REVIEW ARTICLE

Low Level Laser Therapy in the Treatment of Knee Osteoarthritis: A Review

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ABSTRACT

Last few decades have revolutionized medical practice with advancement in biomedical field. This especially applies on finding innovative non-surgical approaches to different medical pathologies. Laser came into existence in 1960's. Usage of Laser got its population with varying degree of applications in medical sciences. The modern use of laser has spanned from skin treatment to surgical procedures. Modern medical science is continuously expanding its horizons to explore the utilization of laser in different pathologies. Osteoarthritis is one of the major debilitating, progressive, degenerative musculoskeletal condition in the world affecting millions of people worldwide. Medical science has been exploring different avenues to treat this pathology with as non-invasive means as possible. Low level laser therapy (LLLT) has been investigated and used in various musculoskeletal conditions for last two decades including knee osteoarthritis. Different search engines and terms were used to find relevant articles. Inclusion and exclusion criteria were set to select the articles. This review looked at different evidences to see how LLLT is effective in treating the knee osteoarthritis and what challenges still exist in LLLT application to treat knee osteoarthritis. Looking at different existing researches, LLLT has mixed results on knee OA. Evidences depict positive outcomes of LLLT and yet do not show significant results. LLLT can show beneficial outcomes but different factors could impact those results. Evidences should focus on different aspects of LLLT in knee OA.

Keywords: Osteoarthritis, Knee joint, Low level laser, Physical therapy, Outcomes

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INTRODUCTION

Low level laser therapy (LLLT) is a type of laser which uses the non-thermal means to produce the desired biological effects in tissues (1). Researches have published the varying effects of LLLT on human body. LLLT has consequential effects on chronic degenerative conditions like OA. Other significant effects include anti-inflammatory and anti-edema effects. One of the key characteristics of LLLT is to decrease pain without any side effects (2). LLLT with right dose, intensity, wavelength and in visible/near visible spectrum has remarkable effects on different MSK conditions using cellular effects on non-photosynthetic cells. These effects depend upon specificity of intensity, wavelength and pulse per second duration (3). LLLT has been shown to provide improved Oswestry Disability Index (ODI) and a possibility of avoidance of operative treatment options for discogenic lower backache. The very effects of LLLT on fibroblasts and collagen synthesis at cellular level promotes the utilization of LLLT to control inflammation, enhance healing and thus control pain and tissue damage (4).

Osteoarthritis (OA) is a very common musculoskeletal disorder globally. One of the common pathological conditions seen in the physician's office is Osteoarthritis (Fig. 1). Prevalence of OA varies according to joint involved, the geographical area. In a study, knee OA is more than 19% in USA (5). Another study indicates the prevalence of knee OA to be more than 30% in adults over the age of 60. Knee OA prevalence is anticipated to rise in countries where geriatric population is rising. Etiology of knee OA

Fig. 1 : Knee OA pathophysiology. [23]

indicates multiple factors which predominantly includes age, weight, gender and hereditary factors. Other factors could include local trauma, arthroscopic procedures, and recreational activities (6). OA is a musculoskeletal condition which is crippling, painful and one of the most debilitating conditions in geriatric population. Progressive cartilage loss, subchondral bone deterioration, osteophytes formation, joint space loss and synovial lining inflammation triggers the typical symptoms of joint pain, crepitus and deformity. Radiological examination is one of the assessment tools but subjective assessment is considered more valuable in treating the OA (7). Aims of this study include;

1) to elaborate the current evidences in the utilization and effectiveness of LLLT.
2) to explore the methodologies and resulting effects.
3) to identify the differences in methodologies, their effects and explore the gap which could lead the researchers and clinicians to investigate and amplify the utilization of LLLT in the treatment of knee OA.

MATERIALS AND METHODS

Literature search

Various search engines and keywords were engaged to investigate the topic of particular interest. Main interest of search was low level laser therapy as the modern modality. Osteoarthritis and knee osteoarthritis as subcategory were looked up as pathological condition of particular interest. Emphasis was made on targeted area of interest. Following search engines were used for the referenced articles;

Search engines: Medline/PubMed, and google scholar were used
Keywords used: this included "knee joint", "low level laser therapy", "low level laser", "osteoarthritis", "low level laser therapy in knee OA", "laser therapy in musculoskeletal conditions".

Inclusion criteria and exclusion criteria

While browsing through the database, reviewers ensured to follow particular inclusion/exclusion to review the appropriate articles. Previous studies were included if those met the following particular criteria: (1) articles must be in English; (2) articles focusing on low level laser therapy in knee OA; (3) articles focusing on OA of the knee joint; (4) articles which were systemic reviews or experimental articles. The exclusion criteria included: (1) articles on laser only; (2) articles on high intensity laser; (3) articles on use of LLLT other than musculoskeletal conditions; (4) articles which were abstract only; (5) duplicate articles; (6) articles engaging animals only. Fig. 2 shows the flow of information used in this systemic review using flow diagram standard from PRISMA.

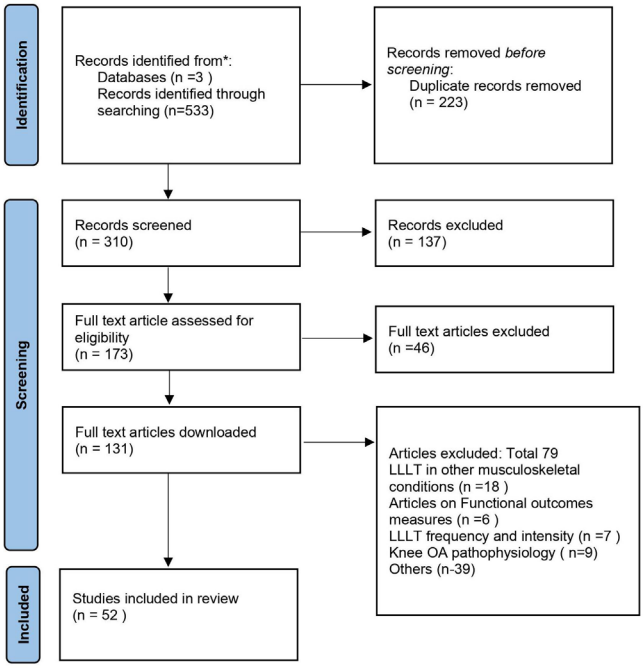

Fig. 2 : Flow diagram of the review work (based on PRISMA 2020 statement at http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

RESULTS

Low level laser therapy as a ripple on the surface of modern medicine

Low level laser therapy (LLLT) is a treatment of choice and is being used in current medical practice in various specialties. Light amplification by stimulated emission radiation (LASER) originally presented by Einstein in early 20th century gained it's popularity in physics. Theodore Maiman was the first person to use the ruby laser to produce the visible and

infrared laser and journey of laser for medical use continued for medical use in decade of 1960's (8). The very first person to produce the infrared laser was Theodore Maiman in middle of 20th century using ruby crystal as a medium. Use of laser in medical field launched from that point on is still the mainstream in medical research on photobiomodulation (8). Area of skin being irradiated and behavior of light are some of the main factors to ensure the photobiological results. Air/tissue and tissue/tissue interface are couple of the main factors to ensure that the desired area is receiving optimal light (9). The energy level at the cellular level is changed with the absorption of light. Absorption of light triggers the photobiomodulation by ensuring the modification of metabolism. This photobiomodulation also impacts on the functional and structural achievements of membranous part of cell (10).

Effects of light have been under research since 19th century. Concentrated light of particular origin like blue or red light filtered from the spectrum of light were known to produce therapeutic effects. N.R.Finsen received the Nobel prize on his work using the concentrated light in the treatment of conditions especially Lupus Vulgaris. Laser is found to be more effective due to its monochromaticity (11). LLLT has been described by North American Association of Laser Therapy as a modality which is non thermal in characteristic from visible and infrared spectrum laser light application to decrease pain and heal the tissues. With laser irradiation, there is temperature gradient at the membrane level promoting the rate of diffusion across the membrane. LLLT is known to produce multiple effects as a result of photobiomodulation including increased procollagen synthesis and activation of macrophages, increased production of serotonin and endorphins, increased in serum reactive factor (SRF) and increased nerve cell action potential (12).

Photobiomodulatory effects include improved microcirculation resulting in increased oxygen supply to hypoxic cells. Tissue hypoxia is controlled as a result of this causing removal of waste products. This helps in controlling the cycle of tissue damage, inflammatory response causing increased pain and edema in the local area. The biomodulatory effects of LLLT can help to decrease inflammation, increased pain tolerance and tissue healing (13). Laser helps relieve pain, repair tissue damage and stimulates acupuncture points. Laser is the light produced by peak electrical stimulation of different mediums like gas, liquid, crystal or semiconductor. Light produced in a coherent beam of single wavelength in visible to infra-red spectrum. Light could be produced in a continuous wave or in a pulsed mode. Therapeutic effects of this light in a non-thermal fashion sometimes call it cold-laser (14).

Osteoarthritis of Knee joint

OA is most common form of arthritis. Modifiable risk factors include obesity, injury and occupation as these contribute towards excessive stress on the joint. Research indicates that mechanical stress due to occupation is more noticed in construction workers and sales departments as that required prolonged standing, lifting and repeated knee bending (15). Knee joint is a modified hinge joint allowing mainly flexion/extension movement at the joint. There is some degree of rotation also involved in movement. It is one of the main weight-bearing joints allowing stability and mobility in various conditions (16). Tibiofemoral and patellofemoral are the two compartments which make the knee joint. Both compartment's ability to transmit the load during weight-bearing or non-weight bearing activities varies upon their shape and geometry (17).

Knee joint biomechanics is complex and contributes in the commencement and advancement of knee OA. Abnormal loading due to injuries involving menisci or internal ligament or high knee adductor mechanism could lead to unusual loading of the medial tibiofemoral compartment (18). Neuromotor performance of the knee depends highly on the proprioceptive function of the knee joint. Consequentially, the very interaction of the muscles especially quadriceps provides the stability during movement and loading to allow the joint surfaces bear the stress (19). In the area of tidemark cartilage, there is remnant of calcified cartilage. With growing age, this area increases pushing the articular cartilage into joint space. This factor contributes towards narrowed joint space (20). American college of rheumatology (ACR) and Kellgren-Lawrence classification are the widely used tools to diagnose and classify the knee OA (21).

Knee OA symptoms are more debilitating with the passage of time. Pain, decreased muscle strength, gait disability, and decreased aerobic performance with the passage of time get more prominent (22). Pain generally gets better with rest and increases with the activities. Joint stiffness sometimes lasting for no more than 30 minutes along with joint swelling, crepitus and limp are other features seen during knee OA assessment (23).

Treatment of knee OA could include pharmacological including analgesics and non-steroidal anti-inflammatory medication. Non pharmcological treatment includes physical therapy, weight loss and use of assistive devices as needed (24).

LLLT and KNEE OA

Physical Therapy is one of the non-invasive and conservative treatments of knee OA patients. Different modalities including thermotherapy, transcutaneous electrical stimulation, acupuncture, LLLT, manual therapy and exercises have varying level of effects on pain and functional performance (25). LLLT is an inexpensive alternative for managing pain and other symptoms in musculoskeletal conditions including knee OA. However, some experimental studies did voice question in effectiveness of LLLT in knee OA. It has also been experimented that LLLT effectiveness could be linked with higher irradiation, increased frequency and number of sessions. It was also concluded that light in the range of 700-1000 nm, the infrared zone appears to have better penetration (26). In a study done by Ferouzan et al. (2017), in Iran, LLLT had no significant impact on reducing the pain and improving the ROM in knee joints. They used LLLT on 8 points at the knee joint with 56 joules/ session. There was no significant improvement in pain or ROM in the group. However, it was suggested that use of LLLT along with acupuncture and exercises could prove better results (27). Patricia Alredo et al. (2012) used the LLLT in a study concluding the using the LLLT could increase neurotransmitters including serotonin production which helps the pain. This benefit of LLLT exerts better effects if exercises are also included in the treatment regimen (28).

One meta-analysis looked at different experimental studies and compared the usage of LLLT in terms of dosage, frequency and outcomes. Study concluded that LLLT is effective as compared to placebo in reducing the pain and disability in knee OA patient. One of the main focuses of this analysis is to observe the response of recommended vs non-recommended dose of LLLT and study found out that dosage recommended by World association of Laser therapy (WALT) is quite effective in ''clinically relevant pain'' relief (29). Another study looked at different modalities including ultrasound, electrical stimulation and LLLT for the effectiveness. This study observed that following the recommended dose of 4 J/point by WALT produces the better pain relief in knee OA patients (30). Fong Li et al. (2019) tested the effectiveness of LLLT on quadriceps strength. His study focused on knee OA and observed that using the LLLT can reduce the pain and also improve the quadriceps strength. His study referenced other studies which also concluded that LLLT was effective in improving the quadriceps strength in elderly women (31). Study done by Fang Liao noticed the pain relief, improved mobility in the joint and pressure sensitivity after irradiating 3 acupuncture points for the treatment of knee OA (32).

Study done by Funda et al. (2004) concluded that LLLT is ineffective in the treating the knee OA. Results suggested that it could be due to use of wavelength, the machine itself and also the treatment area. Study suggested that LLLT may be more effective in treating the smaller joints (33). LLLT effectiveness on knee OA has doubts as compared to other musculoskeletal conditions. Even though LLLT has shown encouraging results in decreasing pain and facilitating clinical outcomes in knee OA. There are number of factors which could impact on the outcomes of LLLT. Pathophysiology of the conditions, severity of the condition, area being irradiated, frequency, wavelength and dosage of the irradiation could impact on the outcomes of LLLT (34). Another possibility of conflicting results of LLLT in knee OA could be due to the variation in treatment application and methods. Since LLLT has been quite promising in progressive and degenerative conditions, the very effect on knee OA has been assorted (35).

One of the challenges patients with knee OA have is to optimally engage the muscles for performance. LLLT is also noticed to improve the torque and extensor muscles activation which is probably due to analgesic effects causing reduced efferent and nociceptive stimulation However, grade III and IV knee OA may not show significant improvement due to increased nociception triggering muscle inhibition. LLLT has been proposed to produce analgesic, anti-inflammatory and regenerative effects (36). LLLT provides a good relief in typical signs and symptoms like pain, stiffness and poor functional mobility seen in knee OA grades 1-3 in comparison with therapeutic Ultrasound modality (37). It is also encouraged to use the appropriate dose of LLLT. As recommended by WALT is a key factor in achieving the right dose. One study compared the LLLT with US. It was noted that patients showed decreased Interleukin-and Interleukin-6 while Cyclooxygenase-1 and Cyclooxygenase-2 were noticed to increasein joint fluid after being treated with LLLT (38).

Duration of LLLT can put an impact on improving the circulation besides managing pain and stiffness in knee OA patients (39). European league against rheumatism (EULAR) recommends to add exercises in addition to using LLLT as a modality for the treatment of knee OA. However, one of the main components of gaining benefit is the dosage of LLLT (40). LLLT is documented to improve the metabolism and structure of the articular cartilage by increasing the synthesis of proteoglycans, mucopolysaccharides, collagen fibers, improving the structural organization of articular cartilage, and thus

overall degenerative process (41). While in a study done on rats with induced OA, LLLT was noticed to show decreased articular deformity and increased cartilage proliferation in 4 weeks of treatment (42). While exercises have a major impact on the functional outcomes in knee OA patients, LLLT has been found to improve the muscle fatigue and performance including the peak and the average force of the muscle. LLLT reduces the negative inflammatory effects and fibrosis and improving the muscle with traumatic injuries (43). Effects of LLLT on chronic arthritis have been noticed to vary based upon the method of application. It was interesting to note that efficacy of LLLT does not depend upon the particular wavelength as long as it varies from 600 nm – 1000 nm (25). In general, Table I is a summary of the reviews on the results of using LLLT in treating musculoskeletal diseases.

DISCUSSION

OA of the knee joint commonly involves both tibiofemoral and patellofemoral compartments. As compared to previous concepts of knee OA being the degeneration of the joint structures due to age; the modern concepts do suggest that there are other factors involved as well in the development of OA in knee joint. (44). The genetic component

Table I : Review of literature

Author	Study Design	Musculoskeletal Condition	Results of LLLT
L. Assis et al. 2016	Experimental on rats	Induced OA in rats	Improved tissue organization; decreased fibrillation and irregularities along the articular surfaces; chondrocytes organization; Lower OARSI score and higher thickness values; low IL1-B, Caspase-3, and MMP-13
Almeida et al. 2012	RCT double blind with crossover	Biceps Brachii	Improved peak force and average force resulting delayed muscular fatigue with exercises
Koutenaei et al. 2017	Double blind clinical trial	Knee OA	No significant difference between active and placebo LLLT results. Both showed decreased pain and improved ROM.
Huang et al. 2015	Systemic review and Meta-analysis	Knee OA	Meta-analysis showed no difference in VAS, WOMAC and ROM scores. Systemic review showed better outcomes with LLLT in KOA patients.
Alfredo et al. 2011	RCT double blind	Knee OA	Significant improvement in VAS and WOMAC scores.
Stausholm et al. 2019	Systemic review and Meta-analysis of randomized placebo-controlled trials	Knee OA	Significantly reduced VAS and disability index score in dose-dependent and non-dose-dependent groups as compared to placebo group. However, dose-dependent group
Melo et al. 2015	Randomized clinical trial single blinded	Knee OA	Compared LLLT with neuromuscular electrical stimulation. Both were equally effective in WOMAC score but no particular difference in muscle strength and morphological status
Fong Li et al. 2019	Randomized clinical trial	Knee OA with focus of irradiating the Quadriceps	Decreased pain, improved quadriceps strength, increased 60 m walking speed, timed five-chair stands,
Ali Ammar, 2015	Randomized controlled trial	Knee OA with focus of comparison between Monochromatic infra red light and LLLT	Both groups showed progress in Pain and Lower extremity functional scale. No significant difference between the two groups.
Cho et al. 2014	Experimental study	Knee OA induced in rabbits	Histologically (increased superoxidase dismutase (SOD)level) and radiographically improved results in LLLT group. However, these results were prominent in after 4 weeks of treatment. After 2 weeks, results were not promising.

Liao et al. 2020	Randomized controlled trial	Knee OA	Improved OA severity index; improved moving and resting knee VAS; improved pain pressure threshold at pes anserinus tendon in after 4 weeks of treatment
Rayegani et al. 2012	Randomized clinical trial double blind study	Knee OA comparing LLLT with therapeutic ultrasound	Improved Visual analog scale score; improved WOMAC for pain and disability in LLLT group.
Tasciogla et al. 2004	Randomized placebo-controlled with single blind	Knee OA	No significant results noted amongst the groups. One group had received 3 J/point and second group was given 1.5 j/point while third group received placebo laser
Pallotta et al. 2012	Experimental study	Induced OA knee in rats	Group with high dose of LLLT showed significantly decreased leukocytes, myeloperoxidase (MPO), increased COX-1 and COX-2 and decreased interleukin-1 interleukin-6 and prostaglandin E2 levels.
Rayegani et al. 2017	Systemic review and meta-analysis	Knee OA	There was improvement in VAS and WOMAC score but ROM did not show significant improvement with LLLT. Also, no side effects were reported in these studies.

in the development of knee OA along with biomechanical overloading and that generally triggers inflammation. Production of IL-1 and TNF-alpha triggers the production of metalloproteinases and Nitric Oxide (NO) (45). Thus, the treatment options of knee OA mainly focus on controlling the symptoms and improving the functions (46). However, the effective management of knee OA offers debatable evidences due to the multifactorial reasons. Between the conservative and surgical management, time, cost and effectiveness of variety of treatment options sometimes become a challenge for the clinicians to manage the symptoms and improve the functional outcomes (47).

LLLT is being considered as an alternative to medicine due to its specific biological effects at cellular level. Inflammation is one of the chief pathological conditions as a result of acute arthritic changes. Chronic conditions when aggravated also indicate the inflammatory changes. LLLT anti-oxidative performance helps to improve healing. It's effects with none or least side effects makes it a therapeutic modality of choice in acute inflammatory conditions (44). Earlier data was not as supportive of LLLT in acute and chronic inflammatory conditions secondary to lack of specific findings. But with the passage of time, different biological and photobiological evidences do promote the use of LLLT in different acute and chronic conditions (45).
Cochrane review also promotes LLLT as an alternative modality for reducing and morning stiffness in rheumatoid arthritis. Literature suggests that prostaglandin E level decreases with depending upon the particular dosage of LLLT (46). As compared to acute inflammatory conditions, this review article focused on OA of the knee joint which is a chronic degenerative pathological condition (47). Considering the chronic characteristic, effectiveness of LLLT in OA has still the debating role as a treatment of choice.

As compared to effectiveness of LLLT in acute conditions like Rheumatoid Arthritis, use of LLLT in chronic degenerative conditions like Osteoarthritis requires robust evidences. When looking at all the evidences in this review, author presents different stimulating thoughts for researchers including but not limited to; (1) Is LLLT the best, and most effective modality in chronic degenerative conditions? (2) Can irradiating maximum area of the tibiofemoral compartments and patellofemoral compartment provide the best results? (3) Can irradiating maximum area provide early and maximal relief? (4) How important is to adhere to the WALT recommended dose in every single case or could the dose vary depending upon the individual case, presenting complaints and intensity of knee OA, gender, prior level of functioning? Effectiveness of LLLT in chronic degenerative conditions like knee OA is still questionable. Author believes that effectiveness of LLLT in knee OA has still controversial aspects and researchers should focus to enhance the particular evidences for clinicians. These evidences should focus on the biomodulatory performance of LLLT in osteoarthritis conditions as a chronic degenerative condition. Researchers need to also look into the strong clinical queries as outlined above and utilize

the necessary laboratory, radiological and functional outcomes to understand the LLLT performance in osteoarthritic conditions. As OA, especially on the knee OA, it is ranked 11th in it's contribution towards disability-adjusted life years (DALY), this requires the attention of researchers to look at ever emerging modalities and evidences for clinicians to provide optimal treatment solutions for patients (48). This review could be resourceful for researchers in focusing on some of the specific areas of research as mentioned earlier.

LIMITATIONS OF THIS STUDY

This study attempted to provide the researchers and clinicians the evidenced-based performance of LLLT in treating the symptoms of knee OA. This review analyzed the effectiveness and ineffectiveness of LLLT in treating the knee OA and other musculoskeletal patients and explore the reasons of ineffectiveness. While looking at these evidences, we realize that there needs to be more thorough investigation to explore the ineffectiveness of LLLT. We also realized that there were studies which we were unable to extract the full text and which could have added valuable material for our review. However, information presented in this review should help the researchers and clinicians to further enhance their peculiar and intellectual minds.

CONCLUSION

LLLT has significant advantageous effects on different musculoskeletal conditions. Modern evidences exhibit inclination towards its utilization as a non-invasive approach without any side effect or hazardous effects. However, these evidences do tend to show stronger effects on certain conditions and possibly conflicting results in some conditions. Knee OA is one of the conditions in which LLLT has conflicting evidences. Clinicians need to ensure that area indicated in previous researches, optimal dosage as indicated by WALT, appropriate frequency and number of sessions to ensure the best outcomes.

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