INTRODUCTION

Foot involvement is an important problem for people with rheumatoid arthritis. The progression of the foot related symptoms is related to the duration and severity of the disease (1,2). The most frequent problems in the foot are pain increased plantar pressure, and decreased functional capacity which have a negative impact on quality of life and increase the risk of falling (1,3–5). The forefoot is commonly affected, especially the metatarsophalangeal joints (1). Common structural problems include hallux valgus deformity, deformities of the lesser toes, subluxation of the metatarsophalangeal joints, and displacement of the plantar fat-pad (3). One of the most prevalent foot deformities in rheumatoid arthritis patients is rearfoot valgus, which is associated with the presence of other deformities (6).

The prescription of different types of foot orthoses is a common practice for patients with rheumatoid arthritis and foot pain symptoms. This treatment provides greater stabilization of the foot and ankle, which can reduce the risk of developing deformities, alleviate pain and the inflammation, and improve the functioning of the foot (3,5). Furthermore, they have been proven to be a cost-effective intervention (7).

Foot orthoses have been used worldwide, but that of present the trial evidence is insufficient to know whether or not they are helpful. Thus, further research in this area is essential. This study aims at determining the effect of custom-made foot orthoses versus placebo flat cushioning insoles on pain, foot functionality, and quality of life in patients with rheumatoid arthritis.

METHODS

Study design and clinical setting

A randomized controlled clinical trial was carried out according to the CONSORT guidelines (8). The study was registered in the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12616000168459). The study was also approved by the Bioethics Committee of the Government of Andalusia (ID: 20161012141038) and authorized by the Head Office of the Clinical Area of Podiatry of the University of Seville (ID: INV22/15).

The participating patients were recruited from the rheumatology unit of the following hospitals: Virgen de Valme, Virgen del Rocio, and Virgen de Macarena in Seville, as well as Hospital Basico de la Defensa in Ferrol (Galicia, Northern Spain). Participants were also recruited from the following patient associations: LIRA (Andalusian Rheumatologic League), AJEREA (Provincial Spondilitis and Arthritis Association), and ASEPAR (Sevillian Association of Patients with Rheumatoid Arthritis). All the participants gave written consent to be included in the study. The data were gathered in the Clinical Area of Podiatry of the University of Seville and in the Podiatric Clinic of the University of La Coruña. The start date and end date of the study were January 2016 and February 2018, respectively. The University of Seville was responsible for the integrity and conduct of the study. This study was non-funded with the exception of the cost of orthoses materials provided by the universities of Seville and La Coruña. These institutions had no influence in the results.

Inclusion criteria and random allocation

The inclusion criteria were age over 18 years, a diagnosis of rheumatoid arthritis according to the criteria of the American Rheumatism Association and the European League Against Rheumatism of 2010 (9), foot involvement, and no foot orthoses treatment for 30 days prior to the study. Patients were excluded if they had rheumatoid arthritis with acute symptomatic flare, ulcers, skin involvement, neurological problems, cognitive deterioration, or a need for walking assistance. Patients were excluded if they refused to change their footwear to use the foot orthoses.

The participants were randomly assigned to one of the study groups. Group A was the experimental group and were given the custom-made foot orthoses, while group B was the control group and received a placebo treatment. Randomization was conducted by flipping a coin after making the foot orthoses and the placebo insoles. The allocation rule was stated in advance, that is, if the side showing a head was uppermost, the person was allocated to group A. This was done in the presence of, at least, two researchers.

Interventions

Two types of foot orthosis were made by a member of the research team prior to the randomization and for all the participants. The foot orthoses for group A were custom made using phenolic foam molds of the feet. They consisted of a polypropylene layer of 2 mm from heel to just proximal to the metatarsal heads, an upper sheet of 30 Shore A polyethylene foam, a 5-mm 50 Shore A ethyl vinyl acetate stabilizer element in the heel, and a 30 Shore A subdigital crest made of polyethylene foam.

The patients of group B were given a flat placebo insole made of the same material as the upper layer of the foot orthoses used for group A, with the only aim of providing cushioning but not functional control. Both types of foot orthoses were made with the same covering color to reduce the risk of bias. After the final evaluation, the control group received the same type of custom-made foot orthoses given to group A, which were kept throughout the 3 months of the study by the staff of the Clinical Area of Podiatry of the University of Seville, who had no relation with the study.

All participants were blinded since they did not know what types of foot orthoses they were given in the study (intervention or placebo). The only information they were given was that the research would evaluate the effectiveness of the foot orthoses to treat pain in patients with rheumatoid arthritis. This procedure is similar to others previously used by other studies (4). The participants were told that the foot orthoses assigned had to be used seven days a week for a minimum of eight hours per day for 3 months. The researcher who performed the measurements at days 0, 30, 60, and 90 (MRB) was not the same researcher who conducted the randomization, adapted the foot orthoses, and gave them to the participants (SPG or MCVB). Thus, they were also blinded. The clinical variables were measured in person at the beginning (baseline) and via phone calls at days 30, 60, and 90.

Data collected

Clinical and demographic data were collected, including age, gender, weight, height, years of development of the disease, foot pain, foot functionality, foot-related disability, and quality of life. Variables measured were pain, foot functionality, disability, and quality of life.

- Pain was measured using the Visual Analogue Scale (10). It ranges from 0 (no pain) to 10 cm (unbearable pain). Pain days were also recorded as the number of days on which the patient felt foot pain in the previous week by assigning a whole number between 0 and 7.
- Foot functionality was measured using the Foot Function Index (11). It is a questionnaire with 23 items that are divided into three domains: foot pain, disability, and functional limitation. The values range from 0 and 46, with higher values corresponding to greater pain, disability, and limitation.
- Disability related to foot pain was measured using the Manchester Foot Pain and Disability Index(12). The values of this index range from 0 and 100, with higher values corresponding to greater disability.
- The SF-12 questionnaire was used to collect data about the quality of life(13), which has values between 0 and 100 with higher values corresponding to lower quality of life.

Sample size calculation

The minimum sample size was calculated using the following formula to compare mean values between populations:

$$n = \frac{2s^2(z_{\alpha/2} + z_{\beta})}{d^2},$$

where s^2 is the sample variance, α is the type I error, β is the type II error, and d is the minimum difference to be detected. According to previous studies, the variance of the visual analogue scale for pain is equal to 400, and the difference found is 16 (14). Therefore, the following result was obtained:

$$n = \frac{2s^2(z_{\alpha/2} + z_{\beta})}{d^2} = \frac{2 \cdot 400 \cdot (1.96+0.84)^2}{16^2} = 24.5 \rightarrow 25$$

Thus, at least 25 people were needed in each group to compare the mean values. In this study, 68 patients were initially recruited with 34 in each group in consideration of possible losses.

Data analysis

The analysis of the data was carried out using the statistical software IBM SPSS Statistics 22 ® (IBM, Armonk, NY, USA). The descriptive data provided the mean values and the standard deviations or the absolute frequencies and percentages depending on whether the variables were scalar or categorical. Shapiro-Wilk tests were conducted for the inferential analysis to determine the most appropriate test to use. When data showed a normal distribution by groups, a t-test was carried out for independent samples. The Mann-Whitney's U test was used for the independent samples when there was no normal distribution.

Since the study variables were measured four times, the tests were conducted by pairs for related samples as well. The t-test was used if the variables showed a normal distribution in the four measurements, and the Wilcoxon's signed-rank test was used for related samples when they did not show a normal distribution. When statistically

significant differences were found according to the p-value, the effect size was calculated using Cohen's *d* or Rosenthal's *r* to analyze the magnitude of the differences. The differences were classified according to the following for both parameters: below 0.2, no effect; 0.2-0.5, small effect; 0.5-0.8, medium effect; above 0.8, large effect (15,16). The confidence level *a priori* was 95%.

RESULTS

All the participants who had been measured at the four time points (0, 30, 60 and 90 days) were included in the data analysis. Six people were eventually lost in group A with 28 remaining, and 9 people were lost from group B with 25 remaining. Flow diagram with reasons for exclusion and withdrawal is presented in Figure 1.

Demographic data and baseline clinical data across all variables are shown in table 1. The groups were similar in sex distribution, age, body mass, disease duration, Foot Posture Index, and baseline values of pain, disability, and quality of life ($P > 0.05$). The characteristics are relevant since clinical and demographic factors have been reported to have an influence on the outcomes of customized foot orthoses (17).

Table 2 shows all clinical data from all follow-up times. As can be observed, values of all clinical variables, except quality of life (SF-12), got improvement for both groups. However, the only variable that showed significant difference between groups was pain measured with VAS at 90 days ($P = 0.048$; Cohen's $d = 0.557$). Although it must be noted that the difference between pain at baseline and at the last time point of follow-up was 2.5 and 0.56 points in group A and B, respectively.

In order to check whether the two types of interventions provided improvement within groups, the evolution of the clinical variables over time were examined (table 3). As can be observed, custom-made foot orthoses produced greater and faster improvement within group A, than cushioning insoles within group B.

DISCUSSION

The results of this study confirm the published data about the effectiveness of custom-made foot orthoses in rheumatoid arthritis patients since they indicate that the foot orthoses applied in group A produced statistically significant improvement in foot pain. Although there were no significant changes in the remaining clinical variables, in our opinion these findings are important since pain is a frequent symptom in rheumatoid arthritis patients and is strongly related to functionality (17). As rheumatoid arthritis affects around 90% of patients' feet and has been reported to be an important reason for incapacity in these patients (1), using a non-pharmacological treatment could involve a reduction in drug consumption and thus a decrease in side effects with positive effects on quality of life.

Pain was chosen as the main outcome measure in this study because it is the main reason why patients look for treatment (18). This outcome has been widely used in previous studies on the effectiveness of foot orthoses in rheumatoid arthritis (2,4,5,17,19–22). Pain was reduced in both groups. However, group A (custom-made foot orthoses) improved earlier and to a greater extent, demonstrating short-term clinical effectiveness of the foot orthosis as previously reported (21). The only variable that maintained a positive development in the last time point in group B was "foot pain days," whereas the rest of the

variables increased again. The pain improvement in the control group could be due to the cushioning effect derived from the thickness (5 mm) of the insoles since it has been demonstrated that thicker foot orthoses reduce pain more effectively (23). However, custom-made foot orthoses provided not only cushioning but also foot functional control, as they were adapted to a foot cast that reflected better foot posture.

Several clinical trials have shown improvement in foot pain with the use of this type of foot orthoses, which is therefore recommended as an intervention for rheumatoid arthritis patients with foot pain (24). In a sample of 35 patients with rheumatoid arthritis, Cameron-Fides and Santos observed that a standard (not custom-made) foot orthosis reduced the pain and the number of inflamed joints after 6 months of use (25). Other studies observed a similar degree of pain reduction in people wearing orthopedic footwear with cushioned insoles and those wearing this type of footwear with custom-made foot orthoses (26). Magalhaes et al. (22) evaluated a group of rheumatoid arthritis patients using FOs during a 6-month period and found that the foot orthoses significantly reduced pain, disability, and activity limitation. However, as there was no control group, a placebo effect of the FO cannot be ruled out for this particular study.

Moreira et al. (2) reported that a custom-made foot orthosis improved pain, but not functionality or quality of life. They observed that both the intervention and control groups had reduced pain, and the reduction was proportional to the length of time for which the foot orthosis was used. The feet of rheumatoid arthritis patients tend to develop a low medial longitudinal arch and everted hindfoot which may be the reason for the pain related to this disease (1–3).

Regarding disability, in the present work, as in other studies (27,28), it was not found significant differences in disability between groups. However, the disability measured through the Manchester Foot Pain and Disability Index was lower in group A at 90 days of follow-up, and the disability domain of the Foot Function Index was lower at the first measurement. In our opinion, an important finding to highlight in the present study is the positive effect observed in the short term and the consistency of the positive effects of the custom-made foot orthosis. In group B, there was also a significant development between the initial measurement and the measurement at 60 days for the Visual Analogue Scale, foot pain days, disability Foot Function Index, and total Foot Function Index. Nevertheless, the only variable that remained the same at 90 days was foot pain days ($p=0.040$) since the values of the rest of the variables increased. In group A, however, the improvement remained at 90 days. Moreover, the Visual Analogue Scale did not show significant differences between the two groups until the last time point of follow-up. Other studies observed a significant reduction in the foot disability score of the Foot Function Index in participants who used a custom-made foot orthosis for several weeks (4,20,21). In the present study the positive effects in foot disability were observed up to the end of the follow-up period in the patients who received the custom-made foot orthoses.

This study has several limitations. We must mention at least two important ones. First, we had a major degree of drop-outs during the follow-up period, and this may seriously compromise the conclusions; despite this, both groups had the minimum number of participants suggested by the sample size calculation. Second, although participants were randomly allocated to both groups, the process of random allocation might be

considered weak; maybe it would have been better to have had a better method of randomization.

Other limitation could be that although a positive effect was shown in the participants who used the custom-made foot orthoses for 3 months, the long-term effect was not evaluated in this study due to the short follow-up period, in contrast to other studies (21). Although the participants were given instructions about the time of use of the foot orthoses, the exact number of hours they wore them cannot be confirmed. In the monthly reviews over the phone, the participants were reminded of the instructions and they claimed to be following them. Lastly, considering that around 80% of the participants were women, it is difficult to extrapolate the results of the study to the general population, although the two groups were balanced in regard to gender. Further studies should include a larger percentage of male participants.

The custom-made foot orthoses reduced foot pain significantly. This study presents a different method for manufacturing foot orthoses. There is a lack of consensus about the selection of the type of foot orthosis that should be used in the management of rheumatoid foot pathology. However, the authors of the present study sustain that foot orthoses that control foot function, apart from provide cushioning to the foot, will have positive effects derived from stress reduction, plantar pressure alleviation, and realignment of the foot joints through the use of the foot orthosis whenever possible. This type of foot orthosis provides an environment that is required to reduce pain, disability, and functional limitation for rheumatoid arthritis patients.

Clinical Messages

- The custom-made foot orthoses significantly reduced foot pain and disability in patients with rheumatoid arthritis.
- The custom-made foot orthoses did not provide positive effects on quality of life in patients with rheumatoid arthritis.

Authorship contributions

MRB have substantial contributions to the conception and design of the work, drafting the work, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MCVB have substantial contributions to the conception and design of the work, revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SPG have substantial contributions to the acquisition, analysis and interpretation of data for the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ADS have substantial contributions to the acquisition, analysis and interpretation of data for the work, drafting the work final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CRB have substantial contributions to the acquisition, analysis and interpretation of data for the work, drafting the work final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PVMM have substantial contributions to the conception and design of the work, drafting the work, revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The Authors declare that there is no conflict of interest

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REFERENCES

1. Novak P, Burger H, Tomsic M, Marincek C, Vidmar G. Influence of foot orthoses on plantar pressures, foot pain and walking ability of rheumatoid arthritis patients--a randomised controlled study. Disabil Rehabil. 2009;31(8):638–45.

2. Moreira E, Jones A, Oliveira H, Jennings F, Fernandes A, Natour J. Effectiveness of insole use in rheumatoid feet: a randomized controlled trial. Scand J Rheumatol. 2016;45(5):363–70.

3. Cuesta-Calleja R, Polo-García A, González-Fernández ML. Evidencia cientifica del tratamiento ortopodologico en pie afectado por artritis reumatoide. Rev Int Ciencias Podol. 2018 Jan;12(1):15–26.

4. Rome K, Clark H, Gray J, McMeekin P, Plant M, Dixon J. Clinical effectiveness and cost-effectiveness of foot orthoses for people with established rheumatoid arthritis: an exploratory clinical trial. Scand J Rheumatol. 2017 Jul;46(3):1–7.

5. Gatt A, Formosa C, Otter S. Foot orthoses in the management of chronic subtalar and talo crural joint pain in rheumatoid arthritis. Foot. 2016 Jun;27:27–31.

6. Barn R, Brandon M, Rafferty D, Sturrock RD, Steultjens M, Turner DE, et al. Kinematic, kinetic and electromyographic response to customized foot orthoses in patients with tibialis posterior tenosynovitis, pes plano valgus and rheumatoid arthritis. Rheumatol. 2014;53(1):123–30.

7. Rome K, Clark H, Gray J, McMeekin P, Plant M, Dixon J. Clinical effectiveness and cost-effectiveness of foot orthoses for people with established rheumatoid arthritis: an exploratory clinical trial. Scand J Rheumatol. 2017 Jul;46(3):187–93.

8. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA. 1996 Aug;276(8):637–9.

9. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580–8.

10. Landorf KB, Radford JA. Minimal important difference: Values for the Foot Health Status Questionnaire, Foot Function Index and Visual Analogue Scale. Foot. 2008 Mar;18(1):15–9.

11. Paez-Moguer J, Budiman-Mak E, Cuesta-Vargas AI. Cross-cultural adaptation and validation of the Foot Function Index to Spanish. Foot Ankle Surg. 2014;20(1):34–9.

12. Gijon-Nogueron G, Ndosi M, Luque-Suarez A, Alcacer-Pitarch B, Munuera PV, Garrow A, et al. Cross-cultural adaptation and validation of the Manchester Foot Pain and Disability Index into Spanish. Qual Life Res. 2014;23(2):571–9.

13. Vera-Villarroel P, Silva J, Celis-Atenas K, Pavez P. Evaluación del cuestionario SF-12: verificación de la utilidad de la escala de salud mental. Rev Med Chil. 2014;142(10):1275–83.

14. Costantini R, Affaitati G, Massimini F, Tana C, Innocenti P, Giamberardino MA. Laparoscopic Cholecystectomy for Gallbladder Calculosis in Fibromyalgia Patients: Impact on Musculoskeletal Pain, Somatic Hyperalgesia and Central Sensitization. PLoS One. 2016;11(4):e0153408.

15. Cohen J. Statistical power analysis for the behavioral sciences. Statistical Power Analysis for the Behavioral Sciences. 1988. p. 567.

16. Rosenthal R, Rubin DB. A simple, general purpose display of magnitude of experimental effect. J Educ Psychol. 1982;74(2):166–9.

17. Van der Leeden M, Fiedler K, Jonkman A, Dahmen R, Roorda LD, van Schaardenburg D, et al. Factors predicting the outcome of customised foot orthoses in patients with rheumatoid arthritis: A prospective cohort study. J Foot Ankle Res. 2011;4(1):8.

18. Chalmers AC, Busby C, Goyert J, Porter B, Schulzer M. Metatarsalgia and rheumatoid arthritis - A randomized, single blind, sequential trial comparing 2 types of foot orthoses and supportive shoes. J Rheumatol. 2000;27(7):1643–7.

19. Tenten-Diepenmaat M, Dekker J, Steenbergen M, Huybrechts E, Roorda LD, van Schaardenburg D, et al. In-shoe plantar pressure measurements for the evaluation and adaptation of foot orthoses in patients with rheumatoid arthritis: A proof of concept study. Gait Posture. 2016;

20. Bongi SM, Rosso A Del, Mikhaylova S, Landi G, Ferretti B, Cavigli E, et al. A comparison of two podiatric protocols for metatarsalgia in patients with rheumatoid arthritis and osteoarthritis. Clin Exp Rheumatol. 2014;32:855–63.

21. Woodburn J, Barker S, Helliwell PS, Woodburn J. A randomized controlled trial of foot orthoses in rheumatoid arthritis. J Rheumatol. 2002;29(7):1377–83.

22. Magalhaes E, Davitt M, Filho DJ, Battistella LR, Betolo MB. The effect of foot orthoses in rheumatoid arthritis. Rheumatology. 2006;45:449–53.

23. Chen WM, Lee SJ, Lee PVS. Plantar pressure relief under the metatarsal heads - Therapeutic insole design using three-dimensional finite element model of the foot. J Biomech. 2015;48(4):659–65.

24. Hennessy K, Woodburn J, Steultjens MPM. Custom foot orthoses for rheumatoid arthritis: A systematic review. Arthritis Care Res. 2012;64(3):311–20.

25. Cameron-Fiddes V, Santos D. The use of "off-the-shelf" foot orthoses in the reduction of foot symptoms in patients with early rheumatoid arthritis. Foot. 2013;23:123–9.

26. Cho NS, Hwang JH, Chang HJ. Randomized controlled trial for clinical effects of varying types of insoles combined with specialized shoes in patients with rheumatoid arthritis of the foot. Clin Rehabil. 2009;23:512–21.

27. Gijon-Nogueron G, Ramos-Petersen L, Ortega-Avila AB, Morales-Asencio JM, Garcia-Mayor S. Effectiveness of foot orthoses in patients with rheumatoid arthritis related to disability and pain: a systematic review and meta-analysis. Qual Life Res. 2018 Jun; 27(12):3059–3069.

28. Conceição CS, Neto MG, Souza AC, Mendes SMD, Baptista AF, et al. Kinetic and Functional Impact of Foot Orthoses in Rheumatoid Arthritis Feet: A Randomized Clinical Trial. J Arthritis. 2015;4:157. doi:10.4172/2167-7921.1000157.