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ORIGINAL ARTICLE

Should open excisions and sutured incisions be treated differently? A review and meta-analysis of animal wound models following low-level laser therapy

Peter Gál[1,2,3] · Martin Bjørn Stausholm[4,5] · Ivan Kováč[1,6] · Erik Dosedla[7] · Ján Luczy[8] · František Sabol[8] · Jan Magnus Bjordal[4]

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Abstract
Although low-level laser therapy (LLLT) was discovered already in the 1960s of the twentieth century, it took almost 40 years to be widely used in clinical dermatology/surgery. It has been demonstrated that LLLT is able to increase collagen production/wound stiffness and/or improve wound contraction. In this review, we investigated whether open and sutured wounds should be treated with different LLLT parameters. A PubMed search was performed to identify controlled studies with LLLT applied to wounded animals (sutured incisions—tensile strength measurement and open excisions—area measurement). Final score random effects meta-analyses were conducted. Nineteen studies were included. The overall result of the tensile strength analysis (eight studies) was significantly in favor of LLLT (SMD = 1.06, 95% CI 0.66–1.46), and better results were seen with 30–79 mW/cm^2 infrared laser (SMD = 1.44, 95% CI 0.67–2.21) and 139–281 mW/cm^2 red laser (SMD = 1.52, 95% CI 0.54–2.49). The overall result of the wound contraction analysis (11 studies) was significantly in favor of LLLT (SMD = 0.99, 95% CI 0.38–1.59), and the best results were seen with 53–300 mW/cm^2 infrared laser (SMD = 1.18, 95% CI 0.41–1.94) and 25–90 mW/cm^2 red laser (SMD = 1.6, 95% CI 0.27–2.93). Whereas 1–15 mW/cm^2 red laser had a moderately positive effect on sutured wounds, 2–4 mW/cm^2 red laser did not accelerate healing of open wounds. LLLT appears effective in the treatment of sutured and open wounds. Statistical heterogeneity indicates that the tensile strength development of sutured wounds is more dependent on laser power density compared to the contraction rate of open wounds.

Keywords Skin wound · Tissue repair · Regeneration · Low-level laser therapy · Power density

Introduction

Although low-level laser therapy (LLLT) was discovered already in the 1960s of the twentieth century [1], it took almost 40 years to be widely used in clinical dermatology/surgery [2]. In general, lasers with output powers in the range between 5 and 50 mW delivering doses of 1–4 J/cm^2 have been found to be most effective in stimulating tissue repair [3]. Since a dose

Peter Gál and Martin Bjørn Stausholm contributed equally to this work.

✉ Peter Gál
galovci@yahoo.com; pgal@vusch.sk

✉ Jan Magnus Bjordal
jan.bjordal@uib.no

1 Department of Biomedical Research, East-Slovak Institute of Cardiovascular Diseases, Inc., Ondavská 8, 040 11 Košice, Slovak Republic

2 Department of Pharmacology, Faculty of Medicine, Pavol Jozef Šafárik University, Košice, Slovak Republic

3 Department of Pharmacognosy and Botany, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic

4 Physiotherapy Research Group, Department of Global Public Health and Primary Care, University of Bergen, Kalfarveien 31, 5018 Bergen, Norway

5 Physical and Occupational Therapy Research Unit, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark

6 2nd Department of Surgery, Louise Pasteur University Hospital and Pavol Jozef Šafárik University, Košice, Slovak Republic

7 Department of Obstetrics and Gynecology, 1st Private Hospital Kosice-Šaca and Pavol Jozef Šafárik University, Košice-Šaca, Slovak Republic

8 Department of Heart Surgery, East-Slovak Institute of Cardiovascular Diseases, Inc. and Pavol Jozef Šafárik University, Košice, Slovak Republic

may only be found effective when it reaches the targeted tissue, it must be taken into consideration that the power of laser is reduced as it penetrates the tissues. Although the penetration profiles for selected lasers may differ [4], in general it can be expected that for example a near infrared laser at 810 nm lose approximately 75% of its power during skin transmission [5] and with red laser, the loss of power is even higher [6].

It is well known that the amount of granulation tissue (GT) that is formed during the proliferation phase depends on the size of the wound. Therefore, an open wound heals with extensive new tissue formation, whereas a primary wound forms no or only a negligible amount of GT [7, 8]. The GT is composed of cells (fibroblasts and endothelial cells) that are present in the normal tissue before injury, cells (immune/inflammatory cells and other bone marrow-derived cells) that are recruited to the wound-associated stroma from distal sites and non-cellular components such as the extracellular matrix (ECM) [9].

A crucial step in accelerating the healing of open wounds is wound contraction (WC) during which the surrounding skin moves centripetally and leaves a remarkably smaller scar [10]. This process includes massive ECM remodeling assured by a more compact organization of collagen fibrils and water elimination. A principal role in WC is played by α-smooth muscle acting (α-SMA) expressing fibroblasts, so-called myofibroblasts, discovered in 1971 [11]. In contrast, sutures can be removed as soon as the wound is fixed and no longer need mechanical support since early suture resection assures a better cosmetic result [12]. During the first days after injury, the ECM is highly hydrated allowing cell invasion and assures only poor wound stiffness. Later during the maturation phase, it becomes more densely composed by collagen associated with an exponential increase of wound tensile strength (TS) [7] assured by gradual replacement of collagen type III by collagen type I [13]. Unfortunately, even a year later, a scar remains weaker and functionally deficient compared to healthy skin.

LLLT has been shown to effectively modulate selected steps in skin wound healing, including generation of myofibroblasts [14], stimulation of collagen deposition [15] and keratinocyte proliferation [16], and/or reduction of oxidative stress and inflammation [17, 18]. In vitro, ex vivo, and in vivo models as well as clinical studies have shown that wound healing is promoted by different laser wavelengths/powers/doses; thus, no optimal set of parameters has yet been identified [19]. Although absorbed energy may differ for each wound type, only a few studies have been focusing on direct comparison of LLLT on the healing of two basic wound models (Fig. 1) [20]. Therefore, in this review, special attention was given to compare the efficiency of the most commonly used red and infrared LLLT on the healing of sutured incisions (focusing on TS) and open excisions (focusing on WC).

Methods

Eligibility criteria

We only included controlled animal studies reported in English language with open wounds (the healing rate measured with wound size) and/or incisional sutured wounds (the healing rate measured with tensile strength) treated with LLLT.

Search strategy

A systematic PubMed search was performed throughout all years until December 31, 2017 to identify studies containing information of LLLT effect on skin wound healing, in terms of TS of sutured wounds and WC of open wounds. The search string for identifying articles contained search and MeSH terms describing open and sutured wounds, TS, WC, wound healing, and LLLT (search keywords in the category sutured wounds/incisions: "tensile strength laser therapy wound," and "tensile strength laser therapy incision," "tensile strength laser therapy incisional wound"; search keywords in the category open wounds/excisions: "laser therapy open wound," "laser therapy excisional wound," "laser therapy excision skin wound," and "laser therapy wound contraction"; search keywords for both categories: "low level laser therapy skin wound repair animal").

Study selection

Initially, one reviewer carefully read the titles and abstracts of the publications, identified by the search, and retrieved them in full text, unless they were clearly irrelevant. The same reviewer evaluated the full texts of all potentially eligible articles and made a careful decision to include or exclude each article, with close attention to the eligibility criteria. Subsequently, another reviewer checked the first reviewers' work by reading the full texts of the articles initially included and excluded. Any retrieved article not meeting the eligibility criteria was excluded and had its details listed with reason for exclusion.

Data extraction and meta-analysis

The data extraction involved a two-person procedure. First, one reviewer extracted the means, variance data and time points of assessment for analysis, and then, another reviewer checked this work. Laser parameters, including mW/spot, mW/cm^2, J/spot, J/session, treatment time, wavelength, distance or contact with laser probe, scanning in the middle, and/or edge of the wound, were additionally collected or calculated when possible, to investigate which ones that might impact healing rate.

All presented meta-analyses were conducted using final score random effects models, weighting the individual trial effect estimates relatively even, when heterogeneity is present. Impact from heterogeneity on the meta-analyses, i.e.,

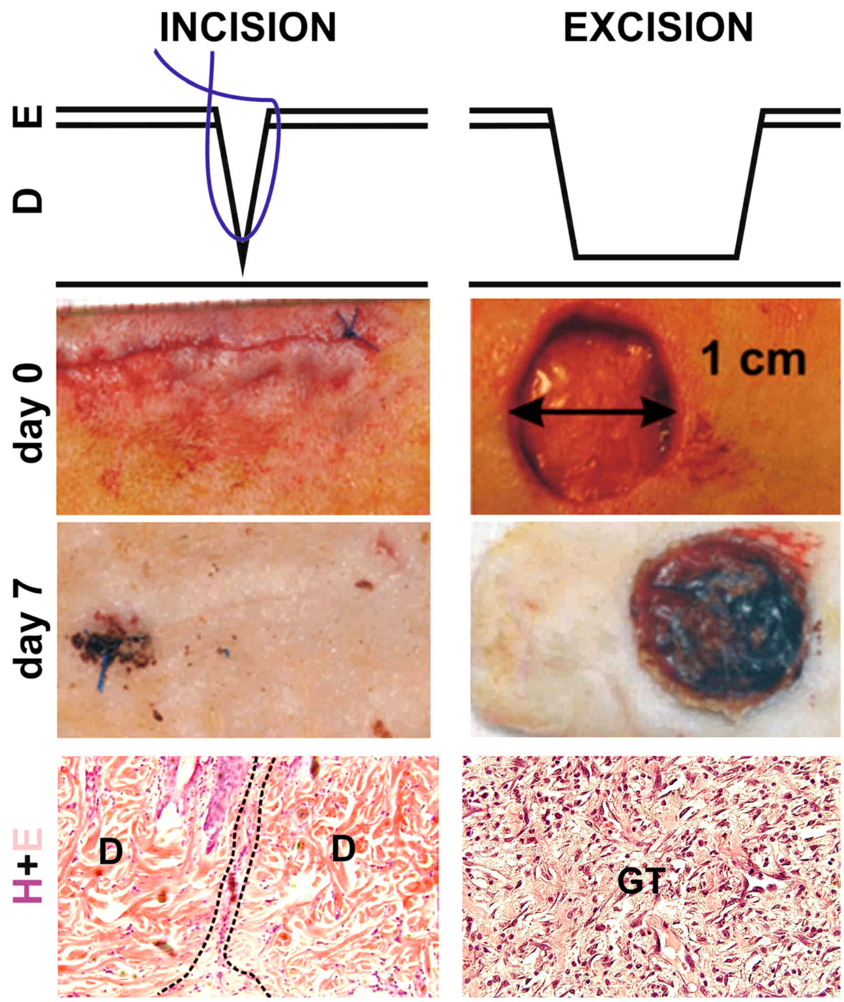

Fig. 1 Schema of sutured incision and open excision (E epidermis, D dermis). Photographs of skin wounds (sutured incision and open excision) at the day of surgery (day 0) and following 7 days of healing (day 7). Histological picture of sutured skin incision with thin incisional gab (I) with only minimal amount of granulation tissue (area between dashed lines) surrounded by intact dermis (D) and open skin excision with extensively formed granulation tissue (GT) rich on cells and high caliber vessels. Both histological pictures show wounds at day 7 stained with hematoxylin and eosin (H+E; ×200)

inconsistency, was examined using I^2 statistics [21]. The level of inconsistency was categorized as low (25%), moderate (50%), and high (75%) [22].

The standardized mean difference (SMD) was calculated as the difference between the final scores of the LLLT and control groups divided by the pooled standard deviation (SD). The SDs were extracted or estimated from other variance data, i.e., standard errors, 95% confidence intervals, *p* values, visually from graphs, and medians of SDs. The SMD was adjusted to Hedges' *g*, using a correlation factor, as Cohens' *d* can exaggerate the results, especially in analyses based on few trials and small sample sizes. The SMD was clinically interpreted as proposed by Cohen, i.e., a SMD of 0.2 represents a small, ~ 0.5 a moderate, and > 0.8 a large effect [23].

All intervention groups have been incorporated in the meta-analyses by splitting their related control groups. That is, except for the studies by Yasukawa et al. [24] and Hegde et al. [25], since they had 10 and 5 intervention groups and only 10 and 7 animals in the control groups, respectively, and consequently, some of their intervention groups were merged.

The meta-analyses were performed using the software programs Excel 2016 for Microsoft Windows and Review Manager, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study selection

The literature search yielded 51 potentially eligible publications of which 19 were judged eligible (Table 1) and 32 judged irrelevant (Table 2). Eighteen articles had data that allowed for meta-analysis of either TS of sutured incisions or WC of open excisions.

Synthesis of results—tensile strength of sutured wounds

Data allowing for meta-analysis of TS of sutured wounds were available from eight studies with 28 comparisons ($n = 378$). The overall result favored LLLT over control after 7–56 days by a significant SMD of 1.06 [95% CI 0.66 to 1.46] with

Table 1 Included studies. The different comparison groups in the same studies are labeled with different uppercase letters (A-J) as in the forest plot figures (Figs. 2–5). Abbreviations: CM continuous mode, PM pulsed mode treatment, ED every day, EOD every other day, SD single dose/number of sessions/follow-up day, DS dose per session, PD power density, TS tensile strength, WC wound contraction, I incision, E excision, ↑ laser therapy was superior

Reference	Wavelength	DS/PD	Mode	Treatment	Wound/effect
Suzuki et al. (2016) A	660 nm	1 J/cm^2/11.3 mW/cm^2	CM	SD/1/7	I/TS ↑
Suzuki et al. (2016) B	660 nm	5 J/cm^2/11.3 mW/cm^2	CM	SD/1/7	I/TS ↑
Suzuki et al. (2016) C	660 nm	10 J/cm^2/11.3 mW/cm^2	CM	SD/1/7	I/TS 0
Dancáková et al. (2014)	810 nm	0.9 J/cm^2/30 mW/cm^2	CM	ED/7/14	I/TS ↑
Dadpay et al. (2012) A	890 nm	0.03 J/cm^2/1.08 mW/cm^2	PM	ED/12/15	I/TS ↓
Dadpay et al. (2012) B	890 nm	0.2 J/cm^2/1.08 mW/cm^2	PM	ED/12/15	I/TS ↑
Dadpay et al. (2012) C	890 nm	0.2/J/cm^2/1.08 mW/cm^2	PM	ED/12/15	I/TS ↑
Vasilenko et al. (2010) A	635 nm	5 J/cm^2/4 mW/cm^2	CM	ED/7/7	I/TS ↑
Vasilenko et al. (2010) B	635 nm	5 J/cm^2/15 mW/cm^2	CM	ED/7/7	I/TS ↑
Vasilenko et al. (2010) C	670 nm	5 J/cm^2/4 mW/cm^2	CM	ED/7/7	I/TS ↑
Vasilenko et al. (2010) D	670 nm	5 J/cm^2/15 mW/cm^2	CM	ED/7/7	I/TS ↑
Yasukawa et al. (2007) A	632.8 nm	2.09 J/cm^2/139 mW/cm^2	CM	ED/6/7	I/TS ↑
Yasukawa et al. (2007) B	632.8 nm	2.09 J/cm^2/139 mW/cm^2	CM	EOD/3/7	I/TS ↑
Yasukawa et al. (2007) C-E	632.8 nm	2.09 J/cm^2/139 mW/cm^2	CM	SD/1/7	I/TS ↑
Yasukawa et al. (2007) F	632.8 nm	4.21 J/cm^{-2}/281 mW/cm^{-2}	CM	ED/6/7	I/TS ↑
Yasukawa et al. (2007) G	632.8 nm	4.21 J/cm^2/281 mW/cm^2	CM	EOD/3/7	I/TS ↑
Yasukawa et al. (2007) H-J	632.8 nm	4.21 J/cm^2/281 mW/cm^2	CM	SD/1/7	I/TS ↑
Stadler et al. (2001) A, E	830 nm	5 J/cm^2/79 mW/cm^2	CM	ED/4/11	I/TS ↑
Stadler et al. (2001) G	830 nm	5 J/cm^2/79 mW/cm^2	CM	ED/4/11	I/TS 0
Stadler et al. (2001) C	830 nm	5 J/cm^2/79 mW/cm^2	CM	ED/4/11	I/TS ↓
Stadler et al. (2001) B, D, F, H	830 nm	5 J/cm^2/79 mW/cm^2	CM	ED/4/23	I/TS ↑
Lyons et al. (1987) A	632.8 nm	1.22 J/cm^2/4.05 mW/cm^2	CM	EOD/3/7	I/TS ↑
Lyons et al. (1987) B	632.8 nm	1.22 J/cm^2/4.05 mW/cm^2	CM	EOD/7/14	I/TS ↑
Lyons et al. (1987) C	632.8 nm	1.22 J/cm^2/4.05 mW/cm^2	CM	EOD/10/21	I/TS ↑
Lyons et al. (1987) D	632.8 nm	1.22 J/cm ^{2}/4.05 mW/cm^2	CM	EOD/14/28	I/TS ↑
Lyons et al. (1987) E	632.8 nm	1.22 J/cm^2/4.05 mW/cm^2	CM	EOD/28/56	I/TS ↑
Allendorf et al. (1997) A	632.8 nm	2 J/cm^2/1.27 mW/cm^2	CM	ED/7/7	I/TS ↑
Allendorf et al. (1997) B	632.8 nm	2 J/cm^2/1.27 mW/cm^2	CM	ED/14/14	I/TS ↓
Allendorf et al. (1997) C	632.8 nm	1 J/cm^2/2.26 mW/cm^2	CM	ED/16/16	E/WC 0
Allendorf et al. (1997) D	632.8 nm	2 J/cm^2/2.26 mW/cm^2	CM	ED/16/16	E/WC 0
Allendorf et al. (1997) E	632.8 nm	4 J/cm^2/2.26 mW/cm^2	CM	ED/16/16	E/WC 0
de Medeiros et al. (2017) A	660 nm	4 J/cm^2/3 mW/cm^2	CM	EOD/3/7	E/WC ↑
de Medeiros et al. (2017) B	660 nm	4 J/cm^2/3 mW/cm^2	CM	EOD/7/14	E/WC ↑
Santana et al. (2015) A	660 nm	1 J/cm^2/38 mW/cm^2	CM	EOD/4/22	E/WC ↓
Santana et al. (2015) B	660 nm	4 J/cm^2/38 mW/cm^2	CM	SD/1/22	E/WC 0
Lau et al. (2015) A	808 nm	5 J/cm^2/100 mW/cm^2	CM	ED/9/9	E/WC ↑
Lau et al. (2015) B	808 nm	5 J/cm^2/200 mW/cm^2	CM	ED/9/9	E/WC ↑
Lau et al. (2015) C	808 nm	5 J/cm^2/300 mW/cm^2	CM	ED/9/9	E/WC 0
Novaes et al. (2014) A	660 nm	3 J/cm^2/25.47 mW/cm^2	CM	ED/21/21	E/WC ↑
Novaes et al. (2014) B	660 nm	30 J/cm^2/25.47 mW/cm^2	CM	ED/21/21	E/WC ↑
Gonçalves et al. (2013) A	830 nm	30 J/cm^2/73 mW/cm^2	CM	ED/21/21	E/WC ↑
Gonçalves et al. (2013) B	830 nm	90 J/cm^2/73 mW/cm^2	CM	ED/21/21	E/WC ↑
Rezende et al. (2007) A	830 nm	1.3 J/cm^2/53 mW/cm^2	CM	SD/1/14	E/WC ↑
Rezende et al. (2007) B	830 nm	3 J/cm^2/53 mW/cm^2	CM	SD/1/14	E/WC ↑
Medrado et al. (2003) A	670 nm	4 J/cm^2/28.27 mW/cm^2	CM	SD/1/14	E/WC ↑
Medrado et al. (2003) B	670 nm	8 J/cm^2/28.27 mW/cm^2	CM	SD/1/14	E/WC ↑

Table 1 (continued)

Reference	Wavelength	DS/PD	Mode	Treatment	Wound/effect
Demidova-Rice et al. (2017)	632.8 nm	2 J/cm^2/90 mW/cm^2	CM	SD/1/8	E/WC ↑
Hegde et al. (2011) A+B	632.8	4.02 mW/cm^2/1–2 J/cm^2	CM	SD/1/7	E/WC ↓
Hegde et al. (2011) C+D	632.8	4.02 mW/cm^2/3–4 J/cm ^{2}/	CM	SD/1/7	E/WC ↓
Hegde et al. (2011) E	632.8	4.02 mW/cm^2/5 J/cm^2	CM	SD/1/7	E/WC ↓
Bisht et al. (1994)	638.2 mm	4 J/cm^2/40 mW/cm^2	CM	ED/14/14	E/WC ↑
Braverman et al. (1989)[a]	632.8 nm	1.65 J/cm^2/3 mW/cm^2	CM	ED/20/21	E/WC 0
Braverman et al. (1989)[a]	904 nm	8.25 J/cm^2/13 mW/cm^2	PM	ED/20/21	E/WC 0
Braverman et al. (1989)[a]	632.8/904 nm	1.65/8.25 J/cm^2/3/13 mW/cm^2	CM/PM	ED/20/21	E/WC 0
Kana et al. (1982)[a]	632.8 nm	4 J/cm^2/45 mW/cm^2	CM	ED/12/12	E/WC ↑
Kana et al. (1982)[a]	514.5 nm	4 J/cm^2/45 mW/cm^2	CM	ED/12/12	E/WC 0

[a] Data did not allow for meta-analysis

moderate inconsistency. Higher mW/cm^2 yielded better point effect estimates and could explain some of the heterogeneity:

A subgroup of nine comparisons ($n = 134$) with infrared 30–79 mW/cm^2 laser favored LLLT over control after 11–23 days by a significant SMD of 1.44 [95% CI 0.67 to 2.21] with moderate inconsistency.

A subgroup of three comparisons ($n = 36$) with 1.08 mW/cm^2 pulsed infrared laser favored LLLT over control after 15 days by a non-significant SMD of 0.69 [95% CI − 1.8 to 3.19] with high inconsistency.

A subgroup of two comparisons ($n = 55$) with 139–281 mW/cm^2 red laser favored LLLT over control after 7 days by a significant SMD of 1.52 [95% CI 0.54 to 2.49] with no inconsistency.

A subgroup of 14 comparisons ($n = 153$) with 1–15 mW/cm^2 red laser favored LLLT over control after 7–56 days by a significant SMD of 0.73 [95% CI 0.34 to 1.12] with no inconsistency (Fig. 2).

Synthesis of results—contraction of open wounds

Data allowing for meta-analysis of contraction of open wounds were available from 11 studies with 23 comparisons ($n = 583$). The overall result favored LLLT over control after 6–14 days by a significant SMD of 0.99 [95% CI 0.38 to 1.59] with high inconsistency. None of the collected laser parameters could explain the heterogeneity, and thus, we subgrouped studies by wavelength and mW/cm^2 as in the TS analysis. Higher mW/cm^2 yielded better point effect estimates:

A subgroup of seven comparisons ($n = 192$) with infrared 53–300 mW/cm^2 laser favored LLLT over control after 6–7 days by a significant SMD of 1.18 [95% CI 0.41 to 1.94] with high inconsistency.

A subgroup of eight comparisons ($n = 285$) with 25–90 mW/cm^2 red laser favored LLLT over control after 7–14 days by a significant SMD of 1.6 [95% CI 0.27 to 2.93] with high inconsistency.

A subgroup of eight comparisons ($n = 106$) with 2–4 mW/cm^2 red laser favored LLLT over control after 6–7 days by a non-significant SMD of 0.11 [95% CI − 0.68 to 0.91] with moderate inconsistency (Fig. 3).

Synthesis of results—LLLT in diabetic animals

Data allowing for meta-analysis of TS of sutured wounds of diabetic animals only were available from three studies with six comparisons ($n = 86$). The overall result favored 1–79 mW/cm^2 LLLT over control after 11–23 days by a significant SMD of 1.84 [95% CI 0.83 to 2.84] with moderate inconsistency (Fig. 4).

Data allowing for meta-analysis of WC of open wounds of diabetic animals were available from two studies with five comparisons ($n = 132$). The overall result favored control over 4–38 mW/cm^2 LLLT after 7–8 days by a non-significant SMD of − 0.51 [95% CI − 1.11 to 0.09] with low inconsistency (Fig. 5).

Discussion

Our previous experimental wound therapy-related works [26–29] demonstrated that identical treatment protocols of sutured and open wounds yielded different outcomes, which may present an aspect with crucial significance for clinical practice. These findings are in line with the overall meta-analysis results of the present study, indicating that LLLT is effective in accelerating healing of open excisions and sutured incisions.

In detail, our meta-analysis indicates that both 53–300 mW/cm^2 infrared laser and 25–90 mW/cm^2 red laser is effective in accelerating WC, whereas less intense red laser in the range 2–4 mW/cm^2 is not effective. In comparison, 30–79 mW/cm^2 infrared laser and 139–281 mW/cm^2 red laser seem to be effective in increasing wound TS, and even red laser with as low as 1.27–15 mW/cm^2 appears moderately

Table 2 Excluded studies/comparisons. Abbreviations: DS dose per session, PD power density, TS tensile strength, WC wound contraction, I incision, E excision, ↑ laser therapy was superior

Reference	Wavelength	DS/PD	Effect	Reason for exclusion
Solmaz et al. (2017)	635 nm	1 J/cm^2/50 mW/cm^2	I/TS ↑	No sutures, WC not evaluated
Solmaz et al. (2017)	635 nm	3 J/cm^2/50 mW/cm^2	I/TS ↑	No sutures, WC not evaluated
Solmaz et al. (2017)	809 nm	1 J/cm^2/50 mW/cm^2	I/TS 0	No sutures, WC not evaluated
Solmaz et al. (2017)	809 nm	3 J/cm^2/50 mW/cm^2	I/TS 0	No sutures, WC not evaluated
D O Guirro et al. (2010)	670 nm	4 J/cm^2/500 mW/cm^2	I/TS ↑	No sutures, WC not evaluated
D O Guirro et al. (2010)	670 nm	7 J/cm^2/500 mW/cm^2	I/TS 0	No sutures, WC not evaluated
Reddy et al. (2003)	904 nm	1 J/cm^2/14 mW/cm^2	I/TS ↑	No incisions, WC not evaluated
Ghamsari et al. (1997)	632.8 nm	3.64 J/cm^2/114 mW/cm^2	I/TS ↑	2-layer suturing, teat healing
Ghamsari et al. (1996)	632.8 nm	3.642 J/cm^2/114 mW/cm^2	I/TS ↑	2-layer suturing, teat healing
Basford et al. (1986)	632.8 nm	0.054 J/cm^2/? mW/cm^2	I/TS 0	Unknown PD
Asghari et al. (2017)	890 nm	0.324 J/cm^2/1920 mW/cm^2	?	TS not evaluated, WC not evaluated
Aragão-Neto et al. (2017)	660 nm	4 J/cm^2/? mW/cm^2	WC ↑	Unknown PD
Keshri et al. (2016)	810 nm	22.6 J/cm^2/40 mW/cm^2	?	TS not evaluated, WC not evaluated
Keshri et al. (2016)	810 nm	22.6 J/cm^2/40 mW/cm^2	?	TS not evaluated, WC not evaluated
Keshri et al. (2016)	810 nm	22.6 J/cm^2/40 mW/cm^2	?	TS not evaluated, WC not evaluated
Tabakoglu et al. (2016)	808 nm	6.38 J/cm^2/1276 mW/cm^2	WC ↑	High-level laser therapy
Pouriran et al. (2016)	890 nm	0.2 J/cm^2/1.08 mW/cm^2	?	TS not evaluated, WC not evaluated
Isman et al. (2015)	810 nm	8 J cm^{-2}/3175 mW cm^{-2}	?	High-level laser therapy
Kurach et al. (2015)	635 nm	1125 J cm^{-2}/? mW cm^{-2}	WC 0	Unknown PD, assumable high-level laser therapy
Kilík et al. (2014)	635 nm	5 J cm^{-2}/1 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Kilík et al. (2014)	635 nm	5 J cm^{-2}/5 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Kilík et al. (2014)	635 nm	5 J cm^{-2}/15 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Colombo et al. (2013)	660 nm	10 J cm^{-2}/318.4 mW cm^{-2}	?	TS not evaluated, WC not evaluated
de Sousa et al. (2013)	660 nm	10 J cm^{-2}/478 mW cm^{-2}	?	TS not evaluated, WC not evaluated
de Sousa et al. (2013)	790 nm	10 J cm^{-2}/398 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Fathabadie et al. (2013)	890 nm	0.03 J cm^{-2}/? mW cm^{-2}	?	TS not evaluated, WC not evaluated
Fathabadie et al. (2013)	890 nm	0.2 J cm^{-2}/? mW cm^{-2}	?	TS not evaluated, WC not evaluated
Dadpay et al. (2012)	890 nm	0.03 J cm^{-2}/1.08 mW cm^{-2}	?	WC not evaluated, no sutures, TS not evaluated
Dadpay et al. (2012)	890 nm	0.2 J cm^{-2}/1.08 mW cm^{-2}	?	WC not evaluated, no sutures, TS not evaluated
Garcia et al. (2012)	660 nm	5.57 J cm^{-2}/420 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Peplow et al. (2012)	660 nm	2 J cm^{-2}/? mW cm^{-2}	?	WC not evaluated, PD not provided
Hussein et al. (2011)	890 nm	1.5 J cm^{-2}/5 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Peplow et al. (2011)	660 nm	6 J cm^{-2}/65 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Bayat et al. (2010)	780 nm	2 J cm^{-2}/50 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Chung et al. (2010)	660 nm	0.8 J cm^{-2}/200 mW cm^{-2}	?	WC not evaluated, used Tegaderm HP dressing
Chung et al. (2010)	660 nm	1.6 J cm^{-2}/200 mW cm^{-2}	?	WC not evaluated, used Tegaderm HP dressing
Chung et al. (2010)	660 nm	3.2 J cm^{-2}/200 mW cm^{-2}	?	WC not evaluated, used Tegaderm HP dressing
Jahangiri et al. (2010)	670 nm	10 J cm^{-2}/500 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Jahangiri et al. (2010)	810 nm	12 J cm^{-2}/250 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Lacjaková et al. (2010)	670 nm	5 J cm^{-2}/5 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Lacjaková et al. (2010)	670 nm	5 J cm^{-2}/15 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Lacjaková et al. (2010)	670 nm	5 J cm^{-2}/40 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Prabhu et al. (2010)	632.8 nm	2 J cm^{-2}/4.02 mW cm^{-2}	WC ↑	Light emitting diode therapy, not laser
Gál et al. (2009)	635 nm	5 J cm^{-2}/1 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Gál et al. (2009)	635 nm	5 J cm^{-2}/5 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Gál et al. (2009)	635 nm	5 J cm^{-2}/15 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Gul et al. (2009)	632.8 nm	1 J cm^{-2}/? mW cm^{-2}	?	TS not evaluated, WC not evaluated, unknown PD
Gul et al. (2009)	632.8 nm	3 J/cm^2/? mW cm^{-2}	?	TS not evaluated, WC not evaluated, unknown PD

Table 2 (continued)

Reference	Wavelength	DS/PD	Effect	Reason for exclusion
Maiya et al. (2005)	632.8 nm	4.8 J cm^{-2}/? mW cm^{-2}	?	TS not evaluated, WC not evaluated, unknown PD
Pinheiro et al. (2005)	685 nm	20 J cm^{-2}/300 mW cm^{-2}	?	TS not evaluated, WC not evaluated
Petersen et al. (1999)	830 nm	2 J cm^{-2}/30 mW cm^{-2}	WC 0	TS not evaluated, Values of WC not provided
Hunter et al. (1984)	632.8 nm	96 J cm^{-2}/64 mW cm^{-2}	WC 0	Only 2 animals (pigs) included

effective (SMD = 0.73). These discrepancies support the hypothesis that the higher amount of granulation tissue in open wounds [7, 8] absorbs more of the laser energy compared to the relatively intact superficial skin in sutured wounds.

The observed differences in the effectiveness of LLLT between healthy and diabetic models may be related to differences in their respective wound microenvironment and/or the use of different laser parameters. Imbalance in the production of growth factors, abnormal ECM function, and poor blood supply are the key factors responsible for delayed wound healing in diabetic patients [30]. Furthermore, diabetic animals have in general decreased expression of α-SMA [31], and subsequently, these wounds exert lower contraction rates [32] which may also explain the poor efficiency of LLLT in this model. The TS analysis of sutured diabetic animals yielded a very large effect estimate in favor of LLLT, whereas LLLT did not improve WC of open wounds in diabetic animals. It is plausible that this discrepancy is due to the higher mW/cm^2 and/or longer wavelength applied to the sutured wounds. On the other hand, the effect of LLLT in diabetic foot ulcers (DFU) has been

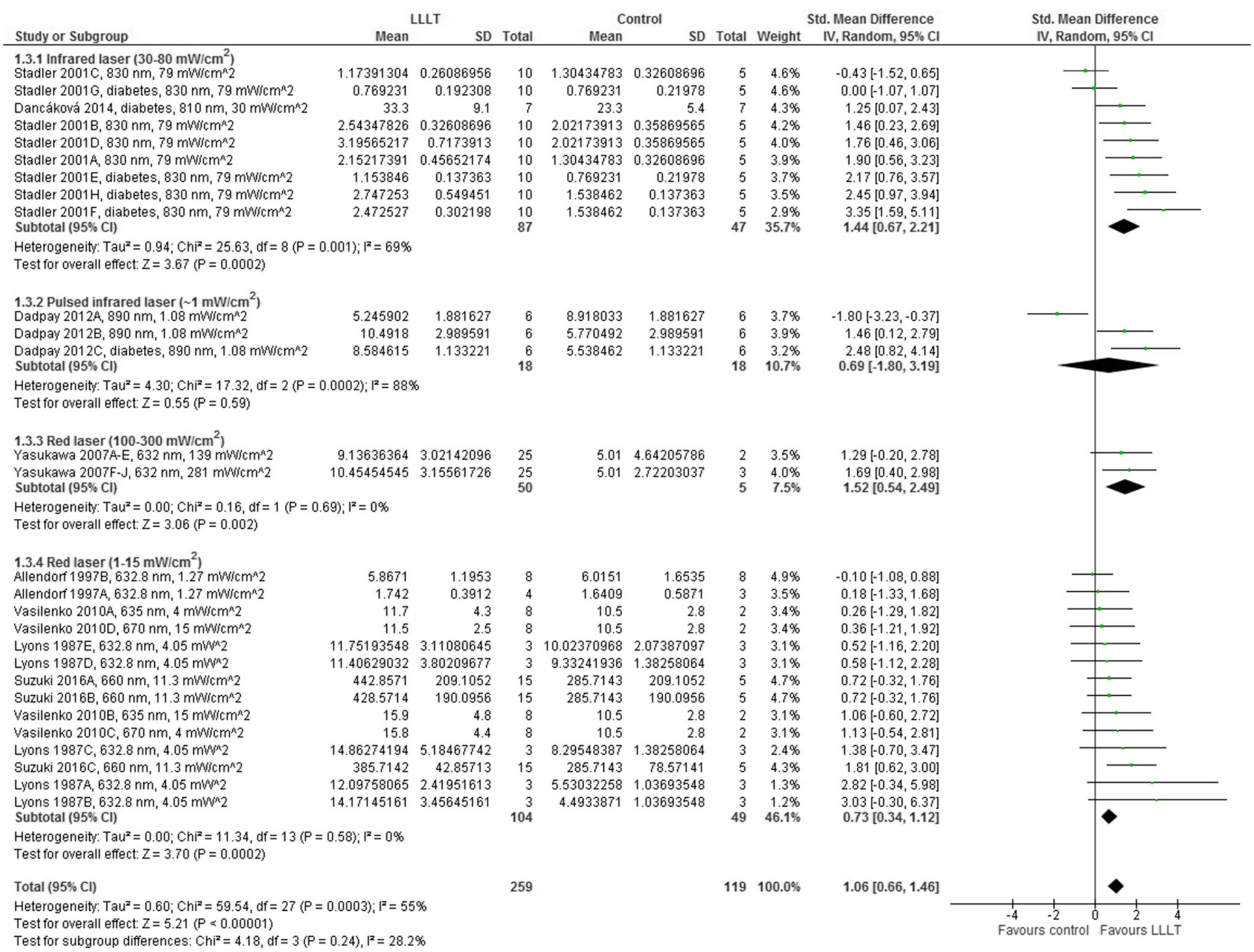

Fig. 2 Forest plot for a meta-analysis based on TS of sutured wounds. Synthesized results are shown as totals in the bottom of the figure. Plots on the right-hand side of the *y*-axis indicate that LLLT is superior. The uppercase letters after author name and publication year refer to the comparison groups in Table 1

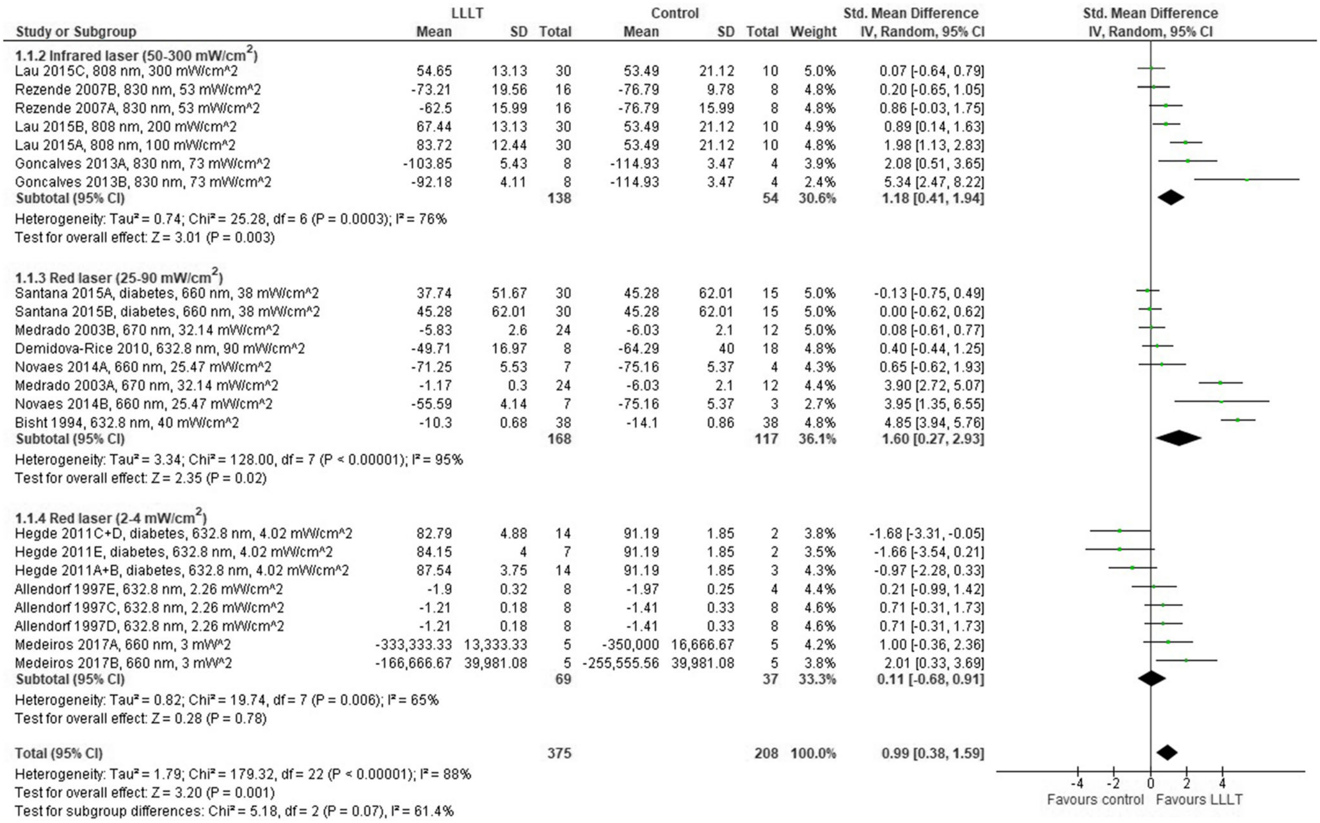

Fig. 3 Forest plot for a meta-analysis based on WC. Synthesized results are shown as totals in the bottom of the figure. Plots on the right-hand side of the *y*-axis indicate that LLLT is superior. The uppercase letters after author name and publication year refer to the comparison groups in Table 1

investigated in an interesting systematic review and meta-analysis and those results showed that LLLT has significant potential to become a portable, non-invasive, easy-to-use, and cost-effective treatment modality for DFU [33].

Since the review revealed different effects of LLLT in both models of wound healing, several underlying biological mechanisms need to be considered. In this context, it has been shown that LLLT with 635-nm diode laser (dose 0.3 J/cm^2, output power 89 mW) inhibited TGF-β1/Smad3-mediated conversion of fibroblasts into myofibroblasts, and this effect involved the modulation of TRPC1 ion channels [34]. These data indicate a potential antifibrotic effect of LLLT and suggest that this therapy is a promising therapeutic tool against tissue fibrosis. On the other hand, open wounds irradiated with a higher dose of HeNe laser (dose 1 J/cm^2, output power 10 mW) contained α-SMA positive cells, reduced inflammation, and better organization of collagen fibrils [35]. Similarly, combined red (685 nm) and blue (470 nm) therapy (both power densities 8 mW/cm^2 and daily doses 3.36 J/cm^2) of sutured skin incisions led to improved formation of cross-linked collagen fibers [36]. The abovementioned data are very interesting, since very low doses, and not high doses, are able to block selected pathways which led to very specific effects of treatment.

Recent progress in wound healing research has also highlighted the significance of the ECM as an essential part of the niche. Important molecules involved in ECM remodeling are matrix metalloproteinases (MMPs), a family of calcium-dependent, zinc-containing endopeptidases that are

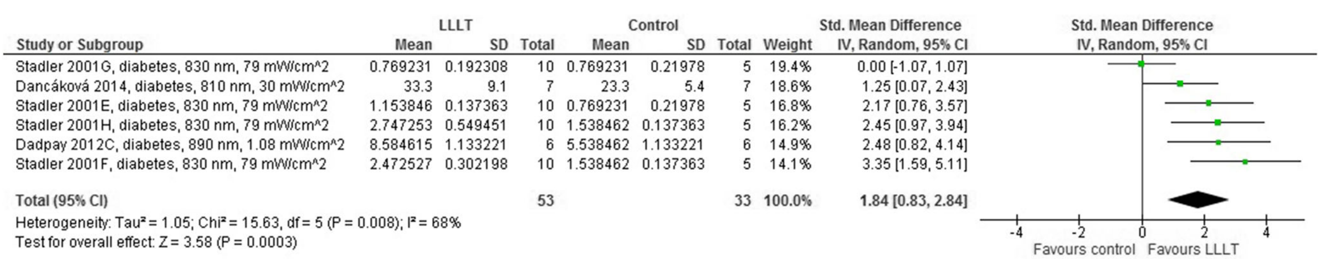

Fig. 4 Forest plot for a meta-analysis based on TS of diabetic sutured wounds. Synthesized results are shown as totals in the bottom of the figure. Plots on the right-hand side of the *y*-axis indicate that LLLT is superior. The uppercase letters after author name and publication year refer to the comparison groups in Table 1

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hegde 2011C+D, diabetes, 632.8 nm, 4.02 mW/cm^2	82.79	4.88	14	91.19	1.85	2	10.7%	-1.68 [-3.31, -0.05]
Hegde 2011E, diabetes, 632.8 nm, 4.02 mW/cm^2	84.15	4	7	91.19	1.85	2	8.5%	-1.66 [-3.54, 0.21]
Hegde 2011A+B, diabetes, 632.8 nm, 4.02 mW/cm^2	87.54	3.75	14	91.19	1.85	3	14.9%	-0.97 [-2.28, 0.33]
Santana 2015A, diabetes, 660 nm, 38 mW/cm^2	37.74	51.67	30	45.28	62.01	15	32.9%	-0.13 [-0.75, 0.49]
Santana 2015B, diabetes, 660 nm, 38 mW/cm^2	45.28	62.01	30	45.28	62.01	15	33.0%	0.00 [-0.62, 0.62]
Total (95% CI)			**95**			**37**	**100.0%**	**-0.51 [-1.11, 0.09]**

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 6.99$, df = 4 (P = 0.14); $I^2 = 43\%$
Test for overall effect: Z = 1.67 (P = 0.09)

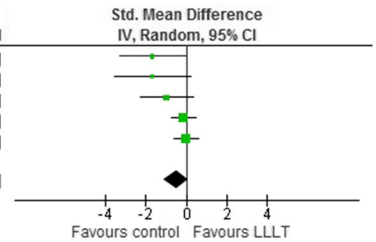

Fig. 5 Forest plot for a meta-analysis based on WC of diabetic sutured wounds. Synthesized results are shown as totals in the bottom of the figure. Plots on the right-hand side of the *y*-axis indicate that LLLT is superior. The uppercase letters after author name and publication year refer to the comparison groups in Table 1

negatively regulated by their inhibitors (TIMPs). In particular, MMP-2 enables endothelial cell migration during angiogenesis and facilitates re-epithelization and fibroblast growth. On the other hand, MMP-2 also digests several structural glycoproteins (including collagen type III) and gelatins [37]. Collagen type III plays an important role in wound stiffness during the early stages of wound healing [7, 13], thus may represent additional mechanisms of wound-type specific differences of treatment. In this context, LLLT has been shown to improve open wound healing by enhancing neocollagenesis, neoangiogenesis, and MMP-2 expression [38]. However, upregulation of MMP-2 has led to a decrease of wound TS in an aged-associated rat model of skin incision [39]. From this point of view, it would be interesting to test this LLLT protocol on the biomechanical parameters of skin incisions.

LLLT parameter/wound-type-dependent effects—red lasers

The first paper comparing both incisions and excisions was published already in 1983. In this work, no significant differences were observed in healing between laser-treated (tested doses 1.1 and 2.2 J/cm^2) and untreated control wounds. Conversely, rat skin incisions exposed to 2.2 J/cm^2 demonstrated significant increase in wound TS over controls [40]. These results have been partially confirmed later, since LLLT at 632.8 nm with a output power of 1.56 mW and a dose of 1.22 J/cm^2 has also resulted in improvement in the wound TS [41]. Nevertheless, no differences were found between control and laser treated (wavelength 632.8 nm; output power 4 mW) groups in the WC of open and TS of closed wounds [42]. Rats received a treatment of 1, 2, or 4 J/cm^2 in the case of excisions and 2 J/cm^2 for skin incisions. In addition, by comparing two parameter settings of HeNe laser, it has been shown that power density of 281 mW/cm^2 with a dose of 4.21 J/cm^2 is more effective than 139 mW/cm^2 and 2.09 J/cm^2 [24]. Furthermore, LLLT produced a better effect when treatment was applied every other day compared to daily treatment.

The first pivotal paper describing inverse relationship between wavelength and power density was published in 2004 [43]. LLLT at 670 and 685 nm (dose 10 J/cm^2; delivered by 2, 15, or 25 mW) has been found more effective when combining higher intensity with shorter wavelength or lower intensity with higher wavelength, using an open wound model. Motivated by this study, we have tested red LLLT, by the means of both basic wound healing models. We have also shown that the LLLT effect depends upon dosing (dose 5 J/cm^2; tested power densities 1, 5, 15, and 40 mW/cm^2), wavelength (635 vs. 670 nm), and wound type (incision vs. excision) [26–28]. In detail, open wounds were effectively stimulated by applying higher intensities with both 635 and 670 nm wavelengths [26, 27], which corresponds to the paper published in 2004. However, the model of sutured incisions revealed that LLLT at 635 and 670 nm was more effective in increasing wound TS when higher intensity was combined with shorter wavelength and/or lower intensity was combined with longer wavelength [28]. Later realized in vivo experiments reinforced the data, demonstrating positive effects of LLLT on wound stiffness. Laser irradiation at 635 nm of both energy densities, 1 and 3 J/cm^2 (delivered by 50 mW), increased wound TS [44]. Similarly, LLLT at 660 nm energy densities of 1 and 5 J/cm^2, but not 10 J/cm^2, enhanced wound TS in a rat incisional wound model [45]. Interestingly, wound treatment at 660 nm (tested doses 3 and 30 J/cm^2, power density 25.47 mW/cm^2) revealed that the higher tested energy density was more effective in modifying the morphology of the scar tissue (increased collagen and glycosaminoglycan content as well as elevated density of blood vessels) and led to a faster course of healing [46]. LLLT at 670 nm (tested doses 4 and 8 J/cm^2, power density: not provided) reduced inflammation and increased collagen deposition and the presence of myofibroblasts [47]. Wound contraction was faster following therapy with the lower tested dose.

LLLT parameter/wound-type-dependent effects—infrared lasers

Other examples of wound-type-specific effects have been demonstrated using infrared lasers. The 808 nm (5 J/cm^2 delivered with different power densities 100, 200, and 300 mW/cm^2) wavelength has been found more effective when energy was delivered at the lowest tested power density. This has been verified by increased GT formation, collagen deposition, and faster rate of wound contraction in an open wound healing model [48]. However, LLLT at similar parameters (809 nm;

tested energy densities 1 and 3 J/cm^2; delivered by 50 mW) did not have any positive effects on wound TS [44]. Other examples of the wound-type-specific LLLT effects may be reflected in our experiment conducted with diabetic rats. In this study, treatment with an infrared 810-nm laser with a power density of 30 mW/cm^2 and daily dose of 0.9 J/cm^2 reverse wound impairment mediated by diabetes induction in open wounds, but was not that effective in increasing wound TS of sutured incisions [49]. A single irradiation at 830 nm produced a slightly better result by applying the dose of 1.3 J/cm^2 when compared to the dose of 3 J/cm^2 (power density 53 mW/cm^2) on open wounds in rats [50]. Our theory regarding a parameter/wound-type efficiency of LLLT was supported by other study where treatment of full-thickness incisions with a laser radiation at 830 nm (dose 5.0 J/cm^2; power density 79 mW/cm^2) resulted in significantly enhanced cutaneous wound TS in healthy and diabetic mice [51]. On the other hand, a direct comparison of two laser doses, 30 and 90 J/cm^2, at 830 nm (power density 73 mW/cm^2) revealed that the higher dose was more beneficial to the healing process via modulating the morphology and oxidative status of open wounds [52]. In another study, healthy and diabetic rats were submitted to a treatment with either 0.03 or 0.2 J/cm^2 dose by a pulsed infrared 890-nm laser with 80 Hz frequency [53]. Interestingly, a lower LLLT dose significantly decreased wound TS in healthy rats, whereas a higher dose significantly increased the maximum load of wounds in both healthy and diabetic animals.

Conclusion

In summary, our review has resulted in two (clinical and experimental) important observations. Firstly, LLLT appears effective in treatment of sutured and open wounds. Laser power density could explain some of the statistical heterogeneity in the TS analysis, but not in the WC analysis. This indicates that TS development of sutured wounds is more dependent on laser mW/cm^2, compared to the contraction rate of open wounds. Thus, it is plausible that optimized treatment of the two wound types require different laser parameters. More comprehensive subgroup analyses with other laser parameters, e.g., dose and irradiation protocol, were prohibited due to poorly reported treatment parameters. However, we may conclude that laser doses around 5 J/cm^2 can accelerate wound healing. Secondly, common use of both basic wound models (sutured incision and open excision) should become the gold standard in all further experimental studies comparing the efficiency of specific treatment protocols/approaches. However, our results should be interpreted with caution, as only one literature database was used and due to statistical heterogeneity, which could be a product of other LLLT parameters than power density and wavelength. Finally, a direct extrapolation from data seen in animal studies to the human clinical situation is not possible due to the inter-species variability. Since the general molecular regulation of wound healing should be similar, further clinical LLLT investigations are encouraged, with comprehensive reporting of LLLT parameters.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

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