

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open-label randomized controlled trial (Protocol)
AUTHORS	Aijaz, Saba; sheikh, sana; Pathan, Asad

VERSION 1 – REVIEW

REVIEWER	Dr Sunil Nadar Sultan Qaboos University Hospital, Muscat, Oman
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	<p>Minor grammatical errors scattered throughout. For example, last sentence of introcution "lastly" should be replaced by "Finally". In the methods section "himself/herself" could be deleted. Similarly "some participants "might be" rather than "can be" It will need to be checked by someone proficient in the language.</p> <p>In your protocol, for the treatment arm, for those who get discharged on the same day, when do you assess for RAO?</p> <p>In the intervention group there is 10 ml air but in control group you start with 12ml air in the TR band</p> <p>Again in the control group, you start deflating much later than the intervention group. So inherently you have a bias towards early deflation in the intervention group. The deflation protocols should be similar in both groups to truly assess any difference in deflation times.</p> <p>When you say that you will exclude patients on anticoagulation post procedure will that include injectable gpIIb/IIIa inhibitors as well?</p> <p>As RAO rates is your primary end point, you have not mentioned when that will be assessed in those being discharged on the same day. Similarly it is not enough to assess it within 24 hours and will need to be examined atleast at 3 months, 6 months or one year. Within 24 hours it could just be spasm.</p>
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REVIEWER	Eneida Rejane Rabelo Da Silva Universidade Federal do Rio Grande do Sul - Nursing School Hospital de Clínicas de Porto Alegre Heart Failure Clinic -Cardiology Division Vascular Access Program Porto Alegre, RS Brazil
REVIEW RETURNED	16-Aug-2020

GENERAL COMMENTS	The primary endpoint could be clear on the aim of the study.
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	<p>I have a concern about block randomization. It can leave weaknesses in the manuscript. I have a suggestion: to make it clear that no researcher will know the proportions in the randomization blocks.</p> <p>I think that compose endpoint could be more clear, because the bleeding could be more frequent than hematoma in transradial procedures. I found the rate of hematoma very high in the pilot.</p> <p>how will the quantitative variables be compared at the baseline?</p> <p>The authors pretend to use the univariate and multivariate analysis be carried out?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer's comments	Responses	Actions
Reviewer 1:		
-Minor grammatical errors scattered throughout. For example, last sentence of introduction "lastly" should be replaced by "Finally". In the methods section "himself/herself" could be deleted. Similarly " some participants "might be" rather than "can be" It will need to be checked by someone proficient in the language.	Thanks for identifying the errors. Document is now checked with the professional English language software.	
-In your protocol, for the treatment arm, for those who get discharged on the same day, when do you assess for RAO?	-A valid question. For patients discharging on the same day, RAO will be checked at the time of TR band removal after leaving it at zero pressure for 30 minutes in both arms. The statement is added in the protocol.	Lines 158-160, pg 6 Lines 182-184, pg 7
-In the intervention group there is 10 ml air but in control group you start with 12ml air in the TR band Again in the control group, you start deflating much later than the intervention group. So inherently you have a bias towards early deflation in the intervention group. The	Reviewer has rightly pointed out the difference in protocol between two arms. We conducted a pilot on 100 patients; InnoSEAL+ TR band and TR band both. The pilot was done to define our intervention protocol. Our intention was to assess the	

<p>deflation protocols should be similar in both groups to truly assess any difference in deflation times.</p>	<p>feasibility of applying same air volume and deflation time as our intervention arm. We found that patients bleed profusely if we reduce the air below 12 cc and start deflating air earlier than 90 minutes in TR band arm. Also, we were able to achieve patent hemostasis in TR band with the given air volume. In order to ensure patient safety we decided to use the mentioned protocol in the control arm.</p>	
<p>-When you say that you will exclude patients on anticoagulation post procedure will that include injectable gpIIb/IIIa inhibitors as well?</p>	<p>Yes, we are excluding patients on injectable gpIIb/IIIa inhibitors.</p>	<p>Lines 105-107, pg 4</p>
<p>-As RAO rate is your primary end point, you have not mentioned when that will be assessed in those being discharged on the same day.</p>	<p>It has been answered above For patients discharging on the same day, RAO will be checked at the time of TR band removal after leaving it at zero pressure for 30 minutes in both arms. The statement is added in the protocol.</p>	
<p>-Similarly it is not enough to assess it within 24 hours and will need to be examined atleast at 3 months, 6 months or one year. Within 24 hours it could just be spasm.</p>	<p>We understand the reviewer's concern regarding primary outcome assessment. However, the literature suggests that RAO is likely to occur within 24 hours. Avdikos et al. in their review stated that 50% of RAO is re-canalized within 1-3 months.</p> <p>-Avdikos G, Karatasakis A, Tsoumeleas A, Lazaris E, Ziakas A, Koutouzis M. Radial artery occlusion after transradial coronary catheterization. Cardiovascular diagnosis and therapy. 2017 Jun;7(3):305.</p>	
<p>Reviewer 2:</p>		
<p>-The primary endpoint could be clear on the aim of the study.</p>	<p>Thanks for pointing out. It is rephrased.</p>	<p>Lines 89-90, pg4</p>

<p>-I have a concern about block randomization. It can leave weaknesses in the manuscript. I have a suggestion: to make it clear that no researcher will know the proportions in the randomization blocks.</p>	<p>We appreciate reviewer's suggestion. The randomization is central by the neutral person not involved in the study. The data collectors are informed about the randomization allocation right before the removal of sheath. None of the study investigators or data collectors is aware of the randomization block sizes in use.</p>	
<p>-I think that composite endpoint could be more clear, because the bleeding could be more frequent than hematoma in transradial procedures. -I found the rate of hematoma very high in the pilot.</p>	<p>Agree with the reviewer that hematoma can be less frequent. Bleeding we have categorized as the adverse event hence cannot be included in composite end point.</p> <p>Rates of hematoma have been reported ranging from 10-23% in literature for transradial PCI.</p> <p>-Garg N, Umamaheswar KL, Kapoor A, Tewari S, Khanna R, Kumar S, Goel PK. Incidence and predictors of forearm hematoma during the transradial approach for percutaneous coronary interventions. Indian heart journal. 2019 Mar 1;71(2):136-42.</p> <p>- Hahalis, G.N., Leopoulou, M., Tsigkas, G., Xanthopoulou, I., Patsilidakos, S., Patsourakos, N.G., Ziakas, A., Kafkas, N., Koutouzis, M., Tsiafoutis, I. and Athanasiadis, I., 2018. Multicenter randomized evaluation of high versus standard heparin dose on incident radial arterial occlusion after transradial coronary angiography: the SPIRIT OF ARTEMIS study. JACC: Cardiovascular Interventions, 11(22), pp.2241-2250.</p>	

-How will the quantitative variables be compared at the baseline?	It is added in the protocol.	Lines 241-243, pg 9
-The authors pretend to use the univariate and multivariate analysis be carried out?	The plan is to conduct univariate analysis. If baseline characteristics of both group were found significantly different then multivariate analysis can be undertaken to adjust those variables. Hope this addresses the question.	

VERSION 2 – REVIEW

REVIEWER	Dr Sunil Nadar Sultan Qaboos University Hospital, Oman
REVIEW RETURNED	13-Oct-2020

GENERAL COMMENTS	The authors have addressed most of my concerns. However I still feel you need to assess the rate of radial artery occlusion at a later time point such as 6 months or one year. The response given by the authors is that 50% recanalisation occurs within 3 months so they only check at 24 hours. However what is clinically relevant is long term radial artery occlusion and not short term occlusion which could be spasm (which the radial artery is very pro
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REVIEWER	Eneida Rejane Rabelo-Silva Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
REVIEW RETURNED	16-Oct-2020

GENERAL COMMENTS	<p>Thank you for the opportunity to review this paper. Please, the file that you sent to the Journal, are still with a word track and I think that it is not a final version, please check it.</p> <p>Please make sure that the only difference between groups will be InnoSEAL ? It is not clear.</p> <p>For patients discharged from the hospital on the same day, how will be assessed the primary outcome?</p> <p>The Barbeau's test will be realize before the procedure or time admission? This is important measure this variable on the baseline.</p> <p>For the interim analysis, you must present the sample estimate for this analysis, it is not simply reaching 50% of this and stop, please make sure of this approach.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

The authors have addressed most of my concerns. However I still feel you need to assess the rate of radial artery occlusion at a later time point such as 6 months or one year. The response given by the authors is that 50% recanalisation occurs within 3 months so they only check at 24 hours. However what is clinically relevant is long term radial artery occlusion and not short term occlusion which could be spasm (which the radial artery is very pro

Response:

The investigators discussed the reviewer's comment and agreed to re-assess the occlusion at 6 months. It is added in the protocol. Line 165, pg 6
Line 190, pg 7

Reviewer 2:

-Thank you for the opportunity to review this paper. Please, the file that you sent to the Journal, are still with a word track and I think that it is not a final version, please check it.

Response: Thanks for pointing it out. The clean copy has been uploaded.

-Please make sure that the only difference between groups will be InnoSEAL? It is not clear.

Response: The difference between the two arms will be InnoSEAL as TR band is applied in both the arms.

The time difference to achieve patent hemostasis in both the arm is inherent.

As explained previously, we decided on the time to achieve patent hemostasis after conducting a pilot on 100 patients; InnoSEAL+ TR band and TR band alone. The pilot was done to define our intervention protocol. Our intention was to assess the feasibility of applying same air volume and deflation time as our intervention arm. We found that patients bleed profusely if we reduce the air below 12 cc and start deflating air earlier than 90 minutes in TR band arm. In order to ensure patient safety we decided to use the mentioned protocol in the control arm.

Even if we would have kept the same time window for both the arms, TR band would have had higher re-bleeds than InnoSEAL.

-For patients discharged from the hospital on the same day, how will be assessed the primary outcome?

Response: For patients discharging on the same day, RAO will be checked at the time of TR band removal after leaving it at zero pressure for 30 minutes in both arms. The statement is added in the protocol.

We have added the follow up of RAO patients at 6 months also. Line 165, pg 6

Line 190, pg 7

-The Barbeau's test will be realized before the procedure or time admission? This is important measure this variable on the baseline.

Response: Valid point. It is being checked before the cath procedure as routine. Barbeau's class D or positive history of RAO is our exclusion hence it is being checked for all patients. Lines 109-110, pg 4

-For the interim analysis, you must present the sample estimate for this analysis, it is not simply reaching 50% of this and stop, please make sure of this approach.

Response: We are thankful to the reviewer for warning us. The statement has been removed.