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ORIGINAL ARTICLE

Rationale and design of the PHYSICALFAV trial: a randomized controlled trial to evaluate the effect of preoperative isometric exercise on vascular calibre and maturation of autologous arteriovenous fistulas

Ines Aragoncillo[1,2], Jose Manuel Ligero[3], Covadonga Hevia[4], Angel Luis Morales[3], Yésika Amézquita[4], Teresa Cervera[3], Almudena Vega[1,2], Soraya Abad[1,2], Nicolás Macías[1,2] and Jose Luño[1,2] on behalf of the PHYSICALFAV Investigators

[1]Servicio de Nefrología, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Spanish Research Network (REDINREN), Madrid, Spain, [3]Servicio de Angiología y Cirugía Vascular, Hospital General Universitario Gregorio Marañón, Madrid, Spain and [4]Servicio de Nefrología, Hospital Universitario Infanta Sofía, San Sebastian de los Reyes, Madrid, Spain

Correspondence and offprint requests to: Ines Aragoncillo; E-mail: inesiglia@hotmail.com; Twitter handle: @almudenavega1

ABSTRACT

Background. A good vascular access (VA) is vital for haemodialysis (HD) patients. HD with an autologous arteriovenous fistula (AVF) is associated with higher survival, lower health care costs and fewer complications. Although a distal forearm AVF is the best option, not all patients are good candidates for this approach and the primary failure rate ranges from 20% to 50%. The optimal AVF depends mainly on the anatomical and haemodynamic characteristics of the artery and the vein chosen for the anastomosis. These characteristics can be modified by performing physical exercise. VA guidelines suggest that isometric exercises should be performed both before and after the AVF is created. While the literature contains few data on the potential efficacy of preoperative exercise, small observational studies point to an improvement in venous and arterial calibre. Postoperative exercise also seems to improve maturation, although there is no consensus on the appropriate exercise protocol.

Methods. The PHYSICALFAV trial (NCT03213756) is an open-label, multicentre, prospective, controlled, randomized trial designed to evaluate the usefulness of preoperative isometric exercise (PIE) in pre-dialysis patients or in prevalent HD patients who are candidates for a new AVF. Patients are randomized 1:1 to the PIE group (isometric exercises for 8 weeks) or the control group (no exercise). The main endpoint is whether the rate of primary failure is lower in the PIE group than in the control group.

Results. The trial has already started, with 40 patients having been enrolled as of 21 March 2018; 26.5% of the estimated sample.

Keywords: arteriovenous fistula, Doppler ultrasound, isometric exercise, maturation, primary failure

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INTRODUCTION

In order to achieve adequate haemodialysis (HD), it is essential to have a good vascular access (VA). Autologous arteriovenous fistula (AVF) is superior to prosthetic fistulas and to the use of central venous catheters (CVCs), both in terms of survival and reduced health care costs [1–4]. Complications derived from VA are one of the leading causes of hospitalization in patients on HD and lead to significant consumption of health care resources [5, 6].

Primary failure is one of the main issues affecting AVFs, either related to early thrombosis or lack of maturation [1–4]. Primary failure of AVFs occurs in 20–50% of cases and varies depending on the definition [7–10]. In most cases, risk factors can be identified through adequate clinical examination and preoperative and postoperative Doppler ultrasonography [11]. Risk factors include an artery and vein calibre <2 mm, which is very frequent in pre-dialysis patients. We have defined primary failure as an AVF unable to provide adequate HD 3 months after its creation. This definition includes 'immediate AVF failure' within 72 h of surgery and 'early dialysis suitable failure', an AVF for which, despite interventions (radiologic or surgical), it was not possible to use the AVF successfully for HD by the third month following its creation, according to the North American Vascular Access Consortium (NAVAC) [8, 9].

Most guidelines on VA recommend performing isometric physical exercise after surgery (low degree of evidence) [1–4]. In recent years, two randomized studies have shown an improvement in maturation with isometric exercise, at least from a clinical point of view, with more evident benefit in distal AVFs, albeit with variable ultrasound results [12, 13]. There is still no consensus on the duration or type of exercise to be performed. Handgrip exercises seem to be the most effective, although benefits have also been reported for elastic band-based exercises and ball contraction [13, 14]. The only observational study that did not find benefits in postoperative isometric exercise was published decades ago and did not have an adequate exercise protocol [15].

Preoperative exercise is recommended in some VA guidelines [1–3], although data confirming the effectiveness of this approach are scarce. Only three observational studies with small samples report an improvement in venous and arterial calibre after 6–8 weeks of isometric exercise [16–18]. One was performed in 15 patients who were not initially candidates for AVF; autologous AVF was successfully performed in 5 of these patients after 8 weeks of exercise [18]. We know that both arterial and venous calibre are key to adequate anastomosis and any intervention that can improve this parameter could result in a greater number of autologous distal AVFs that mature successfully, with the consequent clinical benefits for patients and a reduction in VA-related costs [19]. Despite favourable data from observational studies and the recommendation to carry out new studies, the efficacy of exercise in the preoperative period of AVF has not yet been analysed in a randomized study. Based on this unmet need, the PHYSICALFAV trial, an open label, multicentre, prospective, randomized controlled trial (http://clinicaltrials.gov; NCT03213756), will evaluate the usefulness of preoperative isometric exercise (PIE) in end-stage renal disease patients with indications to perform a new AVF, with an estimated sample size of 158 patients. Besides this trial, there is another randomized, multicentre, single-blinded controlled trial ongoing in The Netherlands for which the protocol has been recently published. This is the PINCH trial, with an estimated sample size of 40 patients and complete recruitment expected by the end of 2019 [20].

ENDPOINTS

The primary endpoint is to evaluate the impact of PIE on AVF primary failure comparing the control group and the PIE group.

The secondary endpoints are to evaluate the following:

- Percentage of candidate patients for autologous distal or proximal AVF in both groups. (The final indication of AVF in the PIE group will be done after 8 weeks of isometric exercise.)
- Differences in the calibre of upper arm arteries and veins in the PIE group before and after isometric exercise. (Calibre, resistance index and flow of radial and brachial arteries and calibre of cephalic and basilic veins.)
- Impact of AVF evaluation with Doppler ultrasound (DU) in the postoperative period in both groups, adding the usual isometric exercise with ball contraction in all patients. This study will allow AVF maturation surveillance with DU in all participating centres, with early detection of stenosis and optimization of the primary assisted patency of AVF in our patients.
- To analyse in both groups of patients the optimal arterial and venous calibres to minimize the primary failure of AVF according to the individual risk factors.

HYPOTHESIS

- Upper arm PIE improves venous and arterial calibres. This facilitates the creation of an arteriovenous anastomosis and allows an absolute reduction of 20% of the primary failure rate of the AVF (evaluated 3 months after its creation), increasing the possibilities of performing autologous distal AVFs.

MATERIALS AND METHODS

Study design

This is an open-label, prospective, controlled, randomized, multicentre study in parallel groups, where, during the preoperative AVF period, one group of patients will perform an isometric exercise protocol for 8 weeks and will be compared with a control group of patients that will not perform this preoperative exercise protocol.

After obtaining written informed consent, the inclusion and exclusion criteria will be verified and randomization (1:1) will be carried out through a centralized computer program.

Population

The population will include patients in pre-dialysis or chronic HD who are candidates for a new AVF.

Inclusion criteria.

- Patients who provide written informed consent (obtained as specified in the International Committee of Medical Journal Editors recommendations).
- Age 18–89 years.
- Patients with advanced chronic kidney disease, Stages 4 and 5, in pre-dialysis or prevalent HD patients requiring new AVF.

Exclusion criteria.

- Absence of adequate arteries and veins to allow autologous AVF (the minimum gauges that will be considered in order

to perform an autologous AVF are artery calibre ≥1.6 mm and vein calibre ≥1.8 mm with a compressor) [3].
- Diagnosis of coagulopathy or haemoglobinopathy of any cause.
- Patients with previous AVF in the elected arm for the new AVF.
- Patients who urgently need an AVF without the possibility of being 8 weeks on the surgical waiting list.
- Impossibility to perform the physical exercise protocol due to physical or mental disabilities or lack of social support.

Subject withdrawal criteria. The investigators may withdraw a patient from the study at any time if the investigator considers it necessary for any reason, including the following:

- Significant protocol deviation or violation
- Abandonment or withdrawal of informed consent
- Transplant
- Change of dialysis technique
- Transfer to another centre
- Exitus.

Study procedures

After signing the informed consent, patients are randomized through a centralized computer program to one of two groups, PIE versus control, with an equal allocation ratio (1:1).

In both groups of patients, a first physical examination of upper arms and an initial DU will be performed, evaluating the anatomical and haemodynamic characteristics of the arteries and veins of both arms. At that time, a first surgical option of AVF will be indicated.

In the PIE group, the patients will receive detailed information about the daily preoperative exercise protocol and they will perform this protocol for at least 5 and ideally >8 weeks based on the criteria given below.

Isometric exercise using hand grip. This exercise consists of two sets of 30 hand-grip contractions with the hand of the upper arm candidate for AVF (in case of doubts about the most appropriate arm for AVF, the exercise should be performed with both arms). The patient will rest 1 min for every 10 contractions and 5 min between both sets. The patient will repeat this protocol twice a day, morning and night (∼15 min each session). The contraction intensity will start with half of the maximum force obtained by dynamometry and will be increased or decreased to be placed on an effort intensity of 2–3 on the 10-point Borg visual analogue scale. This adjustment is based on the findings of a sample of 40 healthy subjects who scored 2 or 3 points on the Borg scale in >80% of the cases. For those patients who score <2 or >3 on the Borg scale, the resistance of the hand grip will be slightly modified until the patient feels a mild to moderate exercise.

Isometric exercise using elastic bands. Once a day the patient will perform a slow contraction session using an elastic band with 20 slow repetitions with the arm in flexion and 20 repetitions with the arm in extension (total duration >10 min).

Clinical follow-up of these patients will be for every 4 weeks to ensure that they perform the exercises correctly and to measure the force through dynamometry. In addition, they will be contacted by telephone fortnightly to assess compliance. Doppler ultrasonography will be performed at the initial visit, and at the 4- and 8-week visits. In the DU performed at Week 8, the final surgical indication will be given depending on the calibre of the vessels in the chosen arm. At the initial visit and at the 8-week visit, biological samples will be obtained to assess the parameters of nutrition and muscle mass.

The date of surgery will be coordinated with anaesthesia and peripheral vascular surgery services to program the intervention during the fortnight after the 8-week isometric exercise period (Weeks 9–10). In prevalent HD patients with CVC presenting greater urgency of AVF, surgery will be scheduled between weeks 6 and 8 of exercises.

Control group patients will follow the usual surgical waiting list protocol (estimated 1.5–2.5 months). Baseline and preoperative ultrasonography will also be performed in these patients, in which it will be verified that there are no significant changes in vascular mapping (punctures sites, hematomas, etc.) and the indication of AVF performed in the initial visit will be confirmed. Dynamometry will be performed both at the onset visit and at the preoperative visit, as well as taking biological samples. The only difference with the PIE group is the 4-week follow-up ultrasound, which will not be performed in control group.

After the AVF creation, the maturation will be monitored with DU and dynamometry at 1, 6 and 12 weeks after the surgery. At 12 weeks, biological samples will be taken (Table 1).

The usual postoperative isometric exercise with ball contraction will be recommended to all patients. Follow-up will be completed 3 months after the surgical procedure, defining whether the AVF has matured or if there has been a primary failure (Figure 1).

Every procedure will be in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2000.

STATISTICS

Sample size calculation

Assuming a primary failure rate of AVF between 20% and 50% according to the literature data by Allon *et al.* [7] and expecting an absolute reduction of 20% in the primary event, with an alpha error of 0.05 and a beta error of 0.20, the required sample size will be 79 subjects in each group. Follow-up losses of 10% and a maximum percentage of primary failure in the control group of 35% were considered. The sample size was calculated using the GRANMO (Sample size calculator) v.7.12 program.

The final sample size will be evaluated through an intermediate analysis when recruitment of half of the sample is achieved.

Statistical analysis

Regarding the statistical analysis, qualitative variables will be presented with their frequency distribution. Quantitative variables are summarized as mean and standard deviation (SD) or median and interquartile range (IQR). The baseline variables will be compared according to the Consolidated Standards of Reporting Trials regulations. In case of detecting some confounding variable, the appropriate models will be adjusted.

The association between qualitative variables will be evaluated with the chi-squared test or Fisher's exact test in case >25% of those expected were <5 observed values.

The primary efficacy variable is the percentage of AVF without primary failure measured 3 months after fistula creation. Kaplan–Meier survival functions for independent variables will

Table 1. Schedule of the activities that will take place after randomization

Study procedures	−8 weeks, Visit 1	−6 weeks	−4 weeks, Visit 2	−2 weeks	−1 week, Visit 3	Week 0, surgery	+1 week, Visit 4	+6 weeks, Visit 5	+12 weeks, Visit 6
Informed consent	x								
Medical History	x								
Demographic data	x								
Physical examination	x				x	x			x
Dynamometry	x		x[a]		x		x	x	x
DU	x		x[a]		x		x	x	x
Access blood flow measurement							x	x	x
Biologic samples (Blood test)	x				x				x
Adherence to exercise	x[a]	x[a]	x[a]	x[a]	x[a]				
Adverse events related to exercise	x[a]	x[a]	x[a]	x[a]	x[a]				

[a]Only in PIE group patients.

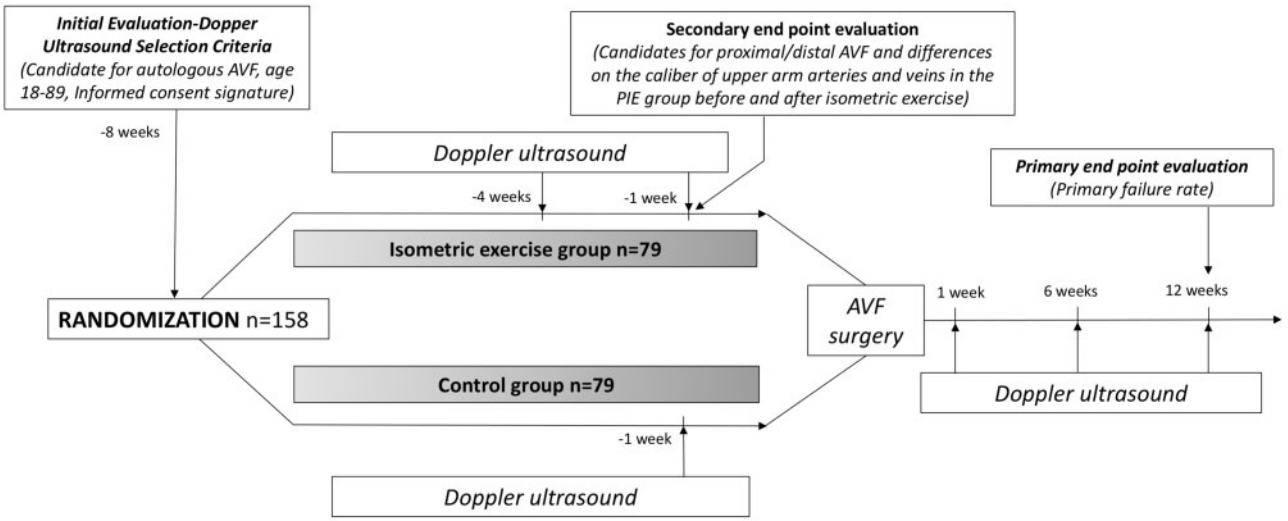

FIGURE 1: Schematic overview of the PHYSICALFAV trial design.

be estimated for the study of primary failure due to a lack of maturation or access thrombosis in the first 3 months after AVF creation. The graphs of the estimated curves and the median of the distribution will be presented together with their confidence interval. Comparison of the survival functions of the different subgroups will be performed using the Breslow exact test. It conforms to a Cox proportional hazards regression model. The hazard ratios are presented along with their 95% confidence intervals.

The assumptions that must fulfil the data to apply this model are especially of the parametric part, since the contribution of the various explanatory variables in the prediction of survival, more precisely, the instantaneous rate of risk, is the same at any point of follow-up time. The non-parametric part of the model does not impose any assumption on the distribution of survival times.

The behaviour of the quantitative variables by each of the independent variables, categorized by the Student's *t*-test (in comparisons of one variable with two categories) and/or the analysis of variance, is analysed. By means of this technique, the differences of means will be evaluated due to the individual effect, the main effect of each factor and/or the effect of their interactions.

In all cases, the distribution of the variable will be checked against the theoretical models and the hypothesis of the homogeneity of variances will be checked. In all the hypothesis tests, the hypothesis will be rejected with an error of type I or error < 0.05.

Patients in the PIE group who do not complete at least 6 weeks of follow-up and those who are classified as poor compliance will be excluded from the protocol analysis but will be included in the intention-to-treat analysis. The computer package used for the analysis will be SPSS (Statistical Package for the Social Sciences) for Windows version 21.0 (IBM, Armonk, NY, USA).

TIME LINE

The trial has already started. The protocol was approved by the Regional Ethical Committee in May 2017. Recruitment started in July 2017. As of 13 April 2018, 42 patients have been enrolled and randomized (26.5% of estimated sample size).

FUNDING

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CONFLICT OF INTEREST STATEMENT

None declared.

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