

# Local ozone (O<sub>2</sub>–O<sub>3</sub>) versus corticosteroid injection efficacy in plantar fasciitis treatment: a double-blinded RCT

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**Purpose:** To compare the efficacy of local ozone injection versus corticosteroid in plantar fasciopathy treatment.

**Patients and methods:** This double-blinded randomized trial was performed on 44 adult patients with plantar fasciopathy. One group (23 patients) received local injection of 40 mg methylprednisolone, while a local injection of 3 cc oxygen-ozone solution was performed for the other group (21 subjects). Severity of pain, functional level, and pressure-pain threshold (PPT) were measured before treatment and 1, 4, and 12 weeks after injection using VAS, Foot and Ankle Ability Measure (FAAM) questionnaire, and algometer for PPT, respectively.

**Results:** The majority (65.9%) of the total 44 patients analyzed, were women. Both treatments efficiently relieved patients' pain and improved their functions at 1 and 3 months follow-up time-points. But one week after injection, the improvement in VAS ( $p<0.001$ ) and FAAM ( $p<0.001$ ) was significant only in the corticosteroid group. During the first month, VAS ( $p=0.35$ ) and PPT ( $p=0.003$ ) were still better in the corticosteroid group. However, FAAM revealed no remarkable difference between the two groups ( $p=0.083$ ). Eventually, at the third month of follow-up, there was no remarkable preference between the treatments regarding any of the outcome measures ( $p>0.05$ ). Nevertheless, both methods efficiently improved patients' symptoms, ie, over the 50% of pain reduction and 30% improvement in functional status.

**Conclusion:** The present results showed no remarkable superiority between the two groups. In other words, although ozone injection showed a slower efficacy than methylprednisolone, it could be used in plantar fasciitis management as an appropriate alternative.

**Keywords:** plantar fasciopathy, ozone, steroids, heel

## Introduction

Plantar fascia, as a thick fibrous sheet, supports the longitudinal arch of the foot and acts as a powerful shock absorber.<sup>1,2</sup> The inflammation of this fascia is called “plantar fasciitis” or more recently plantar fasciopathy, which is usually accompanied by heel spurs resulting from deposition of calcium with tension and inflammation of the attachment site to the calcaneus.<sup>3</sup> Although the definite pathology is still unknown, some probable etiologies include repetitive microtrauma, degeneration, chronic inflammation, prominent heel spurs, entrapment of lateral plantar nerve, overuse, and seronegative arthritis-induced inflammation. It is primarily diagnosed based on symptoms of worsening pain upon morning arising and after long periods of sitting, plus signs

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of point tenderness in the origin of the fascia and increased pain with passive stretching of the plantar fascia.<sup>4–13</sup>

Plantar fasciopathy is the most common cause of heel pain,<sup>14</sup> with a 7–10% lifetime incidence.<sup>15</sup> Despite being self-limiting, its spontaneous resolution takes quite a long time and it significantly affects health-related quality of life.<sup>16</sup> There are several common first-line treatments for this condition, including NSAIDs, night splinting, and therapeutic exercise. Some less common non-invasive methods such as extracorporeal shock wave therapy and platelet-rich plasma (PRP) injection have also been utilized which lack sufficient evidence for routine use.<sup>17,18</sup> Injection of corticosteroid is also a popular treatment.<sup>19,20</sup> It should be noted that although corticosteroid injection can induce a remarkable symptom relief in plantar fasciopathy, might result in a number of complications, including rupture in plantar fascia or local fat-pad atrophy.<sup>21</sup>

A more recent therapeutic option is ozone injection which is now available as a solution of O<sub>2</sub>–O<sub>3</sub>. Its precise mechanism is not well understood. However, it may contribute to reduction of inflammation and pain, namely by downregulation of tumor necrosis factor  $\alpha$  and TNFR2, and blocking phosphodiesterase-A2.<sup>22–27</sup> It has previously been proven to be effective in the management of knee osteoarthritis, myofascial pain syndrome (MPS), and several other conditions.<sup>28–30</sup> To the best of our knowledge,<sup>31–35</sup> except for one article,<sup>31</sup> there are no prospective studies comparing the efficacy of local steroid injection with ozone for the treatment of plantar fasciopathy. Therefore, in this trial we aimed to compare the efficacy and safety of these two injections added to standard conservative treatments available for plantar fasciopathy.

## Materials and methods

### Participants

This double-blinded randomized controlled trial (RCT) was conducted in physical medicine and rehabilitation clinic of Shahid Modarres and Shohaday-e-Tajrish Hospitals in 2017. The study sample consisted of 44 patients aged 20–65 years with at least 3 months of symptoms that was nonresponsive to first-line conservative therapies, such as foot orthoses, stretching exercises, and oral analgesics. The exclusion criteria were as follows: 1) pregnancy; 2) recent use of oral corticosteroids in the previous 2 weeks, or steroid injection in the site of plantar fascia within 6 months prior to the study; 3) vasovagal syncope, or hemodynamic instability; 4) recent

skin or soft tissue infection at the site of injection; 5) neuropathy or radiculopathy associated with heel pain; 6) history of diabetes mellitus; 7) fracture of the surrounding bones; 8) secondary causes of heel pain such as ankylosing spondylitis, other inflammatory joint diseases, or surgery on plantar fascia; 9) glucose-6-phosphate dehydrogenase (G6PD) deficiency; and 10) use of angiotensin-converting enzyme inhibitors. The latter two were the relative contradiction of ozone injection.

### Study design

According to the Declaration of Helsinki issued by the World Medical Association, investigators received ethics approval from Ethics Committee of Shahid Beheshti University of Medical Sciences (No. IR.SBMU.SM.REC.1395.384). After obtaining a written informed consent, the complete history was taken from each of the participants and full physical examination was performed. Demographic data including age, sex, height, weight, job difficulty level, level of education, and pain chronicity were recorded. Subsequently, patients were randomly divided into two parallel groups using a computer-based software of random number generation. In addition to injection, patients in both groups commonly received usual treatments including foot orthoses, ice massage, and stretching exercises for gastrosoleus muscles. One group of patients received a mixture of 1 mL corticosteroid (40 mg methylprednisolone) and 1 mL 2% lidocaine, while the other group received a mixture of 3 mL ozone gas (15  $\mu$ g/mL) (generated using a Ozonibaric P<sup>®</sup> machine; Sedecal, Spain) mixed with 1 mL of lidocaine 2%. Injections were done in the maximal point of tenderness by a senior physiatrist with 15 years of experience in musculoskeletal injections (the second author, SA. R). Patients, as well as the physicians responsible for performing injections and assessments, were totally blinded to the groups. In other words, the syringes of administered mixture were placed in concealed envelopes by a nurse.

Severity of pain, the impact of pain on patients' function, and pressure-pain threshold (PPT) were measured before the injection and after 1, 4, and 12 weeks by means of VAS, Foot and Ankle Ability Measure (FAAM) questionnaire, and an analog algometer (SM100 Sundoo<sup>®</sup>), respectively. VAS is a visual graphic-rating scale of 0–10 in which 0 indicates no pain and 10 shows the worst pain ever experienced. FAAM questionnaire is a self-report outcome instrument to assess physical function consisting of 29 items. Each item is scored on a 5-point Likert scale (4 to 0) from “4= no

difficulty at all” to “0= unable to do”. Maximum possible score is 116 and the results have been reported in percent. PPT is defined as the minimum force applied which induces pain. The algometer was perpendicularly pressed against the skin with a an increment rate of 1 kg/cm<sup>2</sup> per second until pain was elicited. Measurement was done three times with 30-s intervals in the same location and the average value was recorded. Oral tablets of acetaminophen were prescribed for all patients. Besides, the number of tablets used during 3 months was recorded.

## Data analysis

Statistical analysis of data was performed using SPSS software version 22 (SPSS Inc., Chicago, IL, USA). Chi-square method was used to analyze and compare categorical data between the two groups. Also, Student's *t*-test (independent samples *t*-test) was used for comparing continuous variables between the groups, initially and after each follow-up visit. Lastly, evaluation of post-treatment improvement in comparison to baseline level of variables was done using paired-samples *t*-test and repeated measure design across the follow-up time-points. The two-tailed *p*-value  $p < 0.05$  was considered significant.

## Results

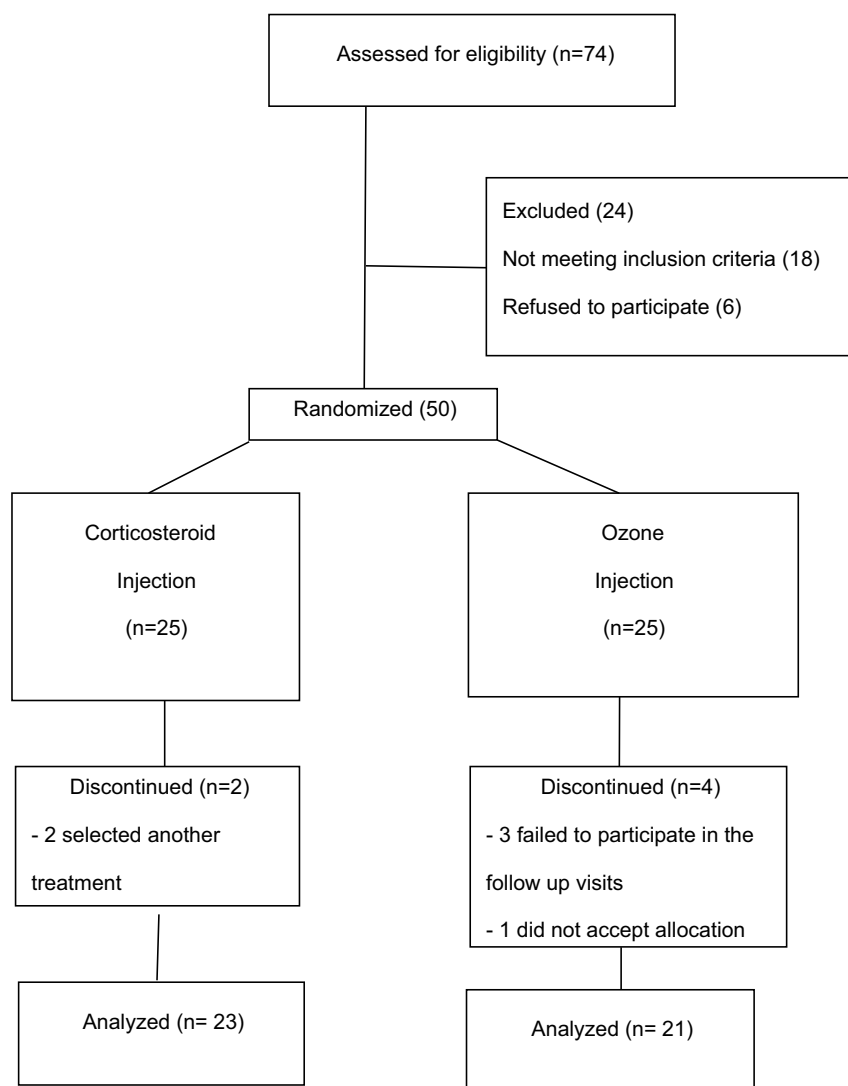
Seventy four patients initially enrolled, among them 50 participants were included in the study. Subjects were randomly divided (using a computer software for random-number generation) into two parallel groups of corticosteroid and ozone injection (25 in each group). However, two patients in the corticosteroid group and four in the ozone group discontinued the study (Figure 1). Two of them decided to receive dextrose prolotherapy, another three subjects failed to participate in the follow-up visits, and one subject asked to receive corticosteroid injection while randomly assigned to the ozone group. Therefore, these six patients received treatment but were excluded from the study. However, none of them exited because of a direct adverse event or other related complications; they were just unsatisfied with the treatment outcome. As a result, collected data from 44 patients including 23 participants in the corticosteroid group and 21 ones in the ozone group were finally analyzed.

The majority of participants, ie, 29 patients (65.9%) were women and 15 subjects (34.1%) were men with a mean age of  $47 \pm 9.0$  years (28–68 years). With regard to job difficulty level, 16 patients (36.4%) had easy jobs (accountant, seller, clerk, manager, etc.); 20 ones (45.4%)

had moderate jobs (teacher, police officer, driver, guard, housewife, etc.); and 8 subjects (18.2%) had difficult jobs (miner, barber, laborer, athletic, etc.). The average body mass index (BMI) calculated as  $\text{weight}/(\text{height})^2$  was  $28.6 \pm 3.2$  kg/m<sup>2</sup> (21.6–36.1 kg/m<sup>2</sup>). Mean duration of pain was  $10.0 \pm 6.4$  months (3–36 months). There was no significant difference between the groups regarding their demographic data, including age, sex, height, weight, BMI, job difficulty, level of education, pain duration, and the number of acetaminophen tablets used within 3 months (Table 1). Thus, the study population had homogeneously been distributed in the groups.

The therapeutic trajectory (within-groups changes) for VAS, PPT, and FAAM scores at the four time-points (before injection, 1, 4, and 12 weeks after treatment) have been demonstrated in Table 2. Also, the inter-group comparisons (Table 3) revealed that VAS was relatively similar before treatment ( $p=0.841$ ); while at the first week and month of follow-up period, it was significantly lower ( $p<0.001$ , and  $p=0.035$ , respectively) in the corticosteroid group, compared to the ozone group. In fact, VAS improvement, according to mean difference (MD) during the first week, was remarkably better following corticosteroid injection ( $\text{MD}=-3.0$ ), compared to ozone injection ( $\text{MD}=0.3$ ) ( $p<0.001$ ). Similarly, VAS changes during the first month were slightly higher in the corticosteroid group but the difference was not clinically important between the groups ( $\text{MD}=-3.9$  for steroid and  $-3.0$  for ozone groups;  $p=0.063$ ). VAS improvement was approximately 58% in both groups during 3 months, without any significant difference ( $p=0.890$ ). Figure 2 demonstrates the therapeutic trajectory at the four time-points, based on VAS improvement in the two groups.

In a similar pattern [Figure 3], PPT was not significantly different between groups before treatment ( $p=0.337$ ). However, it was significantly higher in the corticosteroid group at both the first week and month after injection ( $p=0.019$  and  $p=0.003$ , respectively). Again, at the end of the study, there was not any remarkable difference between groups with regard to their PPT ( $\text{MD}=26.5$  [66%] and  $24.5$  [57%] for corticosteroid and ozone groups, respectively;  $p=0.848$ ). Indeed, PPT changes during the first month after corticosteroid injection were significantly better than ozone injection ( $p<0.001$ ). The therapeutic trajectory on PPT improvement at different time-points has been depicted within the two groups.



**Figure 1** Flowchart of the study population.

Scores of FAAM questionnaire were not significantly different between groups before treatment ( $p=0.393$ ). However, FAAM scores were lower in the corticosteroid group 1 week and 1 month after treatment ( $p<0.001$  and  $p=0.083$ , respectively). However, the difference between groups was statistically significant only after 1 week follow-up. Besides, there was no clinically important difference between the two groups in their total changes from the baseline at the first month visit (MD=-29.4 and -21.7 for corticosteroid and ozone groups, respectively;  $p$ -value=0.041). After 3 months, FAAM score changes were similar between groups (MD=-22.5 [34%] and -17.9 [28%], for corticosteroid and ozone groups, respectively;  $p=0.217$ ). To summarize, Figure 4 has demonstrated FAAM score changes initially and at three follow-up time-points.

## Discussion

The results of this study showed that there was no significant difference between the two groups for VAS, PPT, and FAAM before treatment. However, 1 week after treatment, VAS ( $p<0.001$ ), FAAM ( $p<0.001$ ), and PPT ( $p=0.019$ ) were significantly better in the corticosteroid group compared to the ozone group. One month after treatment, VAS ( $p=0.35$ ) and PPT ( $p=0.003$ ) were still better in the corticosteroid group. However, FAAM was not significantly different between the two groups ( $p=0.083$ ). Eventually, there was no significant difference between groups concerning any of VAS, PPT, or FAAM scores at the third month of follow-up ( $p>0.05$ ).

Few studies have been conducted on the efficacy of ozone injection in chronic inflammatory diseases, and there has been only one previous study,<sup>31</sup> comparing the

**Table 1** Demographic data as compared between the two groups

Variables		Total	Group		p-value
			Corticosteroid	Ozone	
Gender	Male	15 (34.1%)	7 (30.4%)	8 (38.1%)	0.512
	Female	29 (65.9%)	16 (69.6%)	13 (61.9%)	
Job difficulty	Easy	16 (36.4%)	9 (39.1%)	7 (33.3%)	0.954
	Moderate	20 (45.4%)	10 (43.5%)	10 (47.6%)	
	Difficult	8 (18.2%)	4 (17.4%)	4 (19.0%)	
Education	Under diploma	14 (31.8%)	6 (26.1%)	8 (38.1%)	0.419
	Diploma and associate's degree	20 (45.4%)	10 (43.5%)	10 (47.6%)	
	Bachelor's degree or higher	10 (22.7%)	7 (30.4%)	3 (14.3%)	
Age (year)		47.6 (9.0)	47.5 (8.7)	47.7 (9.7)	0.964
Height (m)		1.66 (0.1)	1.64 (0.1)	1.67 (0.1)	0.437
Weight (kg)		78.2 (10.7)	77.0 (10.3)	79.7 (11.2)	0.419
BMI (kg/m <sup>2</sup> )		28.5 (3.2)	28.5 (3.4)	28.6 (3.1)	0.968
Pain duration (months)		10.0 (6.4)	10.2 (7.5)	9.7 (4.9)	0.794
Acetaminophen use (number of tablets)		12.5 (18.0)	11.8 (17.7)	13.2 (18.8)	0.801

**Abbreviation:** BMI, body mass index.

**Table 2** Within-groups comparisons for VAS, PPT, and FAAM scores in four time-points

Change in Variables		Corticosteroid		Ozone	
		Mean (Std. Dev.)	p-value	Mean (Std. Dev.)	p-value
VAS	Before injection – 1 week	–3.0 (1.8)	<0.001	0.3 (1.5)	<b>0.390</b>
	Before injection – 1 month	–3.9 (1.9)	<0.001	–2.9 (1.3)	<0.001
	Before injection – 3 months	–4.2 (1.7)	<0.001	–4.3 (2.0)	<0.001
	After 1 week – 1 month	–0.9 (2.1)	0.045	–3.2 (1.4)	<0.001
	After 1 week – 3 months	–1.2 (1.8)	0.004	–4.6 (2.1)	<0.001
	After 1 month – 3 months	–0.3 (1.8)	<b>0.418</b>	–1.3 (1.7)	0.003
PPT	Before injection – 1 week	13.4 (5.6)	<0.001	3.5 (6.7)	0.028
	Before injection – 1 month	23.4 (9.7)	<0.001	12.3 (7.7)	<0.001
	Before injection – 3 months	26.5 (10.9)	<0.001	24.5 (9.8)	<0.001
	After 1 week – 1 month	10.0 (9.4)	<0.001	8.8 (7.9)	<0.001
	After 1 week – 3 months	13.1 (10.7)	<0.001	20.9 (9.7)	<0.001
	After 1 month – 3 months	3.1 (8.2)	<b>0.080</b>	12.1 (7.3)	<0.001
FAAM	Before injection – 1 week	–17.2 (7.1)	<0.001	2.8 (9.3)	<b>0.190</b>
	Before injection – 1 month	–29.4 (11.1)	<0.001	–21.7 (12.7)	<0.001
	Before injection – 3 months	–22.5 (10.7)	<0.001	–17.9 (13.2)	<0.001
	After 1 week – 1 month	–12.2 (10.7)	<0.001	–24.5 (12.1)	<0.001
	After 1 week – 3 months	–5.3 (11.7)	0.041	–20.7 (12.1)	<0.001
	After 1 month – 3 months	6.9 (12.2)	0.013	3.8 (9.2)	<b>0.080</b>

**Note:** Non-significant p-values have been shown in bold format.

**Abbreviations:** Std. Dev, standard deviation; PPT, pressure-pain threshold; FAAM, Foot Ankle Ability Measure.

effects of local ozone injection versus the corticosteroids for plantar fasciopathy. Therefore, we have firstly compared our results with earlier studies on other treatment methods. McMillan et al evaluated the efficacy of ultrasoundguided injection of 1 mL corticosteroid (dexamethasone sodium

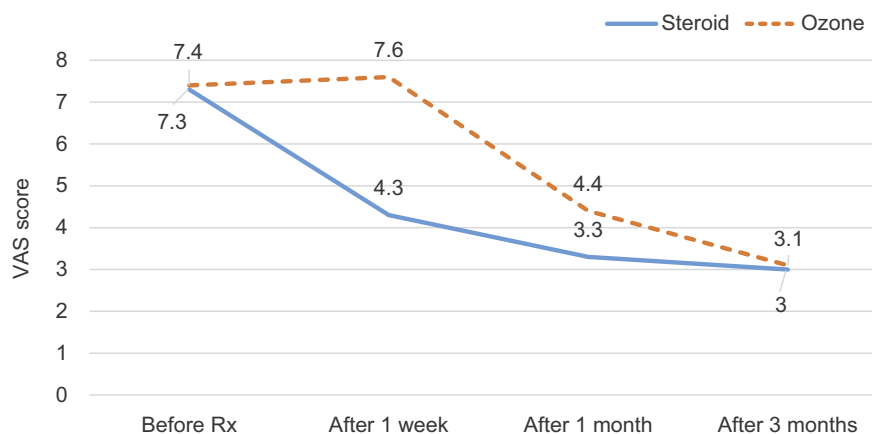
phosphate with dosage 4 mg/mL) versus 1 mL normal saline (placebo), among plantar fasciopathy sufferers. They used the foot health status questionnaire for pain measurement at 4, 8, and 12 weeks.<sup>32</sup> Similar to our study short-term (at 4 weeks) efficacy of corticosteroid was

**Table 3** Between-groups comparisons for VAS, PPT, and FAAM scores in four time-points

Variables		Group		p-value
		Corticosteroid	Ozone	
VAS	Before Injection	7.3 (1.4)	7.4 (1.5)	0.841
	After 1 week	4.3 (1.8)	7.6 (1.5)	<b>&lt;0.001</b>
	After 1 month	3.3 (1.9)	4.4 (1.1)	<b>0.035</b>
	After 3 months	3.0 (1.1)	3.1 (1.5)	0.987
PPT	Before Injection	40.1 (7.6)	42.8 (10.0)	0.337
	After 1 week	53.5 (8.2)	46.3 (10.5)	<b>0.019</b>
	After 1 month	63.5 (9.5)	55.1 (8.0)	<b>0.003</b>
	After 3 months	66.6 (10.8)	67.2 (11.0)	0.848
FAAM	Before Injection	65.5 (7.8)	62.9 (11.4)	0.393
	After 1 week	48.3 (8.3)	65.7 (11.3)	<b>&lt;0.001</b>
	After 1 month	36.0 (9.4)	41.2 (9.5)	0.083
	After 3 months	43.0 (10.1)	45.0 (11.7)	0.546
Change in VAS (mean difference)	After 1 week	-3.0 (1.8)	0.3 (1.5)	<b>&lt;0.001</b>
	After 1 month	-3.9 (2.0)	-3.0 (1.3)	0.063
	After 3 months	-4.2 (1.8)	-4.3 (2.1)	0.890
Change in PPT (mean difference)	After 1 week	13.4 (5.6)	3.6 (6.7)	<b>&lt;0.001</b>
	After 1 month	23.4 (9.7)	12.4 (7.7)	<b>&lt;0.001</b>
	After 3 months	26.5 (10.9)	24.5 (9.8)	0.525
Change in FAAM (mean difference)	After 1 week	-17.2 (7.1)	2.8 (9.3)	<b>&lt;0.001</b>
	After 1 month	-29.4 (11.1)	-21.7 (12.7)	<b>0.041</b>
	After 3 months	-22.5 (10.7)	-17.9 (13.3)	0.217

**Note:** Significant p-values have been shown in bold format.

**Abbreviations:** PPT, pressure-pain threshold; FAAM, Foot Ankle Ability Measure.

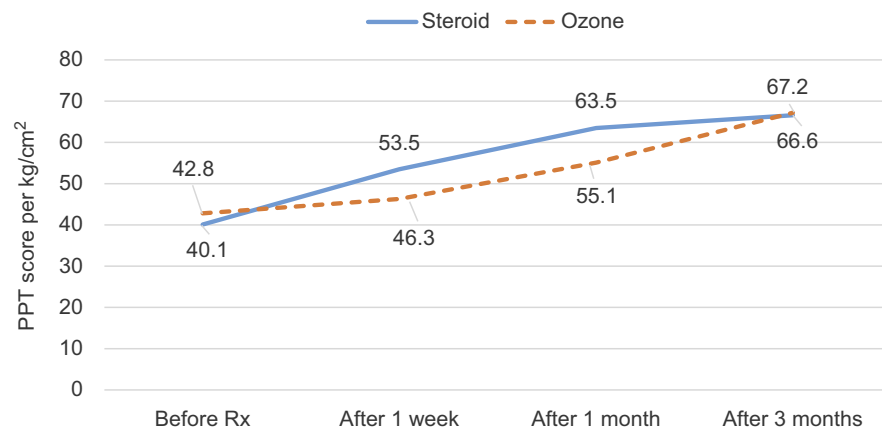
**Figure 2** Therapeutic trajectory based on VAS changes within the two groups.

confirmed, and pain scores were not significantly different between groups after 12 weeks (3 months). However, pain questionnaires, type of corticosteroid, and follow-up intervals utilized in their study were relatively different.

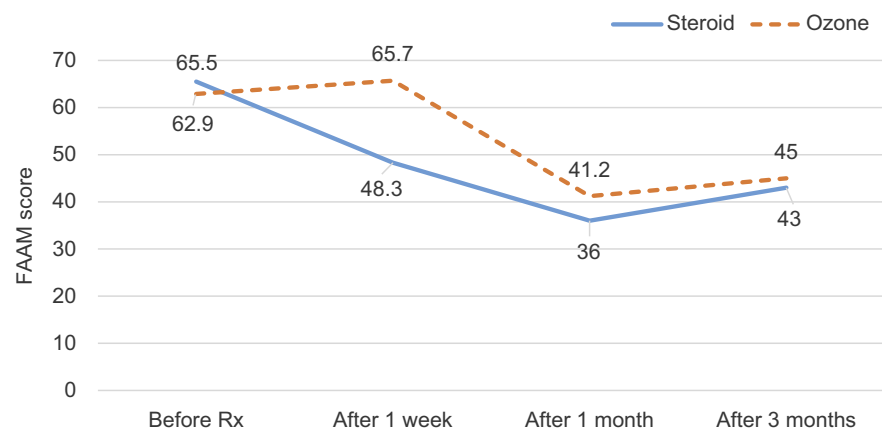
In another study, Karimzadeh et al assessed local injection of autologous whole blood with corticosteroid in the

treatment of plantar fasciopathy.<sup>33</sup> The results were somewhat similar to the present study. The mean value of pain severity (measured by VAS) and average level of PPT in both groups significantly improved during 1 and 3 months after injection. However, the difference between study groups was not statistically significant.





**Figure 3** Therapeutic trajectory based on PPT changes within the two groups.



**Figure 4** Therapeutic trajectory based on FAAM score changes within the two groups.

Mahindra et al compared the effect of PRP versus corticosteroid and placebo in the treatment of chronic plantar fasciopathy.<sup>35</sup> In this study, local injection of PRP was more, or at least as effective as corticosteroid. Both methods were significantly more effective than placebo. Similar to the corticosteroid group of our study, VAS score significantly decreased 3 weeks and 3 months after corticosteroid injection. Functional improvement was also observed with corticosteroid. However, a different functional questionnaire (AOFAS; The American Orthopedic Foot and Ankle Score) was used in their study. While treatment of plantar fasciopathy with ozone has not been studied, some research has been done to evaluate the effect of ozone injection in other musculoskeletal conditions. For instance, ozone has been proved to be effective in pain relief, local inflammation, and systemic inflammation in patients with disc herniation or knee osteoarthritis.<sup>28,36</sup> In another study performed by Morelli et al it was shown that results of ozone therapy

were significantly better than diathermy in the treatment of chronic low back pain.<sup>37</sup> Additionally, the positive effect of ozone therapy on carpal tunnel syndrome, refractory headaches, and MPS has been confirmed.<sup>38,39</sup> A very similar RCT by Babaei-Ghazani et al evaluated two groups of plantar fasciopathy patients with 15 subjects in each group. Participants received either of ozone or corticosteroid injection and were followed during a 3-month period. Finally, authors concluded that both methods were effective in the treatment of chronic fasciopathy patients. They also achieved the same result that steroid injection provided a more rapid and short-term therapeutic effect. On the other hand, they concluded that ozone (O2–O3) injection could be a beneficial option with slow onset and a longer durability.<sup>31</sup> Among their findings, the latter was not supported by the present data. In fact, there was no remarkable difference between ozone and corticosteroid injection durability for any of the outcome measuring tools. In the current investigation, both methods

efficiently improved patients' symptoms; ie, over the 50% of pain reduction and approximately 30% improvement in functional status, without any remarkable superiority between groups.

## Limitations

The first drawback in this research was the absence of a real control group; it would better to recruit a larger sample and assign them into three groups. In addition to the two mentioned groups, we could consider another category receiving only the conservative treatments without any injection. Such a three-arm design could efficiently compare the actual effect size of ozone and corticosteroid injections. As the other limitation, loss to follow-up rate was relatively remarkable (6 patients; 12%) and could potentially result in attrition bias. However, intention to treat analysis was done that revealed no significant difference between the therapeutic trajectory of those participants who discontinued the study with the rest of population at 1 week and 1 month follow-up. In fact, none of them exited because of a direct adverse event or other related complications; they were just unsatisfied with the treatment outcome.

## Conclusion

Our results proved that both groups significantly improved regarding their pain and level of function and PPT. The therapeutic efficacy in corticosteroid effects was more rapid compared to the ozone injection. The results were associated with a better short-term outcome in the corticosteroid group compared to the ozone category (at 1 week and 1 month follow-up), when added to a standard conservative treatment. However, the final outcomes were relatively similar at the third month. Therefore, local injection of ozone, plus the conventional treatments seems to be an appropriate alternative to traditional corticosteroids in plantar fasciopathy management.

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## Disclosure

The authors report no conflicts of interest in this work.

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