

# **Effect of Dextrose Prolotherapy on Pain Intensity, Disability and Plantar Fascia Thickness in Unilateral Plantar Fasciitis: A Randomized, Controlled, Double-Blind Study**

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## Abstract

**Objective:** To evaluate the efficacy of dextrose prolotherapy in the treatment of chronic resistant plantar fasciitis (PF) through comparison with a control group.

**Design:** In this double-blind, randomized, controlled study, the patients were divided into two groups. The prolotherapy group (n=30) was administered 5 cc 30% dextrose, 4 cc saline, 1cc 2% lidocaine mixture (15% dextrose solution) and the control group was given 9 cc saline and 1 cc 2% lidocaine mixture twice at a three-week interval. During the fifteen-week follow-up period, pain intensity was measured using the visual analog scale during activity (VAS-A) and at rest (VAS-R). The foot function index (FFI) was used to measure pain and disability. The plantar fascia thickness was measured by ultrasonography. The measurements were undertaken before treatment and at post-treatment weeks 7 and 15.

**Results:** Improvements in VAS-A, VAS-R, FFI (all subgroups), and plantar fascia thickness measured at the 7th and 15th weeks were significantly higher in the prolotherapy group compared to the control group ( $p > 0.001$ ).

**Conclusion:** Dextrose prolotherapy has efficacy up to 15 weeks and can be used as an alternative method in the treatment of chronic resistant PF.

**Keywords:** dextrose prolotherapy, plantar fasciitis, plantar fascia thickness

**What is Known** Dextrose prolotherapy is a reproducible, inexpensive, safe treatment method and its efficacy has been demonstrated in randomized controlled trials on various tendinopathies. But there was no randomized controlled trial on plantar fasciitis.

**What is New** This randomized-controlled study indicated that effective both clinically and ultrasonographically in the treatment of PF up to 15 weeks.

## **Introduction**

The plantar fascia is an important anatomical structure supporting the longitudinal arch of the foot. The tendinopathy of the insertion of the plantar fascia is called plantar fasciitis (PF), which is the most common cause of heel pain<sup>1</sup>. Mechanical overload and excessive use cause micro tears in the fascia, which initiates the inflammatory process<sup>2</sup>. In PF, the degenerative process is more prominent than the inflammatory process. Over time, PF can cause a calcaneal spur, an additional bony outgrowth in the calcaneus<sup>3,4</sup>. Diagnosis of PF is often made based on patient history and clinical findings, and imaging methods may also be required, albeit rarely<sup>4</sup>. Ultrasonography (US) can be used to support the diagnosis or exclude other pathologies in resistant PF. A plantar fascia thickness of >4 mm and the presence of hypoechogenicity support the PF diagnosis. US is employed for the diagnosis of PF, disease monitoring, and post-intervention follow-up<sup>5,6</sup>.

The first approach in the treatment of PF is conservative treatments, including stretching exercises, non-steroidal anti-inflammatory drugs, arch support, night splints, physical therapy, extracorporeal shockwave therapy (ESWT), and injections<sup>7,8</sup>. As an injection therapy, corticosteroids are the most common and oldest treatment method. Corticosteroid injections are effective for the treatment of PF in the short term, but their long-term effects remain uncertain<sup>9</sup>.

Other injection methods include platelet-rich-plasma (PRP) therapy, administration of botulinum toxin, acupuncture, dry needling, and prolotherapy<sup>10</sup>.

Prolotherapy is a treatment method used especially for the degenerative diseases of the musculoskeletal system and damage due to muscle overuse. The efficacy of prolotherapy has been demonstrated in randomized controlled trials on various tendinopathies, such as those of the common extensor, rotator cuff, patellar and Achilles tendons<sup>11</sup>. However, to the best of our knowledge, there are only two studies on dextrose prolotherapy in PF<sup>12,13</sup>. Although the results of these studies support the efficacy of dextrose prolotherapy in the treatment of PF, there is a need for randomized controlled trials to confirm this efficacy. Therefore, this study aimed to evaluate the efficacy of dextrose prolotherapy by comparing the results of the PF group with the control group both clinically and ultrasonographically.

## **Methods**

### ***Study design and subjects***

This study was planned as a prospective, single-center, double-blind, randomized, controlled, parallel-group trial. Ethics committee approval was obtained in accordance with the Helsinki Declaration (Ankara Numune Training and Research Hospital, approval number: E171615). In addition, the trial was registered with the Clinical Trials Registry (number: NCT03731897). This study conforms to all CONSORT guidelines and reports the required information accordingly (see Supplemental Checklist, Supplemental Digital Content 1, <http://links.lww.com/PHM/A900>).

Written and verbal informed consent was obtained from all patients. The inclusion criteria were as follows: (1) being 18 years of age or older, (2) having unilateral resistant hell pain for at least six months, (3) having undergone non-steroidal anti-inflammatory therapy at least one month,

exercise therapy and arch support among conservative treatments but with no desired outcome, (4) morning pain measured by the visual analog scale (VAS) being above 5, (5) the plantar fascia thickness measured by ultrasonography being >4 mm, and (6) providing informed consent. The exclusion criteria were: (1) bilateral PF, (2) the presence of other diseases of the foot or ankle (arthritis, old or new fractures, tarsal tunnel syndrome, etc.), (3) history of surgical treatment for PF, (4) having received steroid injections for PF within the last six months, (5) having undergone oral non-steroidal anti-inflammatory therapy in the last week, (6) the presence of chronic pain syndromes, (7) being diagnosed with diabetes mellitus, rheumatologic disease, central neurologic diseases (epilepsy, cerebrovascular disease etc.) or mental disorders causing lack of insight and judgment (schizophrenia spectrum and other psychotic disorders, bipolar and related disorders etc.) (8) the presence of peripheral vascular disease or peripheral neuropathy related to the lower extremities, (9) having a disorder or using medication that impairs the bleeding profile, and (10) the presence of infection at the injection site.

The estimated sample size was calculated using G\*Power 3.0.10 (University of Kiel, Kiel, Germany) based on the foot function index (FFI) total score as described by Kim et al.<sup>13</sup>. In order for the study to accurately reveal the differences between the study and control groups, it was determined that 29 patients were required for each group with 5% type 1 error level and 80% power. In the study, 84 patients diagnosed with PF were initially evaluated, and after clinical and ultrasonographic assessments, 65 cases were randomized into two groups: Group 1 (control) and Group 2 (prolotherapy). Randomization was performed by a blinded clinician following simple randomization procedures (computerized random numbers). A random sequence was generated using Excel 2007 (Microsoft, Redmond, WA, USA)

### ***Interventions***

A 10 cc solution (15% dextrose solution) consisting of 5 cc 30% dextrose, 4 cc saline (0.9% NaCl) and 1 cc 2% lidocaine was prepared for the prolotherapy group, and a 10 cc solution containing the combination of 9 cc saline (0.9% NaCl) and 1 cc 2% lidocaine for the control group. Both solutions were of the same color and quantity and administered by the same independent blinded clinician. The application was carried out with palpation guidance by drilling the fascia five times using the peppering technique after providing aseptic conditions with a 22-gauge needle<sup>13</sup>. The injection sites were where the plantar fascia was attached to the metatarsal bones (top of the first and fifth bones) and where it was attached to the heel (medial and lateral), and the midpoint of the plantar fascia. 1 ml of solution was injected into each injection site (total injected solution: 5ml). The injections were performed twice at a three-week interval. The patients were asked not to perform heavy activities or use painkillers other than paracetamol for 72 hours after the injection.

### ***Outcome measures***

All patients were evaluated clinically and ultrasonographically before treatment and at post-treatment weeks 7 weeks (four weeks after the second injection) and 15 (12 weeks after the second injection). The clinical evaluation was performed by the same clinician independent of treatment and ultrasonographic measurements. VAS, a Likert-type scale to measure pain intensity with a score ranging from 0 (no pain) to 10 (most severe pain), was administered to the patients at the post-treatment 7<sup>th</sup> and 15<sup>th</sup> weeks. All patients were asked to indicate the intensity of pain they experienced during activity (VAS-A) and at rest (VAS-R)<sup>12</sup>.

In addition, FFI, a functional index developed for foot diseases, was evaluated for all patients. This instrument contains 23 questions presented in three subscales: pain (nine questions), disability (nine questions), and activity limitation (5 questions). The patient is asked to respond to each item based on a scale of 0 (no pain or difficulty) to 10 (worst pain or most difficulty). The higher the score, the greater the pain and difficulty experienced due to the foot pathology<sup>14</sup>. In the current study, the Turkish version of FFI was used. The validity and reliability study of the Turkish version of FFI was previously undertaken<sup>15</sup>.

All ultrasonographic measurements were performed by the same clinician who had more than five years of musculoskeletal US experience using a 7-12 MHz linear array probe (General Electric, Logic P5, United States), independent of treatment and clinical evaluations. For the US measurements, the patients were placed in the prone position with the ankle in the neutral position. The probe was longitudinally placed on the sole of the foot. The point where the plantar fascia passes in front of the inferior border of the calcaneus was taken as reference. The vertical thickness of the plantar fascia was measured as previously described<sup>16</sup> (figure 1). Each measurement was repeated three times and averaged. The US measurements were undertaken at the same time of day (from 9 to 10 a.m.).

### ***Statistical Analysis***

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS version 23.0, IBM, Armonk, NY, USA). The normality of distribution was evaluated using visual and statistical methods. For the intra-group follow-up assessment, the repeated measures test and paired samples t-tests were applied in the presence of normal distribution. For non-normally distributed variables, the Friedman and Wilcoxon signed-rank tests were conducted. In addition, for the comparison of paired groups, the independent samples t-test

(normal distribution) and the Mann-Whitney U test (non-normal distribution) were employed for the quantitative data. The Pearson chi-square test was used to test the differences in rates. Significance was accepted as  $p < 0.05$ .

## Results

Figure 2 presents the Consolidated Standards of Reporting Trials (CONSORT) diagram showing patient participation and continuity. The study was completed with a total of 60 patients, 30 in the prolotherapy group and 30 in the control group. There was no difference between the demographic data of the two groups ( $p > 0.05$ ) (Table 1). The median values of symptom duration were 7 (6-12) months in both groups ( $p > 0.05$ ). All patients had previously received oral and local non-steroidal anti-inflammatory therapy, arch support, and exercise therapy. One patient in the control group and two patients in the prolotherapy group had previously received ESWT. There was no significant difference between the groups in terms of the treatments they had previously undergone ( $p > 0.05$ ).

No statistically significant difference was observed between the groups in terms of pre-treatment clinical parameters ( $p > 0.05$ ). The results of comparisons revealed that the VAS-A, VAS-R and FFI values were significantly improved within both the control and prolotherapy groups ( $p < 0.001$ ), the improvement in the prolotherapy group was significantly higher than in the control group ( $p < 0.001$ ). The details of clinical improvement are given in Table 2.

The plantar fascia thickness measured by US before treatment did not significantly differ between the prolotherapy and control groups ( $p > 0.05$ ). For both groups, the intra-group improvement in plantar fascia thickness was significant ( $p < 0.001$ ). When the decrease in the

fascia thickness was compared between the groups, it was significantly higher in the prolotherapy group compared to the control group ( $p < 0.001$ ) (Table 3). Furthermore, in the prolotherapy group, by the 7<sup>th</sup> and 15<sup>th</sup> post-treatment weeks, the plantar fascia thickness of the affected and unaffected sides no longer significantly differed ( $p = 0.58$  and  $p = 0.08$ , respectively). In the control group, the facial thickness was still significantly higher at the post-treatment weeks 7 and 15 ( $p < 0.001$ ).

At the post-treatment 7<sup>th</sup> week, the percentage of patients with a VAS-A score of 0 was 46.7 ( $n = 14$ ) in the prolotherapy group and 0 in the control group. At the 15<sup>th</sup> week, there was still no patient in the control group with a VAS-A of 0 while 60% of the patients in the prolotherapy group ( $n = 18$ ) scored 0 ( $p < 0.001$ ). For VAS-R, a score of 0 was observed in 76.6% of the prolotherapy group ( $n = 23$ ) and 13.3% of the controls ( $n = 4$ ) at the 7<sup>th</sup> week while 90% of the former ( $n = 27$ ) but no control scored 0 in VAS-R at the 15<sup>th</sup> week ( $p < 0.001$ ).

The rate of participants with a plantar fascia thickness of  $<4$  mm was 73.3% ( $n = 22$ ) in the prolotherapy group and 23.3% ( $n = 7$ ) in the control group at the 7<sup>th</sup> week and 80% ( $n = 24$ ) and 13.3% ( $n = 4$ ), respectively at the 15<sup>th</sup> week ( $p < 0.001$ ).

No adverse events were observed in either group.

## **Discussion**

This study compared the prolotherapy group that received dextrose + saline + lidocaine and the control group that received saline + lidocaine for the treatment of PF. Both treatments were effective in PF treatment up to 15 weeks. However, the prolotherapy group was found to have

significantly better results at both 7th and 15th weeks in terms of pain intensity, disability, and plantar fascia measurements.

This study indicates a significant reduction in pain intensity both during activity and at rest, measured by VAS after prolotherapy injections. In the literature, an uncontrolled study of 20 patients, the effect of prolotherapy on pain intensity both at rest and during activity was shown. The authors investigated the relief provided by 25% dextrose solution three times at two-week intervals (mean duration 11 months) in cases with resistant PF, and 12 patients (60%) were reported to be completely asymptomatic<sup>12</sup>. In our study, 15% dextrose was applied twice at a three-week interval and clinically tested face-to-face at the 7th and 15th weeks. The improvements in VAS-A and VAS-R scores were significantly better compared to the control group. In addition, at the 15<sup>th</sup> week, the VAS-A and VAS-R scores were found to be 0 in 60% and 90% of the prolotherapy patients, respectively. This result is consistent with the literature and is important for the treatment of PF that severely affects daily life.

In another study comparing the efficacy of PRP and prolotherapy in the treatment of resistant PF, the authors observed improvement in FFI in both groups. They employed a similar method and performed two injections into five areas in the sole of the foot using the peppering technique at two-week intervals. Significant improvement was observed in the FFI total score and all sub-scores at the second and sixth months. However, as limitations of the study, the authors noted that the clinician performing the injection was not independent of the treatment and that the sample size was small<sup>13</sup>. Similarly, in the current study, through prolotherapy injections administered at a three-week interval using the same technique, a significant improvement was observed in the total FFI score, as well as sub-scale scores (pain, disability, and activity limitation). These improvements were superior to the control group. Prolotherapy not only

reduced pain intensity but also improved disability level. In addition, the positive aspects of the current study were that the researchers who administered the injection, performed the clinical evaluation and evaluated US were blinded to the treatment and the sample size was larger.

In this study, in addition to clinical follow-up, ultrasonographic follow-up was performed. In the literature, there are studies using US in the follow-up of PF treatment<sup>17,18</sup>. In a systematic review, it was suggested that US can be used in the diagnosis of PF, as well as in the follow-up of PF treatment<sup>6</sup>. In addition to the favorable clinical findings of the prolotherapy group, their lower plantar fascia thickness compared to the control group showed the efficacy of this therapy ultrasonographically. Furthermore, in the prolotherapy group, the comparison of the affected and intact sides revealed no significant difference at the 7<sup>th</sup> and 15<sup>th</sup> weeks, and the rate of plantar fascia thickness dropped below the PF diagnostic value of 4 mm in 73.3% of these patients at the 7th week, reaching 80% at the 15th week, confirming that prolotherapy is an effective method for the treatment of PF.

Prolotherapy is a regenerative injection therapy and differs from PRP and stem cell injection treatments in that it does not contain biological agents. The effect of prolotherapy on degenerative musculoskeletal diseases is remarkable<sup>19</sup>. The most commonly used prolotherapy agent is hypertonic dextrose, which is an easy-to-prepare, inexpensive and safe solution. When dextrose is introduced around the cells, it causes cellular destruction, resulting in an increase in platelet-derived growth factors, connective tissue growth factor, epithelial growth factor, and complex proteins (cytokines), and consequently leading to a regenerative process<sup>11,12,16,20</sup>. Steroid injections are frequently used for their anti-inflammatory properties in the treatment of PF as an invasive method; however, they are not pathology-based<sup>10-13</sup>. In a systematic Cochrane review, no sufficient evidence was found regarding the long-term efficacy of steroid injections<sup>9</sup>.

Furthermore, in the literature, various adverse events, such as infection, skin atrophy, osteomyelitis of the calcaneus, fascial rupture, and fat pad atrophy have been reported in association with this treatment option. Plantar fascia rupture is a serious adverse effect and has been shown to occur in the range of 2.4-10% after steroid injections<sup>10,21</sup>. While no adverse effects have been reported in the literature concerning dextrose prolotherapy, the most common side effect is increased pain starting from the second day of treatment. Since dextrose is used for its inflammatory effect, rather than an anti-inflammatory agent, paracetamol is prescribed to reduce pain<sup>20</sup>. For the same reason, in the current study, only paracetamol was allowed and no adverse events occurred.

In this study, the improvements in the prolotherapy group were significantly higher than in the control group. However, the control group that received the combination of 9 cc saline and 1 cc 2% lidocaine injection was also observed to significantly improve in terms of intra-group clinical and ultrasonographic parameters, especially at the 7th week. In a PF study comparing PRP, corticosteroid, and placebo groups, Shetty et al. found intra-group improvements in pain intensity and function up to 18 months also in the placebo group in which they used a mixture of 2 ml saline and 1 ml 1% lidocaine<sup>22</sup>. In another study investigating PF injection treatment, the efficacy of PRP and saline treatment was compared. In addition to 3 ml saline or PRP, 5 ml of local anesthetic was prepared and injected into the plantar fascia at 12 points. After the treatment, the control group showed improvement in pain intensity for up to 12 months. The authors attributed this to the fact that they may have triggered an inflammatory process through multiple injections<sup>23</sup>. Similarly, another study using the peppering technique showed improvement in the control group treated with lidocaine alone, but the corticosteroid treatment group using the peppering technique provided better results<sup>24</sup>. Although the exact mechanism has

not yet been elucidated, it is known that *in vivo* platelet activation occurs after contact with thrombin released from tissue collagen through the use of the peppering technique, which may be the trigger of inflammation<sup>13</sup>. In the current study, we attributed the improvements in the control group to the use of multiple injections and the peppering technique in addition to the effect of lidocaine.

The strength of this prospective, randomized, controlled study is that both clinicians and patients were blinded to treatment. The limitations of the study were the short follow-up period (three months) and to not use US guidance during injection.

In conclusion, dextrose prolotherapy was effective in the treatment of PF up to 15 weeks. Based on our results indicating no side effect profile, 60-90% of zero pain intensity, greater improvements in pain, disability and activity compared to the control group, and plantar fascia thickness values being below the PF diagnostic threshold in 80% of the treated cases. Dextrose injection is also reproducible, inexpensive. We consider that dextrose prolotherapy presents as an alternative method for the treatment of chronic resistant PF.

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**Figure 1:** US measures of plantar fascia thickness (A: before treatment; B: at 15<sup>th</sup> week)

**Figure 2.** Consort diagram of study

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**Figure 1**

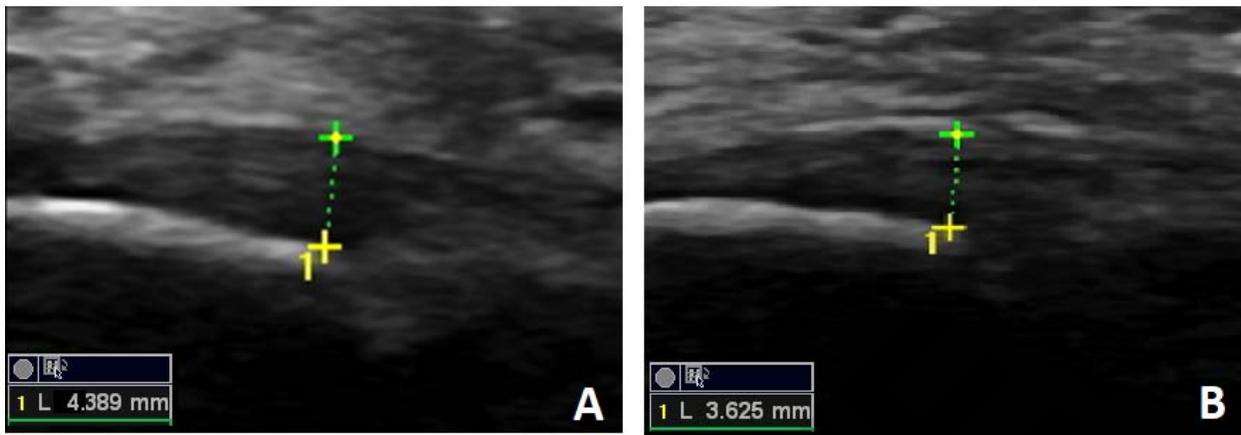
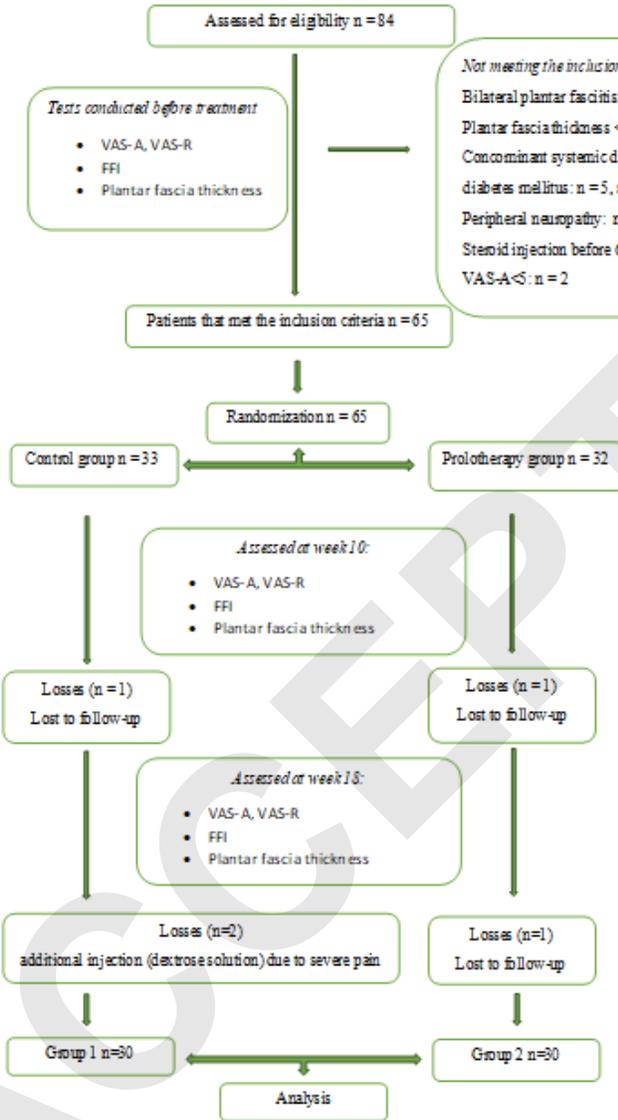


Figure 2

Figure 2. Consort diagram of study



**Table 1:** Comparison of the demographic characteristics of the control and prolotherapy groups.

|                           |                               | <b>Control</b> | <b>Prolotherapy</b> | <b>p<sup>a</sup></b> |
|---------------------------|-------------------------------|----------------|---------------------|----------------------|
| <b>Age</b>                |                               | 46.2 ± 9.6     | 46.7 ± 9.3          | 0.82                 |
| <b>mean ±SD (min-max)</b> |                               | (32 - 64)      | (33 - 64)           |                      |
| <b>BMI</b>                |                               | 29.4 ± 4.8     | 30.8 ± 3.2          | 0.19                 |
| <b>mean ±SD (min-max)</b> |                               | (21.2 – 45.7)  | (26.9 – 37.8)       |                      |
|                           |                               | <b>Control</b> | <b>Prolotherapy</b> | <b>p<sup>b</sup></b> |
| <b>Gender</b>             | Female                        | 23             | 22                  | 0.76                 |
|                           | Male                          | 7              | 8                   |                      |
| <b>Education</b>          | Primary school or none        | 17             | 16                  | 0.95                 |
|                           | Middle school and high school | 9              | 10                  |                      |
|                           | Bachelor's degree and above   | 4              | 4                   |                      |
| <b>Occupation</b>         | Unemployed - Homemaker        | 21             | 22                  | 0.75                 |
|                           | Worker (physical)             | 6              | 4                   |                      |
|                           | Desk job                      | 3              | 4                   |                      |
|                           |                               |                |                     |                      |

*SD: standard deviation, min-max: minimum-maximum, BMI: body mass index, p<sup>a</sup>: Independent simple T test. p<sup>b</sup>: Pearson's chi-square test.*

**Table 2:** Comparison of the clinical data of the groups

|   |               | <b>Control</b>       | <b>Prolotherapy</b>  | <b>p<sup>c</sup></b> | <b>Effect size</b> | <b>Mean difference (95% CI)</b> |
|---|---------------|----------------------|----------------------|----------------------|--------------------|---------------------------------|
| <b>VAS-A Median (IQR)</b>                 | Pre-treatment | 9 (8-10)             | 10 (9-10)            | 0.06                 |                    |                                 |
|   | Week 7        | 5 (4-7)              | 1 (0-3)              | <0.001               | 2.41               | -4.5(-5.4/-3.5)                 |
|   | Week 15       | 6 (4-8)              | 0 (0-2)              | <0.001               | 2.94               | -5.4(-6.3/-4.4)                 |
| <b>p<sup>a</sup></b>                      |               | <0.001 (1>2=3)       | <0.001 (1>2=3)       |                      |                    |                                 |
| <b>VAS-R Median (IQR)</b>                 | Pre-treatment | 7 (6-7)              | 7 (6-8)              | 0,47                 |                    |                                 |
|   | Week 7        | 3 (2-4)              | 0 (0-1)              | <0.001               | 1.66               | -2.6(-3.4/-1.8)                 |
|   | Week 15       | 3 (2-5)              | 0 (0-1)              | <0.001               | 2.11               | -3.2(-4.0/-2.4)                 |
| <b>p<sup>a</sup></b>                      |               | <0.001 (1>2=3)       | <0.001 (1>2=3)       |                      |                    |                                 |
|   |               | <b>Control</b>       | <b>Prolotherapy</b>  | <b>p<sup>d</sup></b> | <b>Effect size</b> | <b>Mean difference (95% CI)</b> |
| <b>FFI-pain Mean ± SD (min-max)</b>       | Pre-treatment | 87.7 ± 17.1 (36-100) | 88.7 ± 10.9 (70-100) | 0.78                 |                    |                                 |
|   | Week 7        | 52.2 ± 24.3 (12-88)  | 11.4 ± 14.5 (0-56)   | <0.001               | 2.09               | -41.8(-52.1/-31.4)              |
|   | Week 15       | 54.5 ± 22.2 (25-89)  | 8.2 ± 12.3 (0-46)    | <0.001               | 2.48               | -47.2(-57.0/-37.4)              |
| <b>p<sup>b</sup></b>                      |               | <0.001 (1>2=3)       | <0.001 (1>2>3)       |                      |                    |                                 |
| <b>FFI-disability Mean ± SD (min-max)</b> | Pre-treatment | 81.7 ± 16.3 (55-100) | 88.2 ± 11.1 (56-100) | 0.08                 |                    |                                 |
|   | Week 7        | 52.1 ± 23.8 (12-84)  | 7.4 ± 12.9 (0-45)    | <0.001               | 2.91               | -51.1(-60.1/-42.0)              |
|   | Week 15       | 53.1 ± 22.8 (14-90)  | 5.6 ± 10.2 (0-36)    | <0.001               | 3.09               | -53.9(-63.0/-44.9)              |
| <b>p<sup>b</sup></b>                      |               | <0.001 (1>2=3)       | <0.001 (1>2>3)       |                      |                    |                                 |
| <b>FFI-activity Mean ± SD</b>             | Pre-treatment | 23.3 ± 11.3 (2-46)   | 28.0 ± 14.5 (2-60)   | 0.17                 |                    |                                 |

|                      |               |                       |                      |        |      |                      |
|----------------------|---------------|-----------------------|----------------------|--------|------|----------------------|
| <b>(min-max)</b>     | Week 7        | 9.7 ± 8.2 (0-30)      | 1.2 ± 2.8 (0-10)     | <0.001 | 1.18 | -13.1(-18.9/-7.3)    |
|                      | Week 15       | 10.5 ± 7.74 (0-30)    | 0.5 ± 2.0 (0-8)      | <0.001 | 1.25 | -14.6(-20.7/-8.5)    |
| <b>p<sup>b</sup></b> |               | <0.001 (1>3>2)        | <0.001 (1>2=3)       |        |      |                      |
| <b>FFI-total</b>     | Pre-treatment | 190 ± 38.6 (103-246)  | 202 ± 32.4 (131-260) | 0.18   |      |                      |
| <b>(min-max)</b>     | Week 7        | 113.4 ± 50.8 (26-187) | 20.1 ± 28.9 (0-103)  | <0.001 | 2.61 | -105.6(-126.4/-84.7) |
|                      | Week 15       | 118.9 ± 47.6 (46-192) | 14.4 ± 23.1 (0-82)   | <0.001 | 3.04 | -116.7(-136.5/-96.9) |
| <b>p<sup>b</sup></b> |               | <0.001 (1>2=3)        | <0.001 (1>2=3)       |        |      |                      |

*IQR: interquartile range, SD: standard deviation, min-max: minimum-maximum, CI: confidence interval, VAS-A: visual analog scale-activity, VAS-R: visual analog scale-rest, FFI: foot function index. p<sup>a</sup>: Friedman's test. p<sup>b</sup>: Repeated measures test. p<sup>c</sup>: Mann Whitney U test. P<sup>d</sup>: Independent sample t-test*

**Table 3:** Measurements and comparison of US plantar fascia thickness

|                     |                        |                          | Control                  | Prolotherapy             | p <sup>b</sup>           | Effect size         | Mean difference (%95 CI) |
|---------------------|------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------|--------------------------|
| <b>PF thickness</b> | <i>Unaffected side</i> |                          | 3.5 ± 0.4<br>(2.8 - 4.2) | 3,7 ± 0.3<br>(2.8 - 4.2) | 0.06                     |                     |                          |
|                     |                        | <i>Affected side</i>     | Pre-treatment            | 5.0 ± 0.6<br>(4.1 - 6.1) | 5.1 ± 0.7<br>(4.2 - 6.7) | 0.57                |                          |
|                     | Week 7                 |                          | 4.4 ± 0.5<br>(3.7 - 5.9) | 3.7 ± 0.2<br>(3.3 - 4.2) | <0.001                   | 1.19                | -0.74 (-1.07/-0.41)      |
|                     | Week 15                | 4.5 ± 0.5<br>(3.9 - 5.8) | 3.5 ± 0.3<br>(3.1 - 4.2) | <0.001                   | 1.69                     | -1.04 (-1.35/-0.73) |                          |
|                     | <b>p<sup>a</sup></b>   |                          | <0.001<br>(1>3>2)        | <0.001<br>(1>2>3)        |                          |                     |                          |

*PF: plantar fascia SD: standard deviation, min-max: minimum-maximum, CI: confidence interval. p<sup>a</sup>: Repeated measures test. p<sup>b</sup>: Independent sample t-test.*