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Aortic Valve Neocuspidization using glutaraldehyde-treated autologous pericardium: A literature review

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Abstract

Background: Aortic Valve Neocuspidization using glutaraldehyde-treated autologous pericardium was first performed by Ozaki et al. in 2007. This technique has become an alternative to tissue and mechanical valve as long-term anticoagulation is not required and shows promising midterm results and durability. Method: A comprehensive search was performed on the major database using search terms "Ozaki technique" AND "Aortic Valve Neocuspidization" AND "AV Neocuspidization" AND "Autologous pericardium" AND "glutaraldehyde-treated autologous pericardium". Articles up to 1st of August 2020 were included in this study. Results: A total of 9 studies with a total of 1342 patients were included. The mean age was 67.36 and 54.23% were male. 66.32% and 23.92% of patients had aortic stenosis and aortic regurgitation, respectively. 66% of patients had a native tricuspid aortic valve and 31.37 % patients' native aortic valve was bicuspid. Three studies reported their experience performing Aortic Valve Neocuspidization via mini sternotomy. Conclusion: Aortic Valve Neocuspidization is an alternative to biological and mechanical prostheses for surgical aortic valve replacement. The short and mid-term outcome are comparable without the need for long term oral anticoagulation. Long term follow-up data is required for this novel approach to be widely adopted.

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Method: A comprehensive search was performed on the major database using search terms "Ozaki technique" AND "Aortic Valve Neocuspidization" AND "AV Neocuspidization" AND "Autologous pericardium" AND "glutaraldehyde-treated autologous pericardium". Articles up to 1st of August 2020 were included in this study.

Results: A total of 9 studies with a total of 1342 patients were included. The mean age was 67.36 and 54.23% were male. 66.32% and 23.92% of patients had aortic stenosis and aortic regurgitation, respectively. 66% of patients had a native tricuspid aortic valve and 31.37 % patients' native aortic valve was bicuspid. Three studies reported their experience performing Aortic Valve Neocuspidization via mini sternotomy.

Conclusion: Aortic Valve Neocuspidization is an alternative to biological and mechanical prostheses for surgical aortic valve replacement. The short and mid-term outcome are comparable without the need for long term oral anticoagulation. Long term follow-up data is required for this novel approach to be widely adopted.

Introduction

Severe Aortic stenosis affects an estimated 3.4% of adults over 75 in North America and Europe. (1) This number is set to increase due to the strong association between advanced age and valvular heart disease. The current gold standard treatment for aortic stenosis is aortic valve replacement, either via surgical or transcatheter approach. The current replacement valve options often present a dilemma for young adults. Mechanical prostheses have been shown to have excellent function and durability. However, but due to their non-organic materials, lifelong anticoagulation often in the form of warfarin is required. (2) This can no doubt increases the risk of haemorrhage, adverse effects, and drug interaction. The current alternative to is the biological tissue valve, usually produced from bovine or porcine tissue, minimising the need for warfarin. However, in younger patients, this presents a significant risk due to degeneration requiring a re-do open-heart surgery and/or valve-in-valve transcatheter aortic valve replacement in a later stage.

AV Neocuspidization (AV Neo) using glutaraldehyde-treated autologous pericardium may be the solution to this dilemma. The technique was originally trialled in the 1960s but fell out of favour due to the lack of standardised procedure and reproducible results. This was revolutionised by Ozaki *et al.* using standardised modelling to size the cusps and allowed reproducibly in other centres. (3) This relatively new technique involves harvesting of patient's own pericardium that is subsequently treated with Glutaraldehyde. The tissue is then shaped to form cusps measured precisely using sizing and templating tools. (3) These new cusps are then used for aortic valve reconstruction. This technique has become an alternative to biological and mechanical valve with multiple centres reporting their promising early (and mid-term) outcomes.(4)

Method

A comprehensive search was performed on PubMed, Ovid, SCOPUS, EMBASE, Cochrane library and Google Scholar. The search terms included "Ozaki technique" AND "Aortic Valve

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Neocuspidization" AND "AV Neocuspidization" AND "Autologous pericardium" AND "glutaraldehyde-treated autologous pericardium". Articles published prior to 31st of August 2020 were included in this study. All articles including outcomes on Ozaki procedure were reviewed. Only full, original articles were included for review. Case reports, expert opinion, editorials, duplicates studies, and conference abstracts were excluded. The literature search was performed independently by two reviewers (SO and KSF). The final review was performed by the third reviewer (JC).

Results:

The literature search yielded 9 eligible studies with a total 1342 patients. The mean age was 67.36 and 54.23% were male. 66.32%, 23.92%,3.58% and 6.18% of patients had aortic stenosis, aortic regurgitation, infective endocarditis and mixed aortic stenosis and regurgitation, respectively. 66.0% of patients had a native tricuspid aortic valve and 31.37 % patients' native aortic valve was bicuspid. Demographics for all patients enrolled in the 9 studies are shown in Table 1.

Intra-operative outcome

Total procedure time was reported by 3 papers with an average of 217.43 minutes (3 hours and 37 minutes) All studies reported their mean cardiopulmonary bypass (143.75 mins) and aortic cross-clamp time (104.54 mins) with isolated AV Neo. 53.41% of the study population received an isolated AV Neo. Overall, 98.14% of patients underwent AV Neo via a median sternotomy. Three studies with a total of 25 patients had their operation via mini-sternotomy. The intra-operative outcomes are included in Table 2.

Post-operative outcome

All studies included their outcomes on the following: a) Moderate and severe aortic valve regurgitation, b) Mortality, c) Postoperative infective endocarditis and d) Reintervention rate. Additionally, 5 studies included their incidence on patients developed stroke post-operatively. The results of the above categories are included in table 3. The mean mortality rate reported was 2.68%. 1.64% of patients had infective endocarditis postoperatively and 5.15% of patients had moderate or greater aortic regurgitation on their first follow up echocardiogram. Overall, 2.16% of patients required reintervention with either a biological or mechanical prosthesis.

Discussion

The average age of population is on the rise, and so is the incidence of valvular disease. (3) Aortic stenosis (AS) is the commonest disease of the aortic valve, commonly due to age-related calcifying degeneration. (5) Current European guideline indicates surgical aortic valve replacement (SAVR) in severe AS in patients with low surgical risk (EuroScore I <10%), young (Age <75), in need of concomitant procedures and for aortic regurgitation (AR). (6) Mechanical valves are preferred in patients less than 50 years old because of a longer durability, and biological valves are utilised with the main advantages of its low thrombogenicity and lack of obligatory long-term anticoagulation. (7) The increasingly popular transcatheter aortic valve replacement (TAVR) has been promising for high risk for open-heart surgery but may not be suitable for the extreme size of aortic annuli and long-term data are currently lacking. (6) All aortic valve bioprostheses are prone to structural degeneration secondary to calcification and stiffening.

Alternative to tissue and mechanical valve

Aortic Valve Neocuspidization (AV Neo) using glutaraldehyde-treated autologous pericardium with the aim to reconstruct the aortic valve using patients' own tissue. AV Neo provided an alternative to the biological and mechanical valve. First performed and reported by Professor Ozaki and his team in 2007, reconstructing the aortic valve using autologous pericardium. AV Neo allows surgeons to preserve natural aortic root expansion in systole with maximal orifice area, and to replace the valve as one complete structure. (3) Due to the lack of foreign materials, no long-term oral anticoagulation is required. Avoiding long term anticoagulation have no doubt being advantageous in both the short and long run. Moreover, avoiding the use of warfarin can be particularly useful in young women who wished to be pregnant in the future due to its teratogenicity nature.

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Maternal warfarin administration could lead to foetal warfarin syndrome causing multiple facial, physical, and intellectual disabilities. This was also noted despite a reduced regime was trailed.

Clinical outcome of AV Neo

Ongoing, full follow-up by Ozaki *et al.* including 850 patients showed positive short- and medium-term outcomes up to 11 years after initial AV Neo. (3) Mourad *et al.* showed good reproducibility of AV Neo procedure with an initial cohort of 52 patients in Germany. (8) They reported several positive findings including safety, reliability, low re-intervention rate, low permanent pacemaker rate and low incidence of valve thrombosis. Additionally, most patients were discharged with no or trace AR or AS and low aortic valve gradients in follow up echocardiogram. (8) Similar results were reported by several other centres suggesting this procedure are reproducible across different centres and surgical teams. (9-11)

Krane *et al.* demonstrated the effectiveness of this technique in a younger population and compared the haemodynamic performance with virtually implanted Trifecta Bioprostheses. They reported a significantly lower mean pressure gradient as well as a higher mean effective orifice area in AV Neo. It was also stable at one-year follow up with a 96.1% freedom from reoperation. (12)

An alternative to autologous pericardium such as bovine pericardium was trialled by Sheng *et al.* (13) The authors reported a comparable early and mid-term outcomes to autologous tissue. This eliminates the drawback of poor quality of patients' own autologous pericardium as well as shorten the procedure time as by eliminating the process of handling and preparing the autologous pericardium with glutaraldehyde solution. The bovine pericardium was also treated with hydroxychromium which was shown to further increase its durability in animal models. (13)

Surgical approach

Several systematic reviews had also reported minimally invasive SAVR (either via right anterior mini-thoracotomy or upper J Ministernotomy) reduced intra-operative blood loss, a small increase in post-operative pulmonary function and a small reduction on intensive care unit stay with comparable Intra- and postoperative outcomes compared with conventional SAVR via median sternotomy. (8, 14) Minimally invasive technique could potentially be translated and adapted to AV Neo. Nguyen *et al.* have reported their experience in performing the AV Neo via mini sternotomy with thoracoscopic harvesting of the pericardium. (15) They concluded that the AV Neo via minimally invasive technique is feasible with low mortality and morbidity, potentially beneficial in younger populations. (15)

The da Vinci Robotic Surgical System has been used in cardiac surgery since its approval from the Food and Drug Administration in 2000. (16) Robotic mitral valve surgery for mitral regurgitation (MR) has been explored. While its efficacy is still being explored, early and midterm outcomes are promising. Incidence of recurrence of MR and reoperation rate remains low. (15) Robotic AV Neo could be a prospect. However, the drawbacks of robotic surgery such as high cost, the size of equipment, and extensive training required must not be forgotten.

Limitations

Due to the novel nature of the AV Neo, limited studies are available to fully evaluate the early, mid and long-term outcomes. Long term outcome and durability remains unknown. This remains an important issue as the operation mainly aims to avoid long term anticoagulation for the young population group. One of the major advantages for AV Neo, avoiding long term anticoagulation seems to be diminished when compared to biological SAVR or TAVR in the elderly population group. Furthermore, due to its novelty, there is no doubt a significant learning curve, suggesting an initial longer cardiopulmonary bypass (CPB) and cross-clamp (CC) time. Similar results are shown in minimally invasive aortic valve surgery using a tissue or mechanical valve, suggesting that average 40-50 cases are required to achieve a stable CBP and CC time.(17, 18)

To harvest the pericardium for the procedure, most surgeons would perform the procedure via a sternotomy,

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hence limiting its popularity. Lately, an upper mini-sternotomy incision with harvesting the pericardium via thoracoscopic technique has been reported but again, a significant learning curve may arise. Moreover, an extra 20 minutes of CPB is normally required for harvesting the pericardium via thoracoscopic technique in order to decompress the heart. (15) A practical difficulty may also arise that the glutaraldehyde substance required to prepared autologous pericardium may not be readily available due to local restrictions. (19)

The procedure is currently performed only by selected surgeons, limiting the availability of data to ascertain its effectiveness. To date, there is no study directly compare the outcomes between conventional aortic valve replacement with biological or mechanical valve with AV Neo. The availability of data on the specific groups of patients (E.g. high-risk patients) are also limited, restricting its use widely.

Conclusion

AV Neo offers an effective alternative to conventionally established tissue and mechanical prostheses. Mid-term outcomes of the procedure have been positive, demonstrating a large haemodynamic improvement in valve function with low rates of adverse events. However, long-term, and large-scale studies are still in progress and the lack of randomised controlled trials may limit its use in a bigger scale.

1. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.

2. Thoren O. Blood flow patterns of the forearm of critically ill post-traumatic patients. A plethysmographic study. Acta Chir Scand Suppl. 1974;443:1-59.

3. Ozaki S, Kawase I, Yamashita H, Uchida S, Nozawa Y, Takatoh M, et al. A total of 404 cases of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. J Thorac Cardiovasc Surg. 2014;147(1):301-6.

4. Ozaki S, Kawase I, Yamashita H, Uchida S, Takatoh M, Kiyohara N. Midterm outcomes after aortic valve neocuspidization with glutaraldehyde-treated autologous pericardium. J Thorac Cardiovasc Surg. 2018;155(6):2379-87.

5. Marathe SP, Chavez M, Sleeper LA, Marx G, Del Nido PJ, Baird CW. Modified Ozaki Procedure Including Annular Enlargement for Small Aortic Annuli in Young Patients. Ann Thorac Surg. 2020;110(4):1364-71.

6. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.

7. Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al. Standardized Definition of Structural Valve Degeneration for Surgical and Transcatheter Bioprosthetic Aortic Valves. Circulation. 2018;137(4):388-99.

8. Mourad F, Shehada SE, Lubarski J, Serrano M, Demircioglu E, Wendt D, et al. Aortic valve construction using pericardial tissue: short-term single-centre outcomes. Interact Cardiovasc Thorac Surg. 2019;28(2):183-90.

9. Reuthebuch O, Koechlin L, Schurr U, Grapow M, Fassl J, Eckstein FS. Aortic valve replacement using autologous pericardium: single centre experience with the Ozaki technique. Swiss Med Wkly. 2018;148:w14591.

10. Iida Y, Fujii S, Akiyama S, Sawa S. Early and mid-term results of isolated aortic valve neocuspidization in patients with aortic stenosis. Gen Thorac Cardiovasc Surg. 2018;66(11):648-52.

11. Arutyunyan V, Chernov I, Komarov R, Sinelnikov Y, Kadyraliev B, Enginoev S, et al. Immediate Outcomes of Aortic Valve Neocuspidization with Glutaraldehyde-treated Autologous Pericardium: a Multicenter Study. Braz J Cardiovasc Surg. 2020;35(3):241-8.

12. Krane M, Boehm J, Prinzing A, Ziegelmueller J, Holfeld J, Lange R. Excellent Hemodynamic Performance After Aortic Valve Neocuspidization Using Autologous Pericardium. Ann Thorac Surg. 2020.

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13. Sheng W, Zhao G, Chao Y, Sun F, Jiao Z, Liu P, et al. Aortic Valve Replacement with Bovine Pericardium in Patients with Aortic Valve Regurgitation. Int Heart J. 2019;60(6):1344-9.

14. Kirmani BH, Jones SG, Malaisrie SC, Chung DA, Williams RJ. Limited versus full sternotomy for aortic valve replacement. Cochrane Database Syst Rev. 2017;4:CD011793.

15. Nguyen DH, Vo AT, Le KM, Vu TT, Nguyen TT, Vu TT, et al. Minimally Invasive Ozaki Procedure in Aortic Valve Disease: The Preliminary Results. Innovations (Phila). 2018;13(5):332-7.

16. Intuitive. da vinci surgery: Intuitive; 2020 [Available from: https://www.davincisurgery.com/.

17. Masuda T, Nakamura Y, Ito Y, Kuroda M, Nishijima S, Okuzono Y, et al. The learning curve of minimally invasive aortic valve replacement for aortic valve stenosis. Gen Thorac Cardiovasc Surg. 2020;68(6):565-70.

18. Murzi M, Cerillo AG, Gilmanov D, Concistre G, Farneti P, Glauber M, et al. Exploring the learning curve for minimally invasive sutureless aortic valve replacement. J Thorac Cardiovasc Surg. 2016;152(6):1537-46 e1.

19. Koechlin L, Schurr U, Miazza J, Imhof S, Maurer M, Erb J, et al. Echocardiographic and Clinical Follow-up After Aortic Valve Neocuspidization Using Autologous Pericardium. World J Surg. 2020;44(9):3175-81.

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