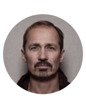
Positive effects of low level laser therapy (LLLT) on Bouchard's and Heberden's osteoarthritis

Article *in* Lasers in Surgery and Medicine · February 2016

DOI: 10.1002/lsm.22480



Axel W Baltzer
Center for Molecular Orthopaedics

Martin Stefan Ostapczuk
St. Josef Hospital, Germany, Moers

Positive Effects of Low Level Laser Therapy (LLLT) on Bouchard's and Heberden's Osteoarthritis

Axel W.A. Baltzer, MD, PhD, PD,[1*] **Martin S. Ostapczuk,** MD, PhD,[2,3] **and Daniel Stosch,** MD, PhD[1]
[1]*Associate Practice at Königsallee / Centre for Molecular Orthopaedics, Königsallee 53-55, Düsseldorf 40212, Germany*
[2]*Clinic for Orthopaedics and Trauma Surgery, St. Josef Hospital, Asberger Str. 4, Moers 47441, Germany*
[3]*Institute of Experimental Psychology, Heinrich Heine-University, Universitätsstr. 1, Düsseldorf 40225, Germany*

Background and Objective: Osteoarthritis (OA) is a common chronic disorder. While research usually focuses on OA of the large joints, OA of the hand receives relatively little attention resulting in a lack of a therapeutic gold standard. Low level laser therapy (LLLT)/photobiomodulation therapy has been successfully used to treat a variety of medical conditions. Nevertheless, its merits in the treatment of (hand) OA remain controversial. The aim of the present study was to examine the longitudinal effect of LLLT on the three major hand OA symptoms—pain, swelling, reduced joint mobility—in patients suffering from Bouchard's and Heberden's OA.

Study Design/Materials and Methods: Thirty-four patients (32 females) aged 61.21 ± 2.13 years were administered 5–10 LLLT sessions to 85 joints (47 proximal and 38 distal interphalangeal joints). Therapy took place twice a week. Pain (Visual Analogue Scale), ring size (perimeter in mm), and range of motion (extension/flexion) were measured at baseline and after five treatments for all patients, and additionally after seven sessions and 8 weeks after treatment ended for patients who received more than five and seven treatments, respectively. Eighteen patients (37 joints) received only five treatments, 10 patients (29 joints) were administered seven treatments, and six patients (19 joints) were administered 10 LLLT sessions.

Results: LLLT significantly reduced pain and ring size and increased range of motion after five and seven treatments (all P's < 0.001). The effects were very large (all η^2's > 0.14). No further significant change occurred between 7 and 10 treatments. The effects achieved after seven sessions persisted for 8 weeks.

Conclusions: LLLT is a safe, non-invasive, efficient and efficacious means to reduce pain and swelling and to increase joint mobility in patients suffering from Heberden's and Bourchard's OA. Further randomized controlled studies are needed to examine medium- to long-term effects as well as the ideal LLLT parameters. Lasers Surg. Med.
© 2016 Wiley Periodicals, Inc.

Key words: conservative treatment; low-power laser; photobiomodulation therapy; osteoarthritis of the hand; distal interphalangeal joint; proximal interphalangeal joint

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic disorders and public health concerns, particularly in the aging Western societies [1]. OA typically leads to pain and loss of function of the affected joint thereby reducing patients' quality of life and/or ability to work [2,3]. Both orthopaedic research and clinical efforts tend to focus on OA of the large joints, such as OA of the knee and hip. In contrast to that, OA of the hand has received relatively little attention [4]. Yet hand OA can also have serious functional consequences, such as pain, swelling, restricted joint mobility and grip strength, loss of muscle force, and fine precision pinch as well as cosmetic deformities leading to activity, and participation limitations [2,5]. As opposed to OA of the large joints, hand OA mainly affects women older than 50 years [6]; in the United States, for instance, approximately 75% of the women aged 60–70 years. suffer from some type of hand OA [5]. The joints most commonly involved are the distal interphalangeal (DIP) joints (Heberden's nodes/OA), the proximal interphalangeal (PIP) joints (Bouchard's nodes/OA) and the carpometacarpal (CMC) joint of the thumb [5,6]. Rheumatoid arthritis (RA) and other rheumatoid conditions affecting the joints constitute an important differential diagnosis, particularly of Bouchard's OA [6].

A variety of treatments for Bouchard's and Heberden's OA are available including analgesics, non-steroidal anti-inflammatory drugs, the supportive use of orthotics and adaptive equipment, hand exercises, cold and heat modalities, intra-articular injections of steroids as well as surgical procedures (e.g., arthrodesis or even arthroplasty) [5,7]. The efficacy and severity of side effects of these therapies, however, vary and often little is known about long-term effects—consequently, no single

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

*Correspondence to: Dr. Axel W.A. Baltzer, MD, PhD, PD, Associate Practice at Königsallee/Centre for Molecular Orthopaedics, Königsallee 53-55, 40212 Düsseldorf, Germany.
E-mail: axel@baltzer.at

Accepted 15 January 2016
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.22480

treatment approach has been established as the gold standard so far [5,6].

Low level laser therapy (LLLT), also known as photobiomodulation, constitutes an alternative non-invasive and presumably safe treatment approach to OA [7,8]. The healing effects of phototherapy have already been demonstrated 40 years ago—since then, lasers have been used in the treatment of a variety of disorders, ranging from musculoskeletal and neurological conditions such as arthritic pain, neck and lower back pain, tendonitis, muscle injuries and carpal tunnel syndrome to chronic wounds, haemorrhoids, and Raynaud's syndrome [9,10]. LLLT/photobiomodulation is a form of phototherapy using red or near-infrared lasers with a wavelength between 600 and 1000 nm and low power wattage from 5 to 500 mW—as opposed to surgical lasers at 1–200 W—and a power density (irradiance) between 1 mW and 5 W/cm^2. Note, however, that some high-peak-power-width devices are in the range of 1–100 W with typical pulse-widths of 200 ns [11]. The laser light is absorbed by the skin without any sensation or thermal damage [2,8]. Although the exact mechanism of its effect still remains tentative, LLLT can apparently penetrate deeply into tissues where it exerts its physiological effects at the cellular level. LLLT has been hypothesized to stimulate cellular repair as well as the immune, lymphatic and vascular systems by regulating DNA synthesis, mitochondrial ATP synthesis, and increasing cellular oxygenation. Further, LLLT has been suggested to have cartilage stimulatory and anti-inflammatory effects [7,8].

Despite its extensive use in treating pain of musculoskeletal origin, studies on the efficacy of LLLT for the treatment of OA are not fully conclusive [7,8]. While most studies investigated the effects of LLLT on knee OA and yielded mainly positive results [12–15], only few studies investigated the effects of LLLT on hand OA [2]. In a randomized controlled trial (RCT), Brosseau et al. found only few significant areas of improvement, that is, carpometacarpal opposition, grip strength, and patient global assessment, in active LLLT patients compared with sham LLLT patients [7]. In another RCT, however, Paolillo et al. demonstrated significant pain reduction in hand OA patients treated with a device combining LLLT with ultrasound [2]. In sum, the effects of LLLT on hand OA remain controversial, too, and warrant further investigation.

The aim of the present study was therefore to investigate the longitudinal effect of LLLT on the three major hand OA symptoms—pain, swelling, reduced joint mobility—in patients suffering from Bouchard's and Heberden's OA.

MATERIALS AND METHODS

Patients and Study Design

Data collection and treatment took place at an orthopaedic centre from November 2013 to October 2015. Inclusion criteria were clinical evidence of Heberden's or Bouchard's OA as judged by the treating orthopaedic surgeon and defined both by the presence of typical symptoms, such as pain, swelling, and restriction of motion, and/or by radiographic evidence of OA. Patients with RA, bacterial infection, clinically relevant haematologic or abnormal clinical chemistry values, bone cancer, metastasis or tumour-like lesions in immediate proximity to the treated joint, and poor general health were excluded. For the duration of the study, patients received no other major treatments, neither pharmacological (such as nonsteroidal anti-inflammatory drugs) nor non-pharmacological ones. All investigations were conducted in conformity with the ethical standards laid down in the 1975 Declaration of Helsinki (as revised in 2008), the ethics review board of the conducting orthopaedic centre approved the study and its subsequent publication. Participation was voluntary and informed consent for participation in the study was obtained.

In total, 34 patients (32 females) aged 61.21 ± 2.13 years participated in the study 16 of the patients (38 joints) suffered from Bouchard's OA, 12 patients (28 joints) from Heberden's OA, and six patients (19 joints) both from Bouchard's and Heberden's OA. The patients were administered 5–10 LLLT/photobiomodulation therapy sessions to the leading joint(s) by an orthopaedic surgeon using the LLLT device as described below. The number of joints treated varied between one and eight joints per patient (2.50 ± 0.26; see Table 1). Both the number of joints treated and sessions administered was guided by clinical considerations. There was no placebo control group. Therapy took place twice a week, and the three outcome measures (ring size, range of motion, pain) were assessed for each joint separately at two points of time in all patients (before treatment started and after five LLLT sessions). For patients who received seven LLLT sessions, the outcome measures were additionally assessed at a third point of time, that is, after seven LLLT sessions. For patients who received 10 LLLT sessions, outcome was measured at baseline, after five LLLT sessions, after seven LLLT sessions, and additionally at a fourth point of time, that is, 8 weeks after treatment ended. Ring size was assessed using European ring sizes which correspond to the perimeter in mm, range of motion (ROM) was measured following the neutral-null-method (extension/flexion), and pain was assessed via the Visual Analogue Scale (VAS) [16] ranging from 0 (no pain) to 10 (most severe pain).

Low Level Laser Therapy (LLLT)/ Photobiomodulation Therapy

The LLLT device used was a Laserneedle Touch, Orthopaedic- and Sports therapy Version, class IIIb (Laserneedle GmbH, Glienicke/Nordbahn, Germany). The device is a diode laser with 10 optical fibres—6 fibres with a wavelength of 658 nm (red) and four fibres with a wavelength of 785 nm (infrared). The chosen modulation was continuous and the output power at the end of each fibre was 40 mW. Two points per joint (the medial and lateral intra-articular space) were simultaneously irradiated with a red and an infrared wavelength. The size of the

TABLE 1. Demographic and Interventional Patients' Characteristics

Characteristic	Total ($N = 34$ patients, $N = 85$ joints)	5 LLLT sessions ($N = 18$ patients, $N = 37$ joints)	7 LLLT sessions ($N = 10$ patients, $N = 29$ joints)	10 LLLT sessions ($N = 6$ patients, $N = 19$ joints)	*P*-value	Effect Size	Posthoc
Age	61.21 ± 2.13	61.94 ± 2.96	57.90 ± 3.97	64.50 ± 5.13	0.56	0.04 (η^2)	—
Joints per patient	2.50 ± 0.26	2.06 ± 0.36	2.90 ± 0.48	3.17 ± 0.62	0.20	0.10 (η^2)	—
Gender							
Female	32 (94.1%)	16 (88.9%)	10 (100%)	6 (100%)	0.39	0.24 (ω)	—
Male	2 (5.9%)	2 (11.1%)	0 (0%)	0 (0%)			
Joints							
Proximal interphalangeal	47 (53.3%)	24 (64.9%)	8 (27.6%)	15 (78.9%)	<0.001	0.42 (ω)	—
Distal interphalangeal	38 (44.7%)	13 (35.1%)	21 (72.4%)	4 (21.1%)			
VAS							
Baseline	5.78 ± 0.26	5.97 ± 0.31	4.72 ± 0.52	7.00 ± 0.50	0.004	0.13 (η^2)	10 LLLT > 7 LLLT
After five LLLT sessions	4.60 ± 0.28	4.22 ± 0.39	3.90 ± 0.49	6.42 ± 0.46	—	—	—
After seven LLLT sessions	—	—	2.86 ± 0.49	5.95 ± 0.55	—	—	—
After 8 weeks	—	—	—	5.16 ± 0.58	—	—	—
ROM							
Baseline	64.51 ± 2.88	63.19 ± 3.93	54.48 ± 4.97	82.37 ± 5.33	0.001	0.15 (η^2)	10 LLLT > 5 and 7 LLLT
After five LLLT sessions	72.35 ± 2.94	71.76 ± 4.53	62.93 ± 4.67	87.89 ± 5.22	—	—	—
After seven LLLT sessions	—	—	70.17 ± 4.07	88.42 ± 5.22	—	—	—
After 8 weeks	—	—	—	88.95 ± 5.28	—	—	—
Ring size							
Baseline	61.32 ± 0.77	61.27 ± 1.06	60.10 ± 1.34	63.26 ± 1.82	0.32	0.03 (η^2)	—
After five LLLT sessions	60.27 ± 0.75	60.35 ± 1.03	59.14 ± 1.38	61.84 ± 1.71	—	—	—
After seven LLLT sessions	—	—	58.69 ± 1.37	61.74 ± 1.84	—	—	—
After 8 weeks	—	—	—	61.63 ± 1.85	—	—	—

LLLT, Low Level Laser Therapy; *OA*, Osteoarthritis; *ROM*, Range of Motion (flexion); *VAS*, Visual Analogue Scale (0 = no pain, 10 = most severe pain).
The figures represent either M ± SE or absolute frequencies (percentages). For continuous variables, *P*-values were calculated by one-way between-subjects analyses of variance (ANOVAs) with the effect size η^2 ($\geq$0.14 = large, $\geq$0.06 = moderate, $\geq$0.01 = small) and Bonferroni corrected posthoc tests. For dichotomous variables, *P*-values were calculated by χ^2-tests with the effect size $\omega\omega$ ($\geq$0.50 = large, $\geq$0.30 = moderate, $\geq$0.10 = small).

respective medial and lateral irradiation point was $0.0016\,cm^2$ each, that is, power density was $25\,W/cm^2$. Treatment time was 20 minutes per joint and hand, as several joints were irradiated simultaneously if necessary. The device was calibrated by a biomedical technologist. All patients and treating physicians wore safety glasses.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Version 17.0 was used for data analysis. Means and standard errors are reported as M ± SE.

The differences between pre- and post-treatment scores were tested with one-way within subjects analyses of variance (ANOVA's) with Bonferroni-corrected post hoc comparisons. Group differences regarding continuous variables were assessed by one-way between subjects ANOVA's with Bonferroni-corrected post hoc comparisons, χ^2 tests were used for dichotomous variables. Associations between continuous variables were examined using Pearson's correlation coefficient.

In all tests, $P < 0.05$ was considered statistically significant. As P-values alone are not exhaustively informative—particularly when samples are very small or large—we followed Cohen's advice to additionally determine effect sizes [17] using the freely available programme G*Power 3 [18]. According to Cohen's criteria for the interpretation of effect sizes, in ANOVA's $\eta^2 \geq 0.14$ indicates a large effect, $\eta^2 \geq 0.06$ a moderate effect, and $\eta^2 \geq 0.01$ a small effect. In χ^2-tests, the measure of effect size is ω, with $\omega \geq 0.50$ a large, $\omega \geq 0.30$ a moderate, and $\omega \geq 0.10$ a small effect. Pearson's correlation coefficient r itself constitutes a measure of effect size, with $r \geq 0.50$ a large, $r \geq 0.30$ a moderate, and $r \geq 0.10$ a small effect.

RESULTS

Patients' Characteristics

In the total sample of $N = 34$ patients, men and women did not differ with regard to age (men: 56.50 ± 8.86 years; women: 61.50 ± 2.22 years; $P = 0.59$, $\eta^2 = 0.01$) or number of joints treated (men: 2.50 ± 1.10; women: 2.50 ± 0.28; $P = 0.99$, $\eta^2 < 0.001$). Sex and type of OA were not associated (PIP joints: 44 females, 3 males; DIP joints: 35 females, 3 males; $P = 0.79$, $\omega = 0.03$). The mean number of joints treated (Bouchard's OA: 2.38 ± 0.39; Heberden's OA: 2.33 ± 0.45; both: 3.17 ± 0.64; $P = 0.52$, $\eta^2 = 0.04$) and age (Bouchard: 63.69 ± 3.12; Heberden: 57.67 ± 3.60; both: 61.67 ± 5.09; $P = 0.46$, $\eta^2 = 0.05$) did not differ between patients suffering from Bouchard's OA, Heberden's OA and both. Age correlated with the number of joints treated ($r = 0.30$, $P = 0.04$, one-tailed).

Of the 34 patients, 18 patients (37 joints) received only five treatments, 10 patients (29 joints) were administered

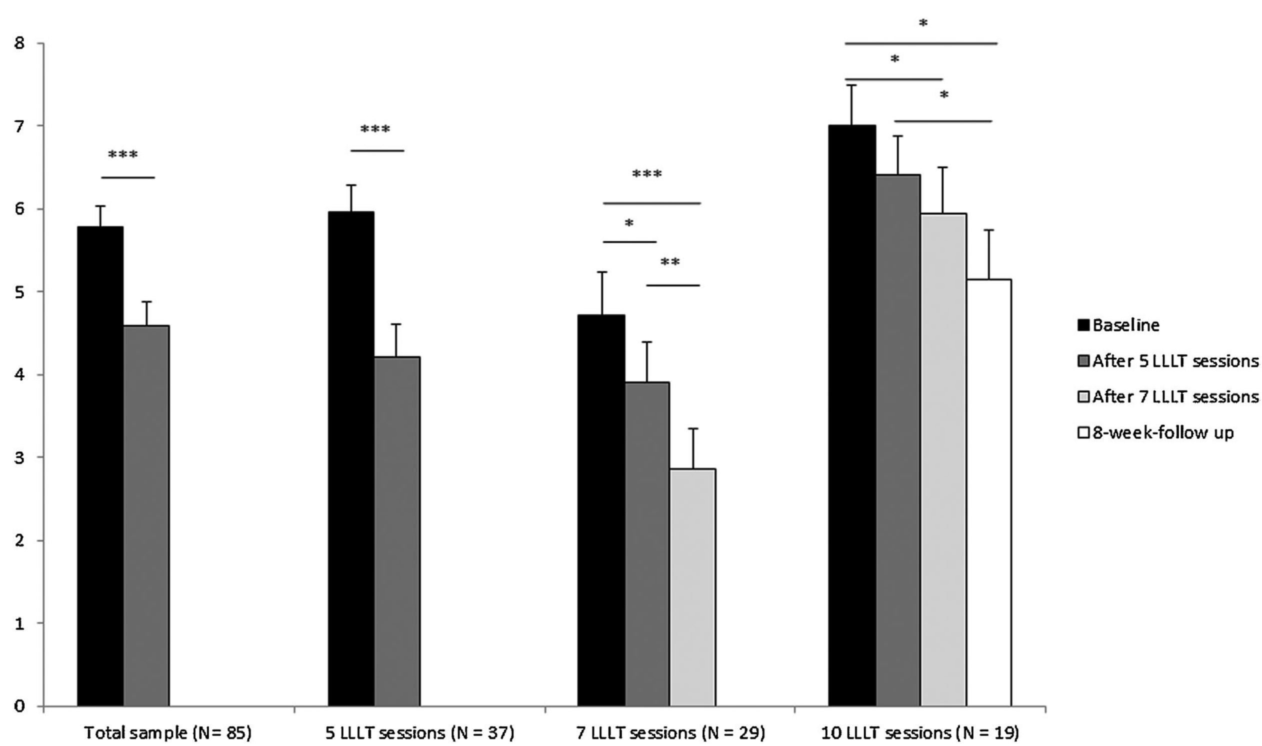


Fig. 1. Mean VAS (Visual Analogue Scale for pain) scores at baseline, after five LLLT sessions, after seven LLLT sessions, and at 8-week-follow-up. Note: Error bars indicate standard errors (SE), P-values were calculated by one-way within subjects analyses of variance (ANOVA's) and Bonferroni corrected post hoc comparisons. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; LLLT, Low level laser therapy; N, number of joints treated.

seven treatments, and six patients (19 joints) were administered 10 LLLT/photobiomodulation therapy sessions. Age, gender, and the number of joints treated did not differ significantly between these groups, only the type of OA was not equally distributed: in patients receiving seven treatments DIP joints were predominant, whereas PIP joints prevailed among patients receiving 5 or 10 LLLT sessions. With regard to the outcome measures, both pre-treatment VAS scores and range of motion were highest in the group who was administered 10 LLLT sessions, whereas pre-treatment ring size did not differ between the three groups (see Table 1).

Treatment Effects

Regarding the total sample, LLLT/photobiomodulation therapy significantly reduced pain ($P < 0.001$, $\eta^2 = 0.37$) and ring size ($P < 0.001$, $\eta^2 = 0.55$) and increased ROM after five treatments ($p < 0.001$, $\eta^2 = 0.29$; see Table 1 and Figs. 1–3). The effects were very large.

The same pattern of results emerged in the subsample analyses regarding patients who received only five LLLT sessions (VAS: $P < 0.001$, $\eta^2 = 0.52$; ROM: $P < 0.001$, $\eta^2 = 0.35$; ring size: $P < 0.001$, $\eta^2 = 0.54$), 7 sessions (VAS: $P < 0.001$, $\eta^2 = 0.41$; ROM: $P < 0.001$, $\eta^2 = 0.30$; ring size: $P < 0.001$, $\eta^2 = 0.49$) and 10 sessions (VAS: $P < 0.001$, $\eta^2 = 0.33$; ROM: $P < 0.001$, $\eta^2 = 0.42$; ring size: $P < 0.001$, $\eta^2 = 0.54$; see Table 1 and Figures 1–3). Again, all effects were unanimously very large. In the seven LLLT group, post hoc comparisons showed a consistent and significant improvement of outcome over time, that is, mean differences of all outcome measures (pain, ring size, range of motion) were significant between all points of time (baseline vs. after five sessions, baseline vs. after seven sessions, and five vs. seven sessions). In the 10 LLLT group, there was a similar trend, yet no significant improvement occurred between 7 and 10 treatments, neither for pain, nor for ring size or range of motion. The improvement achieved after seven sessions, however, persisted at 8-week-follow up and descriptively even intensified.

DISCUSSION

The present study demonstrated highly significant and positive short-term effects of LLLT/photobiomodulation therapy on pain, ring size, and range of motion in patients with Bouchard's and Heberden's OA. Subsample analyses revealed that major improvement in all outcome measures was achieved after five LLLT sessions, followed by further improvement after seven LLLT sessions in the group who received seven treatments. In the group receiving 10 LLLT sessions, outcome did not further significantly improve after 10 treatments, yet remained stable at 8-week-follow up and even showed some trend of improvement. This pattern of results contradicts the notion put forward by

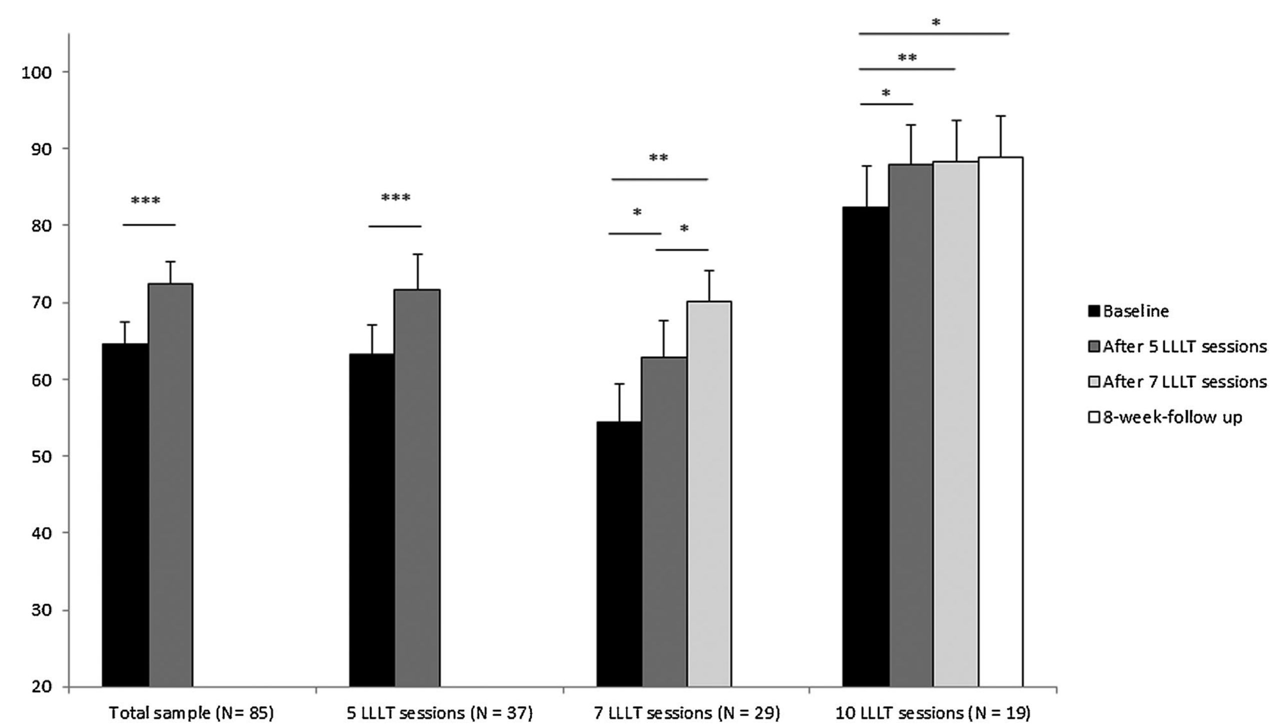


Fig. 2. Mean range of motion (flexion in °) at baseline, after five LLLT sessions, after seven LLLT sessions, and at 8-week-follow-up. Note: Error bars indicate standard errors (SE), P-values were calculated by one-way within subjects analyses of variance (ANOVA's) and Bonferroni corrected post hoc comparisons. For better visibility, the ordinate is truncated at 20°. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; LLLT, Low level laser therapy; N, number of joints treated.

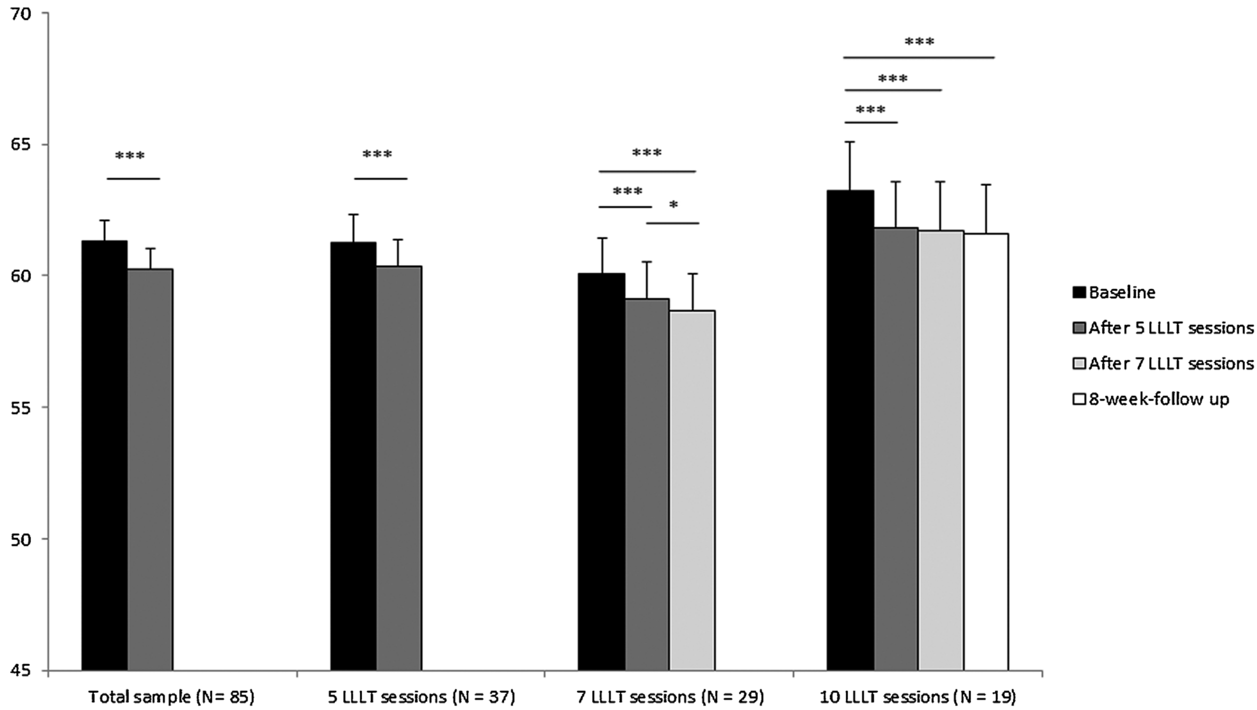


Fig. 3. Mean ring size (perimeter in mm) at baseline, after five LLLT sessions, after seven LLLT sessions, and at 8-week-follow-up. Note: Error bars indicate standard errors (SE), *P*-values were calculated by one-way within subjects analyses of variance (ANOVA's) and Bonferroni corrected post hoc comparisons. For better visibility, the ordinate is truncated at 45 mm. $^{*}P < 0.05$; $^{***}P < 0.001$; LLLT, Low level laser therapy; N, number of joints treated.

Brosseau et al. [7] who hypothesized that compared with RA exhibiting acute inflammatory processes chronic pain conditions, such as OA, require longer treatment of more than 6 weeks to profit from LLLT. Note, however, that the size of our only subsample in which 10 LLLT sessions were administered ($N = 6$ patients, and 19 joints, respectively) was smallest among the three subsamples thus resulting in a lower power to detect significant differences. Further, caution seems warranted when interpreting and comparing the subsample analyses, as the three groups significantly differed at baseline in some aspects and the number of treatments administered was not randomly assigned, but guided by clinical considerations and needs. As one would, for instance, expect patients receiving the maximum of 10 LLLT sessions over 5 weeks reported more pain at baseline than patients receiving fewer treatments. Somewhat surprisingly at first sight, the same subsample had the largest, that is, best, ROM at baseline. This might be either due to the lacking randomization and small sample size of this group ($N = 6$ patients), as in small samples single outliers influence the arithmetic mean to a greater degree than in larger samples. Alternatively, these patients could suffer from the most recent osteoarthritis which is why their joints were most painful, yet still least restricted in motion. Future randomized studies should focus on examining the ideal LLLT treatment duration in Heberden's and Bouchard's OA.

Our results are in line with Paolillo et al. [2] who combined LLLT with ultrasound. The present results are also reconcilable with Brosseau et al. [7] who admittedly found only few significant differences between sham and active LLLT patients, yet demonstrated improvement over time in both groups with a general tendency for greater changes in the main outcome measures, such as pain, morning stiffness, grip strength, and functional status, in the active LLLT group. Although our longitudinal treatment effects were neither placebo-controlled nor blinded, there is good reason to believe that they go beyond pure placebo effects. First, we did not only demonstrate improvement in a rather subjective outcome, such as pain, but also in objective outcome measures, such as ring size and range of motion. Second, our effects were not only significant, but also very large according to Cohen's statistical criteria [17] and thereby larger than the average placebo effects reported in comparable studies on the short-term effects of LLLT on hand OA [2,7]. Nevertheless one might argue that especially the improvement in VAS pain scores (ΔVAS of -1.75 to -1.86 between baseline and the last respective measurement in the three subsamples) is clinically rather small. Note, however, that these positive changes were achieved in a chronic degenerative condition with no therapeutic gold standard and close to no established therapeutic options. Bearing that in mind, we consider these effects as relevant to patients' subjective well-being.

The rather short follow-up interval was another limitation of the present study. Future research should expand follow-up intervals, as still little is known about long-term effects of LLLT on OA in general, and on hand OA in specific [5,6,13]. Furthermore, our results are restricted to female Bouchard's and Heberden's OA patients: almost 93% of our patients were female. This disproportion, however, is typical of hand OA studies [2,7], as it reflects the general epidemiology of Bouchard's and Heberden's OA [5,6]. Nevertheless, studies including more male patients seem desirable to be able to examine the generalizability of results mostly found in women. Further research questions to be answered include the ideal site of LLLT application (joint vs. nerve vs. joint and nerve) as well as the ideal dosage and wavelength [7].

In conclusion, the present study provides evidence for LLLT as a safe, non-invasive, efficient, and efficacious means to reduce pain and swelling and to increase joint mobility in patients suffering from Heberden's and Bourchard's OA. Further randomized controlled studies are needed to examine medium- to long-term effects as well as the ideal technical and therapeutic LLLT parameters.

REFERENCES

1. Baltzer AWA, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthr Cartil 2009;17:152–160.
2. Paolillo AR, Paolillo FR, Joao JP, Joao HA, Bagnato VS. Synergic effects of ultrasound and laser on the pain relief in women with hand osteoarthritis. Lasers Med Sci 2015;30: 279–286.
3. Baltzer AWA, Ostapczuk MS, Stosch D, Seidel F, Granrath M. A new treatment for hip osteoarthritis: Clinical evidence for the efficacy of autologous conditioned serum. Orthop Rev (Pavia) 2013;5:59–64.
4. Mahendira D, Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: An update. Osteoarthr Cartil 2009;17:1263–1268.
5. Valdes K, Marik T. A systematic review of conservative interventions for osteoarthritis of the hand. J Hand Ther 2010;23:334–350; quiz 351.
6. Beasley J. Osteoarthritis and rheumatoid arthritis: Conservative therapeutic management. J Hand Ther 2012;25: 163–171; quiz 172.
7. Brosseau L, Wells G, Marchand S, Gaboury I, Stokes B, Morin M, Casimiro L, Yonge K, Tugwell P. Randomized controlled trial on low level laser therapy (LLLT) in the treatment of osteoarthritis (OA) of the hand. Lasers Surg Med 2005; 36:210–219.
8. De Luigi AJ. Complementary and alternative medicine in osteoarthritis. PM R 2012;4:S122–S133.
9. Fulop AM, Dhimmer S, Deluca JR, Johanson DD, Lenz RV, Patel KB, Douris PC, Enwemeka CS. A meta-analysis of the efficacy of laser phototherapy on pain relief. Clin J Pain 2010;26:729–736.
10. Minatel DG, Frade MAC, Franca SC, Enwemeka CS. Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. Lasers Surg Med 2009;41:433–441.
11. Huang Y, Chen AC, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. Dose Response 2009;7: 358–383.
12. Alfredo PP, Bjordal JM, Dreyer SH, Meneses SRF, Zaguetti G, Ovanessian V, Fukuda TY, Junior WS, Lopes Martins RAB, Casarotto RA, Marques AP. Efficacy of low level laser therapy associated with exercises in knee osteoarthritis: A randomized double-blind study. Clin Rehabil 2012;26: 523–533.
13. Bjordal JM, Johnson MI, Lopes-Martins RAB, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. BMC Musculoskelet Disord 2007;8:51.
14. Gur A, Cosut A, Sarac AJ, Cevik R, Nas K, Uyar A. Efficacy of different therapy regimes of low-power laser in painful osteoarthritis of the knee: A double-blind and randomized-controlled trial. Lasers Surg Med 2003;33: 330–338.
15. Hegedus B, Viharos L, Gervain M, Gálfi M. The effect of low-level laser in knee osteoarthritis: A double-blind, randomized, placebo-controlled trial. Photomed Laser Surg 2009;27: 577–584.
16. Freyd M. The graphic rating scale. J Educ Psychol 1923; 83–102.
17. Cohen J. Statistical power analysis for the behavioral sciences. 2nd edition. New York: Psychology Press; 1988.
18. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39: 175–119.