Design and rationale of the Prevention of radial Artery occlusion after Transradial accEss using NitroglyceriN (PATENS)

NCT03158532

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Abstract

Background

Radial artery occlusion (RAO) is an important access site complications after transradial catheterization (TRC). Acute loss of radial artery patency after TRC is thought be due to a thrombotic process, and a bigger sheath-to-radial-artery ratio could reduce the incidence of RAO. Nitroglycerin acts through the liberation of nitric oxide (NO), which promotes muscle relaxation and vasodilation. Leading to a bigger sheath-to-radial-artery ratio the nitroglycerin administration could help to keep the radial artery patency. The aim is to study if nitroglycerin is superior to placebo concerning incidence of radial artery occlusion, confirmed by vascular Doppler ultrasound, up to 24 hours after catheterization.

Methods/Design

PATENS is a national, multicenter, superiority, 2-by-2 factorial, randomized clinical trial. Two thousand one hundred twenty-eight patients submitted to TRC will be randomized to either nitroglycerin or placebo, administered intra-arterially through the sheath, in two different moments during TRC: after the arterial sheath insertion, at the beginning of procedure, and at the end of the radial procedure, before sheath removal.

Results

The primary efficacy objective is to test the hypothesis that nitroglycerin, dose of 500 mcg, is superior to placebo in decreasing rates of radial artery occlusion on ultrasound Doppler analysis up

to 24 hours after procedures. As secondary objectives, the trial will evaluate the incidence of radial artery occlusion 30 days after catheterization. Enrollment was initiated in August 2017, and the inclusion phase is expected to last until the second half of 2019.

Conclusions

The PATENS trial will help define the role of prophylactic nitroglycerin as a RAO avoidance strategy in patients with submitted to TRC.

Trial registration

ClinicalTrials.gov identifier: NCT03158532

Background

The use of the transradial approach (TRA) for coronary catheterization has increased over the years, worldwide. Radial artery is nowadays utilized by default for percutaneous coronary procedures in many centers, thanks to the reduced rates of vascular and bleeding complications and easier post-procedural management. The use of TRA also improves patient comfort, saves costs and it has an equivalent procedural success when compared to the femoral approach.

Although it is widely accepted by cardiologists and patients, some problems still exist. One of the major limitations is the development of radial artery spasm (RAS), which can reduce success rates, leading to femoral conversion, and cause significant pain to patients. The incidence of RAS varies between 2% and 34%. Aiming prevent RAS, the use of prophylactic intraarterial vasodilators is

routinely recommended by experts, mainly verapamil or nitroglycerin. Most catheterization laboratories habitually use some medication to prevent RAS, however, it is not a consensus.

Another important complication, often underestimated, is the post-procedural radial occlusion (RAO). Incidence of radial pulse loss has been reported to range from 1% to 12%. The benign nature of such an event has been constantly emphasized due to the dual blood supply to hand from the palmar arch. Mostly, the occurrence of radial occlusion is asymptomatic, symptomatic radial occlusion requiring medical attention occurred in only 0.2% of patients, but hand ischemia caused by RAO has been described. The most important aspect is that once artery is occluded, it can not be used neither as access site for future catheterization, nor be used as a conduit for bypass surgery nor fistula formation in hemodialysis patients. The use of small caliber catheters, adequate dose of heparin administration, immediate sheath removal after procedure, patent hemostasis technique and short time of compressive bandage are the key elements to reduce the risk of artery occlusion. Notably the presence of radial pulse does not exclude radial occlusion due to presence of collateral circulation; it can be more accurately evaluated by absence of antegrade flow in vascular doppler ultrasound. In fact, many operators do not assess radial artery patency before discharge.

Acute loss of radial artery patency after cardiac catheterization is thought to be due to a thrombotic process. Sheath insertion leads to local endothelial injury and cessation of blood flow in the radial artery, creating an environment conducive to thrombosis. RAO tends to occur early after transradial catheterization, and roughly 50% of patients have spontaneous recanalization of the artery within 1 month. Direct support for the thrombotic hypothesis has come from recent studies that have confirmed the presence of radial artery thrombus on vascular ultrasound, angiography, and pathology. Transradial catheterization can negatively affect radial artery structure as well. A study using optical coherence tomography found that 67% of radial arteries had intimal tears and 36% had medial dissections immediately after transradial PCI. A study of radial artery function after transradial catheterization found that flow-mediated dilatation was blunted up to 9 weeks. The

radial artery response to nitroglycerin was also decreased, suggesting that the impairment in function was more than just temporary damage to the endothelium and involved long-term changes to the smooth muscle layer.

Nitrates in intra-arterial have been widely studied in prevention of spasm. Nitroglycerin binds to the surface of endothelial cells and undergoes two chemical reductions to form nitric oxide (NO). The nitric oxide then moves out of the endothelial cell and into an adjacent smooth muscle cell, where it promotes the formation of cyclic guanosine monophosphate (cGMP), which promotes muscle relaxation. A bigger sheath-to-radial-artery ratio could reduce the incidence of RAO, indeed current data show that nitroglycerin intra-arterial at the end of the procedure reduce the incidence of radial artery occlusion, so the main objective of this study is to evaluate whether administration of nitroglycerin at the start of a transradial procedure may preserve the patency of the radial artery; as well, confirm if nitroglycerin administration just before sheet removal helps to keep the radial artery patency, probably mediated by vasodilation.

Methods

This is a randomized, multicenter, double-blind, placebo-controlled phase III study (Clinicaltrials.gov identifier NCT 03158532) with an all-comers design, comparing the use of nitroglycerin to decrease the rate of radial artery occlusion after transradial catheterization. Using a 2-by-2 factorial design, we will randomly assign 2128 patients with a clinical indication for coronary angiography (ad hoc angioplasty allowed) or percutaneous coronary intervention (PCI) to receive either 500 micrograms of nitroglycerin or placebo (0,9% sodium chloride), administered intra-arterially through the sheath, in two different moments during transradial catheterization: shortly after the arterial sheath insertion and at the end of the radial procedure, before sheath removal. Written, informed consent will be obtained from each subject. The study protocol has been presented to the institutional medical ethical committee of all participating hospitals to comply with local standards.

Randomization and final acceptance into the study will take place after successful radial artery cannulation and guide wire advanced into the radial arterial lumen through the needle to allow exclusion of failed radial puncture.

Patient population

All eligible patients are aged 18 years or over with a clinical indication for coronary angiography (ad hoc angioplasty was allowed) or percutaneous coronary intervention (PCI) if the following pre-requisites are met: (i) choice of the operator to use the transradial access route and (ii) use of sheath size 5 or 6 French. Allen test was not obligatory performed. The exclusion criteria were: (I) primary angioplasty due to acute myocardial infarction; (ii) intubated patients; (iii) complications during procedure (cardiac arrest, pulmonary oedema, cardiogenic shock, and stroke); (iv) prior inclusion in this trial; (v) known allergy or intolerance to nitrates; (vi) patients medicated with continuous intravenous nitrates or whom received any nitrates on the last hour and (vii) use within 24 hours prior to randomization of phosphodiesterase inhibitors.

Outcomes

Primary outcome

RAO: incidence of radial artery occlusion as confirmed by the absence of antegrade flow in vascular high resolution duplex ultrasound, up to 24 hours after catheterization.

Secondary outcomes

Late RAO: incidence of radial artery occlusion as confirmed by the absence of antegrade flow in vascular high resolution duplex ultrasound, 30 days after catheterization.

Comfort assessment: pain felt by the patient in the forearm, assessed using numeric pain rating scale. The 11-point numeric scale ranges from '0' representing one pain extreme (e.g. "no pain") to

'10' representing the other pain extreme (e.g. "worst pain imaginable"). Only the numbers themselves are valuable answers, meaning that there are only 11 possible answers in the 0–10 interval.

Spasm (operator evaluation): catheter friction, as experienced by the operator (subjective measure), on a predetermined score: 0. No resistance during catheter manipulation or pain reported by the patient; 1. No resistance during catheter manipulation, but with pain reported; 2. Light resistance during catheter manipulation; 3. Moderate to strong resistance during catheter manipulation; 4. Catheter trapping.

Procedure duration: total duration of the procedure, from sheath insertion to last catheter removal.

Radiation exposure: total radiation used in the procedure (mGy).

Study definitions

RAO: the absence of an antegrade flow in radial artery was recorded by doppler ultrasound study.

RAS: will be defined as spasm when: operator evaluation of spasm bigger than 2 by predefined scale; need of spasmolytic medication; access site convertion due to confirmed angiographic evidence of spasm.

Access site convertion: impossibility of complete procedure without another arterial site access. It may be due to spasm or anatomical reason, and should be confirmed with angiography.

Radial puncture attempt: defined as any skin puncture with positive blood draw through the needle.

Local hematoma: will be classified according to the EASY scale: I, ≤5 cm diameter; II, ≤10 cm diameter; III, >10 cm but not above the elbow; IV, extending above the elbow; and V, anywhere with ischemic threat of the hand.

Major bleeding: will be graded according to the Bleeding Academic Research Consortium definition: Type 3 ((3a) bleeding with hemoglobin drop ≥ 3 and < 5 g/dL, or packed red cells transfusion; (3b)

bleeding with hemoglobin drop ≥ 5 g/dL, heart tamponade, bleeding requiring surgical intervention or bleeding requiring intravenous inotropic drugs; (3c) intracranial hemorrhage; subcategories confirmed by autopsy, imaging examinations or lumbar puncture; intraocular bleeding with vision impairment) or type 5 bleeding ((5a) possibly fatal bleeding, (5b) definitive fatal bleeding).

Transradial procedure

Local anesthesia will be administered with a subcutaneous injection of 1% lidocaine after skin preparation. Radial artery access will be obtained using either anterior or counter-puncture technique based on the operator's preference, using a 21-gauge bare needle or 20/22 G sheath covered needle, following which a 5Fr or 6Fr hydrophilic sheath will be inserted over a guidewire. Then, the patient will receive the randomized solution (500 micrograms nitroglycerin or placebo), plus heparin 5,000 units through the radial sheath as an intra-arterial bolus. Additional heparin will be give in cases of PCI (total 100 UI/kg). Doses of heparin are used according to our study protocol. The use of additional medication, either vasodilators or analgesics, is left to operators' discretion. No routine

intravenous sedation was given. Transradial coronary angiography and/or PCI will be performed according to standard techniques, by the choice of operators. At the end of procedure, and before sheath removal, four to five ml of blood will be aspirated through the sheath to remove any residual thrombus and in a blinded fashion, either a 500 micrograms nitroglycerin or placebo will be administered through the radial sheath. Then, the arterial sheath will removed and hemostasis will be achieved.

Arterial hemostasis

A compression device designed to assist hemostasis of the radial artery after a transradial procedure will be applied according to a previously validated protocol. Immediately after procedure

completion, the sheath is initially pulled by approximately 2 to 3 cm. The device is applied to the patient with the green marker (located in the center of the larger balloon) positioned exactly at the puncture hole to aid in the location, visualization and control of possible bleeding. The balloon is inflated with an adequate syringe injecting 15 ml of air with simultaneous and total sheath removal, resulting in the absence of active bleeding. If bleeding occurs, additional 3 ml of air is injected to obtain complete hemostasis. The device is then slowing deflated to the lowest allowable volume (minimum 7 ml) while maintaining hemostasis. If bleeding occurred, 1 ml of air was reintroduced from the bleeding point. Radial artery patency was evaluated utilizing plethysmographic and pulse oximetry evaluation, with sensor placed over the thumb or index finger, and occlusion (manual pressure) of the ulnar artery. Absence of plethysmographic waveform is indicative of interruption of radial artery flow. After 1 hour post diagnostic procedure or 2 hours post intervention, 3 ml of air is removed every 15 minutes. If bleeding occurs during any stage of device removal, the volume of air needed for hemostasis is again injected, restarting the deflation process 60 minutes later. When all the air is removed, and there is no bleeding, the device is removed and the access site is covered with a simple dressing. Dressing should not encircle the entire wrist.

Statistical analysis

The primary analysis of the study is a superiority comparison between the use of nitroglycerin to decrease RAO, in all randomized patients, based on the intention-to-treat principle.

Using our primary end point to estimate the sample size, we suppose to have a 30% reduction in RAO for each trial intervention, considering potential interaction between them. Estimating RAO prespecified in the primary outcome of approximately 11.7% without use of nitroglycerin, with an alpha level of 0.05 and a beta level of 0.20, the minimum estimated sample size per group was established as 1064 individuals. As we do not expected any subsequent loss of follow-up due to the short primary evaluation, the enrolment of 2128 patients would provide sufficient power to the

study. Continuous variables will be described as means and standard deviation and compared using Student's t -test for normally distributed variables or assessed using Mann-Whitney test when not normally distributed. Categorical variables are expressed as frequencies and group percentage and will be compared with the chi-square or Fisher's exact tests. To test the interaction between interventions, we used a multivariable logistic-regression model that included the two randomized treatments and their interaction as parameters. In the analysis of the primary and secondary end points, a two-tailed p value of less than 0.05 will be considered statistically significant. No prespecified interim analysis will be performed. All analyses will be performed using SPSS version 22 (SPSS Inc., Chicago, Illinois).

Discussion

Cardiac catheterization is a common procedure and is need in many clinical scenarios and many times repeated procedures are need. The use of TRA is increasing aiming to improve patient comfort, save costs and reduce rates complications. This implies that the occurrence of RAO should be considered because, once it's occurred, it is impossible to use radial access for future catheterization. In most cases RAO occurs promptly after the procedure and up to 50% of patients have spontaneous recanalization of the artery within 1 month. A palpable pulse does not exclude the diagnosis of RAO: collateral blood flow may supply the periphery of the radial artery distally to the occlusion, giving a false impression of radial artery patency. Therefore, RAO can often be undiagnosed. Radial artery patency is better evaluated with clinical testing as the reverse Barbeau's test and with Doppler ultrasonography. Many interventions are suggested to reduce the risk of RAO, mainly anticoagulation, patent hemostasis and a bigger sheath-to-radial-artery ratio. Although nitroglycerin promotes vasodilation and thus improves the sheath-to-radial-artery ratio, no recommendation is done to its routinely use. Handling confounding factors such as anticoagulation and hemostasis, this test has an ideal design to address the question of whether routine use of the

nitroglycerin approach is superior to not use with respect to the occlusion occurrence, including possible predictors.