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.

EFEITOS DA LASERTERAPIA DE BAIXA POTÊNCIA NA REGENERAÇÃO HEPÁTICA E PARÂMETROS EMPREGADOS DE LASER

RESUMO: Laserterapia de baixa potência tem vários efeitos biológicos, sendo um deles a regeneração de tecido. Sua aplicação no fígado de ratos após hepatectomia parcial para promoção de regeneração hepática tem sido estudada recentemente. O objetivo deste artigo foi revisar os estudos recentes dos efeitos da laserterapia de baixa potência na regeneração de fígado de ratos após hepatectomia parcial de fígado e os parâmetros de laser empregados. Uma revisão da literatura relevante recente foi realizada nas bases de dados Pubmed, Scielo, Medline e Bireme. Artigos sobre a aplicação da laserterapia de baixa potência na regeneração de fígado foram incluídos. Artigos sobre regeneração hepática na presença de patologias foram excluídos. Nove estudos foram encontrados correspondendo aos critérios do estudo. Na maioria dos estudos, a laserterapia de baixa potência promoveu regeneração hepática após hepatectomia parcial, sem causar danos adicionais ao fígado remanescente. Não foram descritos todos os parâmetros necessários para reprodutibilidade dos estudos por todos os autores. O uso terapêutico da laserterapia de baixa potência na regeneração de fígado pode ser promissor, entretanto, como o fígado é um órgão vital e a aplicação do laser é intraoperativa, estudos futuros são necessários, assim como os parâmetros da aplicação de laser precisam ser descritos apropriadamente e padronizados, para permitir a reprodutibilidade do estudo, para que uma janela terapêutica possa ser definida e seu uso clínico possa ser considerado. Também é essencial esclarecer através de quais mecanismos o laser promove regeneração de fígado para garantir sua segurança e eficácia terapêutica.
PALAVRAS-CHAVE: Hepatectomia. Regeneração de fígado. Laserterapia de baixa potência. Fotobiomodulação.

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, 1985; HAMERSKI, STEFANELLO, 2006; GODOY *et al*., 2017), in addition to anti-inflammatory effect (BJORDAL *et al*., 2003; KITCHEN; PARTRIDGE, 1991).

Recently, LLLT has been studied on promoting liver regeneration after partial hepatectomy (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). Regeneretion 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 in 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) labeling index, and liver damage through the measurement of serum aminotransferase level (CASTRO-SILVA *et al*., 2001; GODOY *et al*., 2017; MELO *et al*., 2005; OLIVEIRA *et al*., 2006).

In one study, 5-bromine-2'-desoxyuridine (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	Wavelenght	Peak Power	Dose (ΔE)	FEET	Power density (ΔP)	Anatomical location	Beam distance	Beam área	Time of application
Castro-Silva *et al*. (2001)	DL-A[a]	590 nm	NI[f]	NI[f]	NI[f]	50 mW/cm²	WRL[e]	NI[f]	NI[f]	5 min.
Castro-Silva *et al*. (2003)	DL-A[a]	410 nm, 470 nm, 512 nm, 590 nm, 630 nm	NI[f]	140 J/cm²	NI[f]	50 mW/cm²	WRL[e]	NI[f]	NI[f]	5 min.
Melo *et al*. (2005)	DL-A[a]	590 nm	NI[f]	40 J/cm²	NI[f]	NI[f]	4 points on the RL[g]	NI[f]	NI[f]	1 min. pp[h.]
Oliveira *et al*. (2006)	NI[f]	660 nm	30 mW	22,5 J/cm²	NI[f]	NI[f]	5 points on the RL[g]	NI[f]	NI[f]	30 sec. pp[h.]
Oron *et al*. (2010)	L-GaAlA[d]	810 nm	400 mW	0,6 J/cm²	NI[f]	5 mw/cm²	Shaved skin on the wound.	NI[f]	2 cm²	60 sec. pp[h].
Barbosa *et al*. (2011)	L-HeNe[b]	660 nm	50 mW	22,5 J/cm²	NI[f]	50 mw/cm²	5 points on the RL[g]	NI[f]	NI[f]	30 sec. pp[h.]
Araújo *et al*. (2013)	L-HeNe[b]	632,8 nm	NI[f]	NI[f]	NI[f]	65 mw/cm²	WRL[e]	10 cm.	NI[f]	15 min
Araújo *et al*. (2014)	L-HeNe[b]	632,8 nm	4 mW	0.97 J/cm²	3.6 J	4 mW/cm²	WRL[e]	10 cm.	1,6 cm²	15 min
Godoy *et al*. (2017)	L-InGaIP[c]	650 nm	100 mW	70 J/cm²	2 J	NI[f]	5 points on the RL[g]	NI[f]	2cm²	20 sec. pp[h]

[a]DL-A – Dye Laser pumped by Argonium Laser; [b]L-HeNe – Hélium-Neon Laser [c]L-InGaIP – Indium-Galium-Phosphor Laser; [d]L- GaAlAr: Galium-Aluminum-Arsenic Laser; [e]WRL: Whole remnant liver; [f]NI: Not informed; [g]RL: Remnant liver; [h]pp: Per point; [i]FEET: 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 ($\Delta\psi m$) 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 *Hyptis 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 *Hyptis 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 theses 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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