

The effect of low-level laser therapy on knee osteoarthritis: prospective, descriptive study

Hassan Soleimanpour · Khosro Gahramani ·
Reza Taheri · Samad E. J. Golzari · Saeid Safari ·
Robab Mehdizadeh Esfanjani · Afshin Iranpour

Received: 15 January 2013 / Accepted: 31 March 2014 / Published online: 15 April 2014
© Springer-Verlag London 2014

Abstract

Background Osteoarthritis (OA) is one of the most common joint disorders in the elderly which could be associated with considerable physical disability.

Patients and methods In a descriptive, prospective study, 33 patients enrolled in the study from which 15 people were

excluded due to incomplete course of treatment, leaving the total number of 18 patients with knee osteoarthritis. Gal-Al-As diode laser device was used as a source of low-power laser. Patients were performed laser therapy with a probe of LO7 with a wavelength of 810 nm and 50 mW output power in pulse radiation mode ($F=3,000$, peak power=80 W, $\Delta t=$

Authors' information HS is Associate professor of Anesthesiology and Critical Care, Fellowship in Trauma Critical Care and CPR at the Department of Emergency Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. He is also editorial board member of Emergency medicine journal (EGM) and Pakistan Journal of Biological Sciences (PJBS) and member of World Stroke Organization (WSO), too. KG and RT are anesthesiologists and members of Iranian Medical Laser Association, Tehran, Iran. SEJG is an anesthesiologist at the Department of Anesthesiology, Tabriz University of Medical Sciences, Tabriz, Iran. SS is resident of Anesthesiology and Critical Care Department, Iran University of Medical Sciences, Tehran, Iran and Managing Editor at Anesthesiology and Pain Medicine Journal. RME is member of Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. AI is anesthesiologist at Saudi German Hospital, Dubai, United Arab Emirates.

Electronic supplementary material The online version of this article (doi:10.1007/s10103-014-1576-6) contains supplementary material, which is available to authorized users.

H. Soleimanpour (✉)
Cardiovascular Research Center, Tabriz University of Medical
Sciences, Daneshgah Street, Tabriz 51664, Iran
e-mail: soleimanpourh@tbzmed.ac.ir

K. Gahramani · R. Taheri
Iranian Medical Laser Association, Tehran, Iran

K. Gahramani
e-mail: gahramani_arena@yahoo.com

R. Taheri
e-mail: dr.reza.taheri@gmail.com

S. E. J. Golzari
Liver and Gastrointestinal Disease Research Center, Tabriz
University of Medical Sciences, Tabriz 51664, Iran
e-mail: dr.golzari@hotmail.com

S. Safari
Anesthesiology and Critical Care Department, Iran University of
Medical Sciences, Tehran, Iran
e-mail: drsafari.s@gmail.com

R. M. Esfanjani
Neurosciences Research Center, Tabriz University of Medical
Sciences, Daneshgah Street, Tabriz 51664, Iran
e-mail: mehdizadeh18@yahoo.com

A. Iranpour
Saudi German Hospital, Dubai, United Arab Emirates
e-mail: af6872@yahoo.com

200 ns, density=0.05 W/cm², dose=6 J/cm², area=1 cm²) and also a probe of MLO1K with a power output of 30 mW and a wavelength of 890 nm in pulse radiation mode ($F=3,000$ Hz, peak power=50 W, $\Delta t=200$ ns, density=0.017 W/cm², total dose=10 J/cm²), and were given low-level laser therapy (LLLT) three times a week with a total number of 12 sessions. Data were analyzed using SPSS ver. 15, and the obtained data were reported as mean \pm SD and frequency (%). To analyze the data, repeated measurement and marginal homogeneity approaches were used.

Results In the current study, a significant reduction was observed regarding the nocturnal pain, pain on walking and ascending the steps, knee circumference, distance between the hip and heel, and knee to horizontal hip to heel distance at the end of the treatment course.

Conclusions In brief, the current study focuses on the fact that LLLT is effective in reducing pain in knee osteoarthritis.

Keywords Knee osteoarthritis · Low-level laser therapy · Pain

Abbreviations

LLLT	Low-level laser therapy
TENS	Transcutaneous electrical nerve stimulation
OA	Osteoarthritis
WOMAC	Western Ontario and McMaster Universities

Introduction

Osteoarthritis (OA), one of the most common joint disorders in the elderly, is defined as increased damage and decreased repair processes within the joints following mechanical insults [1]. OA could be associated with considerable physical disability, regardless of the type of the affected joints. Knee osteoarthritis, the most common type of OA, is the chronic degeneration of the articular cartilages. Injured intra-articular cartilage triggers inflammation and swelling of the synovia which in turns could lead to increased pain, stiffness, and bone spurs and decreased range of motion [2–4]. Although non-steroid anti-inflammatory drugs (NSAIDs) are broadly used for the treatment of the pain and rigidity caused by osteoarthritis, their undesirable gastrointestinal complications have contributed to numerous limitations in their administration [5]. To reduce or eliminate these complications, different approaches including ultrasound, transcutaneous electrical nerve stimulation (TENS), and physical exercises have been utilized [6–9]. Low-level laser therapy (LLLT) is used for the treatment of pain in neuromuscular disorders. Despite its broad administration, controversial reports have been made on the efficacy of LLLT. Some of the studies confirm the efficacy of LLLT in pain reduction in cervical osteoarthritis [10] and lateral and medial epichondylitis [11], whereas some

confirm its efficacy on lateral and medial epichondylitis [12], rotator cuff tendinitis [13], and rheumatoid arthritis [14]. Nevertheless, very few studies have been conducted on the efficacy of LLLT on knee osteoarthritis, and the results obtained from these studies are controversial [14–16]. In the study of Stelian et al., LLLT was suggested to reduce pain and disability [15]. However, Bulow et al. found no significant differences between case and control groups [16]. In similar studies carried out by Mokmeli et al., Rayegani et al., and Hegedus et al., the efficacy of LLLT on reducing pain in knee osteoarthritis was proposed [17–19]. Over the years, more than 100 double-blind, placebo-controlled studies have been published on the effects of LLLT emphasizing the favorable anti-inflammatory effects of LLLT [20–22]. LLLT has been used as a non-invasive modality in the pain management of the patients with musculoskeletal disorders. Although the efficacy of LLLT has been compared to that of NSAIDs [23], thanks to its low complication rates and dose-dependent ability of modulating inflammatory processes which can also be titrated, LLLT has turned it into a distinguishable alternative in the pain management of osteoarthritis [24]. Considering the controversial findings and administration of different laser doses and the existing two different criteria for the efficacy of the evaluation i.e., the distance between the hip and heel and the knee to horizontal hip to heel distance, we aimed at evaluating the efficacy of LLLT on reducing pain and disability in patients with knee osteoarthritis.

Methods

In a descriptive, prospective study, 33 patients with history of knee osteoarthritis for more than 1 year were enrolled to the study. All patients had solely been treated with laser and received no medication throughout the study or within the previous months. Later, 15 people were excluded due to incomplete course of treatment, leaving the total number of 18 patients with knee osteoarthritis (Fig. 1). Exclusion criteria from that study were varus or valgus, ankylosis, severe synovitis, degenerative changes in the knee joint confirmed by radiography, and any contraindication for LLLT. After admission of patients, the procedure of using LLLT, the reason for its prescription, and the possible side effects were explained to them, and it was emphasized that LLLT is safe and has the fewest side effects. Written informed consent was obtained from all subjects. Gal-Al-As diode laser device was used as a source of low-power laser. Laser therapy was performed with a probe of LO7 with a wavelength of 810 nm and 50 mW output power in pulse radiation mode ($F=3,000$, peak power=80 W, $\Delta t=200$ ns, density=0.05 W/cm², dose=6 J/cm², area=1 cm²) and probe of MLO1K with a power output of 30 mW and a wavelength of 890 nm in pulse radiation mode

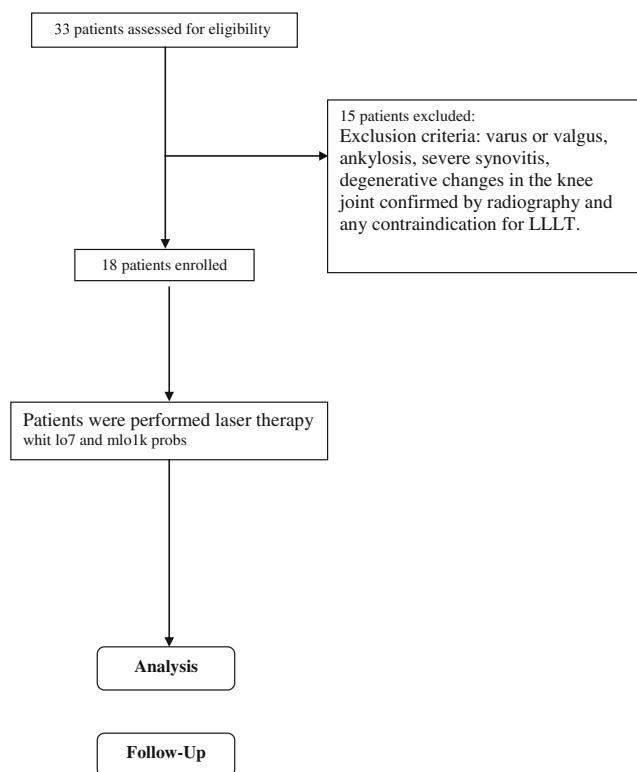


Fig. 1 Flow chart of study

($F=3,000$ Hz, peak power=50 W, $\Delta t=200$ ns, density=0.017 W/cm², total dose=10 J/cm²). The LO7 was used in supra-, mid- and infra-patella (six areas) areas, while the MLO1K was used for the posterior patella area (one area). Each patient received a total of 46 J/cm² energy. Patients were given low-level laser therapy (LLLT) three times a week with a total number of 12 sessions. Patients were asked to identify the degree of their pain using visual analogue pain scale (VAS) in which zero represented painless and 10 was the worst experienced pain. The knee circumference, the distance between the hip and heel in supine position with knee flexion, and the knee to horizontal hip to heel distance with knee extension at the end of treatment course were noted and recorded. It should be mentioned that nocturnal pain, pain on walking, and ascending the steps were defined based on VAS as follows: no pain or negative (VAS score 0) mild pain or +1 (VAS scores 1–4), moderate pain +2 (VAS scores 4–7), and severe pain +3 (VAS scores 7–10). Data were analyzed using the SPSS ver. 15, and the obtained data were reported as mean \pm SD and frequency (%). To analyze the data, repeated measurement and marginal homogeneity approaches were used.

Results

Of the 18 patients, two were males and 16 were females, with the mean age and weight of 64.67 \pm 9.27 years and 74.73 \pm 15.17 kg,

respectively. Nocturnal pain was negative, +1, +2, and +3 in four, two, three, and nine patients on admission, respectively. The scores, however, changed to 5, 9, 4, and 0 cases and 10, 7, 1, and 0 cases in the sixth and 12th sessions, respectively (all $P=0.001$). Pain in walking was negative, +1, +2, and +3 in zero, one, five, and 12 patients on admission, respectively. The scores, however, changed to 1, 10, 7, and 0 cases and 6, 10, 2, and 0 cases in the sixth and 12th sessions, respectively (all $P<0.001$). Pain in ascending the stairs on admission was negative, +1, +2, and +3 in zero, one, two, and 15 patients, respectively. The scores, however, changed to 0, 10, 8, and 0 cases and 5, 11, 2, and 0 cases in the sixth and 12th sessions, respectively (all $P<0.001$) (Table 1). Demographic characteristics of the patients and mean values of VAS, knee circumference, hip to heel distance, and knee to horizontal hip to heel distance are presented in Table 2 and electronic file (Supplementary Material).

Discussion

LLLT, firstly introduced almost a decade ago, is considered as a non-invasive modality for treating joint diseases. Other usages of LLLT include treatment of soft tissue injuries, rheumatoid arthritis, and musculoskeletal pain [25]. Numerous clinical and basic science studies have confirmed medical and physiological effects of LLLT including its positive effect on osteoblastic [26] and fibroblastic [27] proliferation, collagen synthesis [28], and bone regeneration [29]. Laboratory researchers have confirmed the significant effect of LLLT on the activity of alkaline phosphatase enzyme and calcium accumulation [30]. Pathological changes initiate cartilage damage and alter bone metabolism through reduction in

Table 1 Pain reduction at different sessions in patients received low-level laser therapy

Health condition	Pain level			
	No pain	+1	+2	+3
Nocturnal pain				
On admission	4	2	3	9
After sixth session	5	9	4	0
After 12th session	10	7	1	0
Pain in walking				
On admission	0	1	5	12
After sixth session	1	10	7	0
After 12th session	6	10	2	0
Pain in ascending the stairs				
On admission	0	1	2	15
After sixth session	0	10	8	0
After 12th session	5	11	2	0

Table 2 Comparison of the mean value of VAS, the knee circumference, the hip to heel distance, and the knee to horizontal hip to heel distance between patients

	On admission	Sixth session	12th session	<i>P</i> value
VAS	7.39±1.68	3.61±1.91	2.22±1.7	<0.001
Knee circumference (cm)	43.11±4.07	41.88±4.18	41.38±3.88	<0.001
The hip to heel distance(cm)	17.55±5.79	12.55±6.37	11.72±5.83	<0.001
The knee to horizontal hip to heel distance(cm)	5.38±2.06	4.05±1.47	3.55±0.98	<0.001

cartilage circulation and degenerative changes. Increased microvascularization has been reported following LLLT in some studies [31, 32]. Shakouri et al. showed that callus development at the early stages of the healing process could be enhanced following LLLT administration [33]. Lin et al. suggested that the helium–neon (632 nm) low-power laser improves stress protein production in arthritic chondrocytes which is linked to the therapeutic effects of low-power laser via preserving chondrocytes and the repair of arthritic cartilage [34]. Enwemeka et al. highlighted laser phototherapy as a highly effective therapeutic modality which not only repairs the damaged tissues but also alleviates pains [35]. The results obtained from the current study are suggestive of the fact that considerable improvements were achieved in patients following LLLT regarding pain, swelling, and flexion and extension degrees of the knee joint, and this trend continued for 3 weeks during the treatment course.

Alves and colleagues suggested that LLLT is able to modulate inflammatory response at both early as well as late stages of rheumatoid arthritis [36]. Increased temperature in the areas affected by radiation leading to improved clinical symptoms were studied by Hegedus et al. In the present study, thermal effects of LLLT were not studied; however, the results confirmed the efficacy of LLLT on pain reduction [18]. In another study carried out by Stelian et al., 50 patients with knee osteoarthritis were evaluated regarding the effects of red and infrared rays [15]. Patients were given treatment two times a day for 10 days, each time for 7.5 min with total doses of 10.3 and 10.1 J for red and infrared rays, respectively. Finally, it was concluded that LLLT was effective in inducing pain and increasing ability of the patients. In the present study, we used a probe of LO7 (peak power=80 W, λ =810 nm, F =3,000 Hz, dose=6 J/cm²) on six areas and also a probe MLO1K (peak power=50 W, λ =890 nm, Δt =150 ns, F =3,000 Hz, dose=2.4 J/cm²) on the posterior patella. A considerable improvement was observed regarding pain and swelling reduction and increased flexion and extension degrees in the knee joint. In that study of Bulow et al., infrared laser Ga-Al-As with the wavelength of 830 nm was used on the knee joints; this was not associated with significant differences [16]. On the other hand, in that study conducted by Mokmeli et al., significant improvements regarding pain score, nocturnal pain, pain in walking, morning stiffness, and increased range of motion was reported in 386 patients treated by LLLT (λ =860 nm, F =3000 HZ, peak power=100 W, Δt =200 ns, dose=6 J/cm²,

30 J/cm² totally) [17]. Rayegani et al. conducted a study comparing LLLT and ultrasound in which the advantage of LLLT over ultrasound was emphasized as significant improvements were observed regarding pain, stiffness, and disability in the group treated by LLLT [18]. It should be mentioned that very few studies have been performed on the laser therapy of the patients with osteoarthritis and no optimal dose has been suggested so far; explaining the reason of applying different doses in our study compared to the similar ones and the significant results obtained. On the other hand, to evaluate the knee joint efficacy in the patients with osteoarthritis, different indices compared to the similar studies [17, 19] have been utilized; in our research, two novel indices have been introduced:

- (1.) The distance between the hip and heel in supine position with knee flexion
- (2.) The distance between the knee and horizontal hip to heel line with knee extension

Another difference in the present study is the administration of higher total energy doses of Laser (46 vs. 30 J).

Based on the results obtained from our study, it can be assumed that LLLT leads to osteoarthritis improvement from different aspects as pain severity tends to decrease considerably throughout the LLLT sessions. It can be hypothesized that these effects are conducted via reduction in tissue inflammation and vasodilation [37]. On the other hand, as can be seen in Table 2, a significant reduction in knee circumference was achieved following LLLT sessions i.e., LLLT was efficient regarding reducing the peri-articular swelling and inflammation. Furthermore, reduction in the two other previously existing criteria (the distance between the hip and heel and the knee to horizontal hip to heel distance) could indicate improvement in joint range of motion. These findings are in line with those of Stelian et al., Mokmeli et al., and Rayegani et al. [15, 17, 18].

As can be seen, the results obtained from different studies on the efficacy of LLLT in the treatment of the patients with osteoarthritis are controversial. The differences in the used devices and laser types could have contributed to this discrepancy. Another consideration that should be kept in mind is the lack of a definite required dose regarding wavelength, frequency and intensity of laser pulse, and maximum dose of radiation. Therefore, further future studies are required focusing on these pitfalls.

Limitations

The current study was associated with some limitations. As the patients referring to the office were selected, dividing the patients into two groups of case and control was impractical. Furthermore, other evaluation criteria such as WOMAC were not used; a strong correlation between pain criteria and WOMAC tools exists. This does not seem to have had a negative effect on our study. Furthermore, it should be mentioned that our study was a descriptive one rather than a clinical trial which could have been considered as one of the limitations of the present study.

Conclusion

Overall, the results obtained from the present study are suggestive of the fact that LLLT is efficient in reducing pain and increasing ability of the knee joint in patients with knee osteoarthritis.

Acknowledgments We would like to offer our special thanks to the Iranian Laser Association for assisting us throughout the current study.

Financial disclosure The authors declare they have no financial disclosure.

Funding/Support This article is not supported by any funding organization. There is no sponsor for this work.

References

- Brandt KD, Dieppe P, Radin EL (2008) Etiopathogenesis of osteoarthritis. *Rheum Dis Clin N Am* 34(3):531–559
- Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D (1995) The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 38(10):1500–1505
- Felson DT (1993) The course of osteoarthritis and factors that affect it. *Rheum Dis Clin N Am* 19(3):607–615
- Tascioglu F, Armagan O, Tabak Y, Corapci I, Oner C (2004) Low power laser treatment in patients with knee osteoarthritis. *Swiss Med Wkly* 134(17–18):254–258
- Scheiman JM (1996) NSAIDs, gastrointestinal injury, and cytoprotection. *Gastroenterol Clin N Am* 25(2):279–298
- Cheing GL, Hui-Chan CW, Chan KM (2002) Does four weeks of TENS and/or isometric exercise produce cumulative reduction of osteoarthritic knee pain? *Clin Rehabil* 16(7):749–760
- Talbot LA, Gaines JM, Ling SM, Metter EJ (2003) A home-based protocol of electrical muscle stimulation for quadriceps muscle strength in older adults with osteoarthritis of the knee. *J Rheumatol* 30(7):1571–1578
- Kozanoglu E, Basaran S, Guzel R, Guler-Uysal F (2003) Short term efficacy of ibuprofen phonophoresis versus continuous ultrasound therapy in knee osteoarthritis. *Swiss Med Wkly* 133(23–24):333–338
- Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC (2000) Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomised, controlled trial. *Ann Intern Med* 132(3):173–181
- Ozdemir F, Birtane M, Kokino S (2001) The clinical efficacy of low-power laser therapy on pain and function in cervical osteoarthritis. *Clin Rheumatol* 20(3):181–184
- Simunovic Z, Trobonjaca T, Trobonjaca Z (1998) Treatment of medial and lateral epicondylitis-tennis and golfer's elbow-with low laser therapy: a multicenter double-blind, placebo-controlled study on 324 patients. *J Clin Laser Med Surg* 16(3):145–151
- Haker EH, Lundberg TC (1991) Lateral epicondylalgia. Report of noneffective midlaser treatment. *Arch Phys Med Rehabil* 72(12):984–988
- Vecchio P, Cave M, King V, Adebajo AO, Smith M, Hazleman BL (1993) A double-blind study of the effectiveness of low-level laser treatment of rotator cuff tendinitis. *Br J Rheumatol* 32(8):740–742
- Goats G, Hunter JA, Flett E, Stirling A (1996) Low intensity laser and phototherapy for rheumatoid arthritis. *Physiotherapy* 82(5):311–320
- Stelian J, Gil I, Habet B, Rosenthal M, Abramovici I, Kutok N, Khahil A (1992) Improvement of pain and disability in elderly patients with degenerative osteoarthritis of the treated with narrow-bandlight therapy. *J Am Geriatr Soc* 40(1):23–26
- Bülow PM, Jensen H, Danneskiold-Samsøe B (1994) Low power Ga-Al-As laser treatment of painful osteoarthritis of the knee. A double-blind placebo-controlled study. *Scand J Rehabil Med* 26(3):155–159
- <http://www.laserlightcanada.com/article-details.php?ID=1255427194S> at Mokmeli, Anesthesiologist, H. Attarian, Rheumatologist, M. Hosseini, MD, S. Bishea. Low level laser therapy (LLLT) for knee Osteoarthritis: (A clinical study on 386 patients.)
- Rayegani SM, Bahrami MH, Elyaspour D, Saeedi M, Sanjri H (2012) Therapeutic effects of Low Level Laser Therapy (LLLT) in knee osteoarthritis, compared to therapeutic ultrasound. *J Lasers Med Sci* 3(2):71–74
- Hegdu B, Viharos L, Gervain M (2009) The effect of low level laser in knee osteoarthritis: a double-blind, randomised, placebo-controlled trial. *Photomed Laser Surg* 27(4):577–584
- Bjorndal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RAB (2006) Photoradiation in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. *Photomed Laser Surg* 24(2):158–68
- Bjorndal JM, Lopes-Martins RA, Iversen VV (2006) A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinitis prostaglandin E2 concentrations. *Br J Sports Med* 40(1):76–80
- Castano AP, Dai T, Yaroslavsky I, Cohen R, Apruzzese WA, Smotrich MH, Hamblin MR (2007) Low level laser therapy for zymosan-induced arthritis in rats: importance of illumination time. *Lasers Surg Med* 39(6):543–550
- <http://discoverlasers.com/blog/low-level-laser-therapy-vs-nsaids> (Last accessed 11 Dec 2013)
- Bjorndal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RA (2006) Photomed Laser Surg 24(2):158–168
- Cho HJ, Lim SC, Kim SG, Kim YS, Kang SS, Choi SH, Cho YS, Bae CS (2004) Effect of low-level laser therapy on osteoarthropathy in rabbit. *In Vivo* 18(5):585–591
- van Breugel HH, Bär PR (1992) Power density and exposure time of He-Ne laser irradiation are more important than total energy dose in photo-biomodulation of human fibroblasts in vitro. *Lasers Surg Med* 12(5):528–537
- Tamura K, Hosoya S, Hiratsuka K, Abiko Y (1998) Laser stimulation of CDC46 gene expression in murine osteoblasts. *Laser Ther* 10:25–31
- Lam TS, Abergel RP, Meeker CA, Castel JC, Dwyer RM, Uitto J (1986) Laser stimulation of collagen synthesis in human skin fibroblasts cultures. *Lasers Life Sci* 1:61–77

29. Nagasawa A, Kato K, Negishi A (1991) Bone regeneration effect of low-level lasers including argon laser. *Laser Ther* 3:59–62
30. Barushka O, Yaakobi T, Oron U (1995) Effect of low energy laser (He-Ne) irradiation on the process of bone repair in the rat tibia. *Bone* 16:47–55
31. Longo L, Evangelista S, Tinacci G, Sesti AG (1987) Effects of diodes laser silver arsenide aluminium (GaAlAs) 904 nm on healing of experimental wounds. *Lasers Surg Med* 7(5):444–447
32. Lievens P (1988) The influence of laser treatment on the lymphatic system and on wound healing. *Laser* 1(2):6–12
33. Kazem Shakouri S, Soleimanpour J, Salekzamani Y, Oskuie MR (2010) Effect of low-level laser therapy on the fracture healing process. *Lasers Med Sci* 25(1):73–77
34. Lin YS, Huang MH, Chai CY, Yang RC (2004) Effects of helium-neon laser on levels of stress protein and arthritic histopathology in experimental osteoarthritis. *Am J Phys Med Rehabil* 83(10):758–765
35. Enwemeka CS, Parker JC, Dowdy DS, Harkness EE, Sanford LE, Woodruff LD (2004) The efficacy of low-power lasers in tissue repair and pain control. *Photomed Laser Surg* 22(4):323–329
36. Alves AC, de Carvalho Pde T, Parente M, Xavier M, Frigo L, Aimbire F, Leal EC Jr, Albertini R (2013) Low-level laser therapy in different stages of rheumatoid arthritis: a histological study. *Lasers Med Sci* 28(2):529–536
37. Hopkins JT, McLoda TA, Seegmiller JG, David Baxter G (2004) Low-Level Laser Therapy facilitates superficial wound healing in humans: a triple-blind, sham-controlled study. *J Athl Train* 39(3):223–229