Introduction

Knee osteoarthritis is the most prevalent joint disease among peripheral and axial joints of human body. Its prevalence is 10 times more in women than men [1]. Main pathologic characteristics of OA are progressive degeneration of joint hyaline cartilage, marginal osteophyte formation and secondary synovitis alterations. The disease starts with mechanical pain. Mechanical pain refers to pains that occur and exacerbate through working and relieve through resting. Joint stiffness and limited range of motion are the secondary symptoms which occur several years later. In more cute cases, muscles around joints may be subjected to atrophy [2]. Ahlback has classified knee OA intensity into six grades based on radiographical signs. The classification of OA of the knee based on the radiographical signs (by Ahlback) is graded into six levels: Grade 0: Lack of radiographic signs. Grade 1: Decreasing joint space to lesser than 3 mm with or without subchondral sclerosis. Grade 2: Loss of joint space. Grade 3: Destruction or loss of a part of bone smaller than 5 mm. Grade 4: Destruction or loss of a part of bone between 5-10 mm. Grade 5: Destruction or loss of a part of bone more than 10 mm which usually is accompanied with inflammation or joint dislocation.

There are proper protective treatments to treat knee osteoarthritis which varies in terms of injury severity: health advices on how to use joints, physiotherapy exercises, nonsteroidal antiinflammatory drugs (NSAIDs), intra-articular injection, walking aids and finally if the protective treatments failed to treat the injury, surgery (replacing the entire or a part of the damaged joint) is one of few options for treating knee OA [3]. Different methods are used in physiotherapy program of such patients. In the recent years, APS (action potential stimulation) has been used increasingly as a useful method. Since it does not stimulate skin and senses, APS (action potential stimulation) is offered as a good treatment for curing pain. This modality brings about its useful effects through improving blood circulation and extracting the painful metabolites from locus of pain [4].

Equipments which are capable to produce action potential stimulation waves can produce various low-frequency currents special for APS (action potential stimulation). Such current are different in terms of period and intensity. Generally, three important types of action...
APS (action potential stimulation) waves have been introduced for medical applications. In one type, the painful locus is stimulated with a current equal to sensation threshold for 16 minutes, in another type the placebo effect of electrical stimulation without any current is applied, and in the third type, a current set to the highest bearable intensity is applied to the locus of pain [5].

In 1995, Zizic et al. conducted a placebo-controlled trial of pulsed electrical stimulation to assess two main outcomes including the primary outcomes included patient assessment of pain and function and 6 secondary outcomes including range of motion, duration of morning stiffness, knee tenderness, joint swelling, joint circumference, and walking time in patients with knee OA. Pain and function of patients were meaningfully improved, however, no meaningful difference was seen in knee tenderness, swelling and walking time [6].

Berger et al. compared the effects of low-frequency currents (action potential stimulation and placebo, and various types of action potential stimulation and current tense) on knee OA. The results showed that the action potential stimulation is effective to treat patients with knee OA. There was not any meaningful difference between the recovery rate due to transectaneous nerve stimulation (TENS) and APS (action potential stimulation). The study made it obvious that electrotherapy with TENS and APS is helpful to relief pain, nocturnal pain and stiffness caused by knee OA. Likewise, one month after the final therapy session of knee flexibility, the highest recovery rate was observed in the group that has received the highest bearable intensity of action potential stimulation for 8 minutes [5].

Oodendal et al. studied effect of APS on chronic backaches. Eventually, no meaningful difference in terms of recovery rate was found between test and placebo groups. However, some positive results were gained about the goup treated with APS [7]. Van Papendorp et al. studied the effect of action potential stimulation on patients with the chronic pains. Eventually, pain and motion range of patients were improved subjectively and objectively [8]. Seegers et al. examined and approved the effect of direct interrupted currents (frequency: 150 Hz) used to release ATP in healthy individuals [9].

Bunn and Meyers compared the effect of action potential stimulation on patients with OA who have been volunteered for knee arthroplasty and on the placebo. The results showed that in response to action potential stimulation both mornings pain and stiffness were improved meaningfully in the test group in comparison with the placebo [10]. Flenger et al. analyzed the effect of APS on patients with fibromyalgia syndrome. Finally, placebo group showed better results than the APS group. Generally, their study did not find positive and satisfactory results from treating with APS [11].

Regarding high prevalence of osteoarthritis, its long treatment duration and the necessity of introducing nonaggressive and inexpensive for most patients, analysis and determination of proper treatments for this disorder seems necessary. APS is a valid option for alleviating symptoms caused by OA, but the efficiency of its various types is unclear still; thus, the study tries to analyze and find proper method(s) to apply action potential stimulation in knee OA.

**Materials and Methods**

A total of 30 patients with mild to moderate osteoarthritis of the knee were enrolled in this clinical trial. A specialist referred some patients to physiotherapists and their OA range was determined based on Ahlback table. Individuals whose Ahlback rates were determined between grades 1 to 3 were marked as mild to moderate OA patients and after observing other standards were classified as subjects. The qualified people were simply randomized in two 15-person groups. The therapist was aware of the two groups’ difference, but patients were unaware if this, hence, a single-blind controlled clinical trial was executed. The study plan was approved by the Research Ethics Committee (REC).

Having 40-70 years, suffering from primary mild to moderate OA, free from any musculoskeletal disorders in other parts of the body were other quality to include patients in the study. Having injuries other than knee OA or secondary OA, having any systemic disease, being younger than 40 or older than 70 all made patients unqualified to be used in this trial. Also, leaving the study in any stage of the study, any uncontrollable intensification of symptoms let therapists to sack volunteers.

When the patients were divided into two groups, initially their personal profiles including age, gender, height, weight, disease duration, former treatments and radiological signs were recorded. Then, variables of the study were measured and recorded in the questionnaires. Knee pain intensity was set according to the Visual Analogue Scale ten minutes after resting in clinic. The knee flexion and extension ranges were measured by goniometer, time lasted for walking 50 meters in a smooth path, time lasted for ascending and descending three steps were measured with a stopwatch. Knee swelling around patellar top and the possible leg muscle atrophy around 10 cm above patellar base were measured with meter tape. Depending on their pain intensity, patients were allowed to intake NSAIDs and their drug intake amount was being recorded in any step of appraisal.

Variables of the study repeated only one time and were measured and recorded in four stages. A day before beginning treatment process, after fifth therapy session, after tenth therapy session and two weeks after treatment process constituted the appraisal stages. For group 1, initially a hot pack was put on a patient’s knee for 20 minutes. Then, the APS current was set on the patient’s sensation threshold and was applied to his knee for 16 minutes, after that the medical exercise program was begun. Initially, isometric exercises (setting quadriceps femoris muscle) were followed. Then, isotonic exercises including SLR, terminal knee Ext., and progressive resistive exercises with halter were practiced in order to strengthen muscles around knee and leg. The
patients were advised to repeat all exercises three times a day, each 35 times, as they should be 100 exercises during 24 hours. Halter’s weight would be increased to 3 kg, if patients were able to lift them. For group 2, electrodes of the first circuit were placed on the medial and lateral collateral ligaments of knee. One electrode of the second circuit was placed on above the base of patella and the other electrode of this circuit was put behind the knee on the lower part of the popliteal cavity.

The independent t-test was used to analyze and compare data gained from the two groups and the dependent t-test was used to compare data of each single group. p<0.05 was considered meaningful.

Results

Indices (mean, minimum, maximum etc.) pertinent to the demographic variables of the study including age, height, weight, Body Mass Index (BMI) are summarized in table 1.

Table 1. Demographic variables of the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Mean±SD</th>
<th>Group 2</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(year)</td>
<td>60.33±5.61</td>
<td>54.33±8.13</td>
<td></td>
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</tr>
<tr>
<td>Height(cm)</td>
<td>159.40±6.05</td>
<td>160±7.62</td>
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<tr>
<td>Weight(kg)</td>
<td>70.67±10.53</td>
<td>67.60±9.42</td>
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</tr>
<tr>
<td>BMI</td>
<td>27.91±4.44</td>
<td>26.31±2.44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison of changes between two groups: In this stage of study, pain relief degree, muscular atrophy, increased knee flexion, decreased swelling, decreased time to pass 50 smooth path, and decreased time to ascend and descend three steps during three appraisal times, but no meaningful difference was found in comparison to the beginning of the study.

Comparison of changes in each group: pain intensity was analyzed between 1-2, 2-3, and 1-4 times which showed a meaningful reduction, but it did not show any meaningful change between 3-4 times in all groups (table 2).

Table 2. Pain alleviation degree in four appraisals in all studied groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Two comparison times</th>
<th>Mean deviation</th>
<th>SEM</th>
<th>p-Value</th>
</tr>
</thead>
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<tr>
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<td>1.33</td>
<td>0.349</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>2.00</td>
<td>0.349</td>
<td>0.0001</td>
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<tr>
<td></td>
<td>3-4</td>
<td>0.67</td>
<td>0.349</td>
<td>0.239</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>4.00</td>
<td>0.349</td>
<td>0.0001</td>
</tr>
<tr>
<td>2</td>
<td>1-2</td>
<td>1.53</td>
<td>0.365</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>1.13</td>
<td>0.365</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>0.33</td>
<td>0.365</td>
<td>0.786</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>3.00</td>
<td>0.365</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Discussion

Comparing pain intensity, swelling degree and function in the two groups did not show any meaningful difference. Oostendorf et al. compared APS in test and placebo groups for treating the chronic backache and reported similar changes for both test and placebo groups [8]. Oosterhof et al. examined the effect of tense and placebo on OA symptoms (pain and function) and found no meaningful difference [12], so their report verifies the results of our studies. Guerreiro et al. reported that tense, interferential and action potential stimulation do not reduce the superficial sense of normal people, thus, they would not be able to relieve pain [12]. However, Fengler et al. examined the effect of action potential examination and placebo on patients with fibromyalgia, as a result more improving was seen for the placebo group [11] which is in contradiction with the results of this study. The contradiction would be due to different diseases of subjects of two studies. Since, patients with fibromyalgia suffer from very low stimulation threshold, they irritate by stimulation with very low thresholds, so it is expected that they will enjoy the placebo stimulation. While patients with mild to moderate knee OA enjoy normal stimulation threshold, so the difference between patients with fibromyalgia and knee OA in terms of stimulation range seems logical.

Pain intensity of members of the two groups was analyzed among various times which showed a meaningful reduction. Comparing pain intensity between third and fourth times indicated no significant reduction which it verified the sustainability of the medical program. Akbari and Forough, Berger et al. reported sustainable signs one month after termination of therapy [4, 5]. Van Papendorp et al. reported a positive effect of the action potential stimulation on the chronic neck pain [8]. Akbari and Forough reported positive effect of action potential stimulation on knee pain [4]. Pyszora et al. reported the positive effect of action potential stimulation on chronic pain [14]. Johnson et al. introduced the electrical stimulation as a proper treatment to heal musculoskeletal pains [2]. Similarly, the results of this study are in accordance with the report of Zizic et al, Hamilton, McMahon, Seegers et al., Van Papendorp et al., Bunn and Meyers. The mentioned studies have attributed the analgesic effects of APS to increased secretion of beta-endorphins and leu- enkephalin and improved ATP releasing by individuals [6, 9, 10, 15, 16].

Leg muscle atrophy was examined through various times, but no meaningful difference was seen in the two groups. Since subjects started to practice strengthening exercises designed for muscles around knee, particularly quadriceps femoris muscle, since the first session, it was expected that at the end of therapy sessions, leg diameter to be increased about 10 cm above the patella, but not only it was not increased but also for both groups some reduction was observed between first and second times of examination which is normal physiologically, because during the two first weeks of exercising, the muscles feed mainly on the fat resource of its bulk, hence its diameter will be declined over time and the function will be improved because of motion control (improving synapse settings) and in the case of continuing exercises the muscular hypertrophy will be started 4 weeks after beginning exercises [17]. Knee swelling alleviation around the patellar top region was examined between first
and fourth appraisals for group 1 and also between first and second appraisals for group 1 and 2, which the difference was meaningful. Improved swelling mainly may be attributed to the medical exercises and decreased applied load on knee as the result of teaching the proper manner of using a knee suffered from arthritis, which was practiced similarly in both groups. The meaningful results of this examination would be due to different knee swellings in subjects of the two groups upon enrolling in the study.

For group 1, the knee flexion motion range was compared between first and fourth appraisals which were meaningful, but it was not the case for group 2. Maybe the difference can be attributed to the limited motion of subjects upon enrolling in the study. Van Papendorp et al. reported the positive effect of action potential stimulation on motion [16]. Knee extension range and decrease drug intake dose did not show any significant difference during four various appraisals. It can be due to the limited extension motion range when subject enrolled for the study and also low dependency of patients with mild to moderate OA on drugs which no significant change was seen during treatment period.

Two other variables, i.e. time to ascend and descend three steps and time to pass 50 m smooth path showed meaningful differences throughout treatment sessions which can be due to relieved pain, swelling, improved range of motion which have been followed by the improved function. Akbari and Forough [4], Berger et al. [5], and Zizic et al. examined test and placebo groups with electrical stimulation reported improved function of their patients during treatment up to one month after that which are parallel with our results. However, it is not rational to attribute all positive development to the action potential stimulation because, instructing proper methods of using knees during different tasks and the medical exercise program are effective to improve patients. Finding qualified subjects during a certain period of time was one of hindrances of the study.

With regard to the results of the study, it seems that various types of action potential stimulation play similar roles in alleviating symptoms and improving function of patients with the mild to moderate knee OA, thus, applying any type of such treatments along with other non-drug treatments can be effective in improving such patients.

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Author contributions

Razieh Sepehri: research project conception, organization and execution; manuscript writing (writing the first draft).
Mohammad Akbari: research project conception, organization and execution; statistical analysis design and execution; manuscript writing (writing the first draft and making subsequent revisions).

Conflict of Interest

No conflict.

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