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ORIGINAL ARTICLE

Double-blind, single-center, randomized study evaluating the effectiveness of isosorbide mononitrate in preventing radial artery occlusion compared to placebo in patients undergoing elective percutaneous coronary procedure: study protocol

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KEYWORDS

Isosorbide
Radial artery
Percutaneous coronary intervention

ABSTRACT

Objectives: The primary objective of this study will be to evaluate the efficacy of subcutaneous and peri-arterial isosorbide mononitrate in preventing occlusion of the radial artery (ORA) after percutaneous coronary procedures (PCP) performed by the transradial approach (TRA). As secondary objectives define the incidence of ORA in the institution and assess variables related to the risk of occlusion.
Methods: Single-center, double-blind, randomized study, including in- and outpatients from a high complexity hospital, admitted to performing PCP, diagnostic or therapeutic, by TRA, in stable coronary conditions (elective) or acute coronary syndrome. The sample will be randomly divided into a group that will receive the medication and a control group. All participants will be submitted to palpatory assessment of radial artery patency and the Barbeau inverse test within 24 h and seven days after the procedure. This will be the first study to evaluate isosorbide mononitrate as an accessible and inexpensive pharmacological method for preventing OAR after PCP by VTR.

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INTRODUCTION

The diversity and technological improvement of interventional cardiology devices have universalized patients' percutaneous treatment with coronary artery disease (CAD). The transradial approach (TRA) significantly increased as percutaneous intervention route choice compared to the more classic transfemoral approach (TFA). This shift is due to three main reasons:

- Its high success rate;
- Less invasion provided, making it an even more minimalist technique associated with a lower rate of complications when compared to the femoral approach[1-3], allowing earlier discharge in both diagnostic and therapeutic procedures as well as faster return of the patient to his activities[4,5] and;
- The fact that TRA reduces the incidence of hemorrhagic complications, such as hematomas, pseudoaneurysms, and arteriovenous fistulas[6], related to more significant morbimortality[7-10]. The anatomical characteristics of the radial artery explain the lower incidence of hemorrhagic complications: terminal branch of smaller caliber, more superficial and with a more effective underlying bone plane for compression hemostasis, absence of a gauge satellite vein and nerves, which prevents iatrogenic lesions of these structures when compared with the classic route through the common femoral artery.

Therefore, the primary advantage of the TRA over TFA lies in the reduction of severe hemorrhagic events (approximately two-thirds of hemorrhagic complications are related to the femoral approach[11]). Another essential characteristic of TRA is its few contraindications, such as:

- Proximal arterial segments occlusions (brachial, axillary, and subclavian arteries);
- Ulnar route absence of compensatory flow (palmar arch);
- Pathological vasomotor phenomena (Raynaud's phenomenon);
- When the patient refuses to use the transradial approach[12].

On the other hand, anatomical variations of the superficial and deep palmar arches are relatively frequent, especially the incomplete formation of the superficial arch, seen in 46% of cases in na *in vivo* observational study. However, this finding does not translate into a contraindication to the procedure due to mutual compensation between the palm arches[13,14]. Therefore, nowadays, TRA has become the first choice access via performing percutaneous coronary interventions, reaching 80% of the cases[15], and has recently been endorsed by international guidelines[12,16-18].

The assessment of patency and functional competence of the palmar arch is easily accessed by the Barbeau test, which consists of analyzing the variation of plethysmographic waves in the fifth ipsilateral phalanx during digital compression of the radial artery. Type A to C waves do not contraindicate the procedure; on the other hand, type D wave translates into an incomplete and incompetent palmar arch to supply blood to the hand in case of radial artery loss and, therefore, contraindicates the procedure by this approach[19].

Nevertheless, the radial approach is not exempt from complications, among which the most frequent are hemorrhagic complications and radial artery occlusion (RAO). The latter's importance is mainly due to the impossibility of using the route in future percutaneous coronary procedures (PCP).

After percutaneous procedures, RAO incidence can reach 14.4%[19], which may vary widely in the literature. This loss can be caused by vasospasm, reversible in the vast majority of cases, but it can be persistent. In the latter situation, it may present associated thrombosis in approximately 60% of patients[20]. RAO is mostly asymptomatic, and functional sequela represented by the hand's muscular claudication during everyday activities is extremely low, around 0.26% of patients, according to a systematic review[21]. This low incidence can be explained by the mutual compensation between the deep and superficial palmar arches mentioned earlier[13,22].

Evaluation of radial artery patency before discharge is an infrequent practice, as demonstrated in an international survey, where less than 70% of operators performed it in daily practice. Of these, approximately half uses palpation as an evaluation method[23]. The diagnosis of RAO by palpation underestimates its incidence since the radial pulse's tactile sensation can be generated through collateral circulation or palmar arches in a retrograde manner in the absence of radial patency[24,25.] There are other methods of more accurate assessment for radial artery patency before patient discharge. The pulse oximetry with plestimographic curve performed using the reverse Barbeau technique, differentiating antegrade or retrograde wave pulse, previously described, is a good example. The technique consists only of compression of the ulnar artery in place of the radial one to identify patients with occlusion of the radial and pulse palpatory sensation in a retrograde wave through the palmar arch[26]. Another useful tool is the radial artery ultrasound study with Doppler. The first has the advantage of its practicality, low cost, and simple and easily reproducible technique. While ultrasound study direct assessment of radial arterial patency, enabling pathophysiological findings of the arterial occlusion, is more costly, technically more complex to perform, and requires a longer learning curve, making it difficult to reproduce. As there is no evidence of superiority between these two methods, the reverse Barbeau technique should be used as a tool of choice for the diagnosis of RAO, and the ultrasound study with Doppler should be used for a more detailed diagnosis of the cause of this obstruction[16].

The transradial approach has become the first choice route for PCP, and its potential risk for RAO after the procedure encouraged the search for strategies for its prevention. Among the scientifically proven mechanical strategies, we can quote the shortest hemostatic compression time[27], patent hemostasis[28], and simultaneous compression of the ulnar artery with patent hemostasis[29]. Among the pharmacological strategies is the radial intraarterial use of

unfractionated or low molecular weight heparin and direct thrombin inhibitors[22] and the subcutaneous injection of nitroglycerin (NTG)[19]. Although there are studies in the reviewed literature with isosorbide mononitrate (IM), an organic nitrate that is a frequent substitute for nitroglycerin in daily clinical practice due to its similar actions in arterial, venous, and coronary smooth muscle[30], these studies were limited to demonstrate its action on facilitating arterial cannulation and reduction of vasospasm[31]. Therefore, the subcutaneous and periarterial use of IM to prevent RAO after PCP has not yet been evaluated in the scientific community.

The rationale of subcutaneous and periarterial IM in the prevention of RAO in PCP study is based on the fact that in our country, the IM is a frequent and cheaper organic nitrate substitute for nitroglycerin, with a more economical presentation (10 mg / 1 mL ampoules) when compared to NTG (ampoules 25 mg / 5 ml or 50 mg / 10 ml). Besides, there are no studies on the use of IM to prevent RAO after percutaneous coronary interventions. Although there is no subcutaneous use of IM in the reviewed literature, its intra-arterial use in interventional cardiology is well known, and subcutaneous NTG is well described in the literature as effective and safe. IM mechanism of action, like that of NTG, occurs through the increase of nitric oxide through its bioactivation in the endothelium, causing an intracellular reduction of ionic calcium in the smooth muscles of blood vessels with consequent relaxation[30]. The potential side effects of using IM subcutaneously are related to its mechanism of action: inoculation puncture site, ipsilateral hand hyperemia, transient headache, and arterial hypotension. The dose used in MI reviewed studies was 1 mg intraarterial[31], however for a higher concentration of the drug, in the present study, a 10 mg dose (1 mL) subcutaneous adjacent to the radial artery will be used.

The study hypothesis is the subcutaneous IM strategy's superiority over the standard strategy regarding the RAO prevention in the post-procedure, estimating a reduction in arterial occlusion incidence from 14.4% to 5% after PCP. Using a control group is justified for greater statistical strength and will provide the real RAO incidence in our population.

Study design

Prospective, randomized, double-blind, placebo-controlled, single-center, superiority study, with 1: 1 allocation and parallel groups, and a primary outcome of RAO up to 7 days after the procedure.

Objectives

Primary objective:

- To evaluate the effectiveness of subcutaneous and periarterial IM administration compared to placebo in the prevention of RAO occurrence after PCP performed by TRA;

Secondary objectives:

- To define the real RAO incidence after PCP performed by TRA.
- To identify risk factors associated with RAO occurrence after PCP performed by TRA.

METHODS

Study delimitation

The study will include hospitalized or elective patients (outpatient) admitted for diagnostic or therapeutic PCP performed by TRA. It will be carried out at the interventional cardiology service of the Hospital de Clínicas de Itajubá (HCI), a quaternary-level hospital, accredited by the Public Health System for highly complex procedures, in addition to attending private patients or those coming from supplementary health agreements, located in the south of the Minas Gerais state. It is responsible for the direct care of the Alto Sapucaí micro-region, with about 300,000 inhabitants, and indirectly receives patients from all over the south of the state.

Eligibility and exclusion criteria

The study will select for the randomization process: Adult patients ≥ 18 years old, well-oriented, with an adequate level of consciousness and understanding, who will undergo diagnostic or therapeutic PCP through the right or left TRA in a stable (chronic coronary insufficiency) or unstable scenario (acute coronary syndromes) without hemodynamic instability signs (systolic blood pressure <90 mmHg, tachycardia, filiform pulse) after receiving study information by the responsible researcher and signing the Informed Consent Form (ICF).

The study will exclude patients:

- With any degree of impairment of the level of consciousness, hemodynamic instability or;
- Under sedation or general anesthesia or;
- Who have already undergone prior PCP by bilateral TRA or;
- Who have type D curve in the Barbeau test or;
- Who have arterial occlusions in proximal segments (brachial, axillary or subclavian) or;
- Who have a history of Raynaud's Phenomenon.

Among the related-procedure exclusion criteria: moderate to large hematomas-related radial artery puncture sites will be excluded.

The radial artery canulation by the Seldinger technique can be performed through an anterior puncture needle or by a catheter on needle technique (Abocath®). Therefore it will allow arterial transfixation for canulation.

Interventions

Before the intervention, the assistant interventional cardiologist will apply a questionnaire to the participant. This questionnaire will be filed in a parallel medical record containing clinical and procedure-related variables and post-procedure-related complications (Table 1).

Two qualified interventional cardiologists will perform the intervention procedures in a high-volume center with a minimum of five years of experience in PCP by TRA. The study will use the clinical-assistance protocol of the HCI interventional cardiology service during its development, which uses subcutaneous 2% lidocaine hydrochloride without vasoconstrictor as a local anesthetic, in a volume of approximately 3 mL.

Tabela 1 — Parallel medical record model.

Parallel medical record/ Questionnaire
Patient's Variables
Patient's name initials: Medical record number: Phone contact:
Gender: age:
Comorbidities:
( ) SAH ( ) Preview AMI ( ) PAOD
( ) Diabetes mellitus ( ) DLP ( ) *Stents*
( ) CABG ( ) Current smoker
Patient and procedure's general data
Patient's current medications:
Puncture sites'complications: ( ) yes ( ) no which?
Periprocedure's cardiovascular events: ( ) yes ( ) no Which?
Follow-up:
▪ After 24 h: radial pulse: present ( ) absent ( )
▪ At 7±2 day: radial pulse: present ( ) absent ( )
Procedure's variables
Elective: ( ) yes ( ) no
Ad-hoc: ( ) yes ( ) no
Unstable angina ( ) yes ( ) no
NSTEMI: ( ) yes ( ) no
Stent type: ( ) BMS ( ) DES
Predilatation: ( ) yes ( ) no
Post-dilatation: ( ) yes – atm: ( ) no
Treated coronary: ( ) LM ( ) LAD ( ) CX ( ) RCA ( ) DG ( ) MG ( ) PD
Bifucation: ( ) yes ( ) True ( ) false ( ) no
Procedure's timing:
a. Arterial puncture to coronary catheterization:
b. Catheterization to sheath removal:
c. Total time:
Load doses: clopidogrel 600mg / ticagrelor 180mg / prasugrel 60mg: ( ) sim ( ) não
Unfractioned heparin:
Periprocedure's medications:

SAH – systemic arterial hypertension; CABG – coronary artery bypass surgery; AMI – acute myocardial infarction; PAOD – peripheral arterial obstructive disease; DLP – dyslipidemia; ATM – atmosphere; LM – left main artery; LAD – left anterior descendent artery; CX – circunflex coronary; RCA – right coronary artery; DG – diagonal branch; MG – marginal branch; PD – posterior descendent artery

The radial artery will be punctured by the Seldinger technique using a 21 G needle (Terumo®, Japan) or Abocath® and a 0.021" guidewire (Terumo®, Japan). After implantation of the 5 Fr or 6 Fr valve sheath introducer (at the discretion of the interventional cardiologist), sodium heparin 5,000 IU and IM 10 mg will be injected intra-arterially in all cases. At the end of the PCP, a complementary dose of IM 10 mg will be administered, followed by arterial sheath removal and patent hemostasis with TR Band hemostatic compression device (Terumo®, Japan) inflated at the puncture site with up to 13-15 mL of air. The wristband will be gradually deflated at a rate of 2 mL every 10 min after 2 hours of rest from the puncture site, it will be removed, and a non-compressive occlusive dressing will be placed. According to the institution's standard operating protocol, the time of rest and wristband removal do not differ between hospitalized and outpatients[4]. In the case of outpatients, they will receive a guidance document for post-procedure care at the time of discharge.

Eligible patients will be divided into equal proportions into treatment and control groups, receiving or not the subcutaneous injection of IM 1 mL (10 mg) 1 to 2 cm proximal to the radial styloid process, diluted in 2% lidocaine hydrochloride 2 mL, or pure injection of 2% lidocaine hydrochloride 3 mL, respectively. The remaining PCP-related steps will follow the HCI protocol equally in both groups.

All participants will be followed up 24 h and seven days after the procedure for radial pulse palpatory evaluation complemented by the Barbeau reverse test. The results will be divided into the presence or absence of radial pulse. For those with radial pulse, they will still be differentiated by the reverse test by Barbeau[26]. For this test, patients who present an absence of an oximetric curve associated with compression of the ulnar artery will be allocated as RAO. The flowchart of selection and protocol steps is shown in Figure 1.

This protocol is an intention to treat analysis. Therefore, all randomized patients who will already have the radial artery successfully punctured will have no indication of discontinuation at this stage.

The study subject has the right of choice to leave the protocol at any of its stages.

Ethical issues

The study protocol was approved by the Ethics and Research Committee of the Medicine Faculty of Itajubá under the number 3,397,346. Inform consent will be applied to all study participants. The study's subject identity will be confidential through all study's steps. The principal study investigator will hold all data until the moment of its publication.

Sample calculation

The sample calculation of 554 (277 in each arm) is based on a previous study demonstrating an incidence of radial artery occlusion after PCP by TRA of 14.4%[19]. The DIMAM® 1.0 program was used for the chi-square test (samples of equal sizes), single-tailed, to detect a difference of 9.0% between the test and control groups, with 80% power, estimating 20% of losses and a level of significance established at 0.05.

Randomization

Selected participants will undergo simple randomization by the interventional cardiologist who will perform the procedure, using the Randomizer application (for mobile devices with iOS® or Android® operating system. Group 1 will be the test group, therefore receiving IM's subcutaneous and periarterial administration together with lidocaine at the time of local anesthesia; Group 2 will be the control group that will receive the local anesthetic without the addition of periarterial vasodilator drug.

The randomization results will be recorded using an electronic spreadsheet, blind to the statistician and

other members who will work with the database. The interventional cardiologists and the cath lab nursing staff will be "not blind"; however, they will not participate in the pulse evaluation in the post-procedure phase and in the data processing or filling in the database. The radial artery puncture technique will not differ in both groups, and randomization will be carried out only after the puncture's success and the passage of the 0.018" guidewire, neutralizing possible researcher interference in this study's stage. Besides, the same local anesthetic technique will be used in both groups: anesthetic papule at the puncture site and two additional punctures parallel to the radial artery for anesthetic intensification before the sheath implantation, leaving identical scar marks on the patient's forearm regardless of which group he will belong. This information will be shared with the rest of the researcher team and study participants at the end of statistical work.

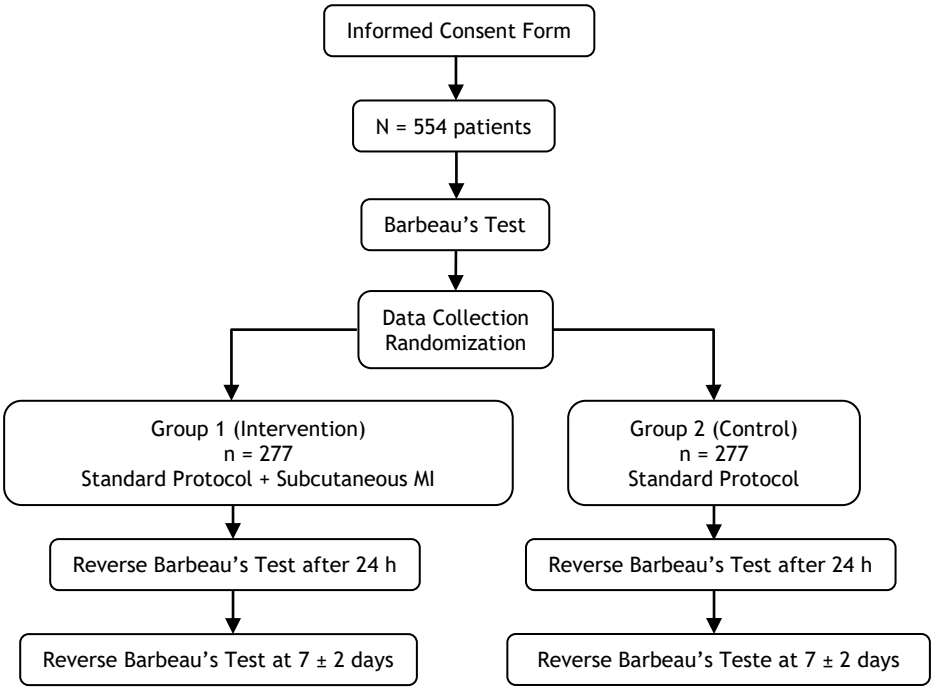

Figure 1 — Flowchart of the study protocol.

Statistical analysis

The clinical variables will be collected through a parallel medical record (Table 1) and will characterize the study groups. Chi-square test will be used to correspondence multivariate analysis. Kolmogorov-Smirnov test will determine normality distribution. Quantitative and categorical variables will be expressed as mean and standard deviation or median and interquartile range, depending on their distribution and absolute numbers and frequency measurements, respectively.

Qualitative variables will be described according to groups and verified their association using chi-square tests or exact tests in low-frequency variables. Quantitative variables will be described according to groups and compared between groups using t-Student or Mann-Whitney tests according to the distribution of probabilities.

The RAO frequency will be described according to the qualitative variables, and the association analysis verified using chi-square tests or exact tests. Quantitative variables will be described according to the RAO occurrence and compared using Student's t-tests or Mann-Whitney tests. Odds ratios (OR) will be calculated with the respective 95% confidence intervals (95% CI) for each variable for the RAO occurrence using bivariate logistic regression.

Variables that have a descriptive level of $p < 0.20$ and that have biological plausibility for the outcome will be inserted in a multiple logistic regression model to verify whether RAO is lower in patients in the group that received subcutaneous and periarterial MI administration regardless of the other characteristics evaluated.

We intend to verify the relationship between categorical variables from double-entry tables and level of significance analysis using the chi-square test for secondary outcomes analysis.

For data analysis, we will use a significance level of 0.05 and 95% CI. The following programs will be used to develop tables and statistical analysis: MS Excel® 2013 and IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.)

Potential damages

Adverse outcomes in the study will be related to the invasive coronary procedure itself, in other words, the complications inherent to the percutaneous coronary procedure:

- Bleeding (BARC Classification): Type 1 - mild bleeding translated into a small hematoma without the need for any medical response to the event; Type 2 - bleeding more significant than expected by the procedure, requiring non-surgical medical intervention, hospitalization, imaging studies, and which does not have Type 3 or 5 criteria; Type 3a - bleeding associated with a 3-5 g/dL drop in baseline hemoglobin, any need for transfusion; Type 3b - bleeding with a drop in baseline hemoglobin > 5 g/dL, need for medical surgical intervention, vasoactive drugs; Type 3c - intracranial or intraocular bleeding identified by imaging exams; Type 5a - bleeding probably fatal without confirmation with an autopsy, but with clinical suspicion; Type 5b - fatal bleeding confirmed by autopsy or image[32].
- In-stent thrombosis: defined by the time of presentation in acute (< 24 h of stent implantation), sub-acute (between 24 h and 30 days), late (between 30 days and one year), and very late (> 1 year). Clinical definition: definitive, when thrombosis is identified by imaging tests or autopsy; likely, when death occurs within 30 days of the stent implantation or regardless of the procedure's time when ischemia findings or acute myocardial infarction are found in the implanted stent territory; possible, when death occurs 30 days after the procedure[33].
- Systemic arterial hypotension: a relatively frequent condition during invasive coronary procedures and its vast majority self-limited and responsive to simple pharmacological measures; therefore, it will not be interpreted as harm.
- Allergic reactions: Grade I - mild symptoms related to one of the organs: cutaneous, upper respiratory tract, ocular conjunctiva; Grade II - symptoms related to two organs mentioned before; Grade III - moderate symptoms related to the lower respiratory tract, gastrointestinal; Grade IV and V related to anaphylaxis: severe manifestations of high and low airways as well as circulatory collapse[34].

TIMELINE

The schedule will be carried out as shown in Table 2.

Table 2 – Schedule of enrolment, interventions, and assessments.

Moment	Study Period						
	adm	SI	PCP	IM	24 h	7 d	late
Enrolment							
Eligibility	X						
FICT	X						
Allocation		X					
Interventions							
Group 1			X	X			
Group 2			X				
Assessments							
RAO					X	X	
Associated Risk factors							X

adm: admission; SI: sheath implantation; PCP; percutaneous coronary procedure, IM: isosorbide mononitrate injection; FICT: application of the free and informed consent form; RAO: radial artery occlusion.

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