Efficacy of prolonged application of low-level laser therapy combined with exercise in knee osteoarthritis: a randomized controlled double-blind study

Laser and Exercises in Osteoarthritis

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ABSTRACT

Objectives: To investigate the effect of prolonged low-level laser therapy application combined with exercise on pain and disability in patients with osteoarthritis of the knee.

Design: A randomised controlled trial.

Setting: Special Rehabilitation Services.

Subjects: Forty-three participants with knee osteoarthritis.

Intervention: Participants were randomly allocated in the laser group (n=22, 44 knees) received low-level laser therapy while the placebo group (n=21, 42 knees) received placebo therapy three times a week for three weeks following initial assessment. Both groups received low-level laser therapy combined with exercise three times a week for the following 8 weeks.

Main outcome measures: The primary outcome was the change in knee pain and disability (Lequesne). Secondary outcomes included change in mobility (Timed Up and Go test), range of motion (goniometer), muscular strength (dynamometer), activity (Western Ontario and McMaster Universities Osteoarthritis questionnaire) and medication intake relief.

Results: The patients' average age was 62.22 (9.8) years. Pain scores at baseline, 3 weeks, 11 weeks, and 6 months follow-up were 9.1 (1.3), 2.6 (2.3), 0.2 (0.9) and 0.2 (0.8) for the Laser Group and 9.5 (8.0), 7.7 (5.3), 5.6 (2.4) and 7.4 (5.0) for the Placebo Group, respectively. Disability scores at baseline, 3 weeks, 11 weeks, and 6 months follow-up were 14.9 (4.7), 7.6 (4.8), 3.9 (4.2) and 3.5 (4.1) for the Laser Group and 17.8 (14.7), 15.2 (11.5), 11.6 (6.4) and 15.8 (11.9) for the Placebo Group, respectively.

Conclusion: In patients with osteoarthritis of the knee, low level laser therapy combined with exercises continued for over 11 weeks reduced pain, disability, and intake of medication over a six-month period.

Keywords: Knee, osteoarthritis, low level laser therapy, exercises.

Clinical Trial Registration number: CT01306435.

INTRODUCTION

Knee osteoarthritis is a large contributor to the global burden of disease, and one of the most common pathologies fueling disability and musculoskeletal pain in the world.[1] Findings of knee osteoarthritis include cartilage degradation, bone remodeling, formation of osteophytes and synovial inflammation, leading to pain, particularly upon weight bearing, stiffness, swelling and loss of normal joint function.[2]

Patients with knee osteoarthritis develop kinesiophobia to evade the onset of pain, especially in the acute phase, limiting their compliance with effective rehabilitation strategies such as regular exercises.[3]

The clinical efficacy of low-level laser therapy in the treatment of osteoarthritis is yet questionable; while some authors have reported pain relief,[4] others have not.[5] These discrepancies may be associated with the variation in low-level laser therapy doses used by different studies.[6]

Different dosimetric aspects must be considered in the therapeutic application of low-level laser therapy in patients with knee osteoarthritis. Stausholm et al[7] in a systematic review and meta-analysis concluded that Laser reduces pain and disability in patients with knee osteoarthritis at doses ranging between 4 and 8 J at wavelengths between 785 and 860 nm. For the 904 nm wavelength, doses should be between 1 and 3J.

Other dosimetric variables, however, still need to be studied to improve the clinical effectiveness of applying Laser in knee osteoarthritis. In a previous study by our research group, we used the application of Laser for 3 weeks prior to performing exercises, with the intention of decreasing the pain and inflammatory process characteristic of knee osteoarthritis, to later start the exercise program, which lasted for 8

weeks.[8,9] The promising results of this study in pain and disability, made us wonder if we could optimize Laser treatment if we used Laser simultaneously with the exercise sessions and in a prolonged manner throughout the 11 week treatment period.

METHODS

This randomized controlled trial was also registered in the Brazilian Clinical Trials Register (ID: CT01306435), before data collection occurred from January 2018 to December 2019. The study was approved by the local Ethics Research Committee (protocol n°0775/08) and performed according to the CONSORT recommendations for non-pharmacological trials.[10]

The study included patients who were attended the Special Rehabilitation Services in Taboão da Serra-SP Brazil, with knee osteoarthritis diagnosed by an independent rehabilitation specialist, and fulfilled the following inclusion criteria: (1) levels 2–4 according to Kellgren–Lawrence grade,[11] (2) aged 50-75 years, (3) both genders,(4) have knee pain and functional disability for at least three months, and (5) according to the criteria of the American College for Rheumatology.[12] The exclusion criteria were follows: cancer, diabetes, symptomatic hip osteoarthritis, or used antidepressants, anti-inflammatory medications or anxiolytics during six months prior to enrolment.

All potentially eligible participants were contacted by telephone and those interested in participating were invited to attend a physical examination for inclusion and exclusion criterion. All participants were informed about the study and provided informed consent before participating. They were assigned by block randomisation, stratified according to treatment group. An independent researcher not involved in outcome assessment was responsible for group allocation, using a computer-generated random number table. Immediately after baseline assessment by the blinded assessor, the treating physiotherapist accessed the allocation schedule from a centrally located locked cabinet. Patients and the physiotherapist responsible for the evaluation and physiotherapist responsible for the treatment were unaware of the randomisation results.

Demographic and anthropometric data, the use of pain relief medications, the duration of knee pain, the knee range of motion, and a range of patient-reported outcomes were collected at baseline (before randomization), 3 weeks from baseline (after Laser application), 11 weeks from baseline (post-treatment) and 6 months from baseline (follow up) by the same blinded evaluator.

The primary outcomes were pain intensity measured by the numeric pain rating scale (0–10) with a minimal clinically important change of two points[13] and disability measured using the Lequesne questionnaire,[14] which consists of 11 questions about pain, discomfort, and function. Scores range from 0 to 24 (from 'no' to 'extremely severe' dysfunction).

Secondary outcomes included medication intake (Paracetamol) for knee pain relief, mobility and balance, range of motion, muscular strength, and activity. Mobility and balance were evaluated by the Timed Up and Go test.[15] The Timed Up and Go test, a measure of functional mobility, quantifies in seconds the time that the individual needs to stand up from a chair, walk 3m, turn back toward the chair and sit down again. Range of motion of the knees was measured with a universal goniometer (AESCULAP) according to the methods described by Marques.[16] Muscular strength was estimated at maximal isometric force for the quadriceps, using a portable dynamometer (Lafayette, USA). Under stabilized conditions, patients, sitting with knees flexed at 60 (measured by a goniometer),[16] were asked to extend the legs as far as they could. Three trials were conducted, and the mean value was obtained. Muscular strength was estimated at maximal isometric force for the quadriceps, using a portable dynamometer. Under stabilized conditions, patients, sitting with knees flexed at 10, 60 and 90 degree (measured by a goniometer),[17] were asked to extend the legs as far as they could. Three trials were conducted and the mean value was obtained. Activity was measured using the Western

Ontario and McMaster Universities Osteoarthritis questionnaire,[18] which is self-administered and measures pain, frozen joints, and physical activity. Increased scores suggest decreased activity.

Participants were randomly allocated into two groups: laser group and placebo group.

In this study, all patients had osteoarthritis of both knees, and in every patient both knees were treated with the allocated treatment.

Participants in the laser group received low-level laser therapy while the placebo group received placebo therapy three times a week for three weeks following initial assessment. Both groups received low-level laser therapy combined with exercise three times a week for the following 8 weeks.

In the laser group, energy was irradiated over the joint line onto five points of the synovial region of the medial side of the knee and in four points at the lateral side, at 3 J per point. Total dose per knee was 27 J per treatment and used previously calibrated equipment (Irradia Class 3B; Stockholm, Sweden). In the placebo group, procedures were identical but without emission of energy. The laser equipment had two identical pens, one for the active treatment and one for the placebo treatment (sealed). The pen's semi-conductor consisted of gallium arsenide with wavelength of 904 nm, frequency of 700 Hz, average power of 60 mW, peak power of 20 W, pulse duration 4.3 ms, 50 seconds per point (area 0.5 cm2). The parameters followed the recommendation of the World Association of Laser Therapy[6] for osteoarthritis. The physiotherapist was blinded for the active and placebo beam.

All patients followed the same training program (Table 1). The intervention was divided into Phase-1, Phase-2 and Phase-3 during eight weeks with three sessions a week. Each session lasted 45 minutes:

- 10 minutes warming-up (treadmill, ergometer bike or rowing machine);
- 30 minutes 2–3 sets with Phase-1, Phase-2 and Phase-3;
- 5 minutes stretching (hamstrings, quadriceps, adductors, and gastrocmenius).

Insert Table 1

Participants were instructed not to use analgesic medications other than paracetamol (500 mg/day) or anti-inflammatory drugs during the study, and not to perform any other type of physical exercise in addition to the exercise performed during the study.

The primary outcome measure Visual Analogic Scale (range: 0-100mm) was used to estimate sample size. Using a minimal clinically important difference of 20mm between the groups, 20mm of standard deviation, with a significance level of 0.05 (2-tailed) and a power of 80%, we required 17 participants in each group.

The data were subjected to analysis of variance by adjusting a mixed generalized linear mixed model appropriate for entirely randomized experiments to test the effect of groups and time as a repeated measure. The random effects were modeled after the first order heterogeneous first-order autorregressive structure and the data distribution was selected according to obtaining the maximum likelihood, assessed using the Akaike information criterion (AIC) and by assessing the adherence of the data. residues to the Gaussian distribution, which was evaluated using the skewness and kurtosis. The significant effects were subjected to the Tukey-Kramer test, giving precedence to the effect of the interaction over the main effects. In all tests applied, the significance level of 5% was adopted and the calculations were made with the support of

the SAS system (SAS Institute Inc. The SAS System, release 9.4, 2012. SAS Institute Inc., Cary: NC.).

RESULTS

In total, 59 subjects were considered for inclusion in the study. Of these 59, 16 were excluded because they did not meet the inclusion criteria or declined to participate. The remaining group of participants were randomly allocated to laser group and placebo group. The whole protocol accomplished with completed data from 40 participants (Figure 1). Thus, the final analysis involved 40 participants (20 subjects in each group).

Insert figure 1

The participant's characteristics are described in Table 2. Both groups were represented predominantly by women, older than 55 years of age, with a predominance of grade 3 osteoarthritis of the knees. Ther variables did not show differences between groups ($p<0,05$).

Insert Table 2

The laser group presented a higher reduction in the use of medication (paracetamol) compared to the placebo group after six months, where the number of days of analgesic use medication for knee pain relief was reduced ($p= 0.0045$).

Between-group differences in the Follow up (3 weeks, 11 weeks, and 6 months), were observed for the variable pain at rest, pain during activities of daily living and disability. The evident improvement observed in the laser group was maintained for the three variables, reaching the larger effect in six months after treatment, being for pain at rest, an estimated mean difference of 5.3 points (95% CI 3.7-6.8), p=0,0001 with an effect size of 2.94, pain during activities of daily living an estimated mean difference of 6 points

(95% CI 4.3-7.5),p= 0.0001 with an effect size of 3.21, and disability an estimated mean difference of 10.4 points (95% CI 6.6-14.1), p=0.0001 with an effect size of 2.48 (Table 3).

Insert Table 3

Table 4 shows that the laser group also presented higher values in all subscales of the activity compared to the placebo group (p=0.0001), in muscular strength of quadriceps with knees flexed at 10, 60 and 90 degrees compared to the Placebo group, with an effect size that increased ranging from 0.38 at the baseline for 90 degrees to 2.26 for 10 degree at 6 months. Significant statistical differences were only observed in mobility at a 6-month follow-up (p=0.0002) and range of motion all follow up time points were significant between groups (p=0.0016).

Insert Table 4

DISCUSSION

The efficacy of prolonged application of low-level laser therapy combined with a programme of exercises in patients with knee osteoarthritis was assessed in this study. Positive results were found in low level laser therapy combined with exercises continued for over 11 weeks reduced pain, disability, and intake of medication over a six-month period, compared to the placebo group.

In our previous studys,[8,9] the low-level laser therapy was applied only in the initial three weeks of treatment and in the following eight weeks only exercises were performed. In these, it was found that the low-level laser therapy when associated with exercises is effective in yielding pain relief, function and activity were maintained for six months on patients with osteoarthritis of the knees. In the current study, with the prolonged application of the low-level laser therapy, it was possible to see an even more significant improvement in these and other variables, also being maintained for six months. We postulated that adding Laser to an exercise-based treatment program might accelerate the improvement of physical function, possibly by controlling the inflammation, resulting in reduced pain and more rapid functional improvement. Hence, Laser may have a more pronounced effect on knee function if the benefit of pain relief is used specifically to optimize exercise parameters.

We believe that analgesia in the laser group may have been a consequence of the anti-inflammatory properties of the low-level laser at 3 J, applied onto specific points, suggested by World Association of Laser Therapy,[6] on the articular capsule. These results can be supported the main findings of previous meta-analyses.[7,19] Stausholm et al.[7] concluded that Laser reduces pain and disability in knee osteoarthritis at 4–8 J with 785–860 nm wavelength and at 1–3 J with 904 nm wavelength per treatment spot. Rayegani

et al.[19] concluded that Laser effectiveness is affected with important factors: wavelength, energy density, treatment duration, numbers of sessions the treatment, severity of knee osteoarthritis and site of application.

As in the present study, Hegedus et al.[20] and MontesMolina et al.[21] carried out clinical trials according to the recommendations of World Association of Laser Therapy[6], using 830 nm laser with average power of 50 and 100 mW, respectively, with a dose of 6.0 J/point. Effective results were recorded in pain relief and improvements in microcirculation in the irradiated area in patients with osteoarthritis knee.

Rashoud et al.[22] used Ga–As laser with wavelength of 830-nm, irradiated each point for 40 seconds with a dose of 1.2 J/point, 6 J per session for each patient. The dose used by the authors was somewhat lower than that recommended by the World Association for Laser Therapy for a 830-nm laser.[6] The application of the laser associated with exercises took place over three weeks. The authors found that short-term application of Laser to specific acupuncture points in association with exercise and advice is effective in reducing pain and improving quality of life in patients with knee osteoarthritis. Alghadir et al.[23] used Ga–As laser with wavelength of 850 nm, power of 100 mW, and spot size of 1.0 mm at eight points of the knee. Each point received energy of 6 J/point for 60s, with a total dose of 48 J/cm2 in each session. The laser application sessions associated with exercises were performed two times per week over a period of 4 weeks. The authors also found that Laser seemed to be an effective modality for short-term pain relief and function improvement in patients with chronic knee osteoarthritis. We believe that the laser application dose and treatment duration, in both studies, may have influenced the absence of results in an evaluation six months follow-up. Unlike these, Tascioglu et al.[24] did not find significant improvement short or long term in pain of patients receiving laser with a wavelength 830 nm, 50 mW of mean power, with doses

ranging from 1.5 to 3 J. They believe that this fact may be related to the laser modality, dosages and wavelength selection used.

A fact that drew attention in the present study was the significant reduction in pain intensity of patients in the laser group in the short and long term and associated with it, also a significant reduction in the consumption of analgesics. The trend, observed in our study, towards a lower consumption of analgesic and anti-inflammatory medications in the intervention groups suggests a line of research in this direction, and coincides with recent studies that highlight this premise.[25]

In articles published so far, the variety of Laser sessions, doses, and differences in the final follow-up time points might have contributed to the significant evidence of heterogeneity, particularly for the possible dose–response patterns, which could have greatly affected the laser performance. Laser was applied prior to exercise performance in order to improve patient symptoms and better execute the exercise; however, most studies applied the Laser after the exercises. Their treatment time was limited to 1-3 sessions in 4 weeks, whereas in our study the sessions were held 3 times a week for 11 weeks. The limited number of trials and insufficient descriptions of treatment parameters are limiting factors in determining which therapy is most effective.

The major study limitations were the small number of patients, the absence of a control group, which would allow us to assess the natural course of the disease.

CONCLUSION

In patients with osteoarthritis of the knee, low level laser therapy combined with exercises continued for over 11 weeks reduced pain, disability, and intake of medication over a six-month period.

CLINICAL MESSAGES

- The previous application of low-level laser therapy for 3 weeks, followed by its association with strength exercises for 8 weeks reduces pain, disability, and intake of medication over a six-month period.
- Patients with knee osteoarthritis can be more responsive to prolonged low-level laser therapy application associated with exercise program.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to all three of the sections below:

(1) Conception and design of the study or acquisition of data, or analysis and interpretation of data.

(2) Draughting the article or revising it critically for important intellectual content.

(3) Final approval of the version to be submitted.

Specifics:

PPA: Conception and design, collection of data, analysis and interpretation of the data, draughting of the article, JMB: Conception and design, interpretation of the data and critical revision of the article for important intellectual content, RABL-M: Conception

and design, interpretation of the data and critical revision of the article for important intellectual content, MIJ: Conception and design, interpretation of the data and critical revision of the article for important intellectual content, WSJ: Analysis and interpretation of the data, Statistical expertise, APM: Conception and design, interpretation of the data, critical revision of the article for important intellectual content. RAC: Conception and design, interpretation of the data, critical revision of the article for important intellectual content. All authors read and approved the final manuscript. The primary author: Patricia Pereira Alfredo (patriciaalfredo@yahoo.com.br) takes responsibility for the integrity of the work as a whole, from inception to finished article.

CONFLICTS OF INTERESTS

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

COMPETING INTEREST STATEMENT

The authors certify that the grant sponsor has no involvement in study design, collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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FIGURES AND TABLES

Table 1: Exercise program conducted over the eight weeks of treatment.

PHASES	EXERCISES
P1 **(**week 1 - week 2) Objectives: Range of Motion Motor Learning Balance Coordination	Each exercise had 30 repetitions and 2 sets: • Sitting in the chair with a weight on the ankle, knee and stretch the foot to rotate alternately in and out then change legs. • Lying prone. Bend the knee slowly as much as possible. Stretch the knee slowly. • Standing with support. Bend the knees to approximately 60 degree. Push up again. • Walk on a 3 m line without stepping besides the line. • Walk-standing. Transfer your body-weight from one leg to the other.
P2 **(**week 3 – week 5) Objective: Strengthening	Each exercise had 20 repetitions and 3 sets: • Standing. Bend your knees to approximately 60 degrees, and up again. • Walk sideward by crossing legs. To right and left. • Standing on a balance board. Hold the balance. • Lying prone. Bend one knee as much as possible. • One foot-standing on a step. Bend your knee until the other foot touch the floor, push up again.
P3 **(**week 6 - week 8) Objective: Strengthening	Each exercise had 20 repetitions and 3 sets: • Walk sideward by crossing steps. To right and left. • Standing on one leg. Bend the knee to approximately 60 degree, and up again. • Standing on a balance board. Keep the balance. More difficult if eyes are closed. • Standing on the floor. Get up on your toes, hold 1-2 sec., and get down again • Sitting with weight around the ankle. Stretch the knee slowly, hold the stretch 3-4 sec., and slowly down again.

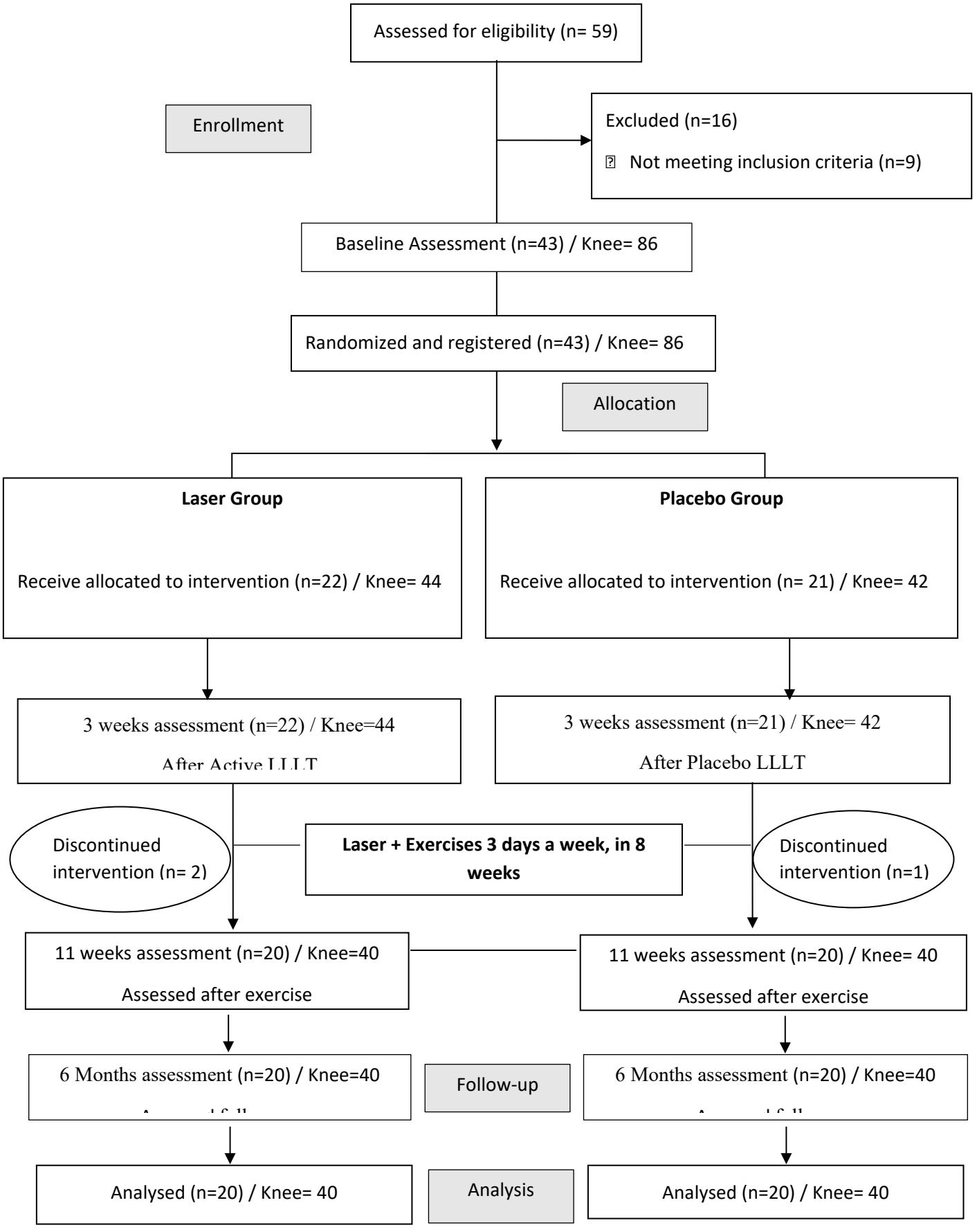

Figure 1- Participant flow diagram.

Table 2: Clinical and demographic characteristics of the participants in both groups.

CHARACTERISTICS	LASER GROUP (N=20/ KNEE= 40) MEAN (SD)	PLACEBO GROUP (N=20/ KNEE= 40) MEAN (SD)	P
AGE (YEARS)	68.55 (9.62)	65.9 (8.82)	0.751
WEIGHT (KG)	76.01 (10.52)	77.37 (7.40)	0.639
HEIGHT (M)	1.65 (0.04)	1.63 (0.06)	0.297
BMI (KG/M^2)	28.39 (4.35)	29.16 (3.65)	0.551
GENDER			
Female	16 (80%)	17 (85%)	0.686
Male	4 (20%)	3 (15%)	0.686
OA DEGREE			
0	1 (2.5%)	1 (2.5%)	1.000
2	1 (2.5%)	1 (2.5%)	1.000
3	33 (82,5)	30 (75%)	0.090
4	5 (12,5)	8 (20%)	0.090

N= number; Kg= Kilograms; M= meters; SD= Standard Deviation; BMI= Body Mass Index; OA= Osteoarthritis

Table 3: T test among the variables pain, mobility, functionality, range of motion, muscle strength and activity at the time of the baseline.

VARIABLES	LASER GROUP (N=20) MEAN (SD)	PLACEBO GROUP (N=20) MEAN (SD)	P
PAIN			
Pain DLA (cm)	8.97 (1.43)	8.50 (1.75)	0.468
Pain Rest (cm)	7.19 (3.30)	6.57 (3.39)	0.627
MOBILITY			
8 meters	14.01 (4.47)	15.04 (3.53)	0.642
TGUG	16.75 (5.17)	19.72 (8.42)	0.357
DISABILITY	14.51 (5.36)	16.27 (3.52)	0.356
RANGE OF MOTION			
(DEGREE)	91.66 (14.30)	85.40 (16.62)	0.135
MUSCLE STRENGTH (H/KG)			
60 degrees	15.99 (9.37)	14.00 (7.28)	0.130
90 degrees	16.49 (11.56)	16.43 (11.08)	0.306
10 degrees	16.41 (15.90)	11.88 (7.38)	0.103
ACTIVITY-WOMAC			
Pain subscale	11.87 (2.83)	13.60 (2.87)	0.142
Stiffness subscale	4.67 (1.50)	5.80 (1.82)	0.403
Function subscale	38.07 (12.46)	39.40 (8.30)	0.583
Total Score	54.60 (15.82)	58.80 (11.36)	0.694

N= number; DLA= daily life activities; TGUG= time get up and go test; SD= Standard Deviation; p value for t Test; WOMAC= Western Ontario and McMaster Universities Osteoarthritis

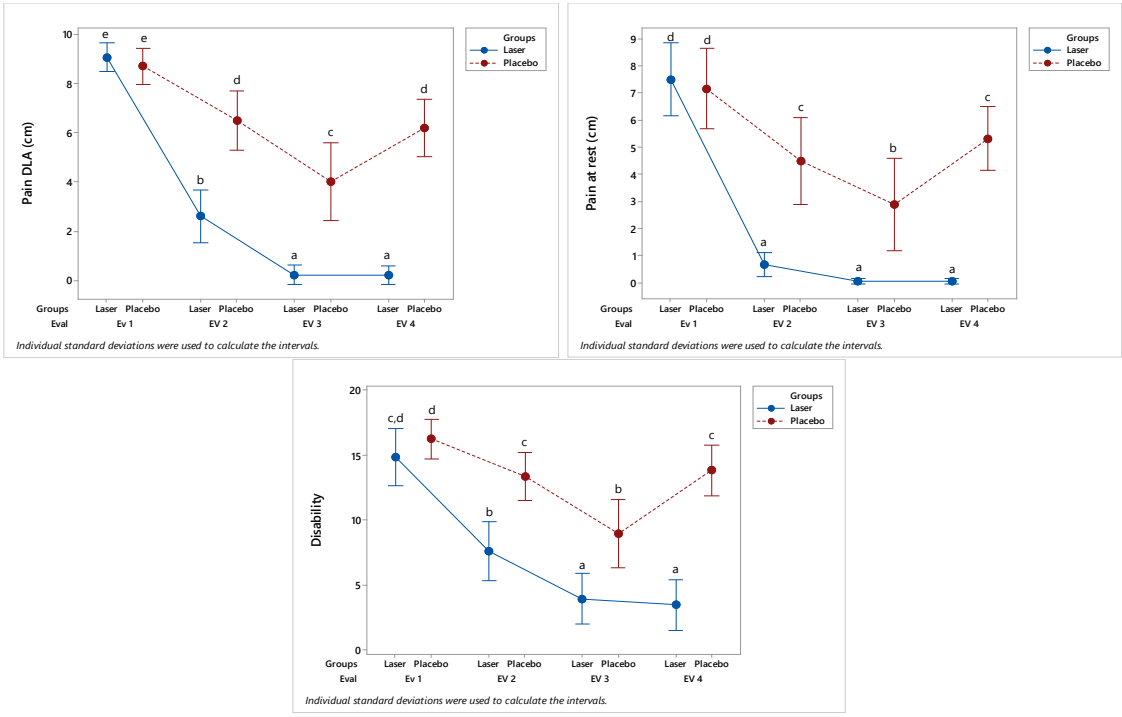

Figure 2- Primary outcomes of the placebo and laser group at baseline (Ev1), three weeks after starting treatment (Ev2), post treatment (Ev3) and six months the extended follow-up (Ev4). DLA= during daily life activities; Ev= evaluation; a = differ of baseline ($p<0.05$), b= differ of post treatment ($p<0.05$), c = differ of group I, d = differ of group II.

Table 4- Comparison between the groups for the variables mobility, range of motion, muscle strength and activity at baseline (T1), three weeks after starting treatment (T2), post treatment (T3) and six months the extended follow-up (T4) of the placebo and laser group.

	LASER GROUP (n=20)	PLACEBO GROUP (n=20)	p value
MOBILITY			
8 meters (time)			
T1	14.01 (4.47)c,d	15.04 (5.97)d	
T2	8.99 (1.52)a,b	13.94 (5.81)b,c,d	**0.00340***
T3	7.48 (2.71)a	12.05 (5.45)a,b,c	
T4	6.55 (2.34)a	13.79(4.98)b,c,d	
8 meters (steps)			
T1	16.33 (2.23)b,c	18.20 (3.53)c	
T2	14.67 (1.35)a	16.00 (2.90)a,b	0,62
T3	14.20 (2.31)a	15.47 (3.07)a,b	
T4	14.15 (2.52)a	15.88 (3.23)a,b	
TGUG			
T1	16.75 (5.17)b,d	19.72 (8.42)d	
T2	11.09 (2.93)a,c	17.37 (8.64)c,b,d	**0,0451***
T3	8.38 (2.77)a	14.82 (8.37)a,b,c	
T4	8.44 (2.98)a	17.06 (5.66)c,b,d	
RANGE OF MOTION (degree)			
T1	91.66 (14.30)a,b	85.40 (16.62)a	
T2	104.07 (11.22)c,d	92.93 (12.88)a,c	0,43
T3	111.47 (10.84)d	103.87 (12.10)b,c,d	
T4	111.58 (9.58)d	93.54 (15.08)a,c	
MUSCLE STRENGTH (H/Kg)			
60 degrees			
T1	15.99 (9.37)a	14.00 (7.28)a,b	
T2	22.53 (8.70)b	16.10 (8.07)a,b	**0.0112***
T3	30.23 (9.86)c	19.23 (8.03)a,b	
T4	30.56 (9.89)c	18.59 (8.03)a,b	
90 degrees			
T1	16.49 (11.56)a	16.43 (11.08)a,b	
T2	23.77 (9.74)b	17.02 (9.33)a,b	**0,008***
T3	30.05 (11.25)c	19.34 (10.21)a,b,c	
T4	32.80 (5.36)c	18.04 (10.21)a,b,c	
10 degrees			
T1	16.41 (15.90)a	11.88 (7.38)a	
T2	23.00 (13.99)a	13.57 (7.67)a	0,085
T3	31.08 (12.30)b	17.50 (8.08)a	
T4	33.51 (13.09)b	14.46 (3.23)a	
ACTIVITY-WOMAC			
Pain subscale			
T1	11.87 (2.83)c,d	13.60 (2.87)d	
T2	6.27 (3.28)b	11.27 (3.31)c,d	**0.00150***
T3	1.67 (2.06)a	8.87 (3.58)b,c	

T4	1.58 (3.05)a	11.38 (4.97)c,d	
Stiffness subscale			
T1	4.67 (1.50)c,d	5.80 (1.82)d	
T2	1.73 (1.62)a,b	3.67 (2.32)b,c	0,43
T3	0.80 (1.52)a	2.60 (2.16)a,b	
T4	0.85 (2.03)a	4.38 (2.89)d	
Function subscale			
T1	38.07 (12.46)c,d.e	39.40 (8.30)d	
T2	19.80 (15.82)b	38.07 (14.57)d	0,24
T3	10.20 (10.76)a	27.47 (15.89)b,c	
T4	11.30 (9.83)a	39.98 (3.57)d	
Total Score			
T1	54.60 (15.82)d,c,e	58.80 (11.36)e	
T2	27.60 (19.79)b	52.93 (18.14)e	**0.000170***
T3	12.67 (13.64)a	38.94 (20.06)b,d	
T4	13.73 (10.89)a	55.74 (13.33)e	
NUMBER OF DAYS OF ANALGESIC USE			
T3	2.45 (1.32)	6.8 (2.54)	**0.0015***
T4	0.21 (1.23)	4.61 (2.19)	

N= number; DLA= daily life activities; TGUG= time get up and go test; SD = standard deviation;

a = differ of baseline ($p<0.05$), b= differ of post treatment ($p<0.05$)

c = differ of group I, d = differ of group II.