The Comparative Pillars Paper

From Validation to Separation

Documenting the Superiority of Multi Radiance Laser Technology

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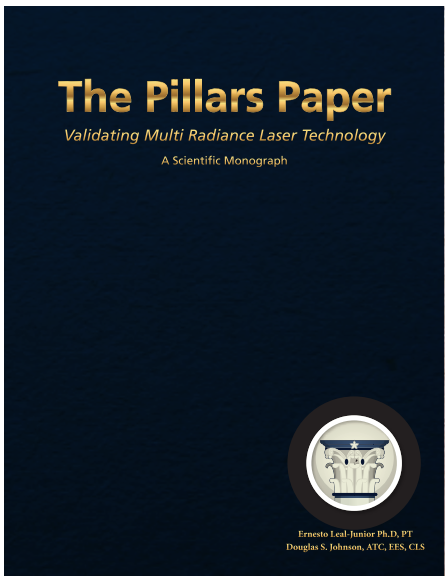
Douglas S. Johnson, ATC, EES, CLS

Anchored in Science

Smarter Technology. Smarter Choice.

Multi Radiance Super Pulsed Laser Technology has been validated In Vitro, In Vivo, in Controlled Laboratory Studied and in Human Clincial Trials.



The Pillars Paper:

Validating Multi Radiance Laser Technology

In-Vitro and In-Vivo Experiments and the Mechanism of Action Pillar

- Validating the Photobiological response.
- Depth of penetration of light through skin.
- Photobiomodulation and the Thermal Effect.

Discovering the Optimal Parameters: The Controlled Laboratory Studies Pillar

- Biphasic dose response and validation.
- Dose validation of inflammatory marker reduction.
- Dose validation for the modulation of pain.
- Power in athletic performance.

Validation of the Outcomes: The Clinical Trial Pillar

- Reducing knee pain in clinical practice.
- Testing a treatment methodology - The Priority Principle.
- The importance of clinical significance for consistent outcomes.

The Comparative Pillars Paper:

From Validation to Sepa ration

Multi Radiance Laser Technology is superior to Class 3B and Class 4 Lasers in mitigating pain without unwanted muscle damage.

- In the past 24 months there have been 12 peer reviewed journal articles published specific to Multi Radiance Medical and with 35 current clinical trials will double or triple that in the next 24 months.

- Multi Radiance Super Pulsed Lasers are Superior to Class 3B and Class 4 Lasers in mitigating pain without associated muscle damage.

- Multi Radiance Laser Technology allows 5x the amount of light to targeted tissue with 75% less energy at the surface.

The Comparative Pillars Paper: From Validation to Separation

Documenting the Superiority of Multi Radiance Laser Technology

A Scientific Monograph

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Introduction

Light as a therapeutic physical agent just celebrated its 50th anniversary. The use of photobiomodulation (PBM), or the use of light-based devices to stimulate or inhibit biological processes, was introduced in the United States in 2002, with the first clearances granted by the Food and Drug Administration (FDA). Since that introduction, PBM or low-level laser/light therapy (LLLT) continues to gain popularity among physicians and therapists and proven to be a superior adjunct or mono therapy in rehabilitation.

Extensive research exists to support the use of light-based modalities for a variety of conditions. Nearly all positive studies have been done with the use of low powered lasers. Anecdotal evidence, expert opinion reports, and an occasional case study provide some insight into clinical use. However, they are not adequate replacements for quality controlled randomized trials.

While the efficacy of laser therapy should no longer be in question, the effectiveness of many commercially available devices should. Clinicians should not confuse the efficacy of a technology with the effectiveness of a product or device. All good products should have a Proof of Concept and detail the steps to prove the effectiveness of their product in both laboratory and clinical trials. Without the proper Proof of Concept, including biphasic dose validation, thermal profiling, and depth of penetration, direct side-by-side comparisons are not possible.

Multi Radiance Medical embarked on the Proof of Concept (POC) process in early 2012 to validate the combined multi-wavelength and magnetic laser and light device, the MR4. All experiments, trials and studies were supervised by the Laboratory of Phototherapy in Sports and Exercise (Sao Paulo, Brazil). The POC was able to validate the combined synergistic effects of the different light sources (laser and LEDs) found in the Multi Radiance Medical devices and identify the optimal doses and treatment parameters for the safe delivery of consistent, clinically relevant patient outcomes. All research articles are published in peer-reviewed journals or pending future publication.

The intention of this work is to unravel many of these false claims and clear any dogma that is based on unscientific principles by presenting only peer-reviewed evidence in an effort to understand the best practices of PBM or LLLT. Additionally, we will discuss the Proof of Concept process that all devices should undergo and how basic device testing and validation can create not only superior clinical devices but move the field of PBM forward into greater use and acceptance in the community.

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From Validation to Separation and the Responsibility of Market Leadership

Multi Radiance Medical develops patented, unique devices that maximize the advantages of multiple wavelengths, light sources and electromagnetic energy. All devices share a common core comprised of 905 nm Super Pulsed Lasers, 875 nm Infrared Emitting Diodes, 640 nm Red Light Emitting Diodes and a static magnetic field of 35 mT. This unique "mix" or synergy of the device's parameters are validated by the Pillars "Proof of Concept" studies completed from 2012-2014. This scientific monograph not only detailed the clinical validations studies, but also crucial details on dose response, absorption characteristics to determine depth of penetration and thermal profiling to ensure safe operation. Extensively tried and tested over 20 years in both lab and in the clinic, the MR4 and TerraQuant product lines continue to consistently deliver the most reliable and significant results available.

Figure 1

Working in Synergy

Wavelength selection, light source and power output play a crucial role in achieving optimal therapeutic benefits from light treatments. Many commercially available devices select Laser or LED diodes based upon commercial availability. Selected parameters should work constructively to create a synergistic effect. [1]

There is strong evidence to suggest that one of the basic mechanisms of photobiomodulation (PBM) is the acceleration of electron transfer by electromagnetic radiation in the visible and near infrared region of the spectrum[2],[3] via the modulation of cytochrome c-oxidase (CCO) activity. It was believed that CCO had a peak of activity at 825 nm, and is thought to be due to the relatively oxidized CuA chromophores[4]. Single wavelength probes (both point and clusters) are limited by the specific absorption spectrum of that specific wavelength. It was suggested that a combination of wavelengths may provide a more robust means of triggering the phototherapeutic response.

Albuquerque-Pontes, et al[5] investigated the effect of different wavelengths on cytochrome c-oxidase (CCO) activity and identified a previously unknown profile for CCO. Not only do multiple wavelengths have the capacity to stimulate CCO activity, they pose an activation time profile that details times of peak stimulation. The findings suggest that the concurrent use of different wavelengths provides an overlapping effect of peak activation that enhances CCO activity. Friedmann, et al confirmed this observation utilizing the Multi Radiance Medical TQ Solo and states the combination of multiple wavelengths produced enhanced Adenosine Triphosphate (ATP) production more efficiently than a single red wavelength with a comparatively larger dose. The combined use of multi wavelength low powered light sources benefits increased CCO activity without having to resort in increased doses from a single wavelength light source. Friedmann, et al[6] found similar increases in ATP production from a smaller dose delivered by a multi-wavelength, lower powered device as compared to Eichler, et al.[7] outcomes with a single wavelength, higher powered device. This suggests that multiple wavelengths can prolong the time profile activation of CCO with much smaller doses delivered across many wavelengths with much lower average powers rather than one single wavelength of higher power.

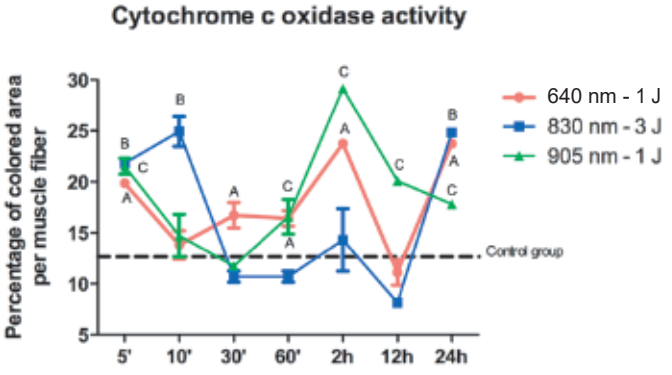

Figure 2

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De Marchi, et al.[8] demonstrated the beneficial effects of multiple wavelengths in the Multi Radiance device in a study that compared to either a single or dual wavelength device. In a randomized, double-blinded, placebo-controlled trial, forty untrained healthy male volunteers preformed eccentric exercise and had the results measured to establish muscle performance and recovery via maximum voluntary contraction MVC, delayed onset muscle soreness (DOMS), and creatine kinase (CK) activity. These included the MR4 triple wavelength 905, 875, 640 nm, a continuous wave single wavelength 808 nm low level laser device and a dual wavelength 810 nm/980 nm Class 4 high power laser device.

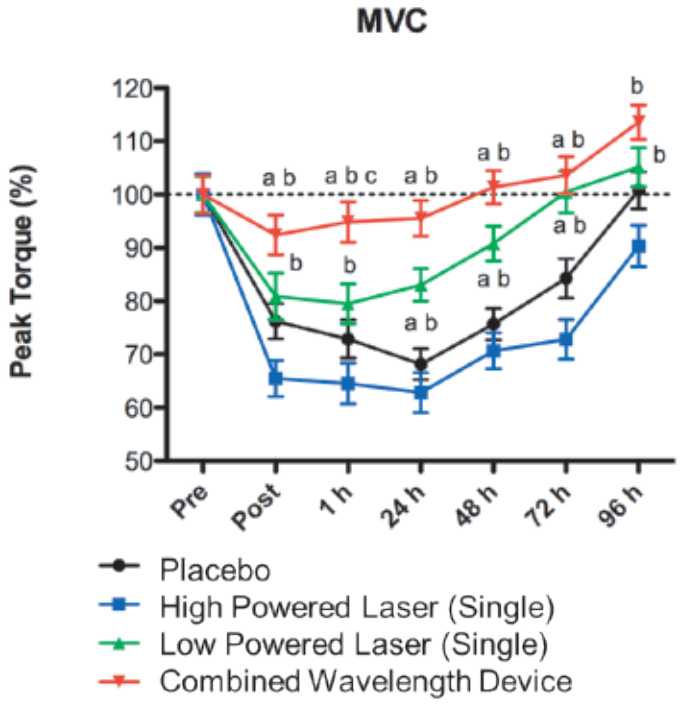

Figure 3

MR4 delivered the greatest enhancement of MVC ($p<0.05$), DOMS ($p<0.05$), CK activity ($p<0.05$) compared to placebo and Class 4 devices and demonstrated the greatest effect on DOMS ($p<0.05$) compared to placebo, Class 3B and Class 4 devices. (Figure 3)

The Multi Radiance combination of Super Pulsed Laser (GaAs 905 nm), infrared and red LEDs (875 nm and 640 nm) ensures an optimized peak activation of CCO across the entire therapeutic window. This enhances ATP production, provides continual photo dissociation of NO and activates ROS. This mix of concurrent multiple wavelengths provides a vastly improved absorption spectrum to interact with a host of different photoreceptors in the body. While the benefits of combined wavelengths are clear, not all combinations of wavelengths, sources and power outputs have proven beneficial. Parr, et al,[9] found no significant differences between either of the treatment groups or the sham group when utilizing a Class 4 high-powered laser containing wavelengths of 810 nm and 980 nm.

Creating Waves

A therapeutic sweet spot exists in the near infrared spectrum between 630 nm and 910 nm, where the absorption of light is not limited by melanin, lipid or water absorption that allows light to enter the body. Researchers have recently been studying the effects of depth of penetration by testing various wavelengths and powers to determine which are better suited for deeper or superficial applications. A review of the available literature has demonstrated that depth of penetration is directly related to the wavelength and actual measurements of the skin penetration by light over a period of time. However, it is necessary to understand how light enters the body.

Researchers have recently demonstrated that depth of penetration is wavelength specific. Brondon, et al[10] found Super Pulsing better able to penetrate through melanin filters and Joensen et al[11] evaluated and found Super Pulsed 904 nm LLLT energy penetrated 2-3 times easier through the rat skin barrier than a CW device of 810 nm. Yet, a common myth perpetuated by several makers of Class 4 devices insists that greater power leads to better photon penetration through the skin. It was determined that 808 nm of light penetrates as much as 54% deeper than 980 nm light[12] and the poor penetration of 980 nm is likely to produce more tissue heating than photochemical effects.[13]

Key Note: Simply put, penetrating the skin barrier cannot be compensated by a higher power output, as it will cause light to be absorbed superficially, more quickly, leading to greater heat generation[14], treatment overdose or possible photodamage.

Leal-Junior, et al performed a depth of penetration time profile on the MR4 LaserShower (640 nm Red LED, 875 nm IRED and 905 nm SPL) following the procedure Joenson, et al employed. Compared to the predicted amount, the combined wavelengths group exhibited nearly a 100% greater penetration time profile at all observed time points (Figure 4). It can

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be concluded that the combination of low level power and multiple wavelengths creates a "synergism" that enhances each individual wavelength's ability to penetrate the skin. This improved skin penetration time profile allows for a greater proportion of the available light energy to reach biological targets beneath the skin. By improving the efficiency of penetration, the necessary energy provided at the surface is significantly less, reduces the conversion into heat and avoids a dangerous rise in tissue temperature. Multi Radiance devices emit wavelengths that reach varying depths of penetration and create a unique non-thermal synergy that improves overall penetration by 100%. This, in turn, creates a favorable mix of the available parameters to maximize therapeutic outcomes in the clinic for consistent and reliable results.

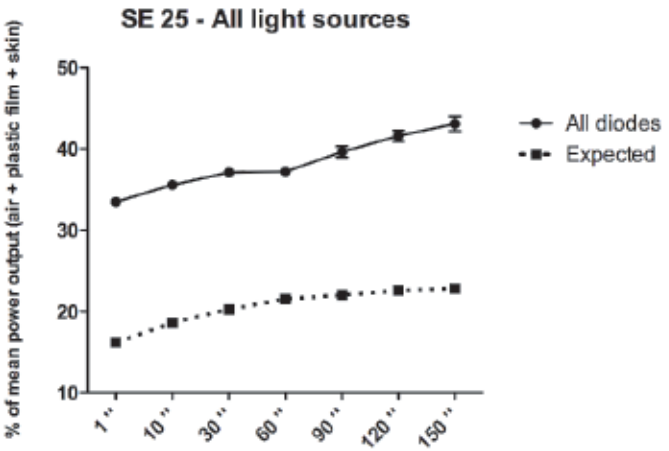

Figure 4

The Argument against High Power is HEATING UP

While a need for adequate power exists, an irradiance either too low or too high can either fail to stimulate a biological process or in some cases inhibit beneficial activity. Creating a balance between power, depth of penetration and absorption is necessary to get the desired tissue response. An irradiance that is too low will fail to stimulate the tissue, give lackluster clinical results and be no more effective than ordinary light. The downside of increasing the average power is heat. Heat is generated as an unwanted byproduct of light, the more intense the light, the greater the amount of heat. This is becoming a larger issue and explains part of the insufficiency of high powered photobiomodulation.

All lasers and LED sources will have a percentage of emitted energy converted into heat. The amount of this conversion is a function of the emitted wavelengths. A wavelength with a poor depth of penetration time profile (DPTP) will transform light into thermal energy more rapidly, possibly increasing the skin surface temperature rapidly. This compromises the phototherapeutic effect, because as the heat continues to increase, the photochemical and photophysical effects are reduced in response to thermal build up. There must be a balance between absorption and penetration to optimize the therapeutic value of the device.

In addition to the favorable DPTP of the Multi Radiance devices, pulsing and Super Pulsing, by nature, have a clean distinctive advantage; their operation, by design, is to minimize heat. Super Pulsed laser creates a desirable higher peak power, however due to the ultrashort pulses, there is little resulting heat accumulating within the target tissue. IREDs and LEDs will, if left on continuously, exhibit the same thermal profile as a continuous wave laser. That is, the increase in power output would also increase the heating effect, due to the inefficiency of the semiconductor processes that generate light. To work in concert with the Super Pulsing laser, both IREDs and LEDs are pulsed to reduce photothermal effects on tissue.

The combination of wavelengths in the Multi Radiance Medical device and pulsing have improved not only the percentage of available light beneath the skin but have reduced the net thermal impact on the skin surface and tissue. This resolves any issues with the inefficient use of higher-powered outputs in continuous wave devices and a poor penetration profile.

Selecting the right PBM device not only dictates understanding the mechanism of how light from that device interacts with the biological target but the diverse set of parameters necessary to produce the therapeutic effects. Even devices that on the surface appear to have similar specifications, can vary tremendously in their therapeutic benefits.

Is a device that can deliver a dose very quickly due to high power a better one? Some may claim that a device is superior because it can deliver a dose in a quick amount of time. This is the argument for the use of high powered Class 4 lasers. Currently there are approximately 60 studies on high-powered laser in

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PubMed, some with questionable outcomes and design biases, which represents less than 1% of all the available research data on PBM and are far from convincing. But they do contribute to the general confusion and are an obstacle in the general acceptance of laser phototherapy.

Key Note: To date there is no evidence based research that supports the efficacy or effectiveness of high powered lasers primarily due to the lack of a true placebo controlled double blinded clinical trial.

Three devices will be compared in a side by side manner (Figure 5). Each device will have a unique set of parameters and while on the surface, a device may appear to be "better" in comparison, a closer look may reveal a different truth. The three devices: a CW device (808 nm 200 mW), a Combined SPL+LED device (133 mW 905 SPL + 875 nm IRED + 640 nm IRED) and a CW Class 4 device (980 nm 500 mW) are examined side by side. Since the DPTP is known for all three devices, a calculation can be made in regards to the available light beneath the skin surface and absorbed by the skin.

For the 808 nm (DPTP is 20%), approximately 2.4 of the 12 J dose delivered in 1 minute would pass through the skin. The remaining 9.6 J are absorbed in the skin and converted to heat. The combined SPL+LED device (DPTP is 43%) would deliver only 8 J in 1 minute, however due to the favorable DPTP, 3.4 J would be delivered below the skin and only 4.6 J would be converted into thermal energy. In very stark contrast, the CW 980 nm (DPTP 97.5%) would convert nearly all of the energy to heat in 1 minute and only .75 J would be available below the skin.

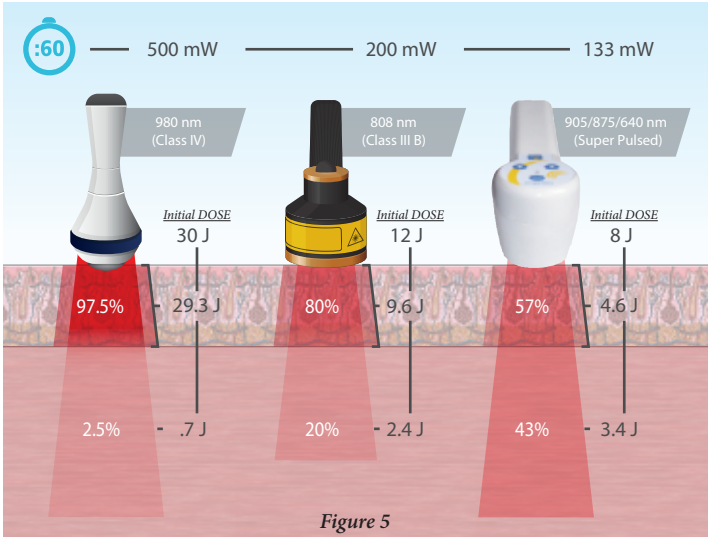

Figure 5

Key Note: Simply, penetrating the skin barrier cannot be compensated by a higher power output, it will just cause light to be absorbed superficially more quickly, leading to greater heat generation, especially if the wavelength selected possesses a weak penetration profile.

In this case, the device that produced the greatest amount of joules also created the greatest amount of heat. It should be noted that the combined SPL+LED device has the greater energy below the surface of the skin due to the favorable DPTP. Therefore, the device most effective at penetrating through the skin, without increasing the temperature, is the ideal device.

Power, Heat, and Phototoxicity

Power is often the most discussed, misunderstood and misrepresented PBM parameter. In the simplest terms, the output of power, measured in watts or milliwatts, determines the time necessary to deliver a set dose. Confusion sets in when evaluating how much power is necessary, what is an acceptable treatment time, and the type of the photobiological reaction that occurs. Thinking that since "a little is good, more must be better" is a critical error. Depending on the intensity of the light, the photobiomodulation effect can quickly transform into a photothermal situation especially if the wavelength selected has a weak penetration profile.

In many instances, power output is limited by the transfer rate of light energy to heat. This creates a technical limitation of many devices and one that can limit the clinical potential of a device as well as its potential safety of use. In order to understand one of the several ways heat can be minimized, a very important distinction is how the energy is delivered either in continuous (CW) or pulsed (P) modes. The type of power delivery can not only impact how heat is managed, but also impact dose and treatment times. The biological responses of cells to Super Pulsed laser therapy can be different from responses to continuous wave, and there is a strong dependence on pulse repetition rate, pulse duration and duty cycle, as well as energy dose and wavelength. [15]

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Primary effects of the PBM are based on photochemical and photophysical changes and not the result of thermal influence in tissue[16],[17]. However, light absorption creates heat as a byproduct. Laser, like ultrasound, at low levels can stimulate while at higher levels it becomes destructive.[18] When a higher dose is delivered, there is a corresponding increase in the surface temperature recorded in darker pigmented skin compared to lighter skin tones. In some instances, there was 3 to 6 times more heat than in the lighter skin color groups.[19] Khan, et al [20] found a correlation between surface temperature greater than 45 °C and significant skin damage irrespective of skin color and conventional laser treatment parameters namely, irradiance and fluence.

Heat is a collateral byproduct of light, and one of the limiting factors in photobiomodulation. Device thermal profiling provides an insight as to how efficient, or inefficient, the device is by measuring the thermal response at the skin surface. Testing ranges should include small and large doses, but also measure dose rates over time. This will give a robust profile that will avoid potentially using PBM in situations where heat may not be indicated, including wounds, acute injuries, and areas of paresthesia.

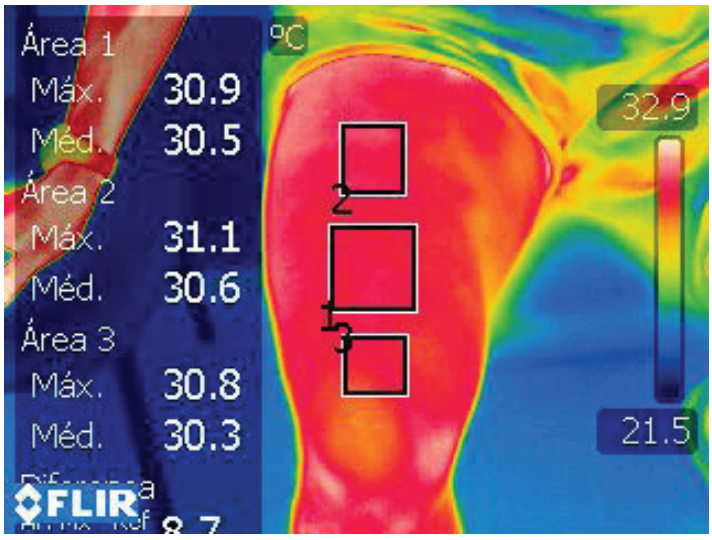

Figure 6

Grandinétti, et al.[21] performed a thermal profile on the MR4 LaserShower (LS50: 640 nm, 875 nm and 905 nm) emitter with a set frequency of 250 Hz to deliver a placebo, 10 J, 30 J and 50 J dose to sixty healthy adult volunteers divided by gender, age, and skin color stratified according to Von Luschan's chromatic scale. In Joensen's prior experiment, using a different super pulsed laser, the higher (and longer) doses significantly increased the skin temperature by 22.3°C in dark pigmented skin. (Figure 6)
At all doses, the MR4 LS50 did NOT increase the skin temperature to same levels reported in the prior studies, that could affect patient safety and comfort. This may be attributed to the ultra-short pulse structure related to the frequency of the Super Pulsed laser and pulsing of the LEDs and IREDs as compared to the devices in the previous study (Joensen, et al).

With virtually no side effects and minimal contraindications, low-level laser and LED Laser therapy treatments are considered safe to use in almost all clinical situations and patient populations. Thermal effects are negligible (<1.5°C) in light, medium, and dark skin at doses recommended by World Association of Laser Therapy-guidelines for musculoskeletal and inflammatory conditions. High-powered lasers cannot claim the same safety. It should be noted that a thermal increase may be even more pronounced for 980 nm Class 4.[22] While heating may elicit a placebo effect due to a tactile response, Kim and Jeong[23] noted while utilizing a Gaussian beam with 3.14 W/cm2 that the hyperthermia lasts for a few minutes. It is possible that significant thermal damage occurs in biological tissues in particular to more superficial skin layers. [24]

Khan, et al.[25] administered high powered Class 4 lasers on laboratory mice to determine the threshold at which laser absorption becomes phototoxic or cytotoxic in order to determine overall safety of the higher powered devices. The conclusion from the research suggested that it is possible to use surface temperature during laser treatment as a clinical indicator of laser phototoxicity. There are molecular markers which are indicators of laser cytotoxicity, including excess ROS. The authors observed that the use of high powered NIR laser resulted in detrimental effects on mice skin that correlate with an increase in surface temperature (≥45 °C). The temperature dependent effects were not just limited to edema and erythema, but also to burns, contractures and even death. It was explained that the excessive heat combined with the excessive release of ROS created the toxicity.

The detrimental effect of high powered laser on intact skeletal muscle can be seen in the comparative study done by De Marchi, et al.[26] The use of the a high powered dual wavelength Class 4 device had no effects in regards to improving muscles strength or modulating

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the pain associated with DOMS, however they observed a significant ($p<0.05$) negative effect greater in CK activity compared to the placebo. (Figure 7)

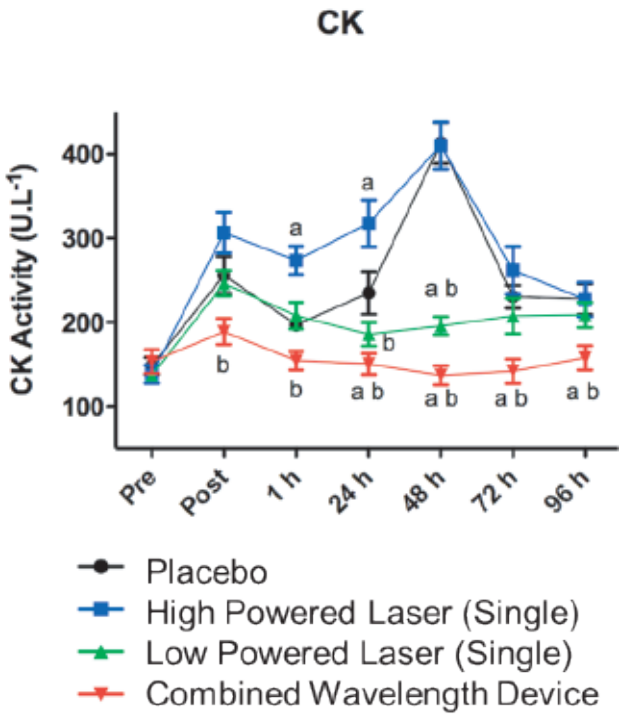

Figure 7

The significant increase in CK appears to suggest that the high powered laser had a damaging effect on the irradiated skeletal muscle of the volunteers. The subjects fatigued faster than those in other groups. This may have caused the muscles to work harder and experience catabolic effects. It is evident that dose delivered by the high-powered laser did not exhibit the same prophylactic and stimulatory effect as demonstrated by the MR4. Tissue heating may be negatively impacting the phototherapeutic outcome as indicated by the significant increase in CK activity noted and possibly a result of photocytotoxcicity. This certainly would "reject" the claim that more power delivered to the tissue provides a beneficial therapeutic effect.

Key Note: All devices should complete thermal time profiles to rule out any possibility of toxicity. The thermal profile done by Grandinétti, et al. showed that no excessive heat was noted in any types of pigmented skin with the Multi Radiance Medical device. This indicates that the Multi Radiance Medical devices are safe to use without concern or worry over photocytoxicity.

Getting Consistent and Reliable Results

Tissue response can be quite different based upon the rate at which energy is delivered. Using the same amount of energy, but with different energy densities, will not necessarily trigger the same biological response. Kim[27] used 1.2 J in plastic and aesthetic surgery. The energy was delivered either by a 1000 mW or a 60 mW 830 nm laser (1000 mW × 1.2 sec or 60 mW × 200 sec). Both were effective, but the 60 mW laser was more effective in the initial period of wound healing, while the 1000 mW laser was more effective in the late period. This response could be attributed to the amount of heat generated by the devices and how that heat affects different stages of healing. Alves et al[28] confirmed effects of a "same" dose can be quite different when the rate of which it is delivered can be altered. Jenkins[29] notes, in short, the power is actually of less importance in determining the outcome of laser therapy than the irradiation time.

If a device is in continuous mode, it will always deliver the same dose in the same amount of time. Imagine how difficult it would be to try to bake a cake with temperature setting of 450'F versus the correct temperature of 350'F, there would be burnt edges and a raw middle. All Super Pulsed lasers operate in pulsed mode and the number of times the laser fires per seconds is the "frequency" of the pulses and affects the mean output of power the laser delivers. This impacts the amount of light the tissue receives. By changing the frequency, the rate of energy delivered is also changed. Based upon tissue response or need, the dose can be delivered in a shorter amount of time by increasing the frequency output of the laser or spreading it out over a much longer time by lowering the rate of laser firing. In essence, it works like a thermostat. This allows for a more customizable delivery of energy, rather than a one-size-fits-all type of situation.

We often think of PBM as being either stimulatory (repair) or inhibitory (pain relief); this is defined as a biphasic dose. These effects are the direct result of the delivered "dose". This is an example commonly known as the Arndt-Schultz principle whereas small doses stimulate the biological process and large doses inhibit them.

The biphasic dose-response has been demonstrated in both in vitro and animal experiments.[30] In reality there appears to be a range of doses that are influenced

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by power output, the thermal profile, and depth of penetration. Examples of the dose variability for the same condition based on wavelength can be seen in the WALT Guidelines. The use of incomplete dose parameters are often the cause of negative outcomes in studies[31] , therefore clinicians should not randomly accept that a universal dose exists.

Antonialli, et al[32] utilized and established a protocol[35] to observe the phototherapeutic effect in the lab settings that can measure both stimulatory and inhibitory effects. Utilizing a randomized, double-blinded, placebo-controlled trial, 40 male healthy untrained volunteers were given one of four doses (80 s, 240 s, 400 s or placebo) with the MR4 LaserShower (640 nm Red LED, 875 nm IRED and 905 nm SPL) prior to performing an eccentric exercise protocol designed to induce muscle fatigue. Visual Analogue Scale (VAS) to assess pain and creatine kinase (CK) test to detect inflammation of muscles (myositis) or serious muscle damage[34] were performed at 1 min, 1, 24, 48, 72, and 96 h post exercise procedures.

While all doses provided a beneficial effect, the specific responses could be linked to a treatment dose. The 240 s dose represented the most stable control of the inflammatory process. The largest of the three doses (400 s) provided the greatest reduction in short term pain in the first 24 hours. (Figure 8) This is an excellent example of the biphasic dose-response or Arndt-Schulz curve. The smallest of the tested doses (80 s) stimulated the biological processes and as the dose was increased (240 s) even more favorable stimulatory results were noted. However once the larger dose (400 s) was applied the biological effects began to diminish and photobioinhibition began to take effect. The placebo has no effect on either pain or inflammation.

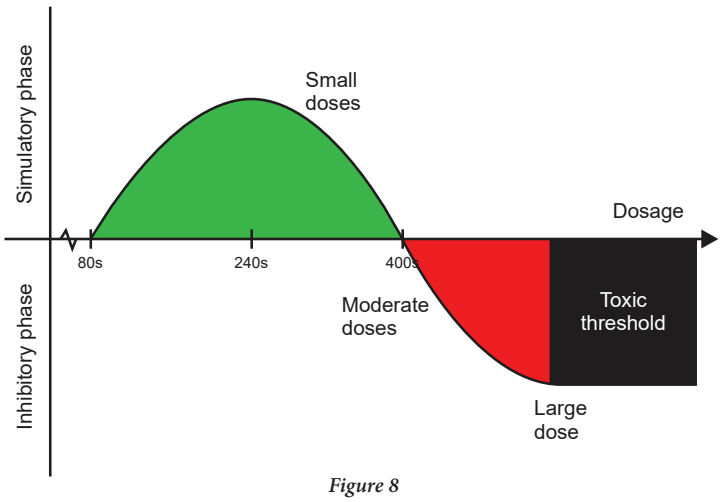

Figure 8

There remains a considerable debate within the community as to how to quantify the dose and more importantly how we should measure the applied energy. Some would note that a joule (the joule, symbol J, is a derived unit of energy, work, or amount of heat in the International System of Units) should be utilized. While on paper, dose or energy, can be easily calculated, but cannot be completely validated. Time is a constant, and therefore a better comparative parameter. The duration of the treatment per location can be measured by the clinician and in most cases, by the device. Recording time along with the device settings attempts to provide some reproducible treatment parameters.

It should be noted that alternative forms for dose calculation have been suggested such as the use of biometric equipped devices, like the TARGET™ equipped MR4 LaserStim™. Other methods such as biofeedback, spectroscopy and thermography may prove useful in the future.

The Reliable Dose

Dose is often one of the most confusing aspects of photobiomodulation and has earned a reputation of being "impossible". Even the suggested dose guideline per condition from the WALT guidelines are so broadly based that their clinical value has been questioned. Compounded by the lack of understanding of the biphasic dose response curve for individual devices, it makes accurate dosing in human subjects nearly impossible.

Multi Radiance Medical recently introduced the first-of-its-kind device to address this issue. The photobiometric MR4 LaserStim™ utilizes biometric data compiled in real-time to optimize treatment parameters to provide the "right" dose, for the right condition, at the right time. The MR4 LaserStim™ adds a neuro-adaptive electrical muscle stimulator to the multi wavelength light and magnetic field to create a new technology that can work in real-time to improve dose delivery.

The MR4 LaserStim™ employs a unique biphasic form of electrical stimulation that provides a continual monitoring of the changes in electrical impedance of the skin and underlying tissue. By identifying areas of decreased resistance (increased impedance), MR4 LaserStim™ can locate areas where inflammation, ede-

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ma, or spasms are present. This is the TARGET™ or Treatment Area Recognition and Guidance Enhanced Technology. It enables users to locate asymmetries or "active sites" through bio-impedance deviations ie: highly-probable laser therapy targets.

Utilizing the same neuro-adaptive biphasic electrical stimulation current, the device employs DOSE™ or Dose Optimization by Skin Electrophysiology, to measure the real-time effects of the combined light and electrical stimulation treatment on the body. When used in conjunction with TARGET™, DOSE™ provides visual and audio feedback when "normalization" of the target tissue has been reached. In essence, the MR4 LaserStim™ acts both like a target finder and a dose meter for the total delivered energy. This unique coupling of technologies improves the overall efficacy of the laser application by ensuring proper target identification and reducing the need for "cookbook" treatments.

Summary

At the core of all Multi Radiance Medical devices is a synergistic combination of Super Pulsed Lasers, Infrared Emitting Diodes, Light Emitting Diodes, and a static magnetic field. This patented "mix" of multi wavelengths, multi-light and energy sources was validated by studies conducted from 2012-2014 by the Laboratory of Phototherapy in Ports and Exercise (Sao Paulo, Brazil) and reported in the Pillars Proof of Concepts White Paper.

It has been demonstrated that multiple wavelengths have the ability to enhance and prolong the time of CCO activation across the entire therapeutic window by delivering much smaller doses across many wavelengths rather than a single wavelength of greater power. This enhances ATP production, provides continual photo dissociates NO and activates ROS.

The tested combination enhanced each individual wavelength's ability to penetrate the skin, to allow for a greater proportion of the available light energy to reach biological targets beneath the surface. This resulted in a vastly improved the efficiency of penetration (up to 100%) of available light beneath the skin without the need for increased power due to heat loss. Combined with the favorable DPTP of the Multi Radiance devices, pulsing and Super Pulsing minimized the photothermal effect accumulating within the target tissue. The combination of wavelengths in the Multi Radiance Medical device and pulsing have improved not only the percentage of available light beneath the skin but have reduced the net thermal impact on the skin surface and tissue. This resolves any issues with the inefficient use of higher-powered outputs in continuous wave devices and a poor penetration profile.

Multi Radiance Medical recently introduced the first-of-its-kind device to address this issue. The photobiometric MR4 LaserStim™ utilizes biometric data compiled in real-time to optimize treatment parameters to provide the "right" dose, for the right condition, at the right time. The MR4 LaserStim™ employs a unique biphasic form of electrical stimulation that provides a continual monitoring of the changes in electrical impedance of the skin and underlying tissue and acts both like a target finder and a dose meter for the total delivered energy. This unique coupling of technologies improves the overall efficacy of the laser application by ensuring proper target identification and reducing the need for "cookbook" treatments.

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Conclusion

Multi Radiance Medical devices have the most favorable mix of the available parameters to maximize therapeutic outcomes in the clinic for consistent and reliable results. With virtually no side effects and minimal contraindications, Multi Radiance Medical Lasers are classified in the safest category of therapeutic lasers to use without concern or worry over photocytoxicity. Combining design and engineering, Multi Radiance Medical does not compromise between power and heat, it maximizes it. This provides clinicians with confidence that the Multi Radiance Medical products are supported by science and clinically proven to produce consistent, positive patient outcomes.

Extensively tried and tested over 20 years, Multi Radiance Medical MR4 and TerraQuant product lines are patented, unique devices that combine multiple wavelengths, light sources and electromagnetic energy to provide the most tested, reliable and clinically significant results available. Each wavelength and light source creates a synergistic effect that when combined with others, summate greater than the individual effects.

On Market Leadership

Multi Radiance Medical remains dedicated to sound research, industry advancement and maintaining the utmost professional integrity. They continue to support educational programs and associations, Laser Therapy U and the North American Association of Photobiomodulation Therapy, which focuses on clinical applications, evidence based and translational research, and the latest discoveries in photobiomodulation. The company partners with the most respected researchers in the field to provide invaluable guidance with regard to the design of the devices and with direction of clinical research.

Multi Radiance Medical, in two scientific monographs, has proven how and why its technology works, without limitations. There are currently over 30 Clinical Trials around the world being funded and supported by Multi Radiance Medical.

Multi Radiance is taking the responsibility to set new standards for the industry by setting the bar high on research and validation. Having proven its technology in vivo, in vitro, in controlled laboratory trials, and in clinical trials, Multi Radiance in now setting its sights on assuming Market Leadership by turning its current research into future treatment opportunities for those disease states and conditions that do not have an adequate current treatment, and in those cases where there is no current treatment at all.

Multi Radiance remains committed to the on-going clinical and scientific studies of its devices, to push new industrial product designs, and become the innovative leader in the field. This commitment will yield many new discoveries and move light based medicine forward into the future and toward mainstream acceptance.

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About the Authors:

Douglas Johnson, ATC, EES, CLS, is a certified athletic trainer with over 20 years of clinical/industrial experience. He attended Wayne State University and The University of Detroit-Mercy where he earned a Summa Cum Laude Bachelors of Science degree in Sports Medicine in 1994.

He is the Senior Vice President, Clinical and Scientific Affairs at Multi Radiance Medical and is involved in numerous research studies involving super-pulsed laser. He was named as a clinical advisor to Laser Therapy U, invited to speak at the Annual 2014 NATA Symposium for Laser Therapy and a member of the NAALT/WALT Scientific Education Committee for the 2014 Program. He studied the effect of super-pulsed laser and light-emitting diodes phototherapy on non-specific knee pain which was published in Lasers in Medical Science, May 2014 and is a reviewer for the Journal of Athletic Training.

Currently he is at work on a comparative study of ice versus combined laser/light for athletic recovery and completing the Laser Methods Post Graduate Course. Mr. Johnson was recently an invited speaker at Euroscience 2015 in London, England and recently elected to the Board of Directors of the North American Association for Photobiomodulation Therapy (NAALT).

Ernesto Cesar Pinto Leal Junior, PT, PhD has a Bachelors Degree in Physiotherapy from 2002 in Brazil. In 2004 he got his Master´s degree in Biomedical Engineering at University of Vale do Paraiba (Univap) in Brazil, and he defended his PhD thesis in 2010 at University of Bergen - Norway (Section of Physiotherapy Science, Department of Public Health and Primary Health Care, Faculty of Medicine and Dentistry). In 2012 he finished his Post-Doctoral at Department of Pharmacology of University of Sao Paulo.

Dr. Leal Junior has been a lecturer at 2 Brazilian universities (Unilasalle University and University of Caxias do Sul) between February 2005 and July 2009. Dr. Leal is a reviewer for several international peer-reviewed journals, he specializes in Phototherapy and the Sports Science fields (Photomedicine and Laser Surgery, Lasers in Medical Science, Physiotherapy Research International, Journal of Sports Sciences, Journal of Photochemistry and Photobiology B: Biology, and Photochemistry and Photobiology). Since April 2014 he has been a member of the editorial board of Photomedicine and Laser Surgery. His current position is as Full Professor at Nove Julho University in Sao Paulo, Brazil.

His expert area of research is photobiomodulation in skeletal muscle disorders. A special interest has been developed in photobiomodulation research (Low-Level Laser Therapy and Light-Emitting Diode Therapy) for skeletal muscle fatigue delaying, performance enhancement, injury prevention and recovery after strenuous physical activity.

Currently Dr. Leal Junior has 70 scientific papers published, 48 of them in international peer-reviewed journals (indexed by Pubmed/Medline), as well as 2 papers recently accepted in international journals. He has presented more than 40 scientific papers in National and International Congresses. In September of 2011, Dr. Leal Junior was awarded by NAALT with Young Clinical Research Award in Phototherapy.

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Appendix:

[1]Friedmann H, Lipovsky A, Nitzan Y, Lubart R. Combined magnetic and pulsed laser fields produce synergistic acceleration of cellular electron transfer. Laser Therapy, 2009, 18(3): 137-141

[2]Karu T. (1998). "The Science of Low-Power Laser Therapy", Gordon and Breach Science Publishers.

[3]Karu T. (2007) "Ten Lectures on Basic Science of Laser Phototherapy" Prima Books AB .

[4]Karu, T. I. (2010). Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. IUBMB life, 62(8), 607-610.

[5]Albuquerque-Pontes GM, Leal-Junior EC, et al. Effect of different doses, wavelengths and application intervals of low-level laser therapy on cytochrome c-oxidase activity in intact skeletal muscle in rats. Lasers Med Sci June, 2014 Epub ahead of print]

[6]Friedmann H, Lipovsky A, Nitzan Y, Lubart R. Combined magnetic and pulsed laser fields produce synergistic acceleration of cellular electron transfer. Laser Therapy, 2009, 18(3): 137-141

[7]Eichler M, Lavi R, Friedmann H. (2007). Red Light-Induced Redox Reactions in Cells Observed with TEMPO. Photomedicine and Laser Surgery 25, 170-174.

[8]De Marchi, T., Schmitt, V., Fabro, C., Lopes da Silva, L.., Sena, J, Salvador, M., Tairova, O,. (2014). Phototherapy in skeletal muscle performance and recovery after exercise: Comparison between three different devices commercially available

[9]Parr J, Larkin K, Borsa P. Effects of Class IV Laser Therapy on Exercise-Induced Muscle Injury. Athletic Training and Sports Health Care. 2010; 2: 267-276. doi: 10.3928/19425864-20100630-04

[10]Brondon P, Stadler I, Lanzafame RJ. Pulsing influences photoradiation outcomes in cell culture. Lasers Surg Med. 2009;41(3):222–226. [PubMed]

[11]Joensen J, Ovsthus K, Reed RK, Hummelsund S, Iversen VV, Lopes-Martins RÁ, Bjordal JM.; Skin penetration time-profiles for continuous 810 nm and Superpulsed 904 nm lasers in a rat model.; Photomed Laser Surg. 2012 Dec;30(12):688-94. doi: 10.1089/pho.2012.3306. Epub 2012 Oct 1.Source

[12]Hudson DE, Hudson DO, Wininger JM, Richardson BD. Penetration of laser light at 808 and 980 nm in bovine tissue samples. Photomed Laser Surg. 2013 Apr;31(4):163-8. doi: 10.1089/pho.2012.3284. Epub 2013 Feb 26.

[13]Mantineo, M., Pinheiro, J. P., & Morgado, A. M. (2014, February). Evaluation of low level laser therapy irradiation parameters on rat muscle inflammation through systemic blood cytokines. In SPIE BiOS (pp. 89320M-89320M). International Society for Optics and Photonics. Chicago

[14]Tunér, J. (2014). No Cure from LiteCure. Annals of Laser Therapy Research, Annals Issue 1 2014. http://www.laserannals.com/2014/03/22/no-cure-from-litecure/

[15]The Science of Low-Power Laser Therapy by Tina Karu, Gordon and Breach Science Publishers 1998 ISBN 90-5699-108-6.

[16]Dyson M. "Primary, secondary and tertiary effects of phototherapy: a review". Abstract from the 7th Congress of North American Association for Laser Therapy, Toronto, Canada, June, 2006

[17]Lanzafame R et al. "Temperature-controlled 830-nm low-level laser therapy of experimental pressure ulcers." Photomedicine and Laser Therapy 22.6 (2004): 483-488.

[18]"Effects of Power Densities, Continuous and Pulse Frequencies, and Number of Session of Low Level Laser Therapy on Intact Rat Brain" by Ilic, S., Leichliter, S., Streeter, J., Oron, A., DeTaboada, L., Oron, U. Photomed Laser Surg, 2006 Augu;24(4):458-66.

[19]Joensen J, Hendrik I, Johnson M, Iversen V, Lopes-Martins R and Bjordal J. The thermal effects of therapeutic lasers with 810 and 904 nm wavelengths on human skin. Photomedicine and Laser Surgery. March 2011, 29(3): 145-153. doi:10.1089/pho.2010.2793.

[20]Khan, I., Tang, E., & Arany, P. (2015). Molecular pathway of near-infrared laser phototoxicity involves ATF-4 orchestrated ER stress. Scientific reports, 5.

[21]dos Santos Grandinétti, V., Miranda, E. F., Johnson, D. S., de Paiva, P. R. V., Tomazoni, S. S., Vanin, A. A., ... & Leal-Junior, E. C. P. (2015). The thermal impact of phototherapy with concurrent super-pulsed lasers and red and infrared LEDs on human skin. Lasers in medical science, 1-7.

[22]Mantineo, M., Pinheiro, J. P., & Morgado, A. M. (2014, February). Evaluation of low level laser therapy irradiation parameters on rat muscle inflammation through systemic blood cytokines. In SPIE BiOS (pp. 89320M-89320M). International Society for Optics and Photonics. Chicago

[23]Kim, S., & Jeong, S. (2014). Effects of temperature-dependent optical properties on the fluence rate and temperature of biological tissue during low-level laser therapy. Lasers in medical science, 29(2), 637-644.

[24]Plaghki, L., & Mouraux, A. (2003). How do we selectively activate skin nociceptors with a high power infrared laser? Physiology and biophysics of laser stimulation. Neurophysiologie Clinique/Clinical Neurophysiology, 33(6), 269-277.

[25]Khan, I., Tang, E., & Arany, P. (2015). Molecular pathway of near-infrared laser phototoxicity involves ATF-4 orchestrated ER stress. Scientific reports, 5.

[26]De Marchi, T., Schmitt, V., Fabro, C., Lopes da Silva, L.., Sena, J, Salvador, M., Tairova, O,. (2014). Phototherapy in skeletal muscle performance and recovery after exercise: Comparison between three different devices commercially available

[27]Kim JW, Lee JO (1998) Double blind cross-over clinical study of 830 nm diode laser and 5 years clinical experience of biostimulation in plastic and aesthetic surgery in Asi- ans. Lasers Surg Med Suppl 10:59

[28]Alves AC, Albertini R, Dos Santos SA, Leal-Junior EC, Santana E, Serra AJ, Silva JA Jr, de Carvalho PD; Effect of low-level laser therapy on metalloproteinase MMP-2 and MMP-9 production and percentage of collagen types I and III in a papain cartilage injury model; .Lasers Med Sci. 2013 Aug 29.

[29]http://www.laserannals.com/2013/06/09/a-brief-word-on-reciprocity/

[30]Huang, Y. Y., Chen, A. C. H., Carroll, J. D., & Hamblin, M. R. (2009). Biphasic dose response in low level lightherapy. Dose-Response, 7(4), 358-383.

[31]Huang, Y. Y., Sharma, S. K., Carroll, J., & Hamblin, M. R. (2011). Biphasic dose response in low level light therapy-an update. Dose-Response, 9(4), 602-618.

[32]Antonialli, F. C., De Marchi, T., Tomazoni, S. S., Vanin, A. A., dos Santos Grandinetti, V., de Paiva, P. R. V., ... & Leal-Junior, E. C. P. (2014). Phototherapy in skeletal muscle performance and recovery after exercise: effect of combination of super-pulsed laser and light-emitting diodes. Lasers in medical science, 29(6), 1967-1976.

[33]Baroni, B. M., Junior, E. C. P. L., De Marchi, T., Lopes, A. L., Salvador, M., & Vaz, M. A. (2010). Low level laser therapy before eccentric exercise reduces muscle damage markers in humans. European journal of applied physiology, 110(4), 789-796.

[34]http://labtestsonline.org/understanding/analytes/ck/tab/test/

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