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REVIEW ARTICLE

Application of Intravenous laser Irradiation of Blood (ILIB) in Physical Medicine: A Narrative Review

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Abstract

Intravenous laser irradiation of blood (ILIB) involves a type of intravascular treatment which applies a helium-neon laser possessing a wavelength of 632.8 nm. Since its first use in 1981 by Russian scientists, it is now widely applied in the treatment of various diseases, including chronic musculoskeletal pain, wound healing, spinal cord injury, stroke, traumatic brain injury, coronary artery disease, type 2 diabetes mellitus, rheumatoid arthritis and acute kidney injury. The underlying mechanism for ILIB may be associated with its anti-oxidative (through regulating the reactive oxygen species systems) and anti-inflammatory effects (by reducing the production of inflammatory cytokines). Moreover, positive effects on the three major blood cell types were also proven, including improving the oxygen-carrying capacity and rheological properties of red blood cells, enhancing mitochondrial activity within white blood cells and modulating immune responses, and inhibiting platelet aggregation to reduce blood viscosity. Although there is currently a lack of robust and compelling evidence to support the use of ILIB in the treatment of various diseases, this minimally invasive complementary treatment method provides another option in the treatment of many intractable diseases.

Keywords: Intravenous laser irradiation of blood (ILIB), Pain, Stroke

1. Introduction

Due to the rapid advancement of technology, the use of physical agent modalities has been continuously evolving and innovating. Physical medicine is referred to as the use of various kinds of physical agents in order to produce the desired therapeutic effects, including cold, heat, sound, electromagnetic waves, electricity and mechanical forces.[1] Among them, low-level laser therapy (LLLT) has been applied in the field of musculoskeletal pain since the1960s, particularly in wound healing.[2] Currently, various related applications, including laser acupuncture, photobiomodulation therapy via the transdermal or intranasal route and intravenous laser irradiation of blood (ILIB) have been widely used in clinical medicine. However, there still remains the lack of a review article in the current literature focusing on the mechanisms and therapeutic effects of ILIB. The goal of this study is to introduce the physics of laser light and briefly summarize the existing evidence regarding the use of ILIB treatment in various diseases.

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2. The physics of lasers

There are two mechanisms contributing to the therapeutic effect of lasers, the thermal and non-thermal effects, defined by the type of interaction which exists between laser light and tissues. The thermal effect occurs when a laser increases the temperature of both cells and tissues, resulting in the denaturation of proteins and collagen, leading to irreversible destructive changes to tissue morphology. Alternatively, the non-thermal mechanism achieves its therapeutic effects through laser light absorption by chromophores, triggering specific photobiological mechanisms.[3] Lasers can be divided into two groups according to their mode of action: pulsed wave and continuous-wave. Pulsed wave lasers are characterized by pulses of energy which occur at a particular pulse repetition frequency, often with high peak power (average power range: milliwatts to several watts; peak power range: megawatts)[4] and a thermomechanical effect. In contrast, continuous-wave lasers exhibit a constant output power (power range: milliwatts up to watts)[1] over a set interval to achieve their therapeutic effects.[5] ILIB, a form of continuous-wave laser, uses the non-thermal mechanism in order to produce its therapeutic effect.

It is believed that the principle behind the generation of laser light is "light amplification", which occurs when an excited and unstable electron transitions from its higher energy state to a more stable state, emitting energy in the form of a single photon. By applying an external power source to a medium, a triggering photon can initiate a chain reaction, resulting in the generation of multiple photons when constrained in a pumping chamber.[1,6] Laser lights contain three properties, namely coherent, monochromatic and collimated. The coherent property implies that light waves are synchronized both spatially and temporally, while monochromatic refers to the light waves as consisting of a single color or wavelength. As for collimation, this implies that the light waves travel in a singular direction with minimal divergence, thus maintaining its parallel nature.[6] It is these three properties which enable clinical workers to create applications of laser light. Lasers can be classified into four categories according to their active medium, solid state, gas, dye (complex organic dye in a liquid solution or suspension) and semiconductor.[7] Traditionally, a non-thermal laser is composed of a low-level laser with a power range of 0.001–500 mW, which will cause insignificant changes in tissue temperature (less than 1 °C), but could have a stimulating effect on target tissues, with the wavelength ranging from infrared to the ultraviolet portion of the electromagnetic spectrum. The wavelength of each laser partially determines the effect it will have on various tissue.[1,6] Briefly, the higher the wavelength, the greater the laser penetrates through the tissue. Ultraviolet wavelengths (10–400 nm) can induce pro-inflammatory cytokine (IL-1α, IL-1β, and IL-6) release, with the red laser (620–740 nm) enhancing the synthesis of procollagen and the releasing of fibroblast growth factor. Infrared wavelengths (780 nm–1 mm) are most popularly used in dermatology, for the purposes of decreasing hand wrinkles and relieving skin tightness.[8]

In the next section, we would focus on the ILIB, including its biomechanisms and applications in various disease. The wavelength used in ILIB and LLLT fell between red to near infrared region of the spectrum (660 nm–905nm).[9]

3. Biomechanisms and physics of ILIB

When directed towards tissue, the majority of laser light is reflected, while the remaining portion penetrates the tissue where it is absorbed and scattered. The degree of light absorption and scattering depends on the physical properties and the color (known as the chromophore) of the tissue, as well as the wavelength of the light.[10] A specific wavelength in a laser can be used to selectively target a specific tissue such as hemoglobin, water or melanin. The chromophore is a type of molecule which imparts its color to a compound, including hemoglobin, myoglobin, cytochromes, flavin, flavoproteins and porphyrins. Among them, the most common target of chromophores is the iron- and copper-containing enzyme cytochrome C oxidase (CCO), a component of the electron transport chain. When absorbing the laser, the CCO becomes excited, leading to an increased production of mitochondrial products such as adenosine triphosphate

(ATP), nicotinamide adenine dinucleotide (NADH) and ribonucleic acid (RNA).[10] Additionally, laser-associated increased antioxidant enzymes and mitochondrial nitric oxide (NO) synthase activities have also been reported in various studies.[11,12] Alternatively, lasers can also regulate the production of the reactive oxygen species (ROS), which play an important role in cell signaling, regulation of cell cycle progression, enzyme activation and production of cytokines and growth factors. Although ROS are often considered as bringing about detrimental effects, the summed effects of low-level lasers in humans include a reduction in both inflammation and oxidative stress.[13,14]

The most commonly utilized wavelength of ILIB is 632.8 nm, using helium–neon as its medium. It is the 632.8 nm that precisely falls within the absorption peak range of CCO (600–830 nm). ILIB was first applied by Russian scientists in 1981 for the treatment of cardiovascular disease and was found to facilitate blood circulation and refine blood cell function.[15] Several studies have reported its positive effects on the three major blood cell types; improving the oxygen-carrying capacity and rheological properties of red blood cells,[16] enhancing mitochondrial activity within white blood cells and modulating immune responses,[17,18] and also inhibiting platelet aggregation, thereby reducing blood viscosity.[18] Therefore, due to its diverse range of advantages, it is currently applied in the treatment of various diseases. A summary of the included articles discussing the application of ILIB in various disease is listed in Table 1.

4. Comparison between ILIB and percutaneous LLLT

ILIB involves the direct administration of laser light to the circulatory system, commonly achieved by use of a fiber optic needle placed into a vein. This direct interaction can potentially lead to more immediate and systemic effects on blood properties,[16–18] microcirculation and biostimulation.[19] Additionally, it reduces the possibility of burns or tissue injury associated with external laser applications, particularly when utilized at higher intensities. On the other hand, percutaneous LLLT allows for targeted treatment of particular anatomical regions, including muscles and joints, which was particularly useful for localized conditions like muscle tears or arthritis.[20] Besides, compared with ILIB, percutaneous LLLT was non-invasive (avoid intravenous access) and required less equipment, which increased its accessibility. In brief, ILIB offers the potential for systemic treatment and direct blood interaction, which can be advantageous for certain medical conditions. On the other hand, percutaneous LLLT is well-suited for the treatment of localized lesions due to its targeted and non-invasive nature. The method selected is based upon the particular medical problems, the goals of therapy, and patient preferences.

In recent years, there has been a growing interest in a novel technique known as semiconductor intravenous laser irradiation of blood, which employs a semiconductor (diode) medium. In comparison to their He–Ne counterparts, semiconductor lasers possess numerous benefits. These include a more compact design, a greater operational life, the capability to emit a wider spectrum of wavelengths, and simplified modulation to accommodate particular therapeutic requirements.[21] Currently, there remains a scarcity of clinical trials that compare semiconductor intravenous lasers to conventional helium-neon lasers. In the future, additional literature will be required to validate their applications.

5. The application of ILIB in the treatment of various diseases

5.1. Chronic pain due to musculoskeletal disorders

Chronic pain is one of the leading causes for patients being referred to clinicians, which can in turn cause heavy burdens on both patients and healthcare providers. LLLT possesses the ability to reduce pain via mechanisms such as decreasing histamine, serotonin and bradykinin, while also increasing acetylcholinesterase, aerobic metabolism, ATP, encephalin and endorphins production. Thus, lasers can notably elevate one's pain threshold and trigger the production of endorphins.[22,23] Currently, the various reports regarding the application of

Table 1. Demographic characteristics, ILIB protocols and main results of the included studies.

Study	Design	Location	Patients	Disease	Protocol	Main result
Pires Diniz et al. (2021)[25]	Case report	Brazil	N = 1 Patient's age = 47 yrs Gender: female (100 %)	Fibromyalgia	Modified ILIB[a] (30 min each time, 10 times/session, total 2 sessions, power density 600 mW/cm^2) + LLLT	Completely pain free for 2 months.
Wu et al. (2018)[26]	Case series	Taiwan	N = 15 Mean age = 53.77 yrs Gender: female (100 %)	Fibromyalgia	ILIB (60 min each time, 10 times/session, total 2 sessions, power output 2.5 mW)	Significantly improved pain severity, sleep, mood disorder, and quality of life.
Momenzadeh et al. (2016)[28]	RCT	Iran	N = 30 (10 in ILIB, 10 in percutaneous low level laser, 10 in placebo laser) Median age = 45.8 yrs Gender: female (30 %)	Shoulder Myofascial Pain Syndrome	ILIB (20 min each time, total 12 times, power output of 2 mW)	Improved pain severity, Pain Disability Index and quality of life in ILIB group and percutaneous low level laser group compared with placebo laser; ILIB group showed more pronounced improvement compared with the percutaneous low level laser group but not statistically significant.
Fu et al. (2022)[29]	Retrospective cohort study	Taiwan	N = 76 Mean age = 57.7 yrs Gender: female (68 %)	Chronic musculoskeletal disorders	ILIB (60 min each time, 10 times/session, total ≥3 sessions, power output 6 mW)	Pain improvement, especially for those initially having moderate to severe pain intensity. (Visual Analogue Scale>4)
Kazemikhoo et al. (2015)[33]	Case study	Iran	N = 1 Patient's age = 45 Gender: female (0 %)	5 cm depth pressure ulcer	ILIB (15–20 min each time, total 24 sessions, power output 1.5 mW) + LLLT	Ulcer healed completely.
Dahmardehei et al. (2016)[34]	Case series	Iran	N = 6 Mean age = 49.1 yrs Gender: female (33.3 %)	Grade 3 burn ulcer	ILIB (16 min each time, total 10–15 sessions, power output 10 mW) + LLLT	Wound healed completely.

Huang et al. (2012)[38]	RCT	Taiwan	N = 24 Patient's age = 45.5 yrs Gender: female (25 %)	Spinal cord injury	ILIB (60 min each time, total 15 sessions, power output 4 mW)	Improved oxidative stress (by molecular biology data), Low-density lipoprotein significantly decreased at Day 10 and 15; increased high-density lipoprotein at Day 45.
Sung et al. (2019)[39]	Case report	Taiwan	N = 1 Patient's age = 73 yrs Gender: female (0 %)	Ischemic stroke	ILIB (60 min each time, 10 times/session, total 9 sessions, power output NS)	Improved brain perfusion in previous ischemic area proven by brain Single Photon Emission Computed Tomography.
Chang et al. (2019)[40]	Case report	Taiwan	N = 1 Patient's age = 50 yrs Gender: female (0 %)	Intracranial hemorrhage and ischemic stroke	ILIB (not stated detailed protocol)	Improved spirit and better sleeping quality, decreased serum homocysteine level.
Yang et al. (2017)[41]	Case report	Taiwan	N = 1 Patient's age = 77 yrs Gender: female (0 %)	Ischemic stroke	ILIB (60 min each time, total 10 times, power output 3.5–4 mW)	Greater perfusion in the affected cerebellar hemisphere proven by brain Single Photon Emission Computed Tomography.
Lai et al. (2022)[42]	Retrospective observational study	Taiwan	N = 34 Mean age = 65.68 yrs Gender: female (53 %)	Ischemic stroke	ILIB (60 min each time, total ≥10 times, power output 2.5–4 mW)	More improvement in Barthel Index, 6-min walk test and Fugl-Meyer Assessment of the upper extremity in ILIB group, but insignificant.
Lin et al. (2023)[43]	Cohort study	Taiwan	N = 30 Mean age = 41.65 yrs Gender: female (16.67 %)	Traumatic brain injury	ILIB (60 min each time, 10 times/session, total 3 sessions, power output 2.5–3.8 mW)	ILIB reduced the occurrence of crossed cerebellar diaschisis but no differences seen in cognitive function.
Derkacz et al. (2014)[47]	RCT	Poland	N = 101 (52 in experimental group; 49 in control group) Mean age = 59.1 yrs Gender: female (25.7 %)	Coronary artery disease	Intravenous laser (90 s each time, power density 100 mW/cm^2, others NS)	Intravenous laser group saw decreased levels of TGF-β1 and FGF2 in patients undergoing coronary intervention
Scheerder et al. (2001)[48]	Clinical trial	Belgium	N = 68 Mean age = 64 yrs Gender: female (12 %)	Coronary artery disease	Intravenous laser (power output 10 mW, others NS	Intravenous laser group showed a reduced expected restenosis rate after coronary stenting.

(*continued on next page*)

Table 1. (continued)

Study	Design	Location	Patients	Disease	Protocol	Main result
Kazemikhoo et al. (2016)[50]	Systematic Review and Meta-analyses	Iran	N = 70 Mean age = 52.2 yrs Gender: not stated	Diabetes mellitus	ILIB (varied in studies)	ILIB significantly decreased glucose levels (mean difference = 14.445, P = 0.007) without significant heterogeneity between trials.
da Silva Júnior et al. (2022)[51]	RCT	Brazil	N = 21 (10 in ILIB group; 11 in control group) Median age = 61 yrs Gender: female (76.1 %)	Diabetes mellitus with periodontitis	Modified ILIB (30 min each time, total 10 times, power output 100 mW)	No statistically significant improvements in HbA1C and fasting blood glucose values.
Razzaghi et al. (2021)[55]	RCT	Iran	N = 20[b] (10 in ILIB group and 10 in placebo group) Mean age = 65 yrs Gender: female (30 %)	Acute kidney injury	ILIB (30 min each time, total 3 times, power output 1.5 mW)	Urine and serum NGAL show declines from the baseline in both groups but the reduction slope occurred faster in the ILIB group in a statistically significant manner.

N = number, yrs = years, ILIB= Intravascular laser irradiation of blood, LLLT = low-level laser treatment (direct exposure to injured area), RCT = randomized controlled trial, N/S = not stated. NGAL = neutrophil gelatinase -associated lipocalin.

[a] Laser is applied through the skin with a bracelet aid located at the radial artery to irradiate blood cells.

[b] Twenty-two participants received randomization, but only twenty participants completed the trials.

ILIB in chronic musculoskeletal pain have mainly focused on fibromyalgia patients, with one review article concluding that the potential benefits of ILIB in fibromyalgia patients have been validated through several basic experimental studies.[24] As for its practice in humans, only one case report[25] and one case series[26] have been found, disclosing improvements in visual analogue scale (VAS), mood disorder, quality of life, sleep quality and the number of tender points in patients receiving ILIB. It is well known that the annoying symptoms surrounding fibromyalgia include non-restorative sleep, fatigue and depression, all of which may be due to central sensitization.[27] Wu et al. believed that ILIB could not only increase the production of endorphins and serotonin but also potentiate antioxidant activities, of which the improved symptoms may be associated with recovery from oxidative stress.[26] Nevertheless, because of the case-series design of the study, the effect of different medication among the participants could not be controlled and could constitute a significant confounding factor in this study.

Another randomized controlled trial (RCT) conducted by Momenzadeh et al. focused on the effects of ILIB in shoulder myofascial pain syndrome. Compared with a placebo low-level laser, ILIB significantly reduced pain severity, while improving quality of life.[28] Recently, a retrospective cohort study published by Fu et al., in 2022 recruited 76 patients diagnosed with musculoskeletal disease who were suffering from multiple sites of pain over a period of at least 3 months. After receiving at least 30 times of ILIB, they found an improvement in pain severity and sleep quality, particularly those who had been experiencing moderate to severe pain intensity (initial VAS score >4).[29] These studies provide evidence that ILIB could be an alternative adjunctive treatment option for those patients with chronic musculoskeletal pain.

5.2. Refractory wound

Current studies surrounding the use of laser treatment in wound healing are mostly either in vitro studies[30] or animal studies,[31] with the majority of them applying laser via direct exposure. One systematic review published by Machado et al. examined the use of LLLT treatment of pressure ulcers and found that only laser light at 658 nm was most beneficial for wound healing. The underlying mechanism here may be related to the fact that laser light at this wavelength is most readily absorbed by CCO, thereby potentiating subsequent ATP synthesis and antioxidant responses.[32]

As for human studies involving ILIB in refractory wound, only two reports have been found. One is a case report[33] and the other a case series.[34] Both reports used LLLT plus ILIB, and showed there was facilitated healing of the pressure ulcer or third-degree burn wound. The underlying mechanism in these cases may be related to the use of lasers promoting fibroblast proliferation, collagen synthesis and epithelialization via bio-stimulation.[35]

5.3. Spinal cord injury (SCI)

Inflammatory response after SCI can contribute to secondary tissue damage, while also impairing neural improvement and regeneration, thus resulting in poor prognosis.[36] Recently, a comprehensive review article focused on LLLT treatment in the recovery of neurological symptoms due to SCI.[37] In this review, the team only addressed the therapeutic effects of LLLT, concluding with a promising result that LLLT was able to reduce inflammation and also attenuate neuronal damage after SCI, thus having a positive effect on functional recovery.

As for specific ILIB treatment in SCI patients, only one RCT investigating the molecular biological results was found. In that study,[38] Huang et al. revealed that ILIB can alleviate oxidative stress and mitochondrial dysfunction (proven by a significantly higher mitochondrial DNA copy number, white blood cell adenosine triphosphate synthesis, and total antioxidant capacity with significantly reduced malondialdehyde) after receiving 1 h of daily ILIB treatment for 15 days over a period of 3 weeks, compared with a sham group. Also, reflecting on the serum biochemical changes, the experimental group found significantly reduced low-density lipoprotein at Day 10 and 15 and significantly higher high-density lipoprotein at Day 45, suggesting that ILIB can act as a potential alternative form of treatment for those diagnosed with SCI.

5.4. Stroke

ILIB had been applied to stroke patients since the 1990s,[16] mainly in Russia and China, however most of the research has not been published in English. Recent studies include mainly case reports,[39–41] with the exception of only one retrospective observational study. Lai et al. found that ILIB led to greater improvements in stroke patients when compared to a control group in several functional indicators, including the Barthel Index, 6-Minute Walk Test and Fugl-Meyer scale, although these differences did not reach any statistical significance.[42] The proposed potential mechanisms regarding about how ILIB may benefit stroke patients may include increased cerebral blood flow, decreased low-density lipoprotein levels, and improved inflammatory responses. However, there has still been no definitive evidence proving the benefits of ILIB treatment in stroke patients. Additional controlled studies of a better quality are still required in order to reach a more solid conclusion on this issue.

5.5. Traumatic brain injury (TBI)

Although ILIB treatment has been more frequently applied to stroke patients ending with promising results, there are still scarce reports surrounding ILIB treatment for those diagnosed with TBI. Currently, there is only one cohort study conducted by Lin et al., in 2023, which has investigated the association between ILIB and the development of crossed cerebellar diaschisis (CCD) in TBI patients. CCD refers to a reduction in oxidative metabolism, glucose utilization, and blood flow in the cerebellum due to a supratentorial lesion in the contralateral cerebral hemisphere. CCD is usually associated with poor neurological outcomes. In the Lin et al. study, the team found that ILIB could reduce the occurrence of CCD in TBI patients but the results failed to show any differences in cognitive function between prior to and after ILIB treatment. The team hypothesized that their findings may be partly attributable to the positive effects of photo-stimulation on mitochondrial proliferation and/or cellular homeostasis, which in turn led to a promotion in cerebellar perfusion.[43]

5.6. Coronary artery disease (CAD)

Upon the discovery of ILIB, heart disease was the first condition it was used to treat.[15] Earlier studies have disclosed that ILIB could increase erythrocyte numbers in the peripheral blood,[44] improve rheologic blood properties and in turn decrease the number of angina attacks, while also reducing the need for nitroglycerine tablet uptake.[45] Recently, one literature review published in 2020 studied the treatment effect of ILIB in chronic diseases, revealing that coronary artery disease was most widely treated with ILIB application (five studies), with most studies showing the positive effects towards the prevention of restenosis after percutaneous coronary interventions.[46]

Restenosis is a common condition in those diagnosed with CAD who are receiving percutaneous angioplasty. The currently proposed mechanism involves the placement of a foreign material, such as a stent, possibly leading to the rupture of endothelial cells, resulting in thrombus formation, vascular remodeling, and smooth muscle cell proliferation. Similar to wound healing, this process involves the spreading of localized inflammatory responses, facilitated by interleukins, vascular endothelial growth factor (VEGF), and fibroblast growth factor-2 (FGF-2), ultimately promoting abnormal intimal hyperplasia and the subsequent narrowing of blood vessels. In one research study conducted by Derkacz et al., in 2014, it was found that ILIB did not affect the concentration of VEGF in the injured endothelium of blood vessels during coronary artery angioplasty. Instead, it was able to reduce the production of certain inflammatory cytokines, such as IL-1β, IL-6, and IL-10.[47] However, this study compared only the cytokine data at different time point instead of the amount of improvement. Therefore, whether there were significant differences in the improvement between the laser group and the control group could still not be determined via this study. Scheerder et al. followed up with a study involving 68 patients diagnosed with coronary artery disease six months after treatment, observing that ILIB could reduce the rate of post-stent restenosis without the occurrence of any complications or adverse events.[48] All these findings suggest that ILIB may be a potential and effective complimentary treatment, while also being relatively safe.

5.7. Type 2 diabetes mellitus (DM)

The application of ILIB in diabetes could be traced back to 34 years ago, when it was primarily used to improve lower limb pain and general health conditions.[21]

Research has found reduced arginine synthesis and increased pro-inflammatory cytokine activity in DM patients.[49] In one research study conducted by Kazemikhoo et al., it was discovered that both arginase and EGFR expression decreased, leading to a reduction in neuroinflammatory responses in 13 DM patients after ILIB treatment.[12] However, the HbA1c level or other severity index of DM were not recorded in this study, which may be a confounding factor for the outcome of this study. Additionally, ILIB could also promote the generation of nitric oxide, thereby increasing vascular dilation. EGFR is a crucial factor in both cell activation and inflammation, while arginine is associated with the secretion of various hormones such as insulin, adrenal and growth hormones. A decrease in EGFR expression and an increase in arginine levels both contribute to better management of diabetes.[12]

However, in recent human studies, the application of ILIB during DM treatment revealed conflicting results. In a systematic review and meta-analysis published by Kazemikhoo et al., in 2016, it was found that there was a significant decrease in blood glucose levels after receiving ILIB (with an average decrease of 14.445 mg/dL, $P = 0.007$ being seen).[50] In contrast, one RCT conducted by da Silva Júnior et al. revealed no statistically significant improvements in glycemic control (HbA1C and fasting blood glucose) in both intergroup and intragroup analyses between ILIB and conventional therapy groups.[51] Although the technique used in the RCT was not the same as that performed in traditional ILIB, where a laser is applied through the skin with a bracelet aid located at the radial artery to irradiate blood cells, it still raised concerns about the effectiveness of ILIB in DM patients.

5.8. Rheumatoid arthritis (RA)

ILIB has been used to treat RA for a long time now, with records of its application dating back to the 1990s.[52] Earlier studies found that ILIB would be less effective in RA patient who had high titers of serum rheumatoid factor and high levels of circulating immune complex (CIC).[53] One study published by Timofeyev et al. found that due to the immunomodulatory effects of ILIB, the pre-existent immune state of the patient was crucial.[53] Patients with low CIC levels and normal T-cell activity tend to experience more noticeable symptomatic improvement after receiving ILIB. On the other hand, if CIC levels are too high or T-cell activity is too strong, these conditions can lead to no significant improvement being seen between the treatment and placebo groups.[53] Recently, Burduli et el. found that ILIB could normalize plasma leptin levels (a marker indicating development of the inflammatory process), and suppress the inflammatory process, leading to a better quality of life.[54] As for studies with a higher level of evidence, there is still a lack of such research. More clinical trials are needed in the future to confirm the effectiveness of the application of ILIB.

5.9. Acute kidney injury (AKI)

Many studies listed above focused on the application of ILIB for chronic diseases. However, one recent RCT in Iran conducted by Razzaghi et al., in 2021 investigated the effectiveness and safety of ILIB in the treatment of AKI. They randomized 10 patients in two groups (ILIB vs placebo laser) and found that the reduction slope of urine and serum neutrophil gelatinase -associated lipocalin (NGAL), an early marker of AKI, occurred faster in the ILIB group in a statistically significant manner, suggesting that ILIB can assist patients diagnosed with AKI to recover better. They hypothesized that this may related to ILIB possibly improving tissue hypoxia, normalizing tissue metabolism, stimulating oxygenation, releasing cytokines and helping to develop new blood vessels.[55]

5.10. Dentistry

The application of ILIB in dentistry had been reported in recent years[56] but most research was not published in English. The primary application of ILIB is through its antioxidant (including enhancing nitric oxide production, and stimulating the enzyme Superoxide Dismutase), anti-inflammatory and analgesic properties for the treatment of various inflammatory diseases, mainly periodontitis, mucositis, post-operative complications, and orofacial pain. By means of promoting tissue repair and controlling inflammatory processes, it makes a valuable addition to dental practice.[56] However, despite the promising applications, the literature suggests a need for more comprehensive studies, including randomized clinical trials, to fully establish ILIB's efficacy and safety in this area.[56]

6. Conclusion

ILIB, utilizing a wavelength of 632.8 nm helium-neon laser, which is readily absorbed by enzymes in the mitochondrial respiratory chain, can lead to anti-oxidative and anti-inflammatory effects as shown through validations published in numerous pieces found in past literature. ILIB has positive effects on all three types of blood cells by improving oxygen-carrying capacity and the rheological properties of red blood cells, modulating the immune response of white blood cells and through its ability to also inhibit platelet aggregation, thereby reducing blood viscosity. Historically, ILIB has been applied as a treatment for various diseases, including chronic musculoskeletal pain, wound healing, SCI, stroke, TBI, CAD, DM, RA and AKI. Although some of the included studies were low on the hierarchy of scientific evidence, most of the results from studies have been both convincing and encouraging. However, larger-scale multicenter studies are still needed in the future in order to get more solid clinical evidence regarding the application of ILIB towards the treatment of various diseases.

Author contributions

Conceptualization, Y.-Y.C; writing—original draft, Y.-C.C.; writing—review and editing, Y.-Y.C.

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Consent for publication

All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

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