

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Axillary versus Innominate Artery Cannulation for Antegrade Cerebral Perfusion in Aortic Surgery: Design of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial
AUTHORS	Garg, Vinay; Peterson, Mark; Chu, Michael; Ouzounian, Maral; Macarthur, Roderick; Bozinovski, John; El-Hamamsy, Ismail; Chu, F Victor; Garg, Ankit; Hall, Judith; Thorpe, Kevin; Dhingra, Natasha; Teoh, Hwee; Marotta, Thomas; Latter, David; Quan, Adrian; Mamdani, Muhammad; Jüni, Peter; Mazer, David; Verma, Subodh

VERSION 1 - REVIEW

REVIEWER	Hiroo Takayama Columbia University, USA
REVIEW RETURNED	20-Dec-2016

GENERAL COMMENTS	<p>The investigators described a randomized control trial comparing axillary vs. innominate artery perfusion strategies for antegrade cerebral perfusion during the open distal anastomosis for the aortic arch surgery. The topic is quite relevant and important for the contemporary aortic surgery. Overall the study is very interesting; however, I have a significant concern on its sample size calculation. The authors defined the 'severe' ischemic lesions, and estimated its incidence to be 50%. This is clearly much higher than the reported incidence of clinically diagnosed strokes/TIAs or neurological complications. Moreover, the referenced study is a neonatal study. Use of this number (50%) as the primary end point of 'severe' ischemic lesions requires more justification either by providing more data, such as other relevant references and/or preliminary data. Another provided reference is stating these lesions as 'silent' ones, which appeared more clinically relevant. Also important, difference of 25% was considered acceptable as 'non-inferiority' margin. This could theoretically result in 75% of the study arm patients developing 'severe' ischemic lesions and being considered 'non-inferior'. This condition seems quite controversial.</p> <p>Other rather minor comments are as follow:</p> <p>Is bilateral perfusion allowed? For instance, if the cerebral oximetry shows impaired perfusion in the contralateral side, can the surgeon insert a perfusion cannula into the left carotid artery, or clamp the left carotid artery?</p> <p>What is the consideration in the occurrences of early postoperative death or significant neurological complication such as coma, which might exclude performing DWMRI?</p> <p>The study will be an important contribution to the cardiovascular surgery, and thank you very much for allowing me to review this</p>
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	proposal.
REVIEWER	Bektas Battaloglu Inonu University Faculty of Medicine Department of Cardiovascular Surgery Malatya-TURKEY
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	<p>Despite important developments in surgical techniques, repairing proximal aortic aneurysms that require open distal anastomosis is still associated with considerable mortality and morbidity. As the authors have noted, this problem is mainly related to intraoperative cerebral protection techniques and brain injury. Therefore studies aimed at finding the best way for cerebral protection have vital importance in terms of preventive measures. In this aspect, this study is very important. However, the study protocol has some weaknesses that I have listed below:</p> <p>1- Although they occur in different locations, for unilateral antegrade cerebral perfusion via axillary and innominate artery cannula the same area are feeded. Especially when axillary artery cannulation is performed through a side graft, perfused area will be identical (exactly the same). Therefore, it is probable that both methods will create the same effect on cerebral protection.</p> <p>2- During surgery of the proximal aortic aneurysms that require open distal anastomosis, direct aortic cannulation for whole body perfusion may not be always possible or this may cause some problems. In the presence of serious aortic calcifications or atheromatous plaques that spread to the aortic arc, severe aortic wall thinning or thickening direct aortic cannulation will not be eligible. In such cases, possible consequences and decision for total body perfusion should be axillary, femoral or innominate artery cannulation. In aortic surgery practice, many surgeons use innominate artery cannulation for whole body as well as unilateral antegrade cerebral perfusion in eligible patients. Hence, surgeons are advised to avoid performing additional incision for cannulation.</p> <p>Recommendations: In addition to assessing brain damage, it may be a good idea to include a comparison of the technical application of both methods and results in order to establish a stronger framework for the study.”</p>
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REVIEWER	Matthew Mosca, MS CCP University of Colorado Hospital, Aurora, CO, USA
REVIEW RETURNED	04-Feb-2017

GENERAL COMMENTS	<p>Overall, the authors have created an impressive and detailed randomized controlled trial that will compare the effectiveness of innominate artery cannulation and axillary artery cannulation for antegrade cerebral perfusion during circulatory arrest. The authors have chosen a variety of clinically relevant endpoints that assess both anatomical and functional neurological status. Please consider the following suggestions as they may improve the quality of the manuscript:</p> <p>Keywords:</p> <p>Consider replacing the 5th keyword (open distal anastomosis) with a</p>
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	<p>keyword related to the temperature at which circulatory arrest will be performed in this RCT (deep hypothermia or moderate hypothermia). The abstract mentions moderate hypothermia but the main manuscript refers to deep hypothermia multiple times.</p> <p>Abstract:</p> <p>Consider highlighting a few secondary endpoints. One of the strengths of this study is that it will incorporate a variety of endpoints that assess both anatomical and functional neurological status. Please also add that this RCT will be a multicenter trial and that the type of antegrade cerebral perfusion being explored is unilateral. The last sentence of the abstract mentions that "...the innominate artery cannulation technique as a safe and potentially more efficient method of antegrade cerebral perfusion..." The study will only be able to conclude this if utilizing 2-sided P testing. This study plans on using 1-sided P testing, so innominate can only be stated as "non-inferior" to axillary.</p> <p>Section titled "Cerebral Protection Strategies in Aortic Arch Surgery":</p> <p>The temperature is reported as 24 to 26 degrees but the paragraph refers to DHCA. If the circulatory arrest was performed at 24-26 degrees then the wording should refer to moderate hypothermia. Please fix this throughout the manuscript as DCHA appears multiple times.</p> <p>Section titled "Proposed frequency and duration of follow-up":</p> <p>Consider including the type of NIRS monitors used as results may vary according to different manufacturers.</p> <p>Other:</p> <p>There are a number of secondary endpoints planned for this study. The authors should consider adding how they might adjust for multiple comparison errors. If the authors plan to do this then it should be included in the statistical analysis methodology.</p> <p>Consider using 2-sided P testing to include the possibility that innominate cannulation may actually be superior to axillary cannulation. The "non-inferiority" design may be attractive because it may limit the required sample size, but a really important conclusion from this study could be that innominate cannulation is superior to axillary. Unless this study is limited by sample size and time, I would recommend using 2-sided P testing.</p> <p>Final Comments:</p> <p>I would like to commend the authors on a well designed study. This type of RCT has been needed for some time, and I enthusiastically await the results.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
 Reviewer Name: Hiroo Takayama
 Institution and Country: Columbia University, USA
 Competing Interests: None declared.

The topic is quite relevant and important for the contemporary aortic surgery. Overall the study is very interesting; however, I have a significant concern on its sample size calculation.

The authors defined the 'severe' ischemic lesions, and estimated its incidence to be 50%. This is clearly much higher than the reported incidence of clinically diagnosed strokes/TIAs or neurological complications. Moreover, the referenced study is a neonatal study. Use of this number (50%) as the primary end point of 'severe' ischemic lesions requires more justification either by providing more data, such as other relevant references and/or preliminary data. Another provided reference is stating these lesions as 'silent' ones, which appeared more clinically relevant. Also important, difference of 25% was considered acceptable as 'non-inferiority' margin. This could theoretically result in 75% of the study arm patients developing 'severe' ischemic lesions and being considered 'non-inferior'. This condition seems quite controversial.

Response: Thank you for the positive comments. While a 50% incidence of ischemic lesions on DW-MRI is higher than the clinical event rate for diagnosed strokes/TIAs or neurologic complications, we intentionally utilized DW-MRI as a marker of neurologic injury given that the clinically diagnosed stroke event rate in the post aortic surgery period is generally acknowledged to underestimate the burden of disease. In addition, the reported incidence of clinical events would require a very large sample size. Furthermore, there is emerging data that ischemic lesions noted on DW-MRI are a reasonable surrogate endpoint for neuronal injury in this patient population, and provide a more objective assessment as opposed to the clinical diagnosis of neurologic events (1-4). Moreover, an estimate of 50% for ischemic lesions on DW-MRI is reasonable given literature which shows a range even as high as 70% for ischemic lesions noted on DW-MRI (4-7) The non-inferiority margin was based on a consensus by experts in cardiac surgery, anaesthesia, and neuroradiology; if the true incidence of DW-MRI lesions is 70% as has been previously reported, we will have 70% power of excluding a 20% non-inferiority margin.

References:

1. Meller SM, Baumbach A, Voros S, et al. Challenges in cardiac device innovation: is neuroimaging an appropriate endpoint? Consensus from the 2013 Yale-UCL Cardiac Device Innovation Summit. *BMC Med* 2013;11:257.
2. Samim M, Agostoni P, Hendrikse J, et al. Embrella embolic deflection device for cerebral protection during transcatheter aortic valve replacement. *J Thorac Cardiovasc Surg* 2015;149:799-805 e1-2.
3. Bolotin G, Huber CH, Shani L, et al. Novel emboli protection system during cardiac surgery: a multi-center, randomized, clinical trial. *Ann Thorac Surg* 2014;98:1627-33; discussion 33-4.
4. Hill MD, Martin RH, Mikulis D, et al. Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2012;11:942-50.
5. Stolz E, Gerriets T, Kluge A, et al. Diffusion weighted- magnetic resonance imaging and neurobiochemical markers after aortic valve replacement: Implications for future neuroprotective trials? *Stroke* 2004;35:888-892.
6. Sun X, Lindsay J, Monsein LH, et al. Silent brain injury after cardiac surgery: A review. *J Am Coll Cardiol* 2012;60:791-7.

7. Song S, Yoo K, Shin YR, et al. Diffusion-weighted magnetic resonance imaging lesions after repair of acute type A aortic dissection: association with neurocognitive outcomes. *Eur J Cardiothorac Surg* 2014;1-7.

Other rather minor comments are as follow:

Is bilateral perfusion allowed? For instance, if the cerebral oximetry shows impaired perfusion in the contralateral side, can the surgeon insert a perfusion cannula into the left carotid artery, or clamp the left carotid artery?

Response: Clamping of the left carotid is allowed. The surgeon is permitted to insert a left carotid catheter if the surgeon has clinical concerns about reduced left carotid perfusion for either group. This would be recorded. Of note, the incidence of unilateral malperfusion, with a single sided perfusion strategy such as described in this study is quite low (1).

Reference:

1. Urbanski P, Lenos A, Kolowca M et al. Near-infrared spectroscopy for neuromonitoring of unilateral cerebral perfusion. *Eur J Cardiothorac Surg* 2013; 43: 1140-1144.

What is the consideration in the occurrences of early postoperative death or significant neurological complication such as coma, which might exclude performing DWMRI?

Response: We would request a post-mortem examination in all causes of early death, to determine if neurological events contributed to the death. We expect the 30-day mortality rate to be quite low, thus it will have minimal effect on the statistical analysis. The postoperative MRI is to be done as soon as feasible postoperatively and our sample size was calculated with a 10% attrition rate to account for such cases as inability to perform the post-operative DW-MRI. We will record and publish reasons as to why these DW-MRIs could not be completed.

The study will be an important contribution to the cardiovascular surgery.

Response: Thank you.

Reviewer: 2

Reviewer Name: Bektas Battaloglu

Institution and Country: Inonu University Faculty of Medicine, Department of Cardiovascular Surgery, Malatya-TURKEY

Competing Interests: None declared

Despite important developments in surgical techniques, repairing proximal aortic aneurysms that require open distal anastomosis is still associated with considerable mortality and morbidity. As the authors have noted, this problem is mainly related to intraoperative cerebral protection techniques and brain injury. Therefore studies aimed at finding the best way for cerebral protection have vital importance in terms of preventive measures. In this aspect, this study is very important. However, the study protocol has some weaknesses that I have listed below:

1- Although they occur in different locations, for unilateral antegrade cerebral perfusion via axillary and innominate artery cannula the same area are feeded. Especially when axillary artery cannulation is performed through a side graft, perfused area will be identical (exactly the same). Therefore, it is probable that both methods will create the same effect on cerebral protection.

2-During surgery of the proximal aortic aneurysms that require open distal anastomosis, direct aortic cannulation for whole body perfusion may not be always possible or this may cause some problems.

In the presence of serious aortic calcifications or atheromatous plaques that spread to the aortic arch, severe aortic wall thinning or thickening direct aortic cannulation will not be eligible. In such cases, possible consequences and decision for total body perfusion should be axillary, femoral or innominate artery cannulation. In aortic surgery practice, many surgeons use innominate artery cannulation for whole body as well as unilateral antegrade cerebral perfusion in eligible patients. Hence, surgeons are advised to avoid performing additional incision for cannulation.

Recommendations:

In addition to assessing brain damage, it may be a good idea to include a comparison of the technical application of both methods and results in order to establish a stronger framework for the study.

Response:

1) Our hypothesis is that the cerebral protection afforded by different unilateral perfusion strategies will provide similar, high quality neuroprotection. However, this has never been formally tested, and it is conceivable that differences exist in the efficacy of neuroprotection, the feasibility of the different strategies, and the complications related to one approach versus the other. Thus, prior to endorsing a shift to the more expeditious innominate strategy, we sought to compare the two techniques in a rigorous, randomized controlled trial, with DW-MRI as the most sensitive and objective endpoint of neurological injury.

2) We are excluding patients with severe aortic arch or innominate artery calcification or atheroma, based on a detailed review of the preoperative imaging. CT is very good at identifying calcium and thickened, atheromatous aortas. Such patients would not be eligible for the study and are listed as exclusions to it.

3) In addition to assessing neurologic outcomes, this study does also look for differences in the technical aspects of both procedures by assessing such variables as total operative time, hypothermic circulatory arrest time, cardio-pulmonary bypass time, and nadir nasopharyngeal temperature. Furthermore, our primary efficacy endpoint is a comparison of total operative time, which is statistically powered to look for superiority.

Reviewer: 3

Reviewer Name: Matthew Mosca, MS CCP

Institution and Country: University of Colorado Hospital, Aurora, CO, USA

Competing Interests: None

Overall, the authors have created an impressive and detailed randomized controlled trial that will compare the effectiveness of innominate artery cannulation and axillary artery cannulation for antegrade cerebral perfusion during circulatory arrest. The authors have chosen a variety of clinically relevant endpoints that assess both anatomical and functional neurological status.

Response: Thank you.

Please consider the following suggestions as they may improve the quality of the manuscript:

Keywords: Consider replacing the 5th keyword (open distal anastomosis) with a keyword related to the temperature at which circulatory arrest will be performed in this RCT (deep hypothermia or moderate hypothermia). The abstract mentions moderate hypothermia but the main manuscript refers to deep hypothermia multiple times.

Response:

As suggested by the reviewer, "moderate hypothermia" has been added to the list of keywords. We

have reviewed the manuscript to ensure that mention of the specific hypothermic technique used for this study is for moderate hypothermia. However, because deep hypothermic circulatory arrest is still in clinical use and has been previously published, DHCA is still mentioned in the Introduction and Discussion.

Abstract:

Consider highlighting a few secondary endpoints. One of the strengths of this study is that it will incorporate a variety of endpoints that assess both anatomical and functional neurological status. Please also add that this RCT will be a multicenter trial and that the type of antegrade cerebral perfusion being explored is unilateral. The last sentence of the abstract mentions that "...the innominate artery cannulation technique as a safe and potentially more efficient method of antegrade cerebral perfusion..." The study will only be able to conclude this if utilizing 2-sided P testing. This study plans on using 1-sided P testing, so innominate can only be stated as "non-inferior" to axillary.

Response: Thank you for your excellent comments and suggestions. We have expanded our description of the study design in the Abstract. The number of new ischaemic lesions on DW-MRI will be compared using 1 sided non-inferiority testing whereas the clinical efficiency outcome (operative time) will be tested using two sided superiority testing.

Section titled "Cerebral Protection Strategies in Aortic Arch Surgery":

The temperature is reported as 24 to 26 degrees but the paragraph refers to DHCA. If the circulatory arrest was performed at 24-26 degrees then the wording should refer to moderate hypothermia. Please fix this throughout the manuscript as DCHA appears multiple times.

Response: The reviewer's comment is well noted and we have indicated that circulatory arrest will be performed under moderate hypothermia. We still however refer to DCHA in the Introduction and Discussion sections to address pertinent points.

Section titled "Proposed frequency and duration of follow-up":

Consider including the type of NIRS monitors used as results may vary according to different manufacturers.

Response: Thank you for this suggestion - this information will be included in the publication of the final manuscript.

Other:

There are a number of secondary endpoints planned for this study. The authors should consider adding how they might adjust for multiple comparison errors. If the authors plan to do this then it should be included in the statistical analysis methodology.

Response: Details about the approach for multiple comparisons will be contained in the Statistical Analysis Plan which will be finalized prior to locking of the database.

Consider using 2-sided P testing to include the possibility that innominate cannulation may actually be superior to axillary cannulation. The "non-inferiority" design may be attractive because it may limit the required sample size, but a really important conclusion from this study could be that innominate cannulation is superior to axillary. Unless this study is limited by sample size and time, I would recommend using 2-sided P testing.

Response: The Statistical Analysis Plan will also include the potential for superiority testing if the primary outcome is found to be not non-inferior.

Final Comments:

I would like to commend the authors on a well designed study. This type of RCT has been needed for some time, and I enthusiastically await the results.

Response: Thank you.

VERSION 2 – REVIEW

REVIEWER	Hiroo Takayama Columbia University , USA
REVIEW RETURNED	19-Mar-2017

GENERAL COMMENTS	I remain hesitant agreeing with use of term, 'severe' neurological injury, for the description of MRI-found injury. While the study is well designed and addresses clinically interesting and relevant question, I am afraid that the publication of the result might introduce fearful interpretation with regard to the neurological risk associated with aortic surgery should the authors decide to use the term, 'severe'.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Hiroo Takayama

Institution and Country: Columbia University, USA

Competing Interests: None

I remain hesitant agreeing with use of term, 'severe' neurological injury, for the description of MRI-found injury. While the study is well designed and addresses clinically interesting and relevant question, I am afraid that the publication of the result might introduce fearful interpretation with regard to the neurological risk associated with aortic surgery should the authors decide to use the term, 'severe'.

Response: Thank you for your comments. Our use of the term “severe” was based on studies used to inform our primary efficacy endpoint (DW-MRI endpoint). Based on previous DW-MRI studies, the risk of neurologic injury with aortic intervention is already cited as 40-70%, and thus our study should not cause any escalation of this fear. Rather, the aim of our study is to see if the new technique has equally acceptable rates of neuronal injury with the innominate artery cannulation cerebral protection technique as compared with axillary artery cannulation, which is the standard of practice for establishing ACP. However, in order to mitigate this concern, we have modified the term “severe” to “radiologically significant”.