Meta-Analysis of Mitral Valve Repair Versus Replacement for Mitral Valve Infective Endocarditis

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Introduction

The indications and benefits of mitral valve repair are ingrained in current clinical practice[1, 2]. It is clear that mitral valve repair offers desirable long term profile with freedom from the durability and anticoagulation issues of mitral valve prostheses[3]. Therefore techniques of repair have become an important part of a surgeon’s skill set and as a result the types of repairs and the types of valves deemed suitable for repair are becoming increasingly complex and broad respectively[2].

One example of this is in the setting of infective endocarditis where there are a number of pertinent issues to contend with. Infective endocarditis is a heterogeneous disease with high mortality, and surgery is frequently indicated for patients with valvular heart failure, uncontrolled infection or embolic prevention[4]. Firstly, there is the primary issue of microbial contamination of the native valve and therefore a desire to minimise the amount of prosthetic material implanted. Secondly, is the degree to which infective processes can disrupt the anatomy of the valve. Finally, the demographics of patients affected by infective endocarditis tend to be different than those affected with other aetiologies of valve dysfunction (i.e. they tend to be include younger patients) [5] and therefore may have more to gain from a successful mitral valve repair. With this in mind the rationale for attempting mitral valve repair in infective endocarditis is clear. However this must

Abstract

Background
Mitral valve repair has superior results to replacement for severe degenerative mitral valve disease, however in the infective endocarditis setting, mixed results have been reported. We compared the outcomes of mitral valve repair and replacement for infective endocarditis in this meta-analysis.

Methods
MEDLINE, Embase and Cochrane databases from 1 January 1980 to 30 June 2018 were searched for original studies. Two authors evaluated these studies for inclusion independently, then data were extracted and pooled.

Results
A total of 4,527 papers was obtained from the search, 121 full-texts were reviewed, and 18 studies which included both mitral valve repair and replacement patients involving 12,339 patients were included for analyses. Pooled rates and odds ratio (95% confidence interval) for operative mortality of repair versus replacement were 4.0% versus 10.5%, 0.37 (0.29-0.48) in 17 studies. Other in-hospital complications of stroke and renal failure were lower for repair than replacement odds ratios 0.65 (0.50-0.84) and 0.42 (0.34-0.52) respectively. Odds ratio for mortality at 1-year (n=4) was 0.31 (0.14-0.72), and at long term follow-up (n=12) was 0.50 (0.41-0.61). There were no differences in long term stroke, recurrent endocarditis and redo-operations (odds ratios 0.55-0.81, P=0.21-0.66).

Conclusions
Mitral valve repair is associated with significant reduction in mortality short and long term, as well as in-hospital stroke and renal failure, with similar rates of long-term stroke, recurrent endocarditis and redo-operation rates at long term follow-up compared to replacement for endocarditis. It should be therefore be the preferred strategy for mitral valve endocarditis surgery.

Keywords: Endocarditis, mitral valve surgery, heart valve surgery


The indications and benefits of mitral valve repair are ingrained in current clinical practice[1, 2]. It is clear that mitral valve repair offers desirable long term profile with freedom from the durability and anticoagulation issues of mitral valve prostheses[3]. Therefore techniques of repair have become an important part of a surgeon’s skill set and as a result the types of repairs and the types of valves deemed suitable for repair are becoming increasingly complex and broad respectively[2].
be balanced against the likelihood of a successful repair in the long term.

A number of retrospective non-controlled studies have reported on outcomes of mitral valve replacement versus mitral valve repair in the setting of infective endocarditis with mixed results. Therefore a review of literature and meta-analysis was performed with the aim of providing short and medium term outcome data of mitral valve repair and mitral valve replacement in the setting of infective endocarditis.

**Materials And Methods**

**Literature Search**

This meta-analysis was conducted following the PRISMA guidelines. Five electronic databases, including MEDLINE, EMBASE, PubMed, Cochrane Central Register for Controlled Trials (CENTRAL), and Web of Science, were searched for original studies from January 1, 1980 to June 30, 2018. The search terms used were “mitral”, or “mitral valve”; and “repair”, “replacement”, “surgery”, or “operation”; and “endocarditis”, or “infective endocarditis”. The search terms were supplemented with corresponding MeSH terms, where possible. The reference lists of retrieved articles were also screened for potentially relevant studies. Two reviewers (MTMW and TKMW) independently conducted the search and evaluated studies for inclusion. Discrepancies were then resolved by discussion and consensus.

**Inclusion and exclusion criteria**

Original studies reporting both mitral valve repair and replacement outcomes, with more than twenty adult human subjects total (over 18 years of age), more than ten patients per surgical arm (repair or replacement) and reporting mortality outcomes were eligible for inclusion. Editorials, reviews and expert opinions were excluded.

**Data Extraction**

Data extraction was conducted independently by two reviewers (MTMW and TKMW), using standardised forms. Discrepancies were resolved by discussion and consensus. Data were extracted on study design, baseline characteristics, and outcome measures. Outcomes of interests include mortality, stroke, recurrent endocarditis and redo-operations at operative (in-hospital or 30 days), 1-year and 5-years where available.

**Statistical analysis**

Statistical analysis was conducted using Review Manager Version 5.3 (Cochrane Collaboration, Oxford, England). Effect measures for dichotomous data were estimated using odds ratios (OR) with the Mantel-Haenszel statistical method, and weighted mean differences (WMD) used for the analysis of continuous data, with 95% confidence intervals reported for both types of measures, unless otherwise stated. Odds ratios were calculated to represent the odds of an event occurring in the mitral valve repair group compared to the replacement group, with a point estimate of <1.0 indicating a lower event rate in the mitral valve repair group. In order to account for potential clinical diversity and methodology variation between studies, random effects statistical modelling was utilised. The I² statistic was used as an indication of the degree in which the total variation across the aggregated studies was a result of heterogeneity instead of chance, and values of >50% were considered to represent considerable heterogeneity. All tests were two tailed and P<0.05 was considered significant.

**Results**

Figure 1 summarizes the study selection process. 4,527 articles were obtained from the literature search. Following abstract evaluation and exclusion, 121 full-text articles were reviewed. Eighteen studies reporting both mitral valve repair and replacement outcomes, involving 12,339 patients (3,390 repairs, 8,948 replacements), were included for the analyses[6-23]. Table 1 lists the characteristics of included studies. Due to clinical characteristics being inconsistently reported across studies they are not separately reported here.

Operative mortality was significantly lower among the mitral valve repair group compared to the replacement group in 17 studies 4.0% versus 10.5%, OR 0.37 (0.29-0.48), P<0.001; figure 2(a). OR (95% confidence intervals) for in-hospital stroke and renal failure were 0.65 (0.50-0.84) in seven studies and 0.42 (0.34-0.52) in five studies respectively in favour of mitral valve repair (figure 2(b)-(c)).

At 1-year follow-up, the mitral valve repair group continued to have significantly lower mortality rates than the replacement group in four studies 5.8% vs. 14.6%, OR 0.31 (0.14-0.72), p=0.006; figure 2 (d).

Long-term mortality rates were significantly lower in the repair group in twelve studies OR 0.50 (0.41-0.61), P<0.001; figure 3(a). There were no significant differences in the two surgical arms for long-term stroke in five studies, recurrent endocarditis in nine studies and redo operations in ten studies (OR 0.55-0.81 but P=0.21-0.66).

One large study made up just over half of the pooled cohort[7], but excluding this study did not change any of the endpoints, such as the pooled operative mortality odds ratios of the other sixteen studies being 0.41 (0.29-0.57), P<0.001. Funnel plots were symmetrical pyramid in shape for all pooled outcomes, that for operative mortality for example is shown in figure 4. This together with Egger’s statistic of all pooled outcomes having P>0.05 suggest no significant publication bias.

**Discussion**

A number of studies have demonstrated mixed results for mitral valve repair in endocarditis compared to mitral valve replacement but this is the first meta-analysis of studies which have compared mitral valve repair and replacement cohorts in the setting of infective endocarditis. This study showed that mitral valve repair was superior to replacement for all in-hospital outcomes for mortality and morbidities as well as long term mortality, with

![Figure 1](image-url)
Encouraging for mitral valve repair in the setting of infective endocarditis, and nearly all outcomes for repair [14], and one study found significantly lower rates of both outcomes for repair combined, in fact one study found significantly lower operative mortality compared to replacement, even with the added technical demand and therefore potential to increase the duration of surgery as well as the risk of repair failure or valvular degeneration requiring re-operation.

In this meta-analysis mitral valve repair had significantly lower operative mortality compared to replacement, even with the added technical demand and therefore potential to increase the duration of surgery as well as the risk of repair failure or valvular degeneration requiring re-operation.

Table 1. Characteristics of included studies (repair, replacement)

<table>
<thead>
<tr>
<th>Article</th>
<th>Repair</th>
<th>Replacement</th>
<th>N</th>
<th>Study dates</th>
<th>Country</th>
<th>Centre</th>
<th>Age</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jung 2011[8]</td>
<td>41</td>
<td>61</td>
<td>102</td>
<td>1994-2009</td>
<td>Korea</td>
<td>Single</td>
<td>34.4 vs 43.1</td>
<td>46.3%, 54.1%</td>
</tr>
<tr>
<td>Knyshev 2001[9]</td>
<td>14</td>
<td>134</td>
<td>148</td>
<td>1982-2000</td>
<td>Ukraine</td>
<td>Single</td>
<td>41.7</td>
<td>78.8%</td>
</tr>
<tr>
<td>Lee 2018[11]</td>
<td>424</td>
<td>1575</td>
<td>1999</td>
<td>2000-2013</td>
<td>Taiwan</td>
<td>Multiple</td>
<td>49.3, 52.4</td>
<td>69.1%, 56.3%</td>
</tr>
<tr>
<td>Ruttmann 2005[16]</td>
<td>34</td>
<td>34</td>
<td>68</td>
<td>1992-2004</td>
<td>Austria</td>
<td>Single</td>
<td>51.5, 53.2</td>
<td>64.7%, 50.0%</td>
</tr>
<tr>
<td>Toyoda 2017[21]</td>
<td>367</td>
<td>1603</td>
<td>1970</td>
<td>1998-2010</td>
<td>United States</td>
<td>Multiple</td>
<td>54.9, 57.4</td>
<td>66.2%, 56.1%</td>
</tr>
<tr>
<td>Wang 2014[22]</td>
<td>25</td>
<td>35</td>
<td>60</td>
<td>2005-2011</td>
<td>New Zealand</td>
<td>Single</td>
<td>43.1, 52.1</td>
<td>56%, 60%</td>
</tr>
</tbody>
</table>

The appeal of surgical repair in the setting of infective endocarditis with respect to long term quality of life is clear[24]. Most of these benefits revolve around avoiding a prosthetic valve and its negatives such as thromboembolism and bleeding with anticoagulation and risk of recurrent endocarditis. However to acquire this benefit mitral valve repair must overcome some hurdles. Specifically, there is the added technical demand and therefore potential to increase the duration of surgery as well as the risk of repair failure or valvular degeneration requiring re-operation.

In this meta-analysis mitral valve repair had significantly lower operative mortality compared to replacement, even with the added technical demand and therefore potential to increase the duration of surgery as well as the risk of repair failure or valvular degeneration requiring re-operation.

Endocarditis however it should be noted that these important outcomes were only reported in a minority of the studies in this analysis, unlike mortality.

Mitral valve surgery has undergone significant progress with the evolution of techniques of repair[25]. As a result, experience with repairing increasingly complex mitral valve disease has grown with some proponents of mitral valve repair believing that all valves are repairable[26]. Clearly, data and clinical practice regarding mitral valve repair in the setting of endocarditis as opposed to degenerative disease is not unconditionally transferrable and this leads to an important point regarding studies comparing mitral valve repair versus replacement in infective endocarditis. For example the severity and or distribution of tissue destruction that is unique to endocarditis pathology is likely to impact both decision making regarding reparability of a valve and certain outcome measures, although unfortunately this was inconsistently reported across studies. Another important concern is that repair rates continue to be low, making up only about 27% of the entire analysis cohort, and in fact only four studies had repair rates over 50%[13, 15, 17, 20]. Further developments of repair techniques and gaining competence are required to increase repair rates, and it is somewhat promising that three of these high repair rates studies were amongst the five most recent studies in this meta-analysis[13, 15, 20].

This meta-analysis has some limitations. All studies were retrospective and observational which have the potential of biases, especially for patient selection for surgical strategy. Differences in baseline characteristics between surgical arms are expected but were inconsistently reported across studies to report and analyse, including meta-regression cannot be performed. This lack of patient-level data also meant we could not pool longitudinal outcomes as hazards ratio or time to endpoint measures. There were heterogeneity across the studies in terms of study design and outcomes recorded, and they were somewhat chronologically diverse. Although this was a meta-analysis, analysis of infrequent outcomes remain underpowered. However as with many challenging clinical presentations the
data and logistical requirement to give robust conclusions are a formidable barrier and therefore meta-analysis of smaller retrospective studies are of substantial value to clarify what would otherwise be anecdotal practice.

In conclusion, this meta-analysis found encouraging and superior outcomes for mitral valve repair compared to replacement for infective endocarditis. The implication is that mitral valve repair, when feasible, should be the preferred strategy for mitral valve endocarditis surgery. We have to be mindful of the limitations of the analysis and manage patient on an individualised basis however, and the next step in this question is perhaps to elucidate the type of patient that is more likely to benefit with mitral valve repair or replacement.

Declarations of interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [27].

References

Figure 2. Forest plot of odds ratio of operative (a) mortality, (b) stroke, (c) renal failure and (d) 1-year mortality after mitral valve repair or replacement in patients with infective endocarditis.

Figure 3. Forest plot of odds ratio of (a) mortality, (b) stroke, (c) recurrent endocarditis and (d) redo-operation at long term follow-up after mitral valve repair or replacement in patients with infective endocarditis.

Figure 4. Funnel plot of included studies pooling and comparing operative mortality.


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