EFFECTS OF LOW-LEVEL LASER THERAPY ON LIVER REGENERATION AND LASER PARAMETERS EMPLOYED

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ABSTRACT: Low-level laser therapy has several biological effects; one of them is tissue regeneration. Recent studies have been held on the application of laser therapy on the liver of rats after partial hepatectomy to promote liver regeneration. The aim of this article was to review the recent studies on the effects of low-level laser therapy on rat liver regeneration after partial hepatectomy and the laser parameters used in those studies. A review of recent relevant literature was performed in Pubmed, Scielo, Medline, and Bireme databases. Articles related to the application of low-level laser therapy on hepatic regeneration were included. Articles with hepatic regeneration in the presence of pathologies were not included. Nine studies were found matching the study criteria. In most studies, low-level laser therapy promoted liver regeneration after partial hepatectomy, without further damage to the remaining liver. Not all laser parameters required for the reproducibility of the study were described by all authors. The therapeutic use of low-level laser therapy in liver regeneration can be promising; however, since the liver is a vital organ, and the laser application is intraoperative, future studies are necessary. The parameters used must be properly described and standardized to allow the reproducibility of the study, in order to define a therapeutic window and thus, consider its clinical use. It is also essential to clarify the mechanisms by which laser promotes liver regeneration to guarantee its safety and therapeutic efficacy.

KEY WORDS: Hepatectomy. Liver regeneration. Low-level laser therapy. Photo-biomodulation.

Introduction

Low level laser therapy (LLLT) has been studied for over 50 years. Its first applications occurred in Hungary, when Professor Endre Mester reported the first application of LLLT in medicine (ENDRE; MESTER; MESTER, 1985). In 1983, Tiina Karu, a russian researcher, published her first article about LLLT, when she started explaining light’s mechanisms on biological tissue (KARU et al., 1983). Over time, the subject interested scientific community, arising researches on the matter. Until today, light’s mechanism of action on biological tissue is not fully understood. However, it is known that cytochrome c oxidase (Cox) is the main photoacceptor (KARU, 1999).

Phototherapy is the application of light amplification by stimulated emission of radiation (LASER) or light emitting diodes (LED), for therapeutic endings, which has several biological effects, as increase in ATP production (PASSARELLA et al., 1983; PASSARELLA et al., 1988), DNA and RNA synthesis (ENDRE; MESTER; MESTER, 1985; KARU et al., 1983; NAGINO et al., 1989), cellular proliferation (ENWEMEKA et al., 2004; HU et al., 2007; PASSARELLA et al., 1988), collagen synthesis (GODOY et al., 2017), and wound healing (ENDRE; MESTER; MESTER, 1988), in addition to anti-inflammatory effect (BJORDAL et al., 2003; KITCHEN; PARTRIDGE, 1991).

Recently, LLLT has been studied on promoting liver regeneration after partial hepaectomty (PH). The liver ability of healing is a sequence of cellular and molecular events that result in DNA synthesis, mitosis, cellular division and progression of the cellular cycle (COURT et al., 2002; KONIARIS et al., 2003). Regeneration means growth process, differing from that undergone by the liver after PH. Liver regeneration is a compensatory growth of the hepatic remnant (FAUSTO; CAMPBELL; RIEHLE, 2006) involving hyperplasia, tightly controlled by the metabolism, until the remaining liver reaches its adequate size (RIEHLE et al., 2011).

Studies about the effect of LLLT on liver

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regeneration after PH on experimental animals suggest effectiveness, but there are differences in the methodology and the laser parameters are not clear (ARAÚJO et al., 2013; ARAÚJO et al., 2014; BARBOSA et al., 2011; GODOY et al., 2017; CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; MELO et al., 2005; ORON et al., 2010; OLIVEIRA et al., 2006). Considering the therapeutic potential of LLLT, the aim of this article was to review the recent studies on the effects of LLLT on rat healthy liver regeneration after PH and the laser parameters employed.

Methods

A review of recent relevant literature was performed PubMed, Scielo, Medline and Bireme, published in a period between 2001 and 2018, using the keywords hepatectomy, laser therapy, liver regeneration, low-level laser therapy, partial hepatectomy and phototherapy.

Literature Review

Biological Parameters Evaluated And Laser Parameters Used To Promote Liver Regeneration

Nine studies were found matching the study criteria. All studies were performed in rats who underwent PH, seven studies realized a 70% PH (ARAÚJO et al., 2013; ARAÚJO et al., 2014; BARBOSA et al., 2011; CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; GODOY et al., 2017; ORON et al., 2010), one 67% PH (MELO et al., 2005) and the other 90% PH (OLIVEIRA et al., 2006).

In order to evaluate the regenerative effects of LLLT in partial hepatectomized rats, the studies evaluated biological parameters as respiratory activity of the mitochondria, phosphorylative activity of the liver (BARBOSA et al., 2011; CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; MELO et al., 2005), mitochondrial membrane potential (BARBOSA et al., 2011; MELO et al., 2005), cell proliferation through proliferating cell nuclear antigen (PCNA) (ARAÚJO et al., 2013; ARAÚJO et al., 2014; CASTRO-SILVA et al., 2003; MELO et al., 2005; OLIVEIRA et al., 2006) or Ki-67 (ARAÚJO et al., 2013; ARAÚJO et al., 2014; CASTRO-SILVA et al., 2003; MELO et al., 2005; OLIVEIRA et al., 2006).

In one study, 5-bromine-2'-deoxyuridine (BrdU) was applied in order to analyze cell proliferation and angiogenesis through immunohistochemical marking (OLIVEIRA et al., 2006). The activation or expression of specific proteins like hepatocyte growth factor (HGF), HGF receptor (MET), protein kinase B (AKT), and protein kinases activated by mitogens (MAPK) were also evaluated to investigate signaling pathways involved in the LLLT mechanism of action (ARAÚJO et al., 2013; ARAÚJO et al., 2014).

All laser application procedures used must be described in detail, not only to validate but also to allow reproducibility of the study. Parameters as wavelength, anatomical location, energy issued on the tissue, energy density or dose (ΔE), beam area, treatment duration, peak power, mean power (in pulsed application), and power density (ΔP) should be described (FUKUDA; MALFATTI, 2008; KITCHEN; PARTRIDGE, 1991). Laser parameters used in each study are described in table 1. Some laser parameters were not reported by the authors in their studies and, therefore, were not mentioned in table 1.

Recent studies are still discussing which parameters are essential for photobiomodulation (FUKUDA; MALFATTI, 2008; HADIS et al., 2016; TUNÉR; JENKINS, 2016). Therefore, a consensus on adequate parameters for reproducibility of the results still needs to be established by the scientific community.

Table 1. Utilized parameters on the studies about the application of LLLT on remnant liver of partially hepatectomized rats.

| Author and year | Laser | Wavelength | Peak Power | Dose (ΔE) | FEET | Power density (AP) | Anatomical location | Beam distance | Beam area | Time of application |
|----------------|-------|------------|------------|-----------|------|--------------------|---------------------|--------------|-----------|-------------------|
| Castro-Silva et al. (2001) | DL-A<sup>a</sup> | 590 nm | NI<sup>b</sup> | NI<sup>b</sup> | NI<sup>b</sup> | 50 mW/cm² | WRL<sup>c</sup> | NI<sup>d</sup> | NI<sup>d</sup> | 5 min. |
| Castro-Silva et al. (2003) | DL-A<sup>a</sup> | 410 nm, 470 nm, 512 nm, 590 nm, 630 nm | NI<sup>b</sup> | 140 J/cm² | NI<sup>d</sup> | 50 mW/cm² | WRL<sup>c</sup> | NI<sup>d</sup> | NI<sup>d</sup> | 5 min. |
| Melo et al. (2005) | DL-A<sup>a</sup> | 590 nm | NI<sup>b</sup> | 40 J/cm² | NI<sup>d</sup> | NI<sup>d</sup> | 4 points on the RL<sup>e</sup> | NI<sup>d</sup> | NI<sup>d</sup> | 1 min. pp<sup>f</sup> |
| Oliveira et al. (2006) | L-P | 660 nm | 30 mW | 22,5 J/cm² | NI<sup>d</sup> | NI<sup>d</sup> | 5 points on the RL<sup>e</sup> | NI<sup>d</sup> | NI<sup>d</sup> | 30 sec. pp<sup>f</sup> |
| Oron et al. (2010) | L-GaAlA<sup>a</sup> | 810 nm | 400 mW | 0,6 J/cm² | NI<sup>d</sup> | 5 mw/cm² | Shaved skin on the wound. | NI<sup>d</sup> | 2 cm² | 60 sec. pp<sup>f</sup> |
| Barbosa et al. (2011) | L-HeNe<sup>b</sup> | 660 nm | 50 mW | 22,5 J/cm² | NI<sup>d</sup> | NI<sup>d</sup> | 5 points on the RL<sup>e</sup> | NI<sup>d</sup> | NI<sup>d</sup> | 30 sec. pp<sup>f</sup> |
| Araújo et al. (2013) | L-HeNe<sup>b</sup> 632,8 nm | NI<sup>d</sup> | NI<sup>d</sup> | NI<sup>d</sup> | 65 mw/cm² | WRL<sup>c</sup> | 10 cm | NI<sup>d</sup> | 15 min |
| Araújo et al. (2014) | L-HeNe<sup>b</sup> 632,8 nm | 4 mW | 0,97 J/cm² | 3,6 J | 4 mW/cm² | WRL<sup>c</sup> | 10 cm | 1,6 cm² | 15 min |
| Godoy et al. (2017) | L-InGaAlP<sup>e</sup> | 650 nm | 100 mW | 70 J/cm² | 2 J | NI<sup>d</sup> | 5 points on the RL<sup>e</sup> | NI<sup>d</sup> | 2 cm² | 20 sec. pp<sup>f</sup> |

<sup>a</sup>DL-A – Dye Laser pumped by Argonium Laser; <sup>b</sup>L-HeNe – Hélium-Neon Laser <sup>c</sup>L-InGaAlP – Indium-Galium-Phosphor Laser; <sup>d</sup>L- GaAlA: Galium-Aluminum-Arsenic Laser; <sup>e</sup>WRL: Whole remnant liver; <sup>f</sup>NI: Not informed; <sup>pp</sup>: Per point; <sup>FEET</sup>: Final Energy Emited to the Tissue.
Effects of LLLT on liver regeneration

The first studies which applied LLLT in hepatocytes emerged in the 80’s, when a group of researchers investigated the effects of LLLT on rat liver mitochondria and showed that its optical and biochemical properties were altered, also mitochondrial metabolism and its membrane potential were increased (PASSARELLA et al., 1983).

From 1984 to 1997, other studies showed positive results regarding LLLT on hepatocytes, such as increase in the electrochemical proton gradient and ATP synthesis in mitochondria (PASSARELLA et al., 1984; PASSARELLA et al., 1988); activation of mitochondrial DNA replication (VACCA et al., 1993); increase in cytosolic and mitochondrial protein synthesis, and free calcium cytosolic concentrations (VACCA et al., 1997); increase in oxygen consumption, energetic metabolism, and enzymatic activity on complex I, III and IV of the respiratory chain in mitochondria (YU et al., 1997).

Part of the mechanism of action proposed for LLLT on hepatocyte was explained. When photons are absorbed directly through the metal on heme complexes in the mitochondrial complex IV, these metals vibrate, increasing the link between cytochrome c and cytochrome c oxidase, accelerating the electron processing and reduction reaction (YU et al., 1997).

Liver regeneration is not a regeneration per se, but a cellular hyperplasia of the remaining hepatocytes, which is necessary to restore the liver normal function (FAUSTO et al., 2006; RIEHLE et al., 2011; TAUB, 2004). This process requires high quantities of energy. This energy is produced through mitochondrial oxidative phosphorylation, making the remnant liver dependent on mitochondrial energy for its regeneration and directly relating the mitochondrial functions to the remnant liver regenerative and metabolic capacity (BARBOSA et al., 2011).

LLLT has promoted increase in mitochondrial state III and IV (BARBOSA et al., 2011; CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; MELO et al., 2005) and respiratory control rate (CASTRO-SILVA et al., 2003). LLLT also stabilized the mitochondrial membrane potential in a 24 hours observation, thus improving mitochondrial function (BARBOSA et al., 2011). Mitochondrial membrane potential (Δψm) is an electrochemical gradient that drives the ATP synthesis in the mitochondria (KARU, 2008). This improvement in mitochondrial function promoted by LLLT leads to increased production of ATP, which can provide the energy needed for liver regeneration after PH.

Some studies have shown the capacity of LLLT to induce an increase in cellular energy production (CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; OLIVEIRA et al., 2006), especially at lower (410 nm) and higher (630 nm) wavelengths (CASTRO-SILVA et al., 2003). The authors believe that lower wavelengths promote a higher cellular excitation and higher wavelengths can penetrate deeper in biological tissue, having effect on a larger number of cells, making it the best wavelength for the purpose (CASTRO-SILVA et al., 2003).

LLLT increased cell proliferation on remnant rat liver, especially in the first 24 hours after PH, and it was assessed by PCNA (ARAÚJO et al., 2013; ARAÚJO et al., 2014; CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; MELO et al., 2005; OLIVEIRA et al., 2006) or Ki-67 (ARAÚJO et al., 2013) labeling index. LLLT did not alter serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), indicating that laser application did not cause liver damage (CASTRO-SILVA et al., 2001; GODoy et al., 2017; ORON et al., 2010; OLIVEIRA et al., 2006).

In most of the studies, LLLT promoted liver regeneration on the remaining liver of PH rats without causing further functional or mutagenic damage (GODoy et al., 2017), alterations in the hepatic functions, weight loss or damage to the tissue (ARAÚJO et al., 2013; ARAÚJO et al., 2014; BARBOSA et al., 2011; CASTRO-SILVA et al., 2001; CASTRO-SILVA et al., 2003; MELO et al., 2005; ORON et al., 2010; OLIVEIRA et al., 2006).

LLLT associated with aqueous extract of Hypitis pectinata promoted greater increase of PCNA count than LLLT by itself (MELO et al., 2005). The same study showed lower levels of AST after PH, when aqueous extract of Hypitis pectinata was applied for 4 days before PH, demonstrating an important hepatoprotective effect (MELO et al., 2005).

Unfortunately, there was only one study analyzing this plant effect associated with laser therapy. Therefore, more evidence and studies are needed. Also, it would be interesting to study another plants and drugs with hepatoprotective effect associated with LLLT, in order to achieve a more efficient regeneration of the remnant liver after PH.

The effect of laser light on angiogenesis in remnant liver after PH was also evaluated (ORON et al., 2010). Mesenchymal stem cells (MSC) were used as a marker of liver regeneration and the region where the LLLT was applied showed a higher density of MSC and newly formed blood vessels (ORON et al., 2010).

Cell proliferation and antiapoptotic effects of HGF, a pleiotropic cytokine of mesenchymal origin, its receptor MET and its downstream signaling pathway have been studied on liver regeneration (ARAÚJO et al., 2013). HGF effects are mediated through the activation of its receptor MET, a transmembrane protein with tyrosine kinase activity. When HGF ligates to MET, autophosphorylation of tyrosine residues of the receptor occurs, leading to the activation of signaling pathways of fosfatidilinositol-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) 48 hours after PH, HGF expression and phosphorylation of MET, AKT and ERK1/2 were increased (ARAÚJO et al., 2013). In animals exposed to LLLT, HGF expression and phosphorylation of MET, AKT and ERK1/2 were significantly higher than in animals not exposed, what suggests the participation of these pathways in the hepatic regeneration induced by LLLT (ARAÚJO et al., 2013).

However, in elder rats, LLLT did not improve liver regeneration (ARAÚJO et al., 2014). The authors believe that it was due to decreased metabolism caused by age, which made Cox unable to absorb the light or simply unable to generate more energy. Furthermore, other factors could have also contributed, such as the increase in reactive oxygen species (ROS) and a lower activation of ERK (ARAÚJO et al., 2014). Therefore, stands the question: can physiological effects of laser light on liver regeneration be affected by age? More studies about it are necessary to answer this question.
Conclusion

Hepatic regeneration is a subject of great interest for the scientific community, because of the large regenerative and metabolic capacity of the liver. It is natural the development of therapies that improve hepatic regeneration. Although LLLT mechanism of action is not clear, its effect on wound regeneration, cell proliferation, increase in mitochondrial activity and energy production for the cell, have been demonstrated. LLLT therapeutic use on liver regeneration is promising, however, as the liver is a vital organ and the laser application is intraoperative, future studies are needed, and, in these studies, the laser parameters, as applied laser, wavelength, anatomical location, energy emitted to the tissue, beam area, treatment duration, peak power, mean power (in pulsed application), power density, and dose should be properly described and standardized to allow the reproducibility of the study, so that a therapeutic window can be defined and its clinical use can be considered. It is also essential to elucidate the mechanisms by which laser promotes liver regeneration to guarantee its safety and therapeutic efficacy.

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