Topical **N**itroglycerine **T**reatment for **R**adial **A**rtery **S**pasm **P**revention (**TNT-RASP**)

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Background:

Vascular access site complications (VASC) during cardiac catheterizations are significantly higher in transfemoral access compared to transradial access. Main disadvantage in radial access is the restriction in size of catheters as well as incidence of radial artery spasm. Radial spasm is identified by pain in the forearm aggravated by movement of the catheter/sheath; difficulty in manipulating the catheter; loss of radial pulse or damping of radial arterial pressure. Tortuosity and loops in upper extremity arterial tree could mimic some findings of radial artery spasm. Incidence of radial spasm has been reported to range between 4% and 20%. Risk factors include smaller radial artery diameter, atherosclerotic lesions, entrance of guidewires into side branches, vessel tortuosity, larger arterial sheath diameters, procedure duration, female sex, younger age, lower BMI, DM, number of catheters used, volume of contrast, unsuccessful access at first attempt, fear and anxiety. Mean size of radial artery is reported at 2.44 mm. Women and persons of south Asian descent tend to have smaller radial arteries with means of 1.91mm and 2.00 mm, respectively. Outer diameters of commonly used 5F and 6F sheaths are 2.16 mm and 2.62 mm, respectively. Ratio of radial artery to sheath size affects post-procedural radial artery flow.

Intraarterial vasodilators reduce radial artery spasm. Transdermal vasodilators prior to vascular access would increase chance for successful arterial access in first attempt and increase radial artery to sheath size ratio both of which should have additive benefit to intraarterial vasodilators in reducing spasm. Transdermal lidocaine would reduce pain during s.c. lidocaine, which can further ameliorate the risk of radial artery spasm. Use of transdermal nitroglycerine has been shown to safely increase radial artery size without significant hypotension.

Aim:

To study the role of transdermal vasodilators as an adjunct to parenteral vasodilators, in reducing radial artery spasm and improving patient comfort and post procedure radial artery patency during transradial coronary angiograms and interventions.

Hypothesis:

Transdermal vasodilators will increase radial artery size and reduce radial artery spasm as well as improve patient comfort and post procedure radial artery patency.

Study Design:

Single center, double blinded, randomized placebo-controlled study comparing effect of transdermal preparations of lidocaine + Nitroglycerine and lidocaine + placebo on radial artery spasm and procedural success in patients undergoing transradial coronary angiograms and interventions. All patients will receive standard parenteral cocktail including intraarterial or intravenous heparin and intraarterial nitroglycerine and / or verapamil. Exact doses and combinations would be at the discretion of individual provider based on patient's hemodynamic status and comorbid conditions.

End Points:

Primary:

1. Radial artery spasm: Incidence of radial artery spasm indicated by a Radial artery spasm score of 1 or more. Radial artery spasm score is sum of:

    a. Verbal or nonverbal expression of discomfort in the forearm during catheter/sheath manipulation - Absent :0; Present:1

    b. Difficulty in manipulating the catheter- Absence :0; Present:1

    c. Difficulty with sheath removal: Absent: 0; Present:1

    d. Additional use of intraarterial nitroglycerine or verapamil after the initial vasodilator cocktail for suspected radial artery spasm- No:0; Yes:1.

Secondary:

1. Change in ipsilateral radial artery cross sectional area (mm^2) before application of topical nitroglycerine / placebo (pre-dilation) vs. prior to arterial puncture after application of topical nitroglycerine / placebo (Post-dilation).

2. Number of patients with Procedural failure: Need to abort procedure or convert to transfemoral approach.

3. Patient forearm discomfort or pain during procedure measured using Visual analog scale 0-10, 0 being no discomfort or pain (best) and 10 being worst discomfort or pain (worst).

4. Ipsilateral radial pulse at end of procedure 0-4+, 0 indicating no palpable pulse (worst); 1 + indicating a faint, but detectable pulse; 2 + suggesting a slightly more diminished pulse than normal; 3 + is a normal pulse; and 4 + indicating a bounding pulse (best).

Safety endpoints:

1. Asymptomatic Hypotension: SBP < 90 mm Hg

2. Symptomatic Hypotension: Dizziness or lightheadedness and SBP < 100 mm Hg

3. Intractable headache unrelieved by 1gm of acetaminophen

Adverse Effects of investigational product:

1. Hypotension: SBP < 90 mm Hg requiring intervention any time after application of investigational product (IP) in Ambulatory Cardiac Unit (Same Day) until removal of IP in Cath lab

2. Dizziness or lightheadedness requiring intervention any time after application of IP in Ambulatory Cardiac Unit (Same Day) until removal of IP in Cath lab

3. Headache requiring intervention any time after application of IP in Ambulatory Cardiac Unit (Same Day) until removal of IP in Cath lab

Complications of Radial artery catheterization:

1. Forearm hematoma > 5cm

2. Absent ipsilateral radial pulse (0) after procedure

Methods:

1. Patient enrollment:

a. Outpatient:

i. Whenever feasible, information about the study would be provided to the patient prior to arrival in Ambulatory Cardiac Unit (Same Day) (preferably at the time of scheduling). When not feasible, patients will be contacted via phone prior to the day of procedure or approached in the Ambulatory Cardiac Unit (Same Day) unit on the day of the procedure by one of the investigators to assess interest in participation.

ii. Patients who are interested and meet all inclusion criteria and none of the exclusion criteria will be enrolled in the trial in the Ambulatory Cardiac Unit (Same Day) on the day of their scheduled procedure. One of the participating investigators will obtain informed consent after the patient has had time to review the consent and all questions have been answered.

b. Inpatient:

i. Hospitalized patients who are interested and meet all inclusion criteria and none of the exclusion criteria may be enrolled in the trial on or before the day of their scheduled procedure, but always prior to transfer to the Catheterization Lab. One of the participating investigators will obtain informed consent after the patient has had time to review the consent and all questions have been answered.

2. After reviewing the most current vital signs, patients without any exclusion criteria will be randomized 1:1 to control arm (40 mg Lidocaine + placebo) or study arm (40 mg lidocaine + 30 mg nitroglycerine)

3. Study drug assignment will be randomized and distributed by a delegated member of the study staff, with oversight by the PI or Sub-Is, for patients consented and enrolled in the trial at least 60 minutes prior to the procedure start time.

4. Pre-medication cross sectional image of ipsilateral radial artery (approximately 1 inch proximal to radial styloid process) will be recorded using bedside sonogram with no more than gentle pressure and site marked with a skin marker.

5. Ipsilateral wrist circumference (1 inch proximal to radial styloid process) will be documented.

6. Pre-procedure ipsilateral radial pulse strength (0-4+) will be documented. (4+ Bounding, 3+ Increased, 2+ Normal, 1+ Weak, 0+ Absent or nonpalpable)

7. Transdermal preparation will be applied to ipsilateral wrist overlying radial pulse (centered approximately 1 inch proximal to radial styloid process) at least 60 minutes before procedure start time at a dose of 40mg (6 ribbons of 2 inches each) of 5% Lidocaine and 30mg (8 ribbons of 2 inches each) of 2% Nitroglycerine/Placebo.

8. Patients will complete the Amsterdam Preoperative Anxiety and Information Scale (APAIS).

9. Vitals signs to be checked every 30 minutes (±10 minutes) after application of the topical preparation for 60 minutes (±10 minutes) then every 60 minutes (±10 minutes) until procedure.

10. If SBP < 100 mm Hg and patient complains of dizziness or light-headedness or if SBP < 90 mm Hg, the topical preparation will be removed promptly, 250 ml of 0.9% Normal Saline (NS) IV bolus will be given over 15 minutes, and provider will be notified immediately.

11. If patient complains of headache, one or two tablets of 500 mg acetaminophen will be given by mouth every 4 hours as needed. One tablet will be given if the patient reports a value of 0-3 on the pain scale, and two tablets will be given if the patient reports a value of 4 or greater on the pain scale. The maximum dose of acetaminophen is 4g in 24 hours.

12. If 30 minutes after acetaminophen administration, headache intensity ≥ 5/10 or patient unable to tolerate intensity of headache, the topical preparation will be removed promptly and provider will be notified immediately.

13. If any of the safety endpoints occur, an investigator will be notified immediately and further decision to proceed with cardiac catheterization or additional workup or treatment would be at the discretion of the investigator.

14. Immediately prior to sterile preparation of access site, transdermal preparation will be removed in Cath Lab and post-dilation cross sectional image of ipsilateral radial artery (approximately 1 inch proximal to radial styloid process) will be captured using bedside sonogram applying no more than gentle pressure.

15. Conscious sedation with intravenous fentanyl and midazolam given with exact dosing at operator's discretion (based on patient's hemodynamic status and comorbid conditions).

16. After sterile preparation 0.5 – 1.0 ml of subcutaneous lidocaine is administered and radial artery cannulated using modified seldinger technique with 5F or 6F hydrophilic sheath.

17. Parenteral radial cocktail (IV/IA heparin +/- IA nitroglycerine +/- IA verapamil) is given with exact combination and dose at discretion of operator based on patient's hemodynamic status.

18. Coronary angiogram and or intervention performed adopting best practices with care to minimize procedure time, contrast volume and catheter exchanges and avoiding side branches.

19. Following parameters are documented:

a. Patient demographics (Age, Sex, BMI, Race)

b. Conscious sedation drugs and doses used

c. Sheath size

d. Number of arterial sticks before arterial access: One or more (Blood in arteriotomy needle equates arterial stick)

e. Wire passage in one or more attempts

f. Sheath insertion in one or more attempts

g. Radial parenteral cocktail used

h. Radial artery spasm score:

i. Verbal or nonverbal expression of discomfort in the forearm during catheter/sheath manipulation – Absent:0; Present:1

ii. Difficulty in manipulating the catheter – Absent:0; Present:1

iii. Difficulty in sheath removal – Absent:0; Present:1

iv. Additional use of intraarterial nitroglycerine or verapamil after the initial vasodilator cocktail for suspected radial artery spasm – No:0; Yes:1

i. Use of long sheath

j. Use of hydrophilic wires or catheters

k. Tortuosity of UE vessels / anatomic variants

l. Catheters used

m. Contrast volume

n. Difficulty in removing catheters and sheath

o. Use of IA/IV NTG and/or verapamil at end of procedure for sheath removal: provisional use when radial artery spasm present or suspected vs. routine pre-emptive use to avoid radial artery spasm per operator standard practice.

p. Length of procedure

q. Change to femoral arterial access and reason

r. Procedures performed

20. Patient's perceived peri-procedure forearm discomfort documented using VAS (1-10) at the completion of the procedure

21. Post procedure strength of ipsilateral radial pulse (0-4+) after radial band removal documented and presence and size of hematoma at access site at time of radial band removal documented

22. For patients who have the sheath left in place for percutaneous coronary intervention (PCI) as a separate procedure at a later time, data will be collected for the initial diagnostic catheterization only. The procedure will be considered completed with removal of last diagnostic catheter. Post procedure pulse will be the radial pulse after the PCI.

23. Patients are monitored for adverse events for the following duration:

a. For patients discharged home from the ambulatory cardiac unit (same day unit) after procedure completion:

i. Until discharged home

b. For hospitalized patients:

i. Until 120 minutes after Radial band, or comparable product, removal

Inclusion criteria:

1. Age: 18 years or older
2. Radial artery catheterization +/- intervention

Exclusion criteria:

1. Hypersensitivity or contraindication to lidocaine
2. Hypersensitivity or contraindication to nitroglycerine
3. Recent use of PDE5 inhibitors (<24 hours after sildenafil or vardenafil; <48 hours after tadalafil)
4. Baseline weak radial pulse (0 or 1+)

5. Baseline hypotension SBP < 100mmHg at the time of enrollment
6. Dizziness or light-headedness at the time of enrollment
7. Severe Aortic Stenosis or HOCM
8. Previous unknown bypass grafts or known LIMA graft
9. Chest pain within 6 hours of IP administration
10. More than 2 episodes of chest pain within 24 hours prior to IP administration
11. Use of sublingual, transdermal, or intravenous nitroglycerine within 6 hours prior to IP administration
12. Likely need for use of nitroglycerine for non-study indication
13. Narcotic or sedative within 4 hours of enrollment
14. Women who are suspected or known to be pregnant or breastfeeding

Processing of cross sectional sonographic images of radial artery:

1. Horizontal diameter
2. Vertical diameter
3. Average diameter
4. Cross Sectional area
5. Presence of atherosclerotic plaque

Data and Safety Monitoring Plan

A data safety monitoring committee will be assigned to review each case for eligibility, adherence to the protocol, occurrence of adverse events, and accuracy of data. This will be completed on a regular basis. The first review will be conducted after enrolling the first 10 patients. Regular reviews will be scheduled at increments of 50 randomized patients until enrollment goals are met. Any deficiencies found during this review will be addressed and reported to necessary parties.

Statistical Analysis

Outcomes will be analyzed by intention to treat analysis using SPSS software. Relationship between use of nitroglycerine and radial spasm will be analyzed using Pearson Chi Square test. The radial artery dimensions before and after application of the study drug or placebo will be compared using paired sample t test. Relationship between use of nitroglycerine and procedural failure will be analyzed using Pearson Chi Square test. Relationship between use of nitroglycerine and forearm discomfort or pain during procedure measured using Visual analog

scale will be analyzed using Mann Whitney test. The post procedure pulse will be analyzed using Mann Whitney test.

Privacy Protections

It is not possible to conduct this research study without access to and the use of the patients' medical record information. The researcher (s) will only obtain the minimum necessary data to achieve the goals of the research. The data collected is not sensitive in nature. In this research project access to and the use of participants PHI involves no more than minimal risk to the privacy of the individual because the investigator(s) is (are) directly involved in the care of respective subjects as part of their patient care responsibilities. Granting of a Partial Waiver of HIPAA authorization for recruitment purposes will not adversely affect the privacy of the involved patients or the confidentiality of their medical record information.

Confidentiality Protections

Identifiable health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted research purposes. Research records will be secured in a locked file cabinet in an access-controlled office. Electronic records will be maintained on an Aultman server using identification and secure password. Records containing PHI will be limited in access to the research team only.

Research records will be securely stored in accordance with retention requirements of local and national regulations. The minimum obligations will be six (6) years following study closure. The ICF states that patient records will be stored up to 10 years. After this time records may be destroyed, the method of destruction will be by shredding per institutional policy.

Information from the study may be published in study reports, scientific journals or presented at scientific meetings; however, the individual and group identity will be kept strictly confidential. Only with specific permission can names or other identifiers used in any publication or teaching material.

HIPAA Authorization

The researcher will obtain an Authorization to Use and/or Disclose of Individually Identifiable Health Information for Research Purposes as part of the informed consent process (see attached consent document). The following individuals/organizations may have access to research data but are required to make sure the information is kept private, unless required by law to provide information:

- The Aultman Cardiology Research Group is sponsoring this study. The following individuals/organizations may inspect the research records. The Human Research Review Board, HRRB, is a group of people who review the research with the goal of protecting the people who take part in the study.

- The research staff, including the Principal Investigator and Sub-Investigators listed on page one of this document, along with other members of the research team responsible for collecting and analyzing data.
- The Food and Drug Administration

Pre- Procedure anxiety evaluation:

The Amsterdam Preoperative Anxiety and Information Scale (APAIS)

	Not at all	1	2	3	4	5	Extremely
1. I am worried about the sedation		☐	☐	☐	☐	☐	
2. The sedation is on my mind continually		☐	☐	☐	☐	☐	
3. I would like to know as much as possible about the sedation		☐	☐	☐	☐	☐	
4. I am worried about the procedure		☐	☐	☐	☐	☐	
5. The procedure is on my mind continually		☐	☐	☐	☐	☐	
6. I would like to know as much as possible about the procedure		☐	☐	☐	☐	☐	

Below information will be calculated later based on patient replies for above questions but will not be included in the patient form

The subscales

Sedation-related anxiety	Sum A = 1 + 2
Surgery-related anxiety	Sum S = 4 + 5
Information desire component	= 3 + 6
Combined anxiety component	Sum C = sum A + sum S (1 + 2 + 4 + 5)

Visual Analog Scale for peri-procedure pain: