Left Atrial or Transeptal Approach for Mitral Valve Surgery: A Systematic Review and Meta-analysis

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Abstract: To compare outcomes of mitral valve surgery through conventional left atriotomy and transeptal approach (TS). Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Primary outcomes were operative mortality and permanent pacemaker (PPM) implantation; secondary outcomes were new onset of atrial fibrillation (AF), stroke and operative times. Sixteen articles met the inclusion criteria with 4537 patients. Cardiopulmonary bypass was longer with TS (weighted mean differences - 16.44 minutes [−29.53, −3.36], *P* = 0.01). Rates of PPM implantation (risk ratio 0.65 [0.47, 0.89], *P* = 0.007) and new onset AF (risk ratio 0.87 [0.78, 0.97], *P* = 0.02) were higher with TS. Subgroup analysis of isolated mitral valve surgery cohort showed no difference in operative times, mortality, new onset of AF, stroke, and PPM implantation. There is equal outcomes between both approaches during isolated mitral

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valve surgery; however, TS was associated with longer operative times and higher postoperative AF and PPM rates when pooling combined procedures. A large randomized controlled trial is required to confirm those findings. (Curr Probl Cardiol 2021;46:100602.)

Introduction

Mitral valve (MV) pathologies constitute a significant proportion of valvular heart disease.[1] Repair or replacement of the valve by surgical intervention is often required to prevent life threatening complications, such as acute heart failure with pulmonary oedema.[1,2] Traditionally, the left atrial (LA) approach through Soonergaard's groove was the ideal access point across many cardiac centers internationally. This access is a well understood, relatively straight foreword procedure that usually allows excellent visualization of the MV.[3] However, in certain cases where access to LA is difficult, adopting a transseptal (TS) approach has been established.[4] This involves a longer incision which extends through the inter-atrial septum to involve the LA as well and is thought to provide better exposure to the valve, either as limited or extended TS approach.[4] Some studies have reported equivocal outcomes in both approaches, while other reported increased cardiopulmonary bypass (CPB) time, and probably a predisposition to arrhythmogenicity and therefore higher permanent pacemaker (PPM) rates.[4-6] Nevertheless, results vary across studies, and pooled evidence supporting the superiority of either technique is lacking.[7-10] Surgical decision-making is therefore primarily based on clinician experience, difficulty of access to the MV and personal preference.[4,5,11] As such, this systematic review and meta-analysis aimed to determine whether LA and TS approaches differed in clinical outcomes during isolated MV surgery and in combined valve procedures.

Material and Methods

Literature Search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] Comprehensive electronic database searches were undertaken on PubMed, Ovid Scopus and Embase to identify all studies

that compared LA and TS approaches during MV surgery. The search timing was done from inception to January 2020. Search terms included "left atriotomy," "transseptal," "high transseptal," "mitral valve," "mitral repair," "mitral replacement," "mitral surgery," and "mitral outcomes." All search terms were combined with Boolean operators and searched as both key words and MeSH terms to ensure maximal sensitivity. Reference lists of papers found in the literature search were manually searched to assess suitability for inclusion in this review. Articles were first screened by 3 reviewers (AH, AN and TK) based on their titles and abstracts. All identified articles were systematically assessed using the inclusion and exclusion criteria for further study.

Inclusion and Exclusion Criteria

Comparative studies that compared TS and LA approach for MV surgery in the same cohort were included. Articles that described only 1 technique during MV intervention was excluded, as well as case reports, editorial, narrative review and consensus documents. In case of duplicate articles, only the latest 1 with entire cohort was included to avoid data and outcome duplications. No limit was placed on timing of publication nor on language. Full-text screening was performed by 3 reviewers (AH, AN and TK). Conflicts over inclusion were resolved by consensus.

Measured Outcomes

The primary outcomes were operative mortality and requirement for PPM. Operative mortality was defined as all-cause death either within same hospital admission or 30-day from the surgery as reported by each relevant study. Requirement for PPM was reported as PPM insertion during the same admission.

Secondary outcomes measured were new onset of atrial fibrillation, stroke and operative times. Stroke was defined as permanent neurological deficit confirmed either clinically or radiologically.

Summary data for all outcomes were extracted manually by 2 reviewers (TK, AN). Other variables were also extracted if deemed appropriate. Conflicts were resolved by consensus.

Left atrial approach is defined as access through Soonergaard's groove while Transseptal approach could be either superior transseptal or conventional transseptal. As there are no significant technical differences

between the later two, we have combined them into one cohort as transseptal (TS) to understand the outcomes.

Methodological Quality Assessment of Included Studies

Qualitative assessment of included studies was performed using the Newcastle-Ottawa scale.[13] The Newcastle-Ottawa scale was devised specifically to assess the quality of non-randomized studies included in meta-analyses. It assesses bias of each study using a star-based rating system, with a maximum score of 9 indicating lowest risk of bias, and a minimum of 0 indicating highest risk. Scores ≥ 7 generally represent a low risk of substantial bias. Quality of included studies was rated by 2 reviewers (AN, SS). Discrepancies were resolved by consensus.

Statistical Analysis

This meta-analysis was performed in-line with recommendations from Meta-analysis Of Observational Studies in Epidemiology guidelines.[14] Clinical outcomes were assessed using standard meta-analysis techniques, with odd ratios (OR), risk ratio (RR) or weighted mean differences (WMD) used as summary statistics for raw data extracted from each included study. Random-effects models were used where significant heterogeneity exists; otherwise, fixed-effect models were used. χ^2 Tests were used to study heterogeneity and the I^2 statistic was used to estimate the proportion of total variation across studies due to heterogeneity rather than chance. A cut-off threshold of 40% was chosen and values exceeding this were considered to signify substantial heterogeneity. Publication bias was assessed visually using funnel plots for all variables reported by at least 10 studies without significantly heterogeneous data. Subgroup analysis was performed to compare LA and TS approaches in studies that reported relevant data for isolated MV surgery, in order to reduce heterogeneity and bias as a result of pooling concomitant surgeries with isolated MV surgery.

To reduce type I error, post hoc trial sequential analysis (TSA) was performed for all variables, including those in the subgroup analysis, without significantly heterogeneous data. The Z score thresholds (trial sequential monitoring boundary) were adjusted using the O'Brien-Fleming α-spending function. Studies reporting no events were handled by adding a constant (1) to both arms. Incidences and required information size were calculated from all included studies that reported the variable

to be analyzed. Permissible 2-sided type 1 error of 5% and type 2 error of 20% were used, therefore giving a power of 80%.

All p values were 2-sided, and p values of 0.05 or less were considered significant. The meta-analysis was performed using Review Manager V.5.2.1 (Cochrane Collaboration, Oxford, UK). The TSA was performed using the Copenhagen trial unit, TSA software version 0.9.5.10 Beta.

Results

Included Studies

The search results are summarized in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (e-Fig 1). Initial search result yielded 567 nonduplicate articles that were screened by title or abstract. After applying inclusion and exclusion criteria, 47 articles were screened in full text; however only 16 studies met the final criteria and were included in subsequent meta-analysis.[9,10,15-28] Two of the included studies were randomized trials,[22,25] the rest were observational studies. E-table 1 summarizes the quality of included studies as assessed by the Newcastle-Ottawa Scale. All studies were of satisfactory quality with low risk of bias. Characteristics of all included studies are summarized in e-Table 2.

A subgroup analysis was performed including only papers that compared isolated MV surgery to minimize confounding factors and risk of reporting bias within the included analysis.[18,23,25,26,28]

Demographics and Preoperative Characteristics

A total of 4537 patients among 16 eligible articles were included in this analysis. TS approach was utilized in 1472 patients while LA approach was used in 3,065 patients. There was no significant difference in mean age between LA and TS cohort (53 $\pm$ 12 years vs 52 $\pm$ 12 years, P = 0.99). Male to female ratio was similar in LA and TS groups (40% vs 44%, P = 0.73). No difference in the mean LVEF was noted in LA vs TS patients (53.8 $\pm$ 9.0% vs 53.7 $\pm$ 9.3%, P = 0.99). Rate of established AF was noted not to be significantly different between LA and TS patients (36% vs 40%, P = 0.68). Only 4 studies reported patients that had previous cardiac surgery,[10,17,26,28] 54.1% of patients in LA cohort patients had previous cardiac surgery compared to only 40.0% in TS patients (P = 0.13). The degree and pathology of MV diseases were similar in both cohorts. Table 1 is summary of details of pre-operative characteristics of both cohorts.

Table 1. Preoperative data of the included studies, all-cohorts

Variable	TS (n = 1472)	LA (n = 3065)	*P* value
Mean age (SD)	52 ± 12	53 ± 12	0.99
Male	645/1472	1241/3065	0.73
Mean LVEF (SD)	53.8 ± 9.3	53.8 ± 9	0.99
AF	579/1432	1074/3025	0.68
Previous cardiac surgery	138/345	432/798	0.13
Mitral stenosis	91/443	314/1192	0.07
Mitral regurgitation	235/280	468/540	0.23

AF, atrial fibrillation; LA, left atrial approach; NYHA = New York Heart Association; TS = transseptal approach.

Operative Data

There were similar rates of MV repair in LA and TS patient (31% vs 35%, OR 0.88, 95%CI [0.64, 1.21], $P = 0.42$; $I^2 = 0.61$, $\chi^2 = 25.9$, $P = 0.004$). The TS cohort had significantly more concomitant tricuspid valve (TV) repair (26.8% vs 13.1%, OR 0.31 [0.15, 0.63], $P = 0.001$; $I^2 = 0.77$, $\chi^2 = 30.78$, $P < 0.0001$), but the rates of concomitant aortic valve replacement (20.3% in TS vs 16.4% in LA, OR 1.01 [0.56, 1.83], $P = 0.97$; $I^2 = 0.76$, $\chi^2 = 24.9$, $P = 0.0004$) and coronary artery bypass graft were similar (24.9% in TS vs 30.2% in LA, OR 1.06 [0.80, 1.41], $P = 0.67$; $I^2 = 0.10$, $\chi^2 = 6.67$, $P = 0.35$). The reported CPB time was much shorter in LA patients (110 ± 29 minutes vs 127 ± 31 minutes, WMD -16.44 minutes [−29.53, −3.36], $P = 0.01$; $I^2 = 0.98$, $\chi^2 = 673.7$, $P < 0.00001$; e-Fig 2). Similarly, aortic cross clamp time (ACx) was shorter in LA patients (74 ± 22 minutes vs 87 ± 23 minutes, WMD -13.51 minutes [−20.81, −6.20], $P = 0.0003$; $I^2 = 0.96$, $\chi^2 = 352.39$, $P < 0.00001$; e-Fig 3). Table 2 is summary of the reported operative and postoperative data of both cohorts.

Postoperative Outcomes

The operative mortality rate was not significantly different between TS and LA cohorts (3.3% vs 4%, RR 0.89, 95%CI [0.60, 1.31], $P = 0.54$; $I^2 = 0.0$, $\chi^2 = 8.69$, $P = 0.80$, e-Fig 4). The mean postoperative blood loss in TS cohort was 488±232 mL vs 446±214 mL in the LA cohort, but this was not statistically significant (WMD -52.27 mL [−108.15, 3.61], $P = 0.07$; $I^2 = 0.82$, $\chi^2 = 27.11$, $P < 0.0001$ e-Fig 5). Furthermore, the reoperation for bleeding was also not significantly different between both LA and TS cohorts (6% vs 5%, RR 0.92 [0.62, 1.37], $P = 0.69$; $I^2 = 0.10$, $\chi^2 = 7.76$, $P = 0.35$). Stroke rate was similar in both LA and TS cohorts

Table 2. Operative and postoperative data of transeptal vs left atriotomy all-cohorts

Operative data	TS (n = 1472)	LA (n = 3065)	*P* value
MV repair	392/1192	623/2347	0.42
MV replacement	729/1192	1423/2347	0.38
CPB time (minute, SD)	127 ± 31	110 ± 29	0.01
ACx time (minute, SD)	87 ± 23	74 ± 22	0.0003
Concomitant TV repair	210/784	87/664	0.001
Concomitant AVR	190/784	179/664	0.97
Concomitant CABG	199/784	322/664	0.67

Postoperative data	TS (n = 1472)	LA (n = 3065)	*P* value
Mean bloods loss (mL, SD)	488 ± 232	446 ± 214	0.07
Operative mortality	44/1322	102/2638	0.98
PPM	66/1362	84/3028	0.007
Reoperation for bleeding	41/947	122/2018	0.69
Stroke	7/579	43/1803	0.34
Renal failure	18/499	88/1726	0.33
New onset AF	304/1276	696/2709	0.02

ACx, aortic cross clamp; AF, atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; LA, left atrial approach; LOS, length of stay; MV, mitral valve; PPM, permanent pacemaker; TS, transseptal approach; TV, tricuspid valve.

(2.4% vs 1.2%, RR 1.41 [0.69, 2.85], $P = 0.34$, $I^2 = 0.00$, $\chi^2 = 2.49$, $P = 0.78$, e-Fig 6). However, new onset AF was more common in the TS cohort (26% vs 25%, RR 0.87 [0.78, 0.97], $P = 0.02$; $I^2 = 0.35$, $\chi^2 = 15.3$, $P = 0.12$, Fig 1). The rate of PPM implantation was also higher in TS patients than LA cohort (5% vs 3%, RR 0.65, 95%CI [0.47, 0.89], $P = 0.007$; $I^2 = 0.0$, $\chi^2 = 10.22$, $P = 0.68$; Fig 2). Table 2 is summary of the reported operative and postoperative data of both cohorts.

Subgroup Analysis

Outcomes in articles that compared isolated MV surgery using both approaches were compared. Only 5 studies.[18,23,25,26,28] reported such data, with a total of 1,513 patients (LA = 1111, TS = 402). There were no differences in CPB and aortic cross clamp times between LA and TS cohorts (98 ± 27 vs 101 ± 26 minutes, WMD −3.20 minutes [−16.02, 9.63], $P = 0.62$; $I^2 = 0.95$, $\chi^2 = 74.72$, $P < 0.00001$; e-Fig 2 and 73 ± 21 vs 77 ± 21 minutes, WMD −2.51 minutes [−14.14, 9.12], $P = 0.67$; $I^2 = 0.66$, $\chi^2 = 11.65$, $P = 0.02$; e-Fig 3, respectively). There was no difference in any of the reported outcomes of operative mortality rates (RR

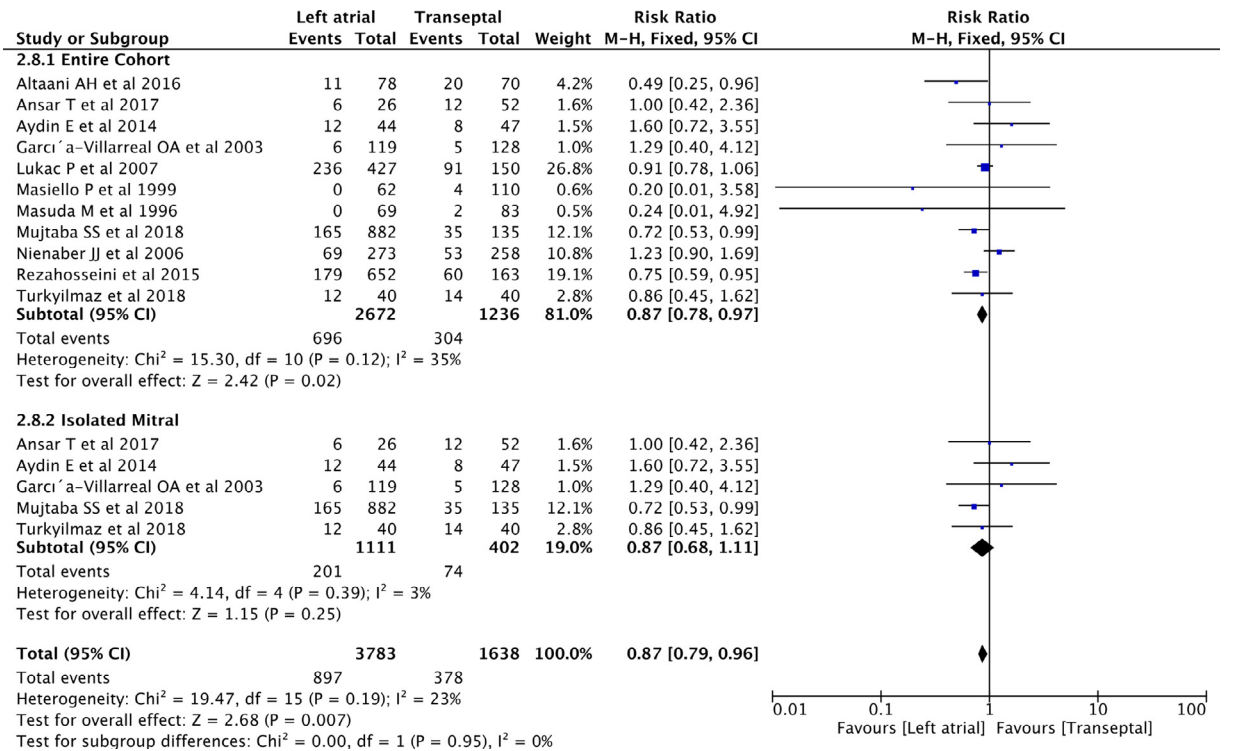

FIG 1. Rate of postoperative new atrial fibrillation in the entire cohort and isolated mitral valve as subgroup

1.02 [0.39, 2.63], $P = 0.97$; $I^2 = 0.34$, $\chi^2 = 6.02$, $P = 0.20$; e-Fig 4), new onset postoperative AF (RR 0.87 [0.68, 1.11], $P = 0.25$; $I^2 = 0.03$, $\chi^2 = 4.14$, $P = 0.39$; Fig 1), requirement for PPM (RR 0.72 [0.41, 1.26], $P = 0.25$; $I^2 = 0.28$, $\chi^2 = 4.14$, $P = 0.25$; e-Fig 2), and stroke rate (RR 1.34 [0.60, 3.00], $P = 0.47$; $I^2 = 0.0$, $\chi^2 = 1.65$, $P = 0.44$; e-Fig 7).

However, analysis of the combined valve cohorts alone, by excluding the 5 studies above, retained the significant differences in longer operative times, higher PPM rate in TS patients (e-Figs 8-10).

Publication Bias

Publication bias of PPM implantation and operative mortality was assessed visually using funnel plots (e-Figs 11 and 12 respectively). The funnel plot for mortality was largely symmetrical which suggests the absence of publication bias. However, the funnel plot for PPM implantation displayed slight asymmetry suggestive of publication bias in favor of TS approach. This may be due to reporting bias, implying that the above-mentioned higher likelihood of PPM implantation in the TS cohort may be underestimated.

Trial Sequential Analysis

TSA was attempted for operative mortality, PPM implantation, new AF, re-operation for bleeding, and stroke. TSA could not be performed for operative mortality and stroke due to information sizes being too small. TSA of both PPM implantation (e-Fig 13) and new AF (e-Fig 14) of all studies showed that the trial sequential boundary was crossed, indicating that the meta-analytical results of TS resulting in higher likelihood of PPM implantation and new AF could be considered conclusive. However, TSA of the isolated MV cohort data showed that the Z scores of both PPM implantation (e-Fig 15) and new AF (e-Fig 16) did not cross the trial sequential monitoring boundary, indicating that more studies are required before the observed effects of LA or TS approach on isolated MV surgeries could be considered conclusive. TSA of re-operation for bleeding in all studies also showed the Z score did not cross the boundary (e-Fig 13), indicating that more evidence is needed for observed effects to be considered conclusive.

Discussion

This systematic review and meta-analysis which is, to the authors' best knowledge, the first meta-analysis in this topic to be reported, is

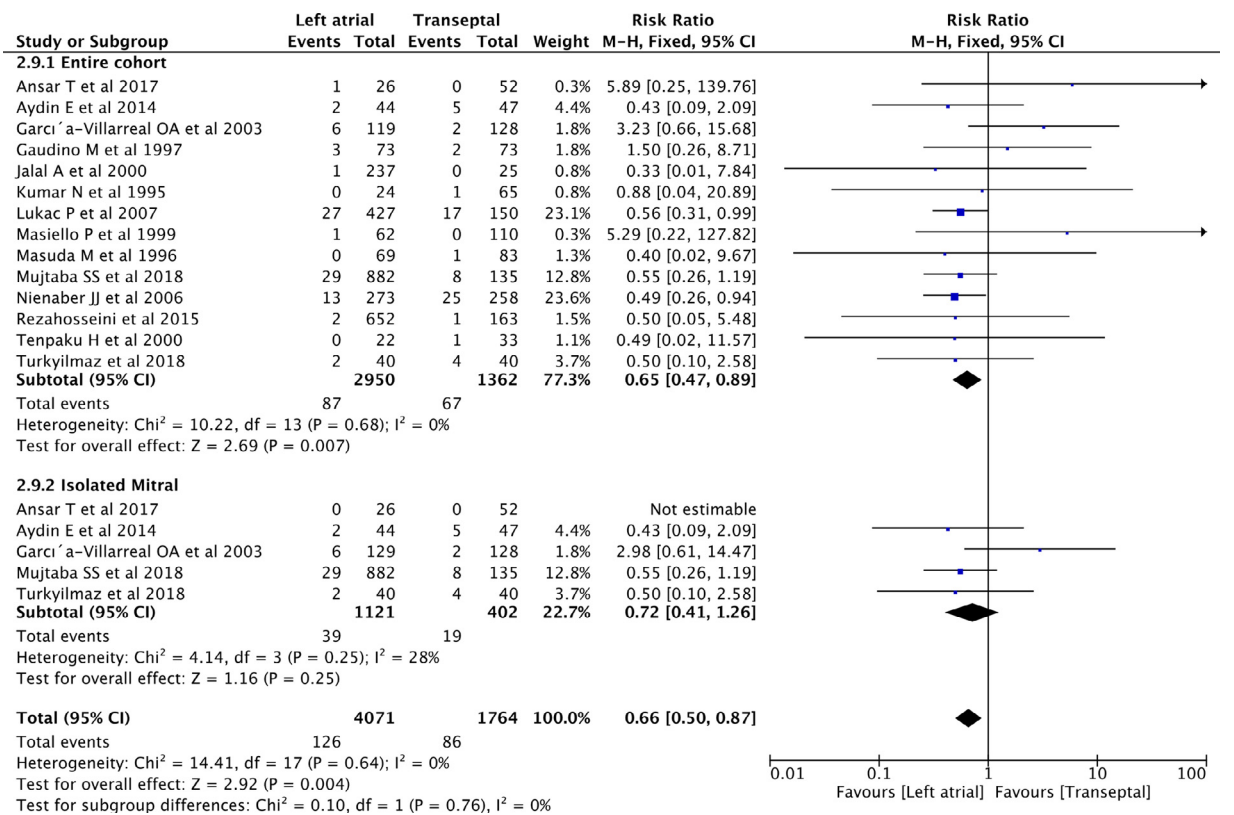

FIG 2. Rate of postoperative permanent pacemaker insertion in the entire cohort and isolated mitral valve as subgroup

comparing clinical outcomes of the LA and TS approach in MV surgery and it drew findings from 16 eligible studies for inclusion. An analysis of 4537 patients; 3065 who underwent MV surgery via the LA approach and 1472 using the TS approach revealed no significant differences in postoperative blood loss, 30-day mortality and stroke rates. While rates of new AF($P = 0.02$), pacemaker implantation ($P = 0.007$), and CPB time ($P = 0.01$) were significantly higher and longer in the TS approach group respectively. It is important to note that patients in TS cohort had higher rate of concomitant TV surgical intervention ($P = 0.001$). those findings we confirmed with TSA and deemed the results to be valid. On the other hand, subgroup analysis of articles that compared outcomes in patients which underwent isolated MV surgery did not show any significant differences in operative times, requirement for PPM and other reported postoperative outcomes.[18,23,25,26,28] Thus, the higher rate of TV intervention in TS cohort could possibly explain the differences in the reported outcomes, but also constitutes a confounding factor contributing to reporting bias among the included studies.

To date, there is no clear consensus over which approach is superior to either. The current reported literature has shown mixed messages, and this has been limited by lack of large sized, multicenter trial. There are only 2 randomized studies by Aydin et al[25] and Gaudino et al[22] and they have reported their outcomes on isolated MV surgery and combined procedures respectively. However, their conclusions are not in line with many of the larger observational studies.[4,17,21] Aydin et al reported no differences in outcomes between either technique for isolated MV surgery, this is similar to what we have reported from our meta-analysis. While Gaudino et al also reported longer operative times with TS, which is similar to our reported analysis, but no difference in outcomes even in combined valve procedures and this is in discrepant to the results from our analysis and several other studies.

The recent propensity-score matched study that aimed to compare the LA and TS approach in 815 patients matched for baseline characteristics,[17] showed no difference in postoperative outcomes, including mortality between the 2 approaches; only pump and cross-clamp times were increased as also seen in this study. This combination of results appears to be the general consensus across the literature.[7,17,27] Nevertheless, controversy surrounding postoperative arrythmias and PPM implantation still exists.[7,17] This study actually suggested that the PPM rate was reduced in the TS group, although this was not significant (5.2% LA vs 3.7% TS; $P = 0.418$). Further study has also indicated that the TS approach does not significantly increase PPM implantation postoperatively when compared

to the conventional LA approach,[7,9,27] albeit with these studies and more demonstrating a loss of sinus rhythm using the TS approach.[3,28]

Our review and meta-analysis revealed a significantly higher rate of PPM insertion in the TS cohort that underwent combined valve procedures with good homogeneity across included studies. TSA confirmed that this finding was conclusive. Previous studies have suggested that such findings may be due to pre-operative characteristics and patient factors.[29] Nevertheless, we found no difference in patient characteristics prior to surgery or preoperative AF rates and therefore cannot support this hypothesis. Our findings suggest that transient postoperative arrythmias are possibly associated with the conventional LA approach.[27] Perhaps this incongruency in the literature is a product of different indications and thresholds for PPMs. This difference in the rate of PPM implantation may also be due to a higher propensity of the TS approach to injure tissues critical for cardiac impulse conduction. This was probably also reflected by the higher rates of new AF in the TS cohort, which would not be surprising considering that the TS approach inevitably involves manipulation and injury of both the left and right atria, after which the resultant scarring may have direct arrhythmogenic effects. This difference in higher rates of new AF was also confirmed by TSA to be conclusive. It is noteworthy though that the observed effects were inconclusive in the isolated MV surgery cohort, and thus further research is required to definitively delineate the effects of TS approach on the rates of new AF and PPM implantation.

Importantly, the operative data suffers from significant heterogeneity. A look at the Forrest plot suggests this cannot be attributed to the time of publication, thus also suggesting that it might be due to different operative procedures used in the included studies. Comparing the data of CPB time and concomitant TV repair and aortic valve replacement (all of which exhibited significant heterogeneity), it appeared that all the studies which reported higher rate of concomitant TV repair in the TS cohort also reported longer CPB time in the same cohort.[16-28] There is no clear and exact explanation of such prolonged CPB and ACx times in combined cohort; this could be due to lack of reporting of second run bypass when failing to come-off CPB at first run, such data has not been reported in each included studies. Another possibility was that the patients had different premorbid state and surgical complexity, causing significant heterogeneity in CPB time. While the latter may be somewhat quantified by the rate of concomitant procedures, assessment of the former was not possible in this study since scoring systems for prediction of postoperative

mortality, such as the Society of Thoracic Surgery score or EuroSCORE, were not measured and reported in each study.

Ultimately, large randomized-control trials comparing the LA and TS approaches are needed in order to provide higher quality evidence to either support or refute the current evidence. Future studies should also explore outcomes associated with the mini-mitral approach. The literature currently suggests that a smaller incision is less likely to result in postoperative arrythmias and PPM implantation. It also suggests that CPB and cross clamp times are comparable to the LA approach.[10] Nevertheless, reducing the size of the incision will result in reduced visualization of the valve and may therefore overcome its purpose/advantage over the conventional approach.[30,31] Studies should therefore report on reoperation rates and intraoperative extension of the mini- incision. For the time being and considering the lack of differences in outcomes for isolated MV surgery and CPB and aortic cross-clamp times, the incisional approach remains at surgeon's preference.

Limitations

Our analysis has several limitations. Most of the included studies were retrospective observational which comes with significant and potential bias such as reporting and performance bias. None of the included studies gave a clear indication of which approach to use but rather it remained the surgeon's decision to decide the type of operation to be performed. In addition, it is unclear and highly unlikely that there are consistent selection criteria for the procedures, especially as it was based on surgeon experience and preference. Furthermore, there is no clear delineation of the outcomes of repair vs replacement as the operating times differs significantly among both procedures. Surgeon experience plays an important role in approach method and possible rate of complications; this has not been mentioned in any of the included studies. Lastly, as previously mentioned there is significant heterogeneity in much of the operative data. Large controlled trials should be able to eliminate those heterogeneity.

Conclusions

The transeptal approach provides comparable operative and clinical outcomes when compared to LA approach in isolated MV surgery. However, TS approach in combined procedures is associated with higher PPM rate and longer operative times. a large, randomized control trial is needed in order to confirm or refute our results.

Author's Contribution

All authors reviewed and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2020.100602.

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