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Permanent pacemaker post-valve surgery: Do valve type and position matter? A propensity score matching study

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Permanent Pacemaker Post-Valve Surgery: Do Valve Type and Position Matter? A Propensity Score Matching Study
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Dear Dr Gatta,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Dec 21, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Dear Authors

Thank you for allowing me to review the manuscript entitled " Permanent Pacemaker Post-Valve Surgery: Do Valve Type and Position Matter? A
Propensity Score Matching Study".

The main goal of the manuscript is to find out the incidence of postoperative pacemaker according to the surgical procedure.

The main outcome is : Valve replacement in the aortic position or mitral position and valve type do not represent independent risk factors for post-operative permanent pacing.

I have some questions and concerns:

Please provide the approval number from the local ethical committee.

The graphical abstract has to many written details on it. I think a graphic chart would be more suitable for the reader.

Please provide a graphic chart for the patient selection criteria according to STROBE II recommendations.

What do you mean by chronic kidney disease? According to the AKIN criteria please provide the creatinine clearance.

What is neurological history? Is it a TIA, a stroke, a debilitating stroke, a history of carotid stenosis? Please be more specific.

In a manuscript describing the incidence of PPM it is imperative to have the presence of AV block I, AV-block II Mobitz 1, AV-block II Mobitz II. This are all factors that predispose to PPM.

According to which classification you say LVEF good, poor or bad. Please provide the numbers.

The Logistic Euroscore is not used anymore. Please provide data with EuroScore II or STS score.

A manuscript describing the incidence of PPM should also report preoperative valve are and post operative effective orifice area (EOA) and indexed iEOA. Also, it should also report the type of surgery such as aortic root enlargement. All these details are important because they

influence the PPM incidence. Therefore, please report them.

Please report the postoperative incidence of AV block I and AV-block II Mobitz 1. These can predispose to PPM.

Please provide the day of PPM implant.

Please provide the type of biological valves and their sizes. My point is that sutureless valves have a higher incidence compared to other biological valves. Therefore, it is important to know the type of prostheses.

Thank you

Reviewer #2: The authors investigated the incidence of permanent pacemaker implantation in patients with AVR or MVR. They found that the valve replacement in the aortic position versus mitral position was not an independent risk factor of post-operative permanent pacemaker implantation. There are several concerns.

1. Their findings might be a little bit different from the general understanding. The incidence of pacemaker implantation would be higher in patients receiving AVR than those with MVR given the anatomical reason. Also, the incidence of pacemaker implantation varies at each valve type.

2. Despite statistical background matching, there are still several critical differences in baseline characteristics including LVEF and operation time, which should have considerable impact on the incidence of pacemaker implantation.

3. Most of tables seem to be inappropriate. They had better be made again appropriately for the academic paper style.

Reviewer #3: Thank you for giving me the opportunity to review this article. A retrospective single-center study is reported, using the 10-years data on aortic valve replacement and mitral valve replacement with respect to post-operative permanent pacemaker implantation. The authors analyzed 617 matched patients in a 9-1 propensity score matching. They found no impact of AVR or MVR on the post-operative PPI rate and they reported worse peri-operative outcomes in the MVR cohort. The article is overall well-written and understandable. Valve surgery is a clear provider of post-operative PPI due to the anatomic interaction between the conduction system and the valve apparatus. Here my main concerns:

- Please provide the definition of MOF and ITU in the abstract section.
- Did the patients provide an inform consent ? Please provide this information.
- The analysis was performed according a 1:9 matching. However, if it can bring more precision, this matching method may generate more bias because the additional matches you made are generally of lower quality than the first one. It should be added to the "limitations" sections of the manuscript or more detailed in the method section.
- Mitral valve presents almost 2 times more endocarditis in the baseline characteristics. Is

there any explanation to this observation?
- What was the median time for PPM in both group?
- The discussion section may benefit from some additional information. Indeed, as this work aimed to compare MVR and AVR with respect to post-operative PPI, it would be better to compare the anatomic position of both valves and their interplay with the conduction system to understand their potentially different impact on post-operative rhythm disturbances. An anatomic illustration of these interactions will help the reader.
- Also, the discussion should explain the difference of the baseline characteristics the authors found between MVR and AVR group. Why was pre-operative non sinus rhythm more frequent in the MVR group? Is there any explanation therefor? Also, the difference regarding pre-operative left ventricle function should be more explained. Do the authors mean that poorest ejection fraction was seen in the AVR cohort ? Additionally, can the authors explain why, for the same age, the MVR cohort has a reduced logistic EUROSCORE (1.54 + 11.22) with respect to the AVR one (8.97 + 10.39)? Please improve the discussion section.
- Please change the description of left ventricle ejection fraction "good - fair - poor" into percent in table 1 if possible.
- In the previous experience of Moskowitz et al in 2019 using the New-York state hospital discharge database, post-operative PPI occurred less frequently after MVR with respect with other valve surgery procedures. Can you please add this reference to the discussion section and discuss the discrepancies of your results ? (ref: Incidence and Risk Factors for Permanent Pacemaker Implantation Following Mitral or Aortic Valve Surgery. J Am Coll Cardiol 2019;74:2607-2620).
- What is the reason of the longer hospital stay of the MVR group ? As the others secondary outcomes are statistically comparable, is there another cause therefor? On the other hand, are the authors able to provide the post-permanent pacemaker implantation complications rate in both group? It should be interesting to analyze these data as the mechanical group for both valve type require an adapted anticoagulation schema, it may have an influence on the post-operative PPI complications.

Authors' response

Reviewer 1

Question 1: Please provide the approval number from the local ethical committee.
Comments 1: Many thanks for the feedback. Such study obtained local institutional review board approval, and was registered as an audit. In our centre, there is a dedicated team for data collection/storage, who has an official role recognised by the Trust.
Changes 1: N/A

Question 2: The graphical abstract has toO many written details on it. I think a graphic chart would be more suitable for the reader.
Comments 2: Addressed. Many thanks
Changes 2: The graphical abstract was changed as per reviewer's instructions

Question 3: Please provide a graphic chart for the patient selection criteria according to STROBE II recommendations.
Comments 3: Addressed. Many thanks
Changes 3: Please note the graphical abstract was changed and a graphic chart was introduced for patients' selection. A full graphic chart as per STROBE II recommendations was introduced in the Manuscript (Figure 1)

Question 4: What do you mean by chronic kidney disease? According to the AKIN criteria please provide the creatinine clearance.
Comments 4: Addressed. Many thanks
Changes 4: Table 1. Chronic Kidney disease defined as GFR < 60 ml/min/1.73 m2.

Question 5: What is neurological history? Is it a TIA, a stroke, a debilitating stroke, a history of carotid stenosis? Please be more specific.
Comments 5: Addressed. Many thanks
Changes 5: Table 1. Neurological history included previous stroke or known carotid artery stenosis.

Question 6: In a manuscript describing the incidence of PPM it is imperative to have the presence of AV block I, AV-block II Mobitz 1, AV-block II Mobitz II. This are all factors that predispose to PPM.
Comments 6: Addressed. Many thanks
Changes 6: The indication for PPM and post-operative arrhythmias were added to Table 3

Question 7: According to which classification you say LVEF good, poor or bad. Please provide the numbers.
Comments 7: Addressed. Many thanks
Changes 7: Table 1. >49% / 30-49% / <30%

Question 8: The Logistic Euroscore is not used anymore. Please provide data with EuroScore II or STS score.
Comments 8: Addressed. Many thanks
Changes 8: New score in Table 1

Question 9: A manuscript describing the incidence of PPM should also report preoperative valve are and post operative effective orifice area (EOA) and indexed iEOA. Also, it should also report the type of surgery such as aortic root enlargement. All these details are important because they influence the PPM incidence. Therefore, please report them.
Comments 9: Many thanks for the feedback. Please note the population matched for the final analysis only included isolated aortic or mitral valve replacement. Associated procedures, such as aortic root enlargement, were exclusion criteria for the study (Figure 1). With regards to the effective orifice area, it would be an interesting data to have and comment upon. Unfortunately, this is not available in our dataset.
Changes 9: N/A

Question 10: Please report the postoperative incidence of AV block I and AV-block II Mobitz 1. These can predispose to PPM.
Comments 10: Addressed. Many thanks
Changes 10: Post-operative arrhythmias and indication for PPM were added to Table 3

Question 11: Please provide the day of PPM implant.
Comments 11: Addressed. Many thanks
Changes 11: The date of PPM implantation was stratified according to the post-operative day (before/after Day 5). Table 3

Question 12: Please provide the type of biological valves and their sizes. My point is that sutureless valves have a higher incidence compared to other biological valves. Therefore, it is important to know the type of prostheses.
Comments 12: Addressed. Many thanks
Changes 12: An additional table with valve type and size was created (Table 2)

Reviewer 2

Question 1: Their findings might be a little bit different from the general understanding. The incidence of pacemaker implantation would be higher in patients receiving AVR than those with MVR given the anatomical reason. Also, the incidence of pacemaker implantation varies at each valve type.
Comments 1: Addressed. Many thanks
Changes 1: An additional table with valve type and size was created (Table 2). The very low incidence of PPM in our database might justify the results in relation to existing literature.

Question 2: Despite statistical background matching, there are still several critical differences in baseline characteristics including LVEF and operation time, which should have considerable impact on the incidence of pacemaker implantation.
Comments 2: Many thanks for the feedback. The 9:1 case-control was performed for the following pre-operative and intra-operative factors: age, sex, BMI, NYHA, ischaemic heart disease, CKD, Diabetes mellitus, NCEPOD and IABP. These are well-known determinants for post-operative PPM. Whilst we acknowledge that LVEF and operation time might have an impact on the incidence of PPM implantation, we decided not to match the AVR/MVR groups for these two variables. Such decision was made in order to provide a reproducible and realistic population, which would preserve some characteristics of those patients that required AVR or MVR in our centre.
Changes 2: N/A

Question 3: Most of tables seem to be inappropriate. They had better be made again appropriately for the academic paper style.
Comments 3: Addressed. Many thanks
Changes 3: Original Tables 2, 3, 4 and 5 were removed. Appropriate new tables were created for the incidence of PPM implantation in all the subgroups considered.

Reviewer 3

Question 1: Please provide the definition of MOF and ITU in the abstract section.
Comments 1: Addressed. Many thanks
Changes 1: Abstract section. No abbreviations

Question 2: Did the patients provide an inform consent? Please provide this information.
Comments 2: Many thanks for the feedback. Patients were not required to provide informed consent. Data was extracted from local storage with the Trust institutional review board approval.
Changes 2: N/A

Question 3: The analysis was performed according a 1:9 matching. However, if it can bring more precision, this matching method may generate more bias because the additional matches you made are generally of lower quality than the first one. It should be added to the "limitations" sections of the manuscript or more detailed in the method section.
Comments 3: Addressed. Many thanks
Changes 3: A section describing such limitation was added.

Question 4: Mitral valve presents almost 2 times more endocarditis in the baseline characteristics. Is there any explanation to this observation?
Comments 4: Many thanks for the feedback. Our 10-year activity originally included a population of 2944 patients, of which 2558 undergoing AVR and 386 undergoing MVR. The application of the exclusion criteria and the case-control matching significantly reduced such numbers (490 AVR; 127 MVR). Of the aortic patients, only 19% were included, whilst for the mitral cohort 34% of patients were considered. In the original database, the incidence of active endocarditis was similar in both groups. This data, however, changed after matching due to the significant decrease of the population size.
Changes 4: N/A

Question 5: What was the median time for PPM in both group?
Comments 5: Addressed. Many thanks
Changes 5: The date of PPM implantation was stratified according to the post-operative day (before/after Day 5). Table 3

Question 6: The discussion section may benefit from some additional information. Indeed, as this work aimed to compare MVR and AVR with respect to post-operative PPI, it would be better to compare the anatomic position of both valves and their interplay with the conduction system to understand their potentially different impact on post-operative rhythm disturbances. An anatomic illustration of these interactions will help the reader.
Comments 6: Addressed. Many thanks
Changes 6: An extensive discussion about the anatomical reasons for PPM post-valve surgery was introduced in the discussion section.

Question 7: Also, the discussion should explain the difference of the baseline characteristics the authors found between MVR and AVR group. Why was pre-operative non sinus rhythm more frequent in the MVR group? Is there any explanation therefor? Also, the difference regarding pre-operative left ventricle function should be more explained. Do the authors mean that poorest ejection fraction was seen in the AVR cohort? Additionally, can the authors explain why, for the same age, the MVR cohort has a reduced logistic EUROSCORE (1.54 + 11.22) with respect to the AVR one (8.97 + 10.39)? Please improve the discussion section.
Comments 7: Addressed. Many thanks
Changes 7: Further characterization of pre-operative non-sinus rhythm was added to Table 1. The difference in the left ventricle function was explained in more details. The final discussion was adjusted for further references and suggestions from the reviewers. Many thanks for highlighting the difference in the EuroSCORE. I agree that such numbers do not portray the actual population, in view of the concomitant demographic data. Therefore, I checked the data and conducted a further analysis. I think there might have been a spelling error, as the MVR EuroSCORE is not 1.5, but 8.5, which would indeed be appropriate.

Question 8: Please change the description of left ventricle ejection fraction "good - fair - poor" into percent in table 1 if possible.
Comments 8: Addressed. Many thanks
Changes 8: Table 1. >49% / 30-49% / <30%

Question 9: In the previous experience of Moskowitz et al in 2019 using the New-York state hospital discharge database, post-operative PPI occurred less frequently after MVR with respect with other valve surgery procedures. Can you please add this reference to the discussion section and discuss the discrepancies of your results? (ref: Incidence and Risk Factors for Permanent Pacemaker Implantation Following Mitral or Aortic Valve Surgery. J Am Coll Cardiol 2019;74:2607-2620).
Comments 9: Addressed. Many thanks
Changes 9: Further discussion was added to the relevant section and the suggested reference commented upon.

Question 10: What is the reason of the longer hospital stay of the MVR group? As the others secondary outcomes are statistically comparable, is there another cause therefore? On the other hand, are the authors able to provide the post-permanent pacemaker implantation complications rate in both group? It should be interesting to analyze these data as the mechanical group for both valve type require an adapted anticoagulation schema, it may have an influence on the post-operative PPI complications.
Comments 10: Many thanks for the feedback. Patients undergoing MVR reported a higher rate of myocardial infarction and a prolonged hospital stay. These same patients had a greater proportion of active endocarditis compared with the AVR group (p 0.02), which could explain the difference in these clinical outcomes. Following PPM implantation, none of our patients developed related early complications. Our current Policy is to start heparin infusion for those with a mechanical valve awaiting for further procedures.
Changes 10: “Patients with a newly-implanted PPM did not report any procedure-related early complications”

2nd Editorial decision
21-Nov-2021

Ref.: Ms. No. JCTRes-D-21-00170R1
Permanent Pacemaker Post-Valve Surgery: Do Valve Type and Position Matter? A Propensity Score Matching Study
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research. Congratulations!

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Journal of Clinical and Translational Research
Peer review process file 07.202106.015

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: