Early or Delayed Surgery for Infective Endocarditis Complicated by Cerebral Embolism: A Meta-Analysis

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Introduction
Cerebral embolism complicates 15-30% of infective endocarditis, and is an indication for surgery alongside severe valvar regurgitation, heart failure and uncontrolled infection[1]. Early surgery is effective and advocated in infective endocarditis with large vegetations for primary prevention of embolic events in one randomised trial and international guidelines [1,2], but the optimal timing of surgery remains controversial in those with cerebral embolism, due to the sparse literature and absence of randomised studies. In this meta-analysis, outcomes of early or deferred infective endocarditis surgery with cerebral embolism was pooled and compared.

Methods
PubMed, MEDLINE, Embase, Cochrane and Scopus databases from 1 January 1980 to 30 June 2016 were searched for original studies. Two authors evaluated these studies for inclusion independently, then extracted and pooled data using random-effects models.

Results
Amongst 2,423 papers obtained from the search, 23 full-texts were reviewed, and 6 studies totalling 701 patients were included for analyses. Rates and pooled odds ratio (95% confidence interval) for operative mortality of early or late surgery set at 7 days were 13.5% vs 10.8%, 1.40 (0.61-3.02); 14 days were 20.7% vs 13.0%, 1.95 (0.95-4.01). Pooled odds ratio of early surgery for long-term mortality was 2.95 (0.35-25.0); and for neurological events, embolic event was 1.22 (0.33-4.56) and intracranial bleeding 1.55 (0.16-15.32).

Conclusions
Although early surgery was not associated with statistically higher rates of mortality or neurological events it does need to be cautiously performed. Data is limited and larger and randomised studies would help to determine the optimal timing.

Keywords: endocarditis, stroke, valve surgery, embolism

Characteristics and outcomes from included studies were recorded using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Pooled odds ratios of outcomes by timing of surgery was calculated using the Review Manager 5.3 (Cochrane Collaboration, London, UK) program.

**Results**

The search yielded 2,423 papers, and after initial screening and exclusions, 23 full-texts were reviewed, with the final 6 studies involving 701 patients were included for analyses. Reasons of exclusions after initial screening include not reporting outcomes of both early or late surgery, and deferred group including both patients with delayed surgery or purely medical management, and having only intracranial bleed patients and case reports or reviews. Early surgery was defined as <7 days from diagnosis in 2 studies and <14 days in 4 studies. Table 1 lists the characteristics of the 6 included studies.

Figure 1 illustrates the pooled odds ratio of operative mortality. Rates and pooled odds ratio (95% confidence interval) of early versus late surgery set at 7 days were 13.5% vs 10.8%, 1.40 (0.61-3.02) in 2 studies; 14 days were 20.7% vs 13.0%, 1.22 (0.95-4.01) in 4 studies. Pooled odds ratio of all studies reporting long-term mortality was 2.95 (0.35-25.0), reported in 2 studies, both using 14 days as cutpoint.

In terms of neurological events, rates and pooled odds ratios of ischaemic stroke or transient ischaemic attack for early versus late surgery were 3.5% vs 2.0%, 1.22 (0.33-4.56) in 3 studies. For intracranial haemorrhage, these were 5.0% vs 2.2%, 1.25 (0.61-3.02) in 2 studies; 14 days were 5.8% vs 2.0%, 2.95 (1.16-7.68) in 2 studies. These analyses are shown in Figure 2.

**Discussion**

The 2015 European Society of Cardiology (ESC) guidelines for infective endocarditis recommend “urgent” surgery, loosely defined as within a few days of diagnosis, for those with left-sided heart valve endocarditis with embolic event(s) [1]. It further describes surgery is recommended “without delay”, for those with silent emboli or transient emboli; in those with ischaemic stroke, surgery is “not contraindicated” unless severe neurological damage without timing recommendations; and with intracranial haemorrhage, generally be postponed to over 1 month later. All these recommendations however are based on small observational studies and/or expert consensus.

Our meta-analysis found no statistically significant differences for the main outcomes evaluated for early versus late surgery. In the current era when urgent early surgery is recommended including by the guidelines [1,2], our finding is reassuring that early surgery is safe. There still needs to be caution because numerically higher pooled adverse event rates (P<0.05), when surgery is performed very soon after cerebral embolism particular those with significant symptoms, at theoretical risk of neurological deterioration.

Beyond timing of surgery, there are a number of other approaches to try and reduce neurological complications in endocarditis patients[1]. Early diagnosis and initiation of antibiotic therapy is critical. Urgent surgery should be considered for those with high risk such as large vegetations for primary prevention of cerebral embolism [1,2]. Multidisciplinary heart team discussion and clinical judgement remains cornerstone to the management also.

This study has several limitations to highlight. There is no randomised data with all the studies being observational, and therefore significant differences in baseline characteristics exist and would affect the pooled results which were unadjusted. The numbers of patients were low for all studies, giving only a modest pooled sample power and inability to look at subgroups. The studies had wide heterogeneity from definitions of early and late surgery to being 7 or 14 days (and none used the 48 hours cutpoint of the randomised trial for primary embolic prevention as cutpoint), of outcomes like neurological events, of follow-up duration amongst others.

In conclusion, there were no significant differences in mortality and neurological outcomes between early and late surgery,

<table>
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<th>Author</th>
<th>Year</th>
<th>Study period</th>
<th>Country</th>
<th>Centre</th>
<th>N</th>
<th>Early surgery (days)</th>
<th>Age (years)</th>
<th>Male</th>
<th>Prosthetic valve</th>
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<td>Korea</td>
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which while confirms the safety of early surgery, there should still be a caution undertaking. Further studies especially larger and/or randomised trials are required to address this important clinical problem.

Conflicts of Interests
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals" [9].

References