Mitral Valve Replacement Using Subvalvular Apparatus: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: To assess clinical outcomes among participants undergoing mitral valve replacement with preservation of subvalvular apparatus.

Methods: Electronic databases, including PubMed, Embase, Science Direct, World of Science, Scopus, Biosis, SciElo and Cochrane library, were probed using an extensive search strategy. Studies that reported at least one clinical outcome, such as morbidity, mortality, early 30-day mortality, myocardial failure, survival, late cerebrovascular events, length of stay, or major operative complications (stroke, prolonged ventilation, and reoperation for bleeding, renal failure, and sternal infection) were considered for inclusion. Data was extracted and pooled into a meta-analysis in RevMan (version 5.3) using a random-effects model.

Results: A total of 21 studies with 5,106 participants (age range: 27.3–69.2 years) were included in this meta-analysis. Preservation of the subvalvular apparatus during MVR significantly reduces the risk of long-term mortality (OR: 0.46; 95% CI: 0.33–0.64), but not early mortality (OR: 0.76; 95% CI: 0.12–4.93). No significant difference ejection fraction was observed (SMD: 0.10; 95% CI: -0.44–0.64). Similarly, there was no significant difference in the risk of stroke, renal failure, and pneumonia between C-MVR and in the control group.

Conclusion: MVR with the preservation of subvalvular apparatus improves clinical outcomes, such as long-term mortality, hospital length of stay, pneumonia, and bleeding. There is no significant difference in the risk of stroke, renal failure, or ICU length of stay. However, there is very limited data available with respect to bleeding, sepsis, and nosocomial infections.

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INTRODUCTION

The prevalence of ischemic mitral regurgitation ranges between 1.6 million to 2.8 million in the United States. Patients with mild or greater degrees of mitral regurgitation after myocardial infarction are at a significantly increased risk of mortality [Rossi 2017; Grigioni 2001; Ellis 2002]. A majority of these patients require mitral valve replacement (MVR) when a repair is not feasible, however, this process can result in a deterioration in the left ventricular (LV) function. As such, preservation of optimal LV function is of great significance in this group of patients [Ellis 2002].

The importance of preserving the subvalvular apparatus was first demonstrated in the early 1960s [Lillehei 1963]. Studies published in the late 1970s reported that the preservation of subvalvular valve apparatus improves LV function and mortality, especially in patients with mitral regurgitation [Hüseyin 2013]. Many studies have been addressed the early and late hemodynamic benefits of preserving the mitral subvalvular apparatus during MVR, however, the issue of complete versus partial chordal preservation has yet to be fully investigated [Yun 2002].

Similarly, in non-rheumatic MVR, preservation of the subvalvular apparatus has maintained annular-papillary continuity, which helps improve LV function in the early and late postoperative period, and subsequently showed short- and long-term survival [Coutinho 2015]. It also has been suggested that MVR with preservation of subvalvular apparatus provides better freedom from mild to moderate mitral regurgitation (MR) in patients with ischemic mitral regurgitation (IMR), with a low incidence of valve-related complications. A study conducted by Reece et al [Reece 2004] reported that mitral valve repair is superior to replacement. However, recent literature suggests that MVR with preservation of the subvalvular apparatus still is a better option in some patients with ischemic mitral regurgitation. In this study, we aimed to assess the clinical outcomes of MVR with complete preservation of subvalvular apparatus as compared with other procedures.
METHODS

Search strategy and study selection: A search of the electronic databases, including PubMed, Embase, Science Direct, World of Science, Scopus, Biosis, SciELO, Cochrane Library, and China National Knowledge Infrastructure (CNKI) database using an extensive search strategy to identify potentially relevant articles. Moreover, the bibliographies and citation sections (i.e., snowballing technique) of the included articles also were searched to identify any additional studies. No language or date restrictions were applied to the searches.

The following steps were conducted during study selection process: (1) identification of titles of records identified through databases searching, (2) removal of duplicates, (3) screening by titles and abstracts, (4) assessment of eligibility by full-texts according to the eligibility criteria explained in Table 1, and (5) finally inclusion. This process was carried out by two independent reviewers; in the case of any disagreement, a consensus was reached by consultation with a third reviewer.

Search strategy:

9. subvalvular[All Fields] AND ("instrumentation"[Subheading] OR "instrumentation"[All Fields] OR "apparatus"[All Fields])

10. ("mitral valve"[MeSH Terms] OR ("mitral"[All Fields] AND "valve"[All Fields]) OR "mitral valve"[All Fields]) AND ("instrumentation"[Subheading] OR "instrumentation"[All Fields] OR "apparatus"[All Fields])

11. #9 OR #10

12. Preserv* [All Fields]

13. #5 AND #8

14. #11 AND #12

15. #13 AND #14

Eligibility criteria: Studies that (1) included patients undergoing MVR with preservation of subvalvular apparatus and (2) reported at least one clinical outcome such as morbidity, mortality, early 30-day mortality, myocardial failure, survival, late cerebrovascular events, length of stay, major operative complications (stroke, prolonged ventilation, and reoperation for bleeding, renal failure, and sternal infection) were considered for inclusion in the review (Table 1).

Data extraction: Data from the eligible studies were extracted in a predesigned extraction spreadsheet by two independent reviewers. Any disagreements were resolved by a consensus among the reviewers. From each study, patient outcomes were extracted and are presented in Table 2.
demographics and characteristics, study design, country, and outcomes (number of events and number of total groups) were extracted.

Definitions of outcomes

1. Primary outcomes
   - Early mortality: Number of deaths within 30 days of the post-operative period (dichotomous data) [Osswald 1999]
   - Long term mortality: Number of deaths at follow up (dichotomous data)
   - Ejection fraction: Measurement of how much blood the left ventricle pumps out with each contraction (continuous data measured using Echocardiogram)

2. Secondary outcomes
   - Hospital length of stay: Number of days spent in hospital pre- and post-MVR (continuous data)
   - Intensive care unit stay: Number of days spent in intensive care unit post-MVR (continuous data)
   - Stroke: Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (The global burden of cerebrovascular disease (dichotomous data))
   - Postoperative need for positive inotropic agents: Patients receiving any inotrope/vasopressor postoperatively up to 12 hours after skin closure, including any agents initiated intraoperatively (dichotomous data) [Williams 2011]
   - Nosocomia infection: Infection occurring 48 hours after hospital admission (dichotomous data) [Kouchak 2012]
   - Pulmonary complication: Complications such as pneumonia, atelectasis, and prolonged ventilation (dichotomous data)
   - Postoperative complications: Any other postoperative complications except the above-mentioned items (dichotomous data)

Statistical analysis: Demographic details were summarised using descriptive statistics. If the data was homogenous, a...
| Author          | Country     | Duration       | Study design   | N  | Group   | Age Mean (SD)/ Median (IQR) | Gender (N) |
|-----------------|-------------|----------------|----------------|----|---------|----------------------------|------------|
| Reece 2004      | NR          | 1995 to 2002   | Retrospective  | 110| C-MVR   | 69.2 (1.2)                 | 38 16      |
| Repair          | NR          | 1995 to 2002   | Retrospective  | 110| C-MVR   | 69.2 (1.2)                 | 38 16      |
| Yun 2002        | US          | Mar 1996 to Apr 1998 | Randomized trial | 47| C-MVR   | 56 (13)                  | 15 7       |
| P-MVR           | 59 (11)     | 1999 to 2000   | Randomized trial | 47| C-MVR   | 56 (13)                  | 15 7       |
| Yun 1999        | US          | Jun 1996 to Jul 1997 | Randomized trial | 30| C-MVR   | 54 (14)                  | 8 3        |
| P-MVR           | 62 (14)     | 1999 to 2000   | Randomized trial | 30| C-MVR   | 54 (14)                  | 8 3        |
| Repair          | 65 (16)     | 1999 to 2000   | Randomized trial | 30| C-MVR   | 54 (14)                  | 8 3        |
| Natsuaki 1996   | NR          | Jan 1992 and Jan 1995 | Retrospective  | 43| P-MVR   | 55 (10)                  | 6 7        |
| C-MVR           | 59 (10)     | 1992 to 1995   | Retrospective  | 43| P-MVR   | 55 (10)                  | 6 7        |
| Repair          | 56 (11)     | 1992 to 1995   | Retrospective  | 43| P-MVR   | 55 (10)                  | 6 7        |
| García-Fuster 2008 | NR        | 1996 to 2006   | Retrospective  | 560| No preservation | 41.7 (16.1)         | 41.7 (16.1) |
| P-MVR           | 62 (9)      | 1996 to 2006   | Retrospective  | 560| No preservation | 41.7 (16.1)         | 41.7 (16.1) |
| C-MVR           | 61 (10)     | 1996 to 2006   | Retrospective  | 560| No preservation | 41.7 (16.1)         | 41.7 (16.1) |
| Chen 2013       | China       | Oct 2003 to Dec 2007 | Prospective study | 128| C-MVR   | 40.8 (15.3)             | 23 35      |
| P-MVR           | 41.7 (16.1) | 1996 to 2006   | Retrospective  | 128| C-MVR   | 40.8 (15.3)             | 23 35      |
| Lee 1996        | NR          | 1992 to 1995   | Retrospective  | 560| No preservation | 41.7 (16.1)         | 41.7 (16.1) |
| C-MVR           | 61.6 (1.5)  | 1992 to 1995   | Retrospective  | 560| No preservation | 41.7 (16.1)         | 41.7 (16.1) |
| No preservation | 62.7 (10.3) | 1992 to 1995   | Retrospective  | 560| No preservation | 41.7 (16.1)         | 41.7 (16.1) |
| Kaul 1992       | UK          | Jan 1992 to Dec 1992 | Retrospective  | 125| C-MVR   | 62.0 (10.2)             | 176 168    |
| No preservation | 59.1 (2.7)  | 1992 to 1995   | Retrospective  | 125| C-MVR   | 62.0 (10.2)             | 176 168    |
| C-MVR           | 66.2 (0.7)  | 1992 to 1995   | Retrospective  | 125| C-MVR   | 62.0 (10.2)             | 176 168    |
| Coutinho 2015   | Portugal    | Jan 1992 to Dec 1992 | Retrospective  | 250| C-MVR   | 62.0 (10.2)             | 176 168    |
| No preservation | 59.8 (10.5) | 1992 to 1995   | Retrospective  | 250| C-MVR   | 62.0 (10.2)             | 176 168    |
| Chan 2011       | Canada      | 2001 to 2010   | Retrospective  | 130| C-MVR   | 68.5 (9.5)              | 22         |
| Repair          | 66.9 (8.6)  | 2001 to 2010   | Retrospective  | 130| C-MVR   | 68.5 (9.5)              | 22         |
| Zakai 2009      | Pakistan    | Jan 2009 to Sep 2009 | Retrospective  | 130| C-MVR   | 68.5 (9.5)              | 22         |
| P-MVR           | 39.28 (15.68) | Jan 2009 to Sep 2009 | Retrospective  | 130| C-MVR   | 68.5 (9.5)              | 22         |
| C-MVR           | 42.19 (15.14) | Jan 2009 to Sep 2009 | Retrospective  | 130| C-MVR   | 68.5 (9.5)              | 22         |
| Sakai 1992      | Japan       | Jan 1985 to Apr 1991 | Retrospective  | 36 | C-MVR   | 47 (10)                 | 6 6        |
| Annuloplasty    | 58 (11)     | Jan 1985 to Apr 1991 | Retrospective  | 36 | C-MVR   | 47 (10)                 | 6 6        |
| Chowdhury 2005  | India       | Jan 1996 to Dec 1999 | Retrospective  | 451| C-MVR   | 44.3 (4.1)              | 17 34      |
| P-MVR           | 33 (19)     | Jan 1996 to Dec 1999 | Retrospective  | 451| C-MVR   | 44.3 (4.1)              | 17 34      |
| C-MVR           | 35 (23)     | Jan 1996 to Dec 1999 | Retrospective  | 451| C-MVR   | 44.3 (4.1)              | 17 34      |
| Cingoz 2004     | Turkey      | Jan 1995 to Feb 1995 | Comparative study | 94 | C-MVR   | 44.3 (4.1)              | 17 34      |
| C-MVR           | 46.3 (4.65) | Jan 1995 to Feb 1995 | Comparative study | 94 | C-MVR   | 44.3 (4.1)              | 17 34      |
| Alizadeh-Ghavidel 2013 | Iran | Jan 1996 to Nov 2006 | Retrospective study | 251| C-MVR   | 42 (18)                 | 14 25      |
| No preservation | 47 (13)     | Jan 1996 to Nov 2006 | Retrospective study | 251| C-MVR   | 42 (18)                 | 14 25      |
| Timala 2013     | Nepal       | Apr 2011 to Apr 2012 | Retrospective study | 93 | C-MVR   | 27.3 (12.8)             | 38 51      |
meta-analysis was performed. Forest plots were generated for graphical presentations of clinical outcomes. Meta-analysis was conducted using a weighted DerSimonian–Laird random-effects model with effect sizes of odds ratio (OR), standardised mean difference (SMD) with 95% confidence interval (CI). This model was weighted by the number of events in each study. All statistical tests were two-sided, with \( P < .05 \) being considered statistically significant, except if otherwise specified. Publication bias was assessed using visual inspection of funnel plots. To assess potential heterogeneity among the included studies, the \( I^2 \) statistic was employed with a value >50% considered as a measure of significant heterogeneity. The meta-analysis was conducted using “RevMan version 5.3” (from Cochrane community). If a meta-analysis was not feasible, the findings of the systematic review were described.

### RESULTS

The literature searches identified 254 records, with five additional records added from the reference search. After removal of duplicates, there were 255 citations, which were screened using title and abstracts. A total of 55 articles were considered potentially relevant, based on the initial screening, and the full text of the articles were evaluated. However, further to researching the full text of the articles, 12 could not be retrieved, thus being discarded; moreover, following an analysis of the full-text against the exclusion criteria in the methods section, 22 articles were excluded for the following reasons: One study was focused on a microsimulation; one article was a commentary of another study; in one study there was no comparator; in 15 articles there were no preservation of the subvalvular apparatus; and four studies did not have data on the relevant clinical outcome measures investigated. Finally, 21 studies (5,106 participants) were included in the meta-analysis. The mean age of the study samples ranged between 27.3 and 69.2 years. Of the 21 included studies, three were randomized studies, 15 were observational studies, and three did not report a study design. The included studies inclusively compared complete preservation of subvalvular apparatus during MVR (C-MVR) with no preservation (N = 10 studies), partial preservation of subvalvular apparatus (P-MVR) (N = 12 studies), mitral valve repair (N = 5 studies), and annuloplasty (N = 2 studies). Most of the patients had undergone MVR for rheumatic disease, or chronic mitral regurgitation. Detailed study characteristics are presented in Table 2.

Table 2. [add title]

| Author          | Country | Duration         | Study design          | N  | Group   | Age Mean (SD)/ Median (IQR) | Gender (N) |
|-----------------|---------|------------------|-----------------------|----|---------|-----------------------------|------------|
| **C-MVR**       |         |                  |                       |    |         |                             |            |
| Dancini 2005    | Brazil  | Apr 2000 to Nov 2002 | Randomized controlled trial | 28 | C-MVR   | 54.1 (15.8)                | -          |
| **P-MVR**       |         |                  |                       |    |         |                             |            |
| Valvuloplasty   |         |                  |                       |    |         |                             |            |
| Ozdemir 2014    | Turkey  | March 2010 to March 2011 | Retrospective study | 70 | MVR-B   | 56.5 ± 13.1                | 7          |
| MVR-P           |         | 52.5±13.9        | 9                     | 14 |         |                             |            |
| Garci’a-Fuster 2011 | Spain | Jan 1994 to Aug 2008 | Retrospective study | 805 | P-MVR   | 61.4 (10.7)                | -          |
| C-MVR           |         | 61.4 (10.4)      | -                     | 141|         |                             |            |
| Anasz 2014      | Turkey  | 2001 and 2007    | Retrospective study   | 51 | P-MVR   | 49.2±11.7                  | 8          |
| C-MVR           |         | 48.6±18.7        | 17                    | 14 |         |                             |            |
| Muthal 2005     | India   | May 1996 to Aug 2002 | Retrospective study | 467 | No preservation | 37 (8-74)           |            |
| P-MVR 47 (18-61)|         |                  |                       |    |         |                             |            |
| C-MVR           |         | 38 (21-56)       |                       |    |         |                             |            |

C-MVR: complete preservation of subvalvular apparatus; P-MVR: Partial preservation of subvalvular apparatus; US: United states; UK: United Kingdom; NR: Not reported
2008; García-Fuster 2011; Alizadeh-Ghavidel 2013; Kaul 1992; Zakai 2009; Muthialu 2005]. A meta-analysis of these studies revealed that preservation of subvalvular apparatus during MVR significantly reduces the risk of long term mortality (odds ratio [OR] 0.46; 95% confidence interval [CI] 0.33 to 0.64; P < .00001; F = 52%) when compared to control procedure.

Ejection fraction (EF): Data on EF was reported in 11 studies (N = 1512) [Yun 2002; Coutinho 2015; Chan 2011; Chowdhury 2005; Chen 2013; Kaul 1992; Zakai 2009; Natsuaki 1996; Sakai 1992; Timala 2016; Yun 1999]. A pooled summary estimate of these 11 studies found no significant difference in EF between C-MVR and no preservation or partial preservation (standard mean difference [SMD]: 0.10; 95% CI: -0.44 to 0.64; P = .72; F = 95%).

Secondary outcomes: Stroke. Incidence of stroke was reported in only four studies [Reece 2004; García-Fuster 2008; Zakai 2009; Muthialu 2005]. A pooled analysis found that there was no significant difference in stroke between C-MVR and the control group (OR: 0.76; 95% CI: 0.30 to 1.92; P = .56; F = 0%).

Hospital length of stay (LOS): Four studies compared hospital LOS in C-MVR versus control group [Coutinho 2015; Reece 2004; Gingöz 2004; Ozdemir 2014]. A meta-analysis of these studies found a significant difference in hospital LOS between C-MVR and control group (mean difference [MD]: 1.52 days; 95% CI: 1.19 to 1.84; P = < .00001; F = 99%).

ICU length of stay: Three studies assessed ICU length of stay. Pooling revealed there was no significant difference between C-MVR with subvalvular preservation when compared with no preservation (MD: -0.09 days; 95% CI: -0.33 to 0.16).

Renal failure: Four studies assessed renal failure among participants undergoing MVR with the preservation of subvalvular apparatus. Summary estimate of these four studies showed slight, but not statistically significant reduction in renal failure in C-MVR group compared with no preservation or partial preservation (OR: 0.72; 95% CI: 0.47 to 1.11; P = .14; F = 0.0%).

Pneumonia: Four studies assessed the effect of C-MVR on the risk of pneumonia [Reece 2004; García-Fuster 2008; García-Fuster 2011; Zakai 2009]. Pooled analysis of these studies demonstrated no significant difference in the risk of pneumonia (OR 0.44; 95% CI 0.06 to 3.34; P = .12; F = 76%). However, when we did sensitivity analysis by removing Reece 2004 study, results were favorable to the C-MVR group (OR 0.20; 95% CI 0.04 to 0.97; P = .05; F = 58%).

Other outcomes: Two studies [Reece 2004; Zakai 2009] reported eight nosocomial infections in the MVR group and five studies in repair, one study in no subvalvular preservation group, and two in partial MVR.

Prolonged ventilation was reported more in no subvalvular preservation group (12.5%; N = 32) and one in C-MVR group (2.7%; N = 36).

Similarly, in two studies [Coutinho 2015; García-Fuster 2011], bleeding was observed less in the MVR group than no subvalvular preservation group (9 versus 33). The study by García-Fuster in 2008 reported that sepsis was observed more in partial MVR (five cases) than in no subvalvular preservation (two cases) and C-MVR (one case).

**DISCUSSION**

All mitral valve components such as the annulus, leaflets, chordae tendinae, and papillary muscles work in coordination to facilitate normal valvular function [Miller 2004; Kodavatiganti 2002; Condado 2003]. The mitral valve consists of two papillary muscles, the anterolateral, and the posteromedial [Piérard 2004]. Mitral regurgitation is a condition that results from disruption of the valve leaflets or any of the above-mentioned components of the mitral apparatus [Maganti 2010].

In the early 1960s, MVR was carried out to manage conditions like mitral regulations by implantation of a Starr-Edwards prosthetic valve, with complete removal of the mitral leaflets, the heads of the papillary muscles, and chordae tendinae [Starr 1961]. However, this procedure was associated with a high incidence of low cardiac output syndrome, other morbidity, and mortality. Too reduce such complications, a subvalvular apparatus preservation (SVP) strategy was introduced [Athanasiou 2008]. David et al, in 1983, revised the process of MVR with the preservation of the chordae tendinae [David 1983]. Convincing clinical evidence was reported in favor of the preservation of papillary muscles in the study by Lillehei et al [Lillehei 1964].

Findings from this meta-analysis indicate that both the risk of mortality and pneumonia were found to be reduced in the C-MVR group as compared with the control group. It was observed that C-MVR reduced ICU length of stay, and bleeding as compared with the control group. One study reported that prolonged ventilation was reduced in C-MVR group compared to no preservation.

Although the results of our analysis on long-term mortality were in favor of C-MVR, no statistically significant difference was observed for 30-day mortality between the experimental and control groups. A previous meta-analysis conducted by Athanasiou et al reported that excision of the subvalvular apparatus was found to be significantly associated with an increased risk of overall mortality and 30-day perioperative mortality [Athanasiou 2008]. In left ventricular contraction, the papillary muscles play a vital role by drawing the mitral ring toward the apex to shorten the axis for the ejection of blood [Solomon 2006]. Hence, preserving subvalvular apparatus during MVR may improve the ejection fraction, thereby reducing mortality.

The risk of stroke, renal failure, and pneumonia were slightly on the lower side in the C-MVR group than in control group. However, the results were not statistically significant.

Strengths and limitations: A few limitations of this meta-analysis should be considered. First, most of the included studies were single-center retrospective observational studies, which are a high risk for inherent biases, such as recall bias. Second, while inspection of funnel plots indicated a fairly symmetrical distribution, the possibility of such bias still exists and should be considered when interpreting this study's findings. Third, substantial statistical heterogeneity was present,
but we were not able to explore the sources due to the low number of studies included in each analysis. However, we suspect that the main source of heterogeneity was the different comparators employed for the control group. Very limited data was available with respect to bleeding, sepsis, ionotropic usage, and nosocomial infections, as such, there is a need for further investigation of these parameters in future studies.

CONCLUSION

In conclusion, MVR with the preservation of the subvalvular apparatus improves clinical outcomes, such as long-term mortality, hospital length of stay, pneumonia, and bleeding. There is no significant difference in the incidence of stroke, renal failure, and ICU length of stay.

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