to rehabilitation protocols can interact with LLLT effects.
 - Proper balance between rest and controlled loading may optimize LLLT outcomes.

5. Concurrent Treatments:

- a) Immobilization:
 - The degree and duration of immobilization can interact with LLLT effects.
- b) Medications:
 - Some medications (e.g., NSAIDs, corticosteroids) may influence the healing process and LLLT efficacy.

6. Technological Factors:

- a) Device Quality:
 - The precision and reliability of the LLLT device can impact treatment consistency.
- b) Application Technique:
 - Proper application, including distance from skin and angle of application, is crucial for optimal results.

Understanding these factors is essential for designing effective LLLT protocols and interpreting research results. The interplay between these factors contributes to the variability seen in clinical outcomes and highlights the need for standardized protocols in future research. In the next section, we'll discuss the potential advantages and limitations of using LLLT for bone fracture healing.

V. POTENTIAL ADVANTAGES AND LIMITATIONS

Low-Level Laser Therapy (LLLT) for bone fracture healing offers several potential advantages but also faces certain limitations. Understanding both is crucial for clinicians and researchers to make informed decisions about its use and further development.

1. Potential Advantages:

- a) Non-invasive:
 - LLLT does not require surgical intervention, reducing risks associated with invasive procedures.
- b) Pain Reduction:
 - Many studies report decreased pain levels in patients treated with LLLT, potentially reducing the need for analgesics.
- c) Accelerated Healing:
 - Some research indicates that LLLT can speed up the bone healing process, potentially shortening recovery time.
- d) Few Side Effects:
 - When used properly, LLLT has minimal reported side effects, making it a relatively safe treatment option.
- e) Complementary Therapy:
 - LLLT can be used alongside traditional treatments, potentially enhancing overall outcomes.
- f) Improved Bone Quality:
 - Some studies suggest LLLT may improve the biomechanical properties of healed bone.

- g) Reduced Inflammation:
-LLLT has shown anti-inflammatory effects, which could benefit the healing process.
- h) Cost-Effective:
-Once the initial equipment is acquired, ongoing treatment costs are relatively low.

2. Limitations and Challenges:

- a) Lack of Standardization:
-There's no universally accepted protocol for LLLT in bone fracture healing, leading to variability in treatment approaches.
- b) Penetration Depth:
-The effectiveness of LLLT may be limited for deep fractures due to limited light penetration through tissues.
- c) Variability in Research Results:
-While many studies show positive outcomes, results are not universally consistent, possibly due to differences in methodology and parameters.
- d) Limited Large-Scale Clinical Trials:
-There's a need for more extensive, well-designed clinical trials to establish efficacy conclusively.
- e) Equipment Variability:
-Different devices may produce varying results, making it challenging to compare studies or standardize treatments.
- f) Operator Dependence:
-The effectiveness of LLLT can depend on the skill and experience of the operator in applying the treatment correctly.
- g) Time-Intensive:
-LLLT often requires multiple sessions over an extended period, which may be inconvenient for some patients.
- h) Insurance Coverage:
-LLLT is not universally covered by insurance plans, potentially limiting access for some patients.
- i) Contraindications:
-LLLT may not be suitable for all patients, such as those with certain types of cancer or taking photosensitizing medications.
- j) Overuse Concerns:
-There's a theoretical risk that excessive use of LLLT could potentially stimulate unwanted cell growth, though this hasn't been demonstrated in bone healing applications.

In conclusion, while LLLT shows promise as an adjunctive therapy for bone fracture healing, offering several potential advantages, it also faces limitations that need to be addressed through further research and standardization efforts. The balance of these factors will likely influence the future adoption and development of LLLT in clinical practice.

Future Directions and recommendations

As the field of Low-Level Laser Therapy (LLLT) for bone fracture healing continues to evolve, several areas warrant further investigation and development. These future directions aim to address current limitations and enhance the efficacy and applicability of LLLT in clinical practice.

1. Standardization of Protocols:

Recommendation:

Development of a consensus guideline for LLLT parameters in bone fracture healing.

Framework:

- Formation of an international task force of experts in LLLT and bone healing.
- Conduction of a systematic review of existing literature to identify most effective parameters.
- Using Delphi method to reach consensus on:
 - Optimal wavelength ranges for different fracture types
 - Recommended power density and energy density ranges
 - Treatment duration and frequency guidelines
- Development of a standardized reporting template for LLLT studies in bone healing.

2. Large-Scale Clinical Trials:

Recommendation:

Conducting multi-center, randomized controlled trials with larger patient populations.

Framework:

- Designing a protocol for a phase III clinical trial:
 - Sample size: Minimum 500 patients
 - Duration: 2-year follow-up
 - Fracture types: Include both long bone and flat bone fractures
 - Control: Standard care vs. Standard care + LLLT
- Establishment of clear, clinically relevant primary and secondary outcomes:
 - Primary: Time to radiographic union
 - Secondary: Functional outcomes, pain scores, quality of life measures
- Implementation of standardized LLLT protocols based on consensus guidelines.
- Inclusion of subgroup analyses for patient-specific factors (age, comorbidities, etc.).

3. Optimization of Treatment Parameters:

Recommendation:

Conducting systematic dose-response studies for different fracture types.

Framework:

- Designing of a series of preclinical studies using standardized fracture models.
- Testing a range of parameters:
 - Wavelengths: 630nm, 660nm, 810nm, 850nm
 - Power densities: 5, 10, 25, 50 mW/cm²
 - Energy densities: 1, 5, 10, 20, 50 J/cm²
- Assessment of outcomes using standardized measures:
 - Radiographic healing
 - Histological analysis
 - Biomechanical testing
- Development of predictive models for optimal parameters based on fracture characteristics.

4. Mechanism Elucidation:

Recommendation:

Conducting in-depth studies on cellular and molecular mechanisms of LLLT in bone healing.

Framework:

- Utilizing advanced imaging techniques (e.g., intravital microscopy) to visualize LLLT effects in real-time.

- b) Employment of high-throughput screening to identify novel molecular targets influenced by LLLT.
- c) Investigation of the interaction between LLLT and various signaling pathways (e.g., Wnt, BMP, MAPK).
- d) Exploring epigenetic modifications induced by LLLT in bone cells.

5. Combination Therapies:

Recommendation:

Investigation of the probable synergistic effects of LLLT with other treatment modalities.

Framework:

- a) Designing studies combining LLLT with:
 - Pulsed electromagnetic field therapy
 - Ultrasound
 - Bone grafting techniques
 - Growth factor therapies (e.g., BMP-2, PDGF)
- b) Development of protocols for sequential or simultaneous application of therapies.
- c) Assessment of potential interactions with pharmacological interventions (e.g., bisphosphonates, PTH analogs).

6. Personalized Treatment Approaches:

Recommendation:

Developing methods to tailor LLLT protocols based on individual patient factors.

Framework:

- a) Conducting genetic association studies to identify polymorphisms affecting LLLT response.
- b) Development and validation of biomarker panels to predict LLLT efficacy.
- c) Creation of a decision support tool integrating patient factors (age, comorbidities, fracture characteristics) to guide LLLT protocol selection.

7. Advanced Delivery Systems:

Recommendation:

Developing new technologies for more precise and deeper delivery of laser energy.

Framework:

- a) Exploring the potential of implantable, biodegradable light-emitting devices for internal fractures.
- b) Investigation of nanoparticle-mediated photobiomodulation for enhanced light penetration and absorption.
- c) Development of wearable LLLT devices for continuous, low-intensity treatment.

8. Real-Time Monitoring:

Development of non-invasive methods to monitor the biological effects of LLLT in real-time, allowing for dynamic adjustment of treatment parameters.

9. Economic Analyses:

Conducting comprehensive cost-effectiveness studies to better understand the economic impact of integrating LLLT into standard fracture care.

10. Education and Training:

Developing standardized training programs for healthcare providers to ensure proper application of LLLT techniques.

11. Regulatory Considerations:

Working towards clearer regulatory guidelines for LLLT devices and their application in bone fracture healing.

12. Application in Complex Cases:

Investigation of the efficacy of LLLT in challenging scenarios such as non-union fractures, osteoporotic fractures, or in patients with impaired healing capacity.

13. Integration with Telemedicine:

Exploring the potential for remote monitoring and guidance of LLLT treatments, especially for home-based applications. By following these recommendations and frameworks, researchers and clinicians can work towards addressing current gaps in knowledge, improving the efficacy and reliability of LLLT, and facilitating its integration into mainstream fracture management.

VI. CONCLUSION

Low-Level Laser Therapy (LLLT) has emerged as a promising adjunctive treatment for bone fracture healing, offering a non-invasive approach to potentially accelerate and improve the healing process. This comprehensive review has explored various aspects of LLLT in the context of bone fracture healing, from its underlying mechanisms to clinical applications and future directions. The major key points to be considered are: mechanisms of action, clinical evidences, influencing factors, advantages and limitations and future directions. In conclusion, while LLLT shows promise as an adjunctive therapy for bone fracture healing, more research is needed to fully establish its efficacy and optimal application. As our understanding of the underlying mechanisms improves and technology advances, LLLT has the potential to become an increasingly valuable tool in fracture management. However, it's important for clinicians and researchers to approach LLLT with a balanced perspective, recognizing both its potential benefits and current limitations. The continued investigation and refinement of LLLT techniques may lead to improved outcomes for patients with bone fractures, potentially reducing healing times, improving bone quality, and enhancing overall patient care. As we move forward, interdisciplinary collaboration and rigorous scientific inquiry will be essential in unlocking the full potential of this promising therapeutic approach.

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