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Design of a Clinical Trial to Determine the Effects of Low Level Laser on Pain and Function in Patellofemoral Pain Syndrome: Protocol for a Triple-Blinded Randomized Clinical Trial

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Original Article

Abstract

Introduction: We aimed to design a triple-blinded randomized clinical trial study to assess the effect of low-level laser (LLL) on pain and function in patients with patellofemoral pain syndrome (PFPS).

Materials and Methods: This designed study will involve 60 subjects with PFPS. Eligible subjects will be divided randomly into control (physical therapy), physical therapy plus active LLL, and physical therapy plus placebo laser. The physical therapy program will be exactly the same for all groups including exercise and education for ten sessions, every other day. The LLL group will receive 808 nm, 200 mW, 4 J gallium-aluminum-arsenide (GaAlAs) laser over 5 points for 20 seconds per point. The laser will be deactivated in placebo group, and for the control group, the laser will not be used. The outcomes include pain and function, which will be measured using visual analogue scale (VAS), the Persian version of the Kujala patellofemoral questionnaire, and the step-down test. Following Shapiro-Wilk test, the paired t and one-way analysis of variance (ANOVA) tests, if data distribution followed normal distribution, or the Kruskal-Wallis and Mann Whitney tests, if data distribution did not follow normal distribution, will be administered at the significance level of less than 0.05.

Conclusion: Therapeutic exercise is the treatment of choice for PFPS. LLL is a commonly favorable modality prescribed as a part of physical therapy program for musculoskeletal disorders. However, the effect of laser in subjects with PFPS has not been thoroughly investigated. In designed study, it will be examined whether adding LLL to standard physical therapy has a clinical benefit in subjects with PFPS.

Keywords: Low-level laser therapy, Patellofemoral pain syndrome, Pain, Function

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Introduction

Patellofemoral pain syndrome (PFPS) is one of the most common orthopedic problems with controversial etiology in adolescents and young adults (1,2). The pain appears following loading on the knee extension mechanism and activities with knee flexion (3,4). While there are no known specific diagnostic tests for PFP, the diagnosis is usually based on clinical symptoms and physical examinations (5). There is persistent joint inflammation in PFPS (2). Generally, non-surgical treatments for PFPS at early stage include medications or physical therapy (6).

There are only two studies about the role of laser therapy in PFPS (7,8) which both lack appropriate laser application and outcome measurements. Since there have been only two previous studies of laser on PFP with contradictory results, a new study is needed to examine the clinical impact of using laser in people

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with PFPS that tackles the limitations of previous studies. Therefore, the aim of this study was to design a protocol that could investigate the effect of low-level laser (LLL) on pain and function in subjects with PFPS.

Materials and Methods

Trial design: This study will be a triple-blind randomized clinical trial (participant, clinician, and assessor) with a parallel design.

Approval and registration: Ethical approval was obtained from the local medical ethics committee (http://ethics.research.ac.ir/IR.MUI.RESEARCH.REC.1397.035). The committee will monitor data collection phase through random visit by randomly-selected reviewer. This study is being funded by Vice Chancellery of Research and Technology, Isfahan University of Medical Sciences, Isfahan, Iran (Budget Code: 297030). Protocol of this study is registered at the Iranian Registry of Clinical Trials (IRCT) (IRCT20150131020888N9).

Participants: 60 men and women with PFPS who do not have other problems and diseases associated with knee pain and function will be recruited in the study. Subjects will be recruited through local advertisement in public and private health centers and sports committee, social media, "house of health" and the cultural centers of various urban districts in Isfahan, and using the database of the Musculoskeletal Research Center of School of Rehabilitation Sciences, Isfahan University of Medical Sciences. The inclusion criteria will be age of 18 to 40 years, presence of anterior or retropatellar pain only in one limb, and the report of pain during a day at least in 2 functional activities including prolonged sitting, climbing stairs, squatting, running, double kneeling, and jumping. The pain is required to be started at least in the past 3 months and scored not less than 3 on the visual analog scale (VAS). To be included in the study, the subject should report the pain during 10 seconds of one leg squat. Participants will be excluded if they report traumatic injuries, surgery, or other infectious or systemic disorders involving the low back and lower extremities, any signs or symptoms or magnetic resonance imaging (MRI) findings based on intra-articular pathologic conditions such as effusion, meniscal, cruciate, or collateral ligament involvement, subluxation and dislocation of the patella or other musculoskeletal injuries in lower extremities, hip or lumbar-referred pain, any symptoms or evidence of knee osteoarthritis in X-rays, corticosteroid injections, participating in physical therapy in the last 3 months especially with history of using laser due to prejudices about the effect of the intervention, administration of opioid and/or analgesic drugs in the last 72 hours, epilepsy, heart problems and heart pacemaker, and body mass index (BMI) > 30 kg/m^2.

All participants will enter the study with voluntary sampling. The purpose and method of the study will be described to the participants and the written and formal consent will be obtained from all volunteers. A physical therapist who is blind to the randomization results will evaluate the subject for inclusion/exclusion criteria.

Study procedure: Participants have 48 hours to decide on participation in the research. The day before start of the study, participants will be requested to wear comfortable outfits and attend Hatef Physical Therapy Center in Isfahan. All the subjects will fill the demographic information form; the form asks for contact details, age, gender, job status, educational level, weight, height, and BMI. Also, the step-down test will be explained to the subject.

Eligible subjects will be divided randomly using the random number table into three groups:

1. Physical therapy only
2. Physical therapy plus active LLL
3. Physical therapy plus placebo laser

Assessment procedures: A physiotherapist assessor, that is unaware of the therapeutic groups' allocation, will perform the clinical assessments at baseline and after 10 sessions. Measurements include pain and function. The subjects will score the severity of their pain on the scale of VAS, before and immediately after performing the step-down test. Then, they will be asked to fill the Kujala questionnaire.

The function will be measured by the Persian version of the Kujala questionnaire and the step-down test. The day before the first session of treatment, subjects will practice the step-down test for five times familiarization rehearsal. The details for each research instrument are described below.

- VAS: VAS is a unidimensional continuous measuring tool. It is a horizontal or vertical line, usually 10 centimeters (100 mm) in length, to assess pain intensity during last 24 hours in subjects with PFPS. To explain the severity of pain, VAS uses "no pain" (score of 0) and "worst imaginable pain" (score of 100) (Figure 1).

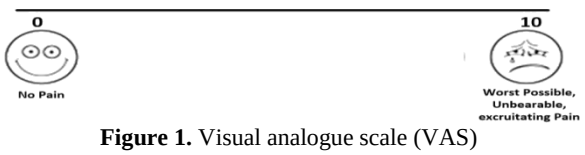

Figure 1. Visual analogue scale (VAS)

The VAS is self-administered; the subject shows the intensity of the pain by placing a line on the ruler. The time to complete this scale is less than one minute, and the validity of this tool has been proven in previous studies (9,10).

- Step-down test: This test is a unilateral test that will be performed on an 8 inches high platform. Subject will bear the weight on the affected limb and healthy limb will step forward and then down toward the floor. The heel will touch the floor and then the subject will return to full knee extension in affected knee. The number of steps in 30 seconds will be reported as subject's record [intraclass correlation coefficient (ICC) = 0.94] (Figure 2) (10). In the present study, step-down record will be reported for both lower limbs.

Figure 2. Step-down test

- Anterior Knee Pain Scale (AKPS) or Kujala: The questionnaire is a 13-item screening tool designed to evaluate PFP in adolescents and young adults. It contains questions about different levels of knee function, for example the scores for "limp" are as follows: none (5), slight/periodic (3), and constant (0). The total score ranges from zero to one hundred. The score of 100 indicates no functional limitation (11–13). This questionnaire was translated and culturally adapted in Iran (14) [correlation coefficient (CC) > 0.70, ICC = 0.96, 95% confidence interval (CI) = 0.93–0.98].

Interventions: Eligible subjects will be divided randomly into three groups using the random number table. The standard physical therapy program will be the same in all three groups consisting of 10 sessions every other day. This program includes education with a pamphlet and an exercises protocol. The physical therapy procedure will be conducted by the same qualified and registered physiotherapist who is unaware of the study groups.

Patient education: Patient education consists of modifying activities of daily living such as avoidance of prolonged sitting, sitting on low chair, cross-legged sitting, kneeling, climbing stairs, and squatting (11). A detailed brochure is prepared for this purpose that contains basic information about the mechanism of the disease, symptoms, principles of self-care, and simple exercises.

Laser therapy: Before using the laser, it will be calibrated. Exercise will be accompanied by an increase in local blood flow that may have a negative effect on the penetration depth of the laser beam due to increased hemoglobin content in the tissue (15). Therefore, laser will be used at the beginning of the session before any other intervention. Subjects will receive laser in supine position. The probe will be in direct and full contact with the tissue at 90° angle.

Laser will be radiated point by point. The participants and the physiotherapist will wear safety goggles to protect their eyes. The laser group will be treated with low level gallium-aluminum-arsenide (GaAlAs) laser, (LASER 680X, Novin Medical Engineering Company, Isfahan, Iran), with a wavelength of 808 nm, output power of 200 mW, continuous mode, beam spot size of 1 cm^2, dose of 4 J/cm^2 (each point) (equation 1), and energy of 4J (equation 2) for 20 seconds on each point (Table 1).

Table 1. Laser parameters

Device information, irradiation and treatment parameters	
Device information	
Manufacturer	LASER 680X, Novin Medical Engineering Company
Number of emitters	1
Emitter type	GaAlAs Diode
Beam delivery system	Hand-held probe
Irradiation parameters	
Wavelength (nm)	808
Mode	CW and Pulse
Maximum Output (mW)	500
Frequency	10-5000Hz & CW
Treatment parameters	
Beam spot size at target (cm^2)	1
Number of points irradiated	5
Application technique	Contact with pressure
Output power (mW)	200
Treatment mode	CW
Radiant energy (J)	4
Dose (J/cm^2)	4
Radiation time (sec)	20
Total radiant energy (J)	20
Total radiant time (sec)	100

GaAlAs: Gallium-aluminum-arsenide; CW: Continuous wave

Equation 1. Calculation of low-level laser (LLL) dose

$$\text{energy density } (^{j}/_{cm^2}) = \frac{\text{power(w)} * \text{time(S)}}{\text{area}} = \frac{0.2 * 20}{1} = 4\,^{j}/_{cm^2}$$

Equation 2. Calculation of low level laser (LLL) energy

$$\text{energy(j)} = \text{power(w)} * \text{time(S)} = 0.2 * 20 = 4\ \text{j}$$

Laser will be radiated over five points around the patella (Figure 3). The total energy and total radiation time for each session will be 20 J and 100 s (one minute and 40 seconds), respectively (16,17).

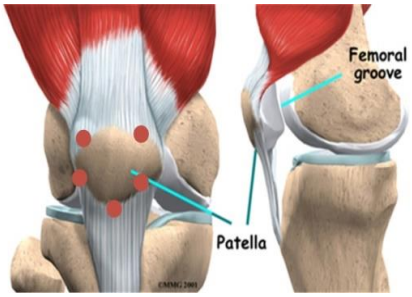

Figure 3. Laser radiation points in two groups

Participants will receive laser therapy prior to standard physical therapy. For participants in the placebo group, the treatment procedure will be identical to that of laser group although the laser apparatus will be off all the time. For the control group, the laser will not be used.

Exercises: According to Manchester consensus statement, therapeutic exercise is the treatment of choice for PFPS (18). At first, ultrasound (US) probe in "off" mode will be used over the patella (to ensure blinding of the participants) for 1 minute. Each training session will begin with 5 minutes warm up, continue with stretching and strengthening exercises, and finally, cool down for 5 minutes (Figure 4) (11).

Figure 4. Warm up and cool down

- Stretching exercises (Figure 5) for hamstring, plantar flexors, quadriceps, and iliotibial band: 3 repetitions of 30s for each muscle (19).

- Strengthening exercises (Figure 5): semi squat (0-45 degrees), seated knee extension (90-45 degrees), straight leg raise (SLR), hip abduction with weights (side lying), hip abduction against elastic band (standing), and hip lateral rotation against elastic band (sitting). Each exercise will be performed in three sets of 10 repetitions. Interval for rest and recovery between sets will be 3 minutes. External resistance during training will be standardized as 70% of the 1-repetition maximum (1RM).

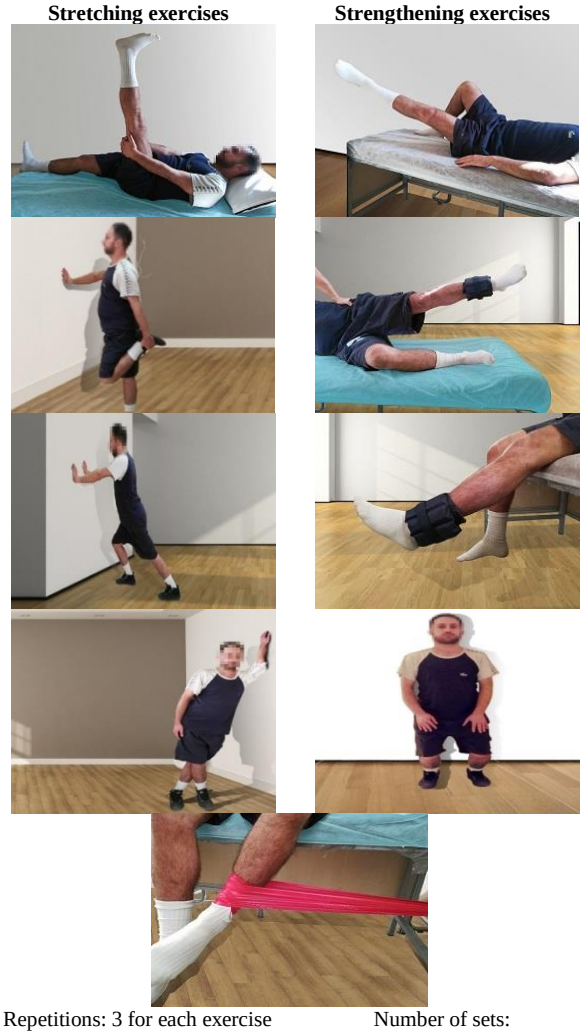

Figure 5. Exercises

The elastic resistance band will be individualized as maximum resistance which each subject can perform

in 10 repetitions (10 RM for TheraBand). The 1RM and 10 RM for TheraBand will be determined for any subject the day before the study (11,19).

Randomization and allocation concealment: The randomization schedule for subjects with PFPS will be done using the random number table by principal investigator (PI) who will have no role in data collection. A 1:1:1 allocation ratio is considered for each group. Subjects will be divided into three groups, and participants will not be aware of the groups they are in. For this purpose, all the groups will experience 1 minute off US placement on their affected knee. US probe will be saved unmoving on the treatment points around the patella without administering US gel. The laser and US apparatuses are covered by a thick material. The program of physical therapy is common to all three groups but the laser may be on, off, or not used. For blinding clinician, laser therapy will be performed by a physiotherapist who has no role in evaluating participants and recording information while the exercises will be done under the supervision of a qualified and registered physiotherapist who is unaware of the study groups. The assessor is also blind to the study groups.

Blinding strategy: -The physical therapist who is responsible for primary assessment of the volunteers will be informed about the inclusion/exclusion criteria, while he will not receive any information about the details of the study protocol.

– The selected individuals will be informed about the study protocol in detail. They will know that they will be randomly assigned into one of the study groups that all will receive standard physical therapy including exercise. They will realize there will be 33.33% chance of receiving true laser radiation. Thus, the participants will be blind to their own group.

– The PI will assign the participants into groups based on random number table.

– Employed physical therapist, who will be the assessor too, will manage all the groups through standard physical therapy program. He will be blinded to study groups, and he will evaluate all the subjects before and after 10 sessions of treatments.

– Laser and US will be administered by a physical therapist who will be blind to study details and will have no role in subject primary assessment, allocation, and measuring outcomes.

– Data will be coded by PI and will be analyzed by an analyzer who is blind to the study protocol.

Statistical analysis: Shapiro–Wilk test will be conducted to determine if the distribution of test variables follow normal distribution. The paired t-test and one-way analysis of variance (ANOVA) will be used to determine if the variables' distribution follows the normal distribution. Otherwise, the Kruskal-Wallis and Mann Whitney tests will be applied. The analysis will be performed using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). The significance level for all analyses will be $\alpha = 0.05$. The power of the test will be determined by G*Power software (20,21). The subjects' adherence and the cause for which people leave the study or reject joining the program will be mentioned using Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Intention-to-treat (ITT) analysis will be performed.

Sample size calculation: Considering $\alpha = 0.05$, $\beta = 0.80$, and using the G*Power software (20,21), according to Akbari et al. (8), the sample size was 111 subjects for pain and 30 subjects for function [based on Knee injury and Osteoarthritis Outcome Score (KOOS)] in each group. According to Rogvi-Hansen et al. (7), 4 subjects in each group will be enough if pain and disability be considered. Because both studies had considerable flaws in the outcome measurements, the sample size in this study will be considered to be 20 subjects in each group as a preliminary study.

Timeline: Ethical approval was obtained in May 2018 from the local medical ethics committee (protocol #297030). Recruitment of subjects with PFPS commenced in June 2018. All participants will complete the study in December of 2019. We decided to finish the statistical analysis by end of

January of 2020 and after that start the elaboration of scientific paper.

Discussion

PFPS is a common musculoskeletal disorder that has a high prevalence in general practice, orthopedic, and sport medicine (22,23). Pain may be caused due to abnormal stresses on the patellar joint surface or cartilage lesion (24). Risk of patellofemoral osteoarthritis increases in individuals with PFPS involvement (23). Therapeutic exercises is the treatment of choice for PFPS that can reduce the pain by restoring the hemostasis of the patellofemoral joint and prevent cartilage damage (2,18).

This paper is a research design study that will compare the effect of standard physiotherapy plus LLL and standard physiotherapy plus placebo laser with standard physical therapy alone on pain and function in subjects with PFPS. The aim of this study will be to determine if there is any added clinical benefit over standard physical therapy using LLL in subjects with PFPS. The results of this study will determine how much the laser will actually improve the pain and function in subjects with PFPS.

Limitations

Due to the large number of groups, and the time constraint of the project implementation, the follow-up phase was not considered for this study.

Recommendations

In future research, it is recommended to follow up the participants in the short and long term.

Conclusion

In designing, this clinical trial attempted to resolve the limitations and weaknesses of existing studies.

Acknowledgments

The study was funded and ethically approved by Isfahan University of Medical Sciences (Ethics Code: http://ethics.research.ac.ir/IR.MUI.RESEARCH.REC.1397.035) as a part of a thesis for Master's Degree in physical therapy by Mohammad Sedighi Pashaki (Registration code: 297030). The authors appreciate contribution of physical therapists: Reza Baba Ahmadi, Parisa Manzari, Fateme Beheshti Zadeh, Alireza Dashti, and Mohammadreza Talari in data collection. The authors also thank all the participants who kindly gifted their time, and supported the project. The Protocol of this study was registered at the Iranian Registry of Clinical Trials (IRCT20150131020888N9).

Authors' Contribution

Mohammad Sedighi Pashaki: Conception and design, Provision of study materials or patients, Data Collection, Data analysis and interpretation, Critical revising of the article for important intellectual content, Final approval of the article; Hosein Akbari Aghdam: Conception and design, Provision of study materials or patients, Data analysis and interpretation, Critical revising of the article for important intellectual content, Final approval of the article; Mehran Radi: Conception and design, Provision of study materials or patients, Data analysis and interpretation, Critical revising of the article for important intellectual content; Michael Callaghan: Conception and design, Data analysis and interpretation, Statistical expertise, Critical revising of the article for important intellectual content, Final approval of the article; Zahra Sadat Rezaeian: Conception and design, Funding and obtaining financial support, Administrative, technical, or logistic support, Provision of study materials or patients, Data analysis and interpretation, Statistical expertise, Drafting the manuscript, Critical revising of the article for important intellectual content, Final approval of the article, Integration of study protocol from design to dissemination.

Funding

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Pashaki. The sponsor has no role in data collection, analysis of the data and drafting the manuscript.

Conflict of Interests

Nothing to declare. Dr. Rezaeian is an assistant professor in Isfahan University of Medical Sciences since 2011. She worked as "Industry invited professor" with Novin Company since April 2017 to April 2018. The company is not aware of this study and has no role in data collection, analysis of the data and drafting the manuscript.

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