Title: Randomized C**O**mparison of Isolated Radial Artery Com**Pr**Essio**N** versus **Radial** and Ipsilateral Ulnar Artery Compression in Achieving Radial Artery Patency: OPEN-Radial Trial

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STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

The study was conducted at a tertiary care center in India. The protocol was reviewed and approved by the local institutional review board.

Inclusion criteria: Patients referred for cardiac catheterization using TRA.

Exclusion criteria:

1: Patients with a history of previous ipsilateral TRA.

2: Warfarin anticoagulated patients or patients on novel oral anticoagulant compounds.

3: Patients requiring continuous intravenous heparin infusion for any indication.

4: Presence of plethysmographic waveform when both radial and ulnar arteries were occlusively compressed (suggestive of presumed interosseous artery related digital plethysmographic waveform).

5: Absence of palpable ulnar pulse.

6: Lack of informed consent.

Primary study endpoints:

The primary study endpoint was achievement of patent hemostasis, defined as presence of radial artery patency at 15 minutes after onset of hemostatic compression of radial artery, using plethysmographic technique as described below.

Secondary study endpoint:

The secondary study endpoint was RAO evaluated by plethysmographic technique, 1-hour after the removal of hemostatic compression device was the secondary study endpoint.

All patients underwent Barbeau's test before the procedure, although TRA was performed if inclusion criteria were met. Reverse Barbeau test was also performed before the procedure, when the ipsilateral ulnar artery was transiently compressed in conjunction with radial artery compression, while plethysmographic waveform monitoring was in progress with the sensor placed on ipsilateral index finger. Total absence of waveform while both arteries were compressed was necessary for inclusion into the trial. Upon release of the radial artery, return of the waveform was considered evidence of patency of radial artery at baseline. Randomization scheme is depicted in the CONSORT diagram shown in Figure 1. Patients randomized to Group 1 received hemostasis post-procedure using TR Band (Terumo Interventional Systems, Japan), and Group 2, using VASOBand (VASOInnovations Inc., Los Angeles, California, USA).

Transradial Procedure:

The patients underwent standard preparation with infiltration of lidocaine using a 25-gauge short needle at the distal forearm in the vicinity of the radial pulse, 2 to 3 finger breadths above the wrist joint. Using a micropuncture system and counter-puncture technique,[11] a 5-French hydrophilic-coated 7 cm introducer sheath (Radiofocus^{TM}, Terumo, Japan) was placed

in the radial artery. A vasodilator cocktail containing of 200 µg of nitroglycerin and 2.5 mg of verapamil was administered intra-arterially via the introducer. 5000 U bolus of unfractionated heparin was administered intravenously after placement of the sheath. The remainder of the procedure was completed following the standard routine with coronary angiography performed using catheters deemed necessary by the primary operator.

Hemostasis protocol:

Group 1: Patients randomized to Group 1 received hemostatic compression using TR Band. The band was applied by placing the green centering marker 2 to 3 mm proximal to the skin entry site, at the presumed arteriotomy site, and after securing the band around the forearm circumferentially using Velcro, the inflatable bladder was inflated using air in a standard fashion. The introducer sheath was then gently removed and the inflated bladder was gently deflated to the point where a small amount of bleeding was noted at the skin puncture site, at which point the bladder was re-inflated to achieve dry hemostasis using the lowest necessary amount of air injected into the bladder. The care team was allowed adjustment in hemostatic pressure throughout the hemostatic compression period and followed the patent hemostasis protocol. The band was left in place for a minimum duration of 120 minutes. After 120 minutes, the band bladder was gradually deflated over 15 minutes and the band was removed if there was no bleeding. Inadequate hemostasis was treated with hemostatic pressure adjustment at any time during the hemostatic process. If rebound bleeding occurred, the band was re-inflated and hemostatic compression was reapplied for 30 minutes after which the weaning process was repeated, and the band was removed.

Group 2: Patients randomized to Group 2 received hemostatic compression using VASOBand. VASOBand was placed on the forearm, with the distal edge of the band aligned with the crease of the wrist and the band was secured circumferentially around the forearm using Velcro. Ulnar balloon was inflated using 15 ml of air. Radial balloon was inflated using 15 to 20 ml of air, the introducer sheath was removed, and the radial bladder was then deflated to observe a small amount of bleeding at the skin puncture site, after which it was inflated with the smallest necessary volume of air to achieve dry hemostasis. Ulnar balloon was deflated after 60 minutes of onset of compression by the care team. At this point, hemostatic pressure adjustment was allowed if deemed necessary by the care team. No other adjustments in hemostatic pressure were made. After 120 minutes, as per the institution's protocol, the band compression pressure was weaned over 15 minutes and the band was removed. If rebound bleeding occurred, the band was re-inflated and hemostatic compression was reapplied for 30 minutes after which the weaning process was repeated, and the band was removed. A dry dressing was applied with minimal pressure at the puncture site to cover the dermotomy. Inadequate hemostasis was treated with hemostatic pressure adjustment at any time during the hemostatic process.

Evaluation of radial artery patency:

In Group 1 patients, radial artery patency was evaluated by performing reverse Barbeau test. Ipsilateral ulnar artery at the distal forearm, and the radial artery proximal to the band were occlusively compressed while observing the plethysmographic waveform with a plethysmograph sensor placed on the ipsilateral index finger. Absence of waveform was noted. Then while transiently maintaining ulnar artery occlusive compression, radial artery was released. Presence of plethysmographic waveform was considered evidence of radial artery patency.

In Group 2 patients, the plethysmographic sensor was placed on the ipsilateral index finger. Absence of waveform was considered evidence of radial artery occlusion. If waveform was present, the radial artery was compressed proximal to the band, in the mid-forearm, with adequate compression to eliminate the palpable pulse at that point. Absence of a plethysmographic waveform at this time confirmed occlusive ipsilateral ulnar artery compression. Upon release of radial artery compression proximal to the band in the mid-forearm region, return of plethysmographic waveform was considered evidence of radial artery patency with presence of antegrade flow.

A separate team evaluated radial artery patency after the application of the band, and at 15 minutes, 60 minutes, 90 minutes and 120 minutes after band application. If the band compression exceeded 120 minutes, patency was evaluated at 30-minute intervals after 120 minutes. Radial artery patency was evaluated at the time of discharge, at a minimum of 60 minutes after the band was removed and the dressing was applied. Findings of radial artery patency obtained by the monitoring team were blinded from the clinical care team. The care team performed their own patency evaluation following the local “patent hemostasis” routine after onset of hemostatic compression. All equivocal plethysmographic tests were evaluated by performing radial artery duplex Doppler ultrasonography.

Demographic, laboratory, as well as procedural variables were recorded upon enrollment. Post procedural variables including systolic blood pressure, diastolic blood pressure, presence of pain at the forearm, and difficulty in hardware transit during the procedure suggestive of spasm, and occurrence of hand pain throughout the procedural and post-procedural predischarge course were also recorded.

Statistical Analysis:

Categorical variables were expressed as proportions, and differences between the two groups were assessed using Chi-square test, or Pearson test as deemed appropriate. Numeric variables were assessed for normality of the distribution and were expressed as mean and standard deviation for normally distributed variables, and median as well as interquartile range for those without normal distribution. Parametric tests were used to compare differences between the two groups for normally distributed numeric variables, and nonparametric tests were used in those variables with a non-normal distribution. Paired t-test was performed to compare serial blood pressure observations. Binary logistic regression was performed to identify independent predictors of RAO. Mediation analysis was performed to identify potential mechanistic basis of the effect observed in the treatment (VASOBand) group.

Sample Size Calculation:

Based on the available literature, using the current standard of care TR Band, sample size was calculated for our primary study endpoint, achievement of patent hemostasis as defined above. We used an optimistic 80% patent hemostasis rate in the TR Band group in view of the high level of training of the research site in preventing RAO. The only published randomized trial using prophylactic ipsilateral ulnar artery compression during radial artery hemostatic compression has shown 96% achievement of patent hemostasis at 15 minutes after onset of compression. Using 80% rate of patent hemostasis in single-balloon band (TR Band) group and 95% rate of patent hemostasis in the dual-balloon band (VASOBand) group, a Chi-square model provided a sample size of 194 patients equally divided between two groups, necessary to achieve a 90% power with an alpha error of .05. Average incidence of RAO 1-hour after removal of

hemostatic compression device, using the findings from recent trials reporting RAO rates at < 24 hours sampling[5,9,12] was expected to occur in 11% of patients in TR-Band group and 1.5% in the experimental group, providing a sample size of a total of 250 patients in order to have a 90% chance of detecting a difference in the secondary end-point of RAO with an alpha=.05. It is important to note that RAO incidence is very dependent on time of evaluation after the procedure, data from recent studies mentioning the time point of RAO evaluation were used for sample size calculation. SPSS 26 (IBM Corporation, Armonk, NY) statistical software was used for the analyses.