Safe Use of Glutaraldehyde to Repair the Destroyed Valve in Active Infective Mitral Valve Endocarditis

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Background: The aim of this study was to review our experience of mitral valve (MV) repair for acute and active infective endocarditis (AAIE) and to identify the feasibility of a new approach together with the mid-term results.

Methods and Results: A retrospective analysis was performed on 35 consecutive AAIE patients surgically treated in the isolated mitral position. Mean follow-up after the surgery was 4.3±3.7 years. 30 of the 35 patients were successfully treated by MV plasty (MVP); however, MV replacement (MVR) was necessary in the remaining 5 patients. Our novel approach included resection of the infective lesion, approximation with direct suture and/or patch repair with bovine or autopericardium after 2-min treatment of it and the defective leaflet edge(s) with 0.625% glutaraldehyde solution, reconstruction with artificial chordae and ring annuloplasty. The success rate of MVP was 85.7%. The longest postoperative follow-up echocardiography showed no mitral regurgitation (MR) in 4, trivial MR in 4, mild MR in 16 and moderate MR in 5 patients in the MVP group. The 5-year survival rate in the MVP group was 89±6%. MVR was required in 1 patient 2 months after MVP because of increasing MR. Recurrence of endocarditis has not been observed in any case.

Conclusions: Glutaraldehyde was safely used in a surgical intervention for AAIE in the mitral position with acceptable early and mid-term results.

Key Words: Acute infective endocarditis; Mitral valve repair

Mitrval valve plasty (MVP) is a well-established procedure for degenerative MV disease and offers multiple advantages for patients, compared with MV replacement (MVR). In addition to fewer requirements in terms of anticoagulant therapy, MVP allows the subvalvular apparatus and left ventricular motion to be maintained. Although several institutions have reported good results of MVP for acute and active infective endocarditis (AAIE), the re reparability in AAIE patients ranges from 35% to 81%, because the repair procedure is technically demanding. The purpose of this study was to review our 10-year experience of MVP for AAIE and to determine whether our new approach is both reliable and long-lasting.

Methods
From January 2004 through August 2015, a consecutive series of 35 patients (21 males [60.0%] and 14 females [40.0%]) underwent isolated MV surgery for AAIE at the Jikei University Hospital. The mean age was 57±17 (range, 22–84) years. The patients’ preoperative profiles are listed in Table. Preoperative NYHA class was I in 1, II in 24, III in 5, and IV in 5 patients. Preoperative stroke occurred in 10 patients. No patients who consulted a cardiologist were excluded from indication for surgery during this study period.

Causative Organisms We could identify the causative organisms in 21 cases; 14 cases were culture-negative. Streptococcus was identified in 12 cases, Staphylococcus aureus (MRSA), and Pseudomonas was detected in 2 cases. Immediately after the diagnosis, appropriate antibiotics were selected and administered before and during surgery. The mean duration of intravenous antibiotic treatment was 6 weeks after operation. The choice of antibiotics was based on the sensitivity of causative organisms. If the culture was negative, we followed the Japanese guidelines for the prevention and treatment of infective endocarditis.

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**Infected Lesions of MV**  In terms of the infected lesions of the MV leaflets, 23 cases involved the anterior mitral leaflet (AML) and 29 cases on the posterior mitral leaflet (PML), and among these cases, both the AML and PML were involved in 17 cases. When the lesions were described in terms of the segments of the leaflets, there were 18 cases involving a P2 lesion, 13 cases of an A2, 11 cases of an A3, 9 cases of a P1, 9 cases of a P3 and 8 cases of an A1. The P2 was the most vulnerable type of lesion, and the infection extended to the mitral annulus in 11 patients. The preoperative echocardiography findings are shown in **Figure 1**.

**Diagnosis of AAIE and Timing of Surgery**  We diagnosed AAIE according to Duke’s criteria, such as on-going active infection with a fever, prolonged elevation of the white blood cell count and C-reactive protein level. We essentially followed the Japanese guidelines for the medical treatment and surgical intervention of infective endocarditis, but we preferred to perform surgery as early as possible.

Congestive heart failure caused by progression of mitral valve regurgitation (MR) and associated large (>10 mm) vegetations were also important factors in surgery-related decision making.

**Operative Techniques**
All patients underwent surgery through a median sternotomy and under routine cardiopulmonary bypass (CPB). Cardioplegia was induced by both antegrade and retrograde methods. All surgical procedures, both repair and replacement, were performed by several surgeons, including surgeons-in-training under direct supervision. After exposing the MV through a right-side incision of the left atrium, annular sutures for a ring were first placed to obtain a better view. Fragile vegetations were resected first, and the infected lesions were eliminated by rubbing with a small ball of gauze and rinsing with water until the native valve, chorda, papillary muscles and annular tissue could be seen clearly.

The operative techniques can be summarized into the following 5 procedures: (1) triangular or rectangular resection, depending on the extent of the destruction by the infective lesion; (2) patch repair with bovine pericardium or treated autopericardium after treatment of the defective edge(s) for 2 min with 0.625% glutaraldehyde solution; (3) reconstruction with polytetrafluoroethylene (PTFE) artificial chordae for unsupported lesions; (4) edge-to-edge repair to create a new commissure in some commissural lesion cases; and (5) ring annuloplasty. Glutaraldehyde fixation, in both the infected area and nearby intact tissue, was used for its bactericidal and reinforcing effects, in addition to the autopericardium. If the infected lesion was limited to one segment of the PML, the surgeons used a simple triangular or quadrangular resection and direct suturing technique. Unfortunately, elimination of the infected lesion occasionally complicates direct suturing. In such cases, patch repair with artificial chordae was performed after reinforcing the remaining tissue by soaking with glutaraldehyde solution. If it related to annular disruption, the patch was secured at the intact left atrial wall near the destroyed annulus.

**Table. Patients’ Preoperative Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±17 (22–84)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>21/14</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I 1, II 24, III 5, IV 5</td>
</tr>
<tr>
<td>Preoperative stroke</td>
<td>10</td>
</tr>
<tr>
<td>Causative organism</td>
<td>10</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>12</td>
</tr>
<tr>
<td>MSSA</td>
<td>2</td>
</tr>
<tr>
<td>MRSE</td>
<td>1</td>
</tr>
<tr>
<td>MRSA</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>14</td>
</tr>
<tr>
<td>AML</td>
<td>23 (A1: 9, A2: 13, A3: 11)</td>
</tr>
<tr>
<td>PML</td>
<td>29 (P1: 9, P2: 18, P3: 9)</td>
</tr>
<tr>
<td>Both</td>
<td>17</td>
</tr>
<tr>
<td>Annulus</td>
<td>11</td>
</tr>
</tbody>
</table>

AML, anterior mitral leaflet; MRSA, methicillin *Staphylococcus aureus*; MRSE, methicillin-resistant *S. epidermis*; MSSE, methicillin-sensitive *S. epidermis*; PML, posterior mitral leaflet.

**Figure 1.** Summary of study of treatment of mitral valve infective endocarditis.
If the infected lesion was located in the AML or in a whole segment or 2 segments of the PML, patch repair with artificial chordae was inevitable. We used the loop-in-loop technique for placing the artificial chorda. When we used patch repair, glutaraldehyde fixation at suture sites was routinely performed. The autopericardium was treated with 0.625% glutaraldehyde solution for 2 min. Bovine pericardium, usually thicker than the leaflet tissue, (Edwards Lifesciences, Irvine, CA, USA) was occasionally used, particularly if the remaining leaflet tissue was thick. For commissural lesions, triangular or rectangular resection was the preferred choice, and then the edge-to-edge technique with or without a combination of patch repair was used to create a new commissure. Finally, we did not hesitate to perform a semi-rigid type ring annuloplasty.

Statistical Analysis
Event-free survival was defined as the primary outcome measure to compare efficacy. All cases of death, valvular reoperation and recurrent endocarditis were regarded as events. Actual survival and freedom from events were analyzed with the Kaplan-Meier method. All values are expressed as mean±standard deviation.

Data documentation and statistical analysis were performed with StatMate V (ATMS Inc., Tokyo, Japan).

Results
Of the 35 AAIE cases in our cohort, 5 underwent MVR; in 3 cases the lesions were found to be unsuitable for MVP at surgical inspection because of the large amount of destruction, which existed in >3 segments with or without calcified annulus. In the other 2 cases, MVP were converted to MVR during surgery because of unsatisfactory results after MVP. In the end, we completed the MVP procedure in 30 cases, and the initial success rate was 85.7% (Figure 1). Mean CPB and operation times were 206.36±52 min and 367.39±60 min, respectively. The procedures (MVP or MVR after failed MVP) obviously took much longer to complete than simple MVP or MVR.

Frequency of Techniques Utilized
The resection and direct suture technique was performed in 12 cases and patch plasty was performed in 17 cases, utilizing autopericardium in 7 and bovine pericardial patch in 10. Neochordoplasty was performed in 7 cases after patch repair. In terms of the approach to anterolateral or posteromedial commissure lesions, the edge-to-edge technique was utilized in 7 cases. Ring annuloplasty was performed in 27 cases with 26 semi-rigid type rings and only 1 pericardial band.

Early Outcomes
The results of postoperative echocardiography are shown in Figure 2. All patients were followed, with observation periods ranging from 1 week to 11 years (mean follow-up period: 4.3±3.7 years). The mean ejection fraction in 30 patients was 61.0±0.1%, and the mean left ventricular Dd/Ds value was 48±5/32±5 mm. The mean MV area (MVA) was 2.4±0.6 cm², and only 1 patient...
was considered to have mild stenosis (BSA 1.81 m², ring size 28 mm; MVA 1.8 cm²). In all but 1 case, there was postoperative improvement in the degree of MR and NYHA classification to I or II. In the 1 non-improved case the patient required MVR 2 months after MVP, because of increasing MR and deterioration of NYHA class to IV.

Postoperative echocardiography showed no MR in 4, trivial MR in 4, mild MR in 16 and moderate MR in 5 on the follow-up final examination. There was 1 hospital death in the MVP group of a patient who needed re-intubation because of suffocation by sputum. Her condition deteriorated into sepsis and recurrence of MR, progressing to multi-organ failure. The cure rate of AAIE was 97%, and the 5-year actuarial survival was 89±6% after MVP (Figure 3). Cerebral bleeding after a fall occurred in 1 case of MVR at 1 month after the surgery, but no neurological events were seen in the MVP group.

Discussion

Ruttmann et al demonstrated a significantly improved event-free survival of MVP over MVR in comparable groups of patients with severe native MV endocarditis.8 Their report showed a 10-year event-free survival of 80.4% in the repair group and 46.2% in the MVR group. Although we did not have enough MVP data to compare, the actuarial survival and freedom from events in our MVP patients was almost identical to their results and so was considered to be satisfactory. Ruttmann et al also reported that an optimal repair was essential in preventing the recurrence of IE because underlying valve disease was the main risk factor for the development of IE.9 Postoperative echocardiography showed no MR in 4, trivial MR in 4, mild MR in 16 and moderate MR in 5 on the follow-up final examination. There was 1 hospital death in the MVP group of a patient who needed re-intubation because of suffocation by sputum. Her condition deteriorated into sepsis and recurrence of MR, progressing to multi-organ failure. The cure rate of AAIE was 97%, and the 5-year actuarial survival was 89±6% after MVP (Figure 3). Cerebral bleeding after a fall occurred in 1 case of MVR at 1 month after the surgery, but no neurological events were seen in the MVP group.

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Because of decreasing incidence of rheumatic disease and the excellent long-term results of MVP for degenerative uninfected MV regurgitation, MVP rather than MVR has become a popular procedure for treating MV diseases. Although many surgeons have also adopted MVP for mitral IE,9 MVP for AAIE remains controversial because of the technical difficulties in reconstruction after eradication of the infected tissue. Therefore, MVR after elimination of the entire MV, including intact lesions, has been thought to be a simpler and safer procedure for obtaining reliable results in AAIE patients. The wide range in reparability rates (from 35% to 81%)8 may be explained by the degree of infection and the surgeon’s skill and experience. Dreyfus et al10 demonstrated that almost 20% of IE patients required MVR without a successful Carpentier’s French correction.14 We believe that our high success rate (85.7%) with MVP for AAIE patients was because of our use of 5 techniques and reinforcement of residual tissue by 0.625% glutaraldehyde solution with its bactericidal effects on infected lesions. The reinforcement of residual tissue edges through treatment with 0.625% glutaraldehyde solution can reduce the resected area and sometimes allowed for direct suturing without a patch. We cut the vegetation off the leaflet and then rubbed the area with a small ball of gauze while rinsing with water. If the remaining leaflet tissue looked intact and usable, we soaked it for 2 min in 0.625% glutaraldehyde solution. Gorman et al reviewed the antimicrobial activity, uses and mechanism of action of glutaraldehyde, and concluded that a 0.2–2% solution can inactivate common microorganisms within 2 min.15 After this maneuver, we rinsed the lesion with water.

A lesion associated with prolapsed redundant degenerative change of the PML can be repaired using a simple resection and suture technique for up to one-half of the posterior leaflet. However, if the lesions involve >50% of the posterior leaflet, or to even a lesser degree with vegetations, a patch plasty is frequently needed. In the case of AML lesions, we used the patch plasty technique regardless of the extent of infection (except in 2 cases). If the patch size was large, we created an artificial chorda using the loop-in-loop technique to support a large patch or the edge-to-edge technique for commissure lesions. The combination of our surgical procedures allowed us to repair multi-lesion infections, in which the conditions were not complicated. When annular disruption existed at the PML, after eradication of the annulus, we covered the void with a patch securing the adjacent intact leaf wall and the remaining leaflets, and then the artificial chordae were placed between the patch and the papillary muscle in order to function as part of the leaflet segment. For 3 patients in our cohort, we found it initially difficult to perform MVP because there was significant destruction of the leaflet and annulus (early in this study when we were less experienced), and 1 patient had associated severe calcification of the mitral annulus. In 2 of the cases, we had to convert from MVP to MVR during surgery. One of these 2 patients had a limited infection of the PML, but inflammatory change in the AML had caused the leaflet to shrink, which led to unbalanced leaflets. Another case involved significant destruction at both A2 and P2 lesions. We repaired both areas using large patches with artificial chordae, but failed to eliminate regurgitation. In terms of the limitations of MVP for AAIE cases, multi-segment infected lesions are not always irreparable. Indeed, some reports have demonstrated that MVP can be used for cases involving large destruction of both leaflets by using a large patch and reconstructing the neochordae.16 Omar et al showed that despite destruction of the leaflet’s free margin and an AML that was >50% affected, MVP could be successfully performed with these techniques.17

The material available for patch plasty was fresh pericardium, glutaraldehyde-treated autologous pericardium or xenopericardium, which consisted of heterologous pericardium that had been preserved with a glutaraldehyde chemical fixation process. In the present cases, the autologous pericardium was treated with 0.625% glutaraldehyde for 2 min, which is the duration required to obtain antimicrobial activity. In our clinical experience of using glutaraldehyde-treated autopericardium, we consider that 1–2 min of treatment is enough for the cross-linking action of protein, and preferable with regard to handling. Our main consideration when selecting the pericardium (auto or xeno) was the thickness of the remaining leaflet tissue. We think that less difference in leaflet thickness is better for preserving leaflet movement. We could not find any difference in results between the 2 materials according to postoperative echocardiographic evaluation. One patient required MVR 2 months later, but this was not related to the patch material. In that patient, we used a teardrop-shaped patch of autopericardium and the elongated narrow part of this teardrop-shaped strip was used as an artificial chorda instead of PTFE. A twist in the teardrop strip caused the development of MR and we abandoned this...
Another factor influencing the results is the causative microorganisms. We identified the causative organism in 60% of cases. *Streptococcus* was the most common microorganism, and accounted for 34% of all detected causative microorganisms in this series. *Staphylococcus* represented 14% (5 cases; 2 cases of MRSA; 1 patient died of sepsis, 1 patient needed a second operation for uncontrolled MR). We believe that the efficacy of antibiotic therapy was important in the decision-making process for MV repair. If the selected antibiotics were effective against the causative organism, we actively tried to accomplish valve repair, and the effectiveness was very important in determining how much tissue can be resected at the infectious site. Caes et al reported that the independent predictors of hospital death were age, female sex, previous cardiac surgery, preoperative serum creatinine level >2 mg/dL, *S. aureus* infection, emergency or salvage operation and concomitant coronary artery bypass grafting. In particular, emergency or salvage surgery and IE caused by *S. aureus* were significant determinants for a worse early outcome. Our previous report suggested that *Staphylococcus* infection was more frequently complicated by abscess formation and faster destruction of leaflets than were infections with other causative organisms; therefore, we recommend surgical intervention as early as possible and complete elimination of infected sites.

In conclusion, MV repair with fundamental techniques offered excellent results and glutaraldehyde was safely used in surgical interventions for AAIE in the mitral position with acceptable early and mid-term results.

**References**