REVIEW

Is early surgery beneficial in infective endocarditis?
A systematic review

La chirurgie précoce est-elle bénéfique dans l’endocardite infectieuse ? Revue systématique

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Summary We do not know whether surgery during the active phase of infective endocarditis improves prognosis, as no randomized trial data exist. Several observational studies published recently have examined the influence of surgery on prognosis by performing a propensity score analysis. The aim of the present paper is to review these studies, in order to determine whether or not early surgery decreases mortality in adult patients with infective endocarditis. Among nine published studies, 4199 patients were included overall. The rate of surgery during the active phase of infective endocarditis ranged from 23 to 53%. Surgery was significantly beneficial in six studies (adjusted hazard ratios or odds ratios ranging from 0.27 to 0.47), neutral in two studies and without benefit in one study (hazard ratio 1.9; 95% confidence interval 1.1—3.2). Conflicting results appear to be related to differences in statistical methods. When using appropriate models, surgery is significantly associated with reduced long-term mortality. Results from these observational studies suggest that current surgical practices in infective endocarditis are beneficial in terms of long-term survival. However, we cannot conclude that surgery is beneficial and must be performed in all patients with infective endocarditis. Surgery was associated with a favourable outcome in those patients in whom infective endocarditis presentation and

Abbreviations: AEPEI, l’Association pour l’étude et la prévention de l’endocardite infectieuse/Association for the Study and Prevention of Infective Endocarditis; ARR, absolute risk reduction; CHF, congestive heart failure; CI, 95% confidence interval; HR, hazard ratio; ICE, International Collaboration on Endocarditis; IE, infective endocarditis; NVE, native valve infective endocarditis; OR, odds ratio; PVE, prosthetic valve infective endocarditis.

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Background

Although relatively rare, IE remains a severe disease; the in-hospital mortality rate is around 20% overall, but is much higher in complicated cases. Prognosis can be improved in several ways, one of which is avoiding delay to cardiac surgery in complicated cases; this remains the main issue for physicians involved in the care of patients with IE.

Historically, the dogma was to avoid surgery during the active phase because tissues are inflamed and infected, which makes surgery very difficult and leads to high postoperative mortality and a high risk of valve dysfunction. This belief has changed dramatically over the past two decades owing to improvements in surgical technique. Cardiac surgeons no longer refuse to operate at a very early stage in the course of the disease. In France, the rate of surgery increased by 7% per decade between 1969 and 2000 [2].

Indications for surgery are well defined in guidelines, but they are based on expert opinion [3,4]. We still do not know whether surgery during the active phase of IE improves a patient’s prognosis, as no randomized trial data exist. Several observational studies published recently have examined the influence of surgery on prognosis by using propensity score analysis [5–13]. In 1983, Rosenbaum and Rubin proposed ‘propensity scores’ as a method of controlling for selection (here, treatment-selection) bias in observational studies [14]. A patient’s propensity score is his/her conditional probability of a particular exposure (here, surgery) versus another, given the observed confounders; it can be estimated using logistic regression, modelling the exposure as the dependent variable and the potential confounders as the independent variables [14–19]. The most recent studies [6,8,10,11] controlled for another bias, survivor bias, which occurs because patients who live longer are more likely to undergo surgery than those who die early.

The aim of the present paper is to review these studies, in order to determine whether or not early surgery is beneficial in adults with IE. Papers were identified using Medline (http://www.ncbi.nlm.nih.gov/sites/pubmed). The search strategy selected articles that contained ‘propensity’ and ‘endocarditis’ as text words or Medical Subject Headings, and papers cited in the reference list of the selected articles. Papers are presented in chronological order of publication. Data from the studies are summarized in Table 1.

Study review

Vikram et al. conducted a retrospective, observational cohort study of 513 patients with complicated, left-sided NVE [12]. Complication was defined as ‘clinical complication for which surgery is considered in current clinical practice: CHF; new valve regurgitation; refractory infection; systemic embolization to vital organs; or presence of a vegetation on echocardiography’. Forty-five percent of patients underwent surgery. In the 6-month period after baseline (defined as the date of surgery or the date of decision not to operate), 26% of the patients died. In unadjusted analyses, surgery was associated with reduced mortality (16% vs 33%; HR 0.43; CI 0.29–0.63).

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<td>Vikram et al. [12]</td>
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<td>1990—99</td>
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<td>45</td>
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<td>Treatment-selection bias</td>
<td>Operated patients 16%; non-operated patients 33%; HR 0.43; p &lt; 0.001</td>
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<td>Group 1 (lowest likelihood for surgery): medical therapy, 9.5%; surgical therapy, 20.0%; p = 0.16</td>
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<td>Group 5 (strongest likelihood for surgery): medical therapy, 38.0%; surgical therapy, 11.2%; p &lt; 0.001</td>
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<td>Reference</td>
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<td>Wang et al.</td>
<td>International registry</td>
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<td>PVE</td>
<td>355; 136 propensity-matched</td>
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<td>OR 0.56; 95% CI 0.23—1.36; $p = 0.20$</td>
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<td>Aksoy et al.</td>
<td>Duke University, Durham, NC, USA</td>
<td>1996–2002</td>
<td>Left-sided NVE or PVE without intracardiac device</td>
<td>333; 102 propensity-matched</td>
<td>23</td>
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<td>Estimated; operated patients 30%; non-operated patients 47%; $p = ?$</td>
<td>HR 0.27; 95% CI 0.13—0.55; $p = ?$</td>
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<td>1980–98</td>
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<td>546; 186 propensity-matched</td>
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<td>Matched cohort: HR 1.3; 95% CI 0.5—3.1; $p = 0.56$</td>
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<td>Whole cohort, surgery as a time-dependent covariate: HR 1.9; 95% CI 1.1—3.2; $p = 0.02$</td>
<td>After adjustment for early (operative) mortality: HR 0.9; 95% CI 0.5—1.8; $p = ?$</td>
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<td>Study</td>
<td>Design</td>
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<td>Study Population</td>
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<td>Bias</td>
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<td>Bannay et al. [6]</td>
<td>Prospective, population-based study in several French regions</td>
<td>1999</td>
<td>Left-sided NVE or PVE</td>
<td>449</td>
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<td>Treatment-selection bias; survivor bias</td>
<td>Operated patients 30%; non-operated patients 52%; p &lt; 0.0001</td>
<td>Within 14 days after intervention, mortality was higher in the surgery group: adjusted HR 3.69; 95% CI 2.17–6.25; p &lt; 0.0001</td>
<td>Thereafter, it was lower in the surgery group: adjusted HR 0.55; 95% CI 0.35–0.87; p = 0.01</td>
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<td>Sy et al. [10]</td>
<td>Two university teaching hospitals in Sydney, Australia</td>
<td>1996–2006</td>
<td>Left-sided NVE or PVE</td>
<td>223</td>
<td>5.2-year all-cause mortality</td>
<td>Treatment-selection bias; survivor bias</td>
<td>Operated patients 32%; non-operated patients 51%; p = 0.02</td>
<td>After adjustment for baseline differences in propensity for surgery and risk of mortality: HR 0.50; 95% CI 0.28–0.88; p = 0.02</td>
<td>After time-dependent analysis: HR 0.77; 95% CI 0.42–1.40; p = 0.39</td>
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Table 1: (Continued)

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| Lalani et al. [8]  | International registry | NVE | 2000–2005 | 532/1238 in the propensity groups | In-hospital mortality | After adjustment for heterogeneity (baseline features that were associated with mortality: hospital site; comorbidity assessed using the Charlson index [20]; CHF; microorganism; immunocompromised state; abnormal mental status; and refractory infection), surgery remained associated with reduced mortality (HR 0.35 [0.23–0.54]; p < 0.001), as in further analyses of 218 patients matched by propensity scores (15% vs 28%; HR 0.45 [0.23–0.86]; p = 0.02). After additional adjustment for confounding (patient selection bias due to non-randomized assignment of treatment) within the propensity-matched group, surgery remained significantly associated with reduced mortality (HR 0.40 [0.18–0.91]). In this propensity-matched group, patients with moderate-to-severe CHF showed the greatest reduction in mortality with surgery (14% vs 51%; HR 0.22 [0.08–0.53]; p = 0.01), whereas there was no benefit of surgery among patients with none-to-mild CHF. Vikram et al. did not study the impact of surgery on the prognosis of all IE: they included only patients with complicated IE (those for whom surgery is usually advised) and they excluded prosthetic valve IE (PVE) and right-sided IE. We do not know which subgroup analyses other than CHF the investigators performed. All hospitals participating in the study had surgical facilities. This first paper using propensity analysis confirmed what we, as clinicians, intuitively knew about the beneficial effect of surgery in complicated IE.

A retrospective study was performed in the two medical intensive care units of a French teaching hospital [9]. To evaluate the potential role of surgery in the prognosis of NVE, the investigators performed a nested case-control study comparing 27 operated with 27 non-operated patients using propensity scores. Among 228 patients with definite IE (146 NVE and 82 PVE), 46% underwent cardiac surgery. The overall in-hospital mortality rate was 45%. In patients with NVE, mortality was significantly lower in operated patients than in non-operated patients (p = 0.014). Cardiac surgery was independently associated with in-hospital mortality (OR 0.47). In contrast, in the nested case-control study, operated patients did not have lower in-hospital mortality than non-operated patients (OR 0.96; not significant). In patients with PVE, mortality was lower in the surgery group (p = 0.04). However, surgery was not an independent predictor of lower mortality. The authors concluded that surgery appears to improve in-hospital mortality. The in-hospital mortality rate was very high because patients were recruited from intensive care units. There were very few propensity-matched patients, which may explain why the authors did not observe a beneficial effect of surgery in these patients, whereas there was a significant beneficial effect of surgery in the cohort as a whole.

The ICE merged database is a large, multicentre, international registry of patients with definite IE, as defined by the Duke criteria. Surgery was performed in 40% of 1516 patients with NVE [7]. In-hospital mortality was 13.6% in the surgery group and 16.4% in the no surgery group (not significant). The investigators constructed a multiple logistic regression model to create equally sized propensity groups for the likelihood of surgery. Within group 1 (lowest likelihood of surgery), medical therapy had a non-significant advantage over surgery in terms of in-hospital mortality (Fig. 1). This observation was reversed in groups with a moderate likelihood of surgery (groups 2 to 4), with a suggestion of survival benefit with surgery. In the group of patients
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In-hospital mortality rate in the five propensity groups in the study by Cabell et al. (adapted from [7]).

Figure 1.

with the strongest indicators for surgery (group 5), surgery had a significant survival benefit compared with medical therapy alone (p<0.001) even after adjustment for multiple comparisons. Patients with the fewest predictors for surgery (group 1) were more likely to be female and to have an oral streptococcal infection compared with the other groups. Patients with the most predictors for surgery (group 5) were more likely to be male, and to have aortic valve involvement, CHF or an intracardiac abscess. The authors concluded that the benefits of surgery are not seen uniformly in all patients with NVE, but are mostly demonstrated within a target population. Surgery was performed in 42% of the 355 patients with PVE [13]. In-hospital mortality was similar for patients treated with surgery compared with those treated with medical therapy alone (25.0% vs 23.4%; not significant). After adjustment for factors independently related with medical therapy alone (25.0% vs 23.4%; not significant) was to evaluate the effect of surgery on 5-year mortality [6]. Among 449 patients with definite left-sided IE, 53% were operated on. Association between surgery and all-cause 5-year mortality was examined using a Cox model, adjusted for survival prognostic factors and predictors of surgery, with surgery as a time-dependent covariate. Unadjusted 5-year mortality was 30% in operated patients and 52% in non-operated patients (p = 0.0001). Surgery, assessed as a time-dependent variable, was associated with a non-significant lower mortality (HR 0.78 [0.56—1.1]). This association disappeared after adjustment for prognostic factors and surgery predictors (1.01 [0.67—1.51]). However, there was an interaction between HR for death and time (p = 0.02): within 14 days after intervention, mortality was higher in the surgery group than in the no surgery group (HR 3.69 [2.17—6.25]; p < 0.0001), but thereafter, it was lower in the surgery group than in the no surgery group (HR 0.55 [0.35—0.87]; p = 0.01). For the whole sample, the equity point (the time at which the area between the surgery group curve and the no surgery group curve during the short-term period is equal to the area between the surgery group curve and the no surgery group during the long-term period) was obtained 188 days after surgery. In other words, a minimum of 188 days of follow-up was required for the long-term beneficial effect of surgery to compensate for the high postoperative mortality rate. The authors concluded that surgery was significantly associated with reduced long-term mortality.

Among 223 patients admitted with left-sided IE to two university teaching hospitals in Sydney, Australia, 28% were...
operated on [10]. The authors used propensity scores and time-dependent analyses (to account for survivor bias). Compared with non-operated patients, operated patients had lower mortality during a median follow-up of 5.2 years (32% vs 51%; unadjusted HR 0.54 [0.33–0.88]; p = 0.01). After adjustment for baseline differences in propensity for surgery and risk of mortality, there remained a significant benefit for surgery (HR 0.50 [0.28–0.88]; p = 0.02). However, this was diminished and no longer significant after time-dependent analysis (0.77 [0.42–1.40]). Conditional Kaplan–Meier analyses at day 15, day 30 and day 60 (day 1 was the day of hospital admission) found no significant difference in mortality between non-operated patients and operated patients and thus confirmed the effect of sur-

vivor bias, as the apparent benefit of surgery was primarily attributable to excess mortality in the non-operated group during early hospitalization when surgery was not frequently performed. The authors concluded that survivor bias significa-


tantly affects the evaluation of surgical outcomes in IE. Survivor bias is not corrected by propensity analysis alone but may be reduced by time-dependent survival analysis. Surgery was beneficial in unadjusted analysis and propensity analysis but it was no more beneficial in time-dependent analysis. One reason why this result differs from most of the previous results may be a lack of power because of the small size of the population, especially the operated group, in which the rate of surgery was particularly low.

The present paper and the previous paper have almost the same follow-up duration and very similar death rates, in both operated and non-operated patients, although the rates of surgery are very different ([10]: 28%; [6] 53%). The two populations do not look very different. We have not found a satisfactory explanation for these differences and would welcome explanations.

ICE very recently published again on the impact of surgery on NVE mortality [8]. The authors used propensity-based matching, adjusting for survivor bias and instrumental variable analysis. Patients were stratified by propensity quintile, paravalvarular complications, valve perforation, systemic embolization, stroke, *Staphylococcus aureus* infection and CHF. Of the 1552 patients with NVE, 46% underwent early surgery. Compared with medical therapy, early surgery was associated with a significant reduction in mortality in the overall cohort (12.1% vs 20.7%; ARR −8.6%; OR 0.53 [0.40–0.70]; p < 0.001) and after propensity-based matching and adjust-

ment for survivor bias (ARR −5.9%; OR 0.55 [0.31–0.96]; p < 0.001). Using a combined instrument, the instrumental-variable-adjusted ARR in mortality associated with early surgery was −11.2% (OR 0.44 [0.33–0.59]; p < 0.001). Clinically plausible variables known to affect the decision to perform valve surgery were used to perform subgroup anal-

ysis to determine characteristics associated with maximum mortality benefit. Surgery was found to confer a survival benefit compared with medical therapy among patients with a higher propensity for surgery (ARR −10.9% for quintiles 4 and 5; p = 0.002) and those with paravalvular complications (ARR −17.3%; p < 0.001), systemic embolization (ARR −12.9%; p = 0.002), *Staphylococcus aureus* NVE (ARR −20.1%; p < 0.001) and stroke (ARR −13%; p = 0.02), but not with valve perforation or CHF. The authors concluded that early surgery for NVE is associated with an in-hospital mortality benefit compared with medical therapy alone.

**Impact of biases**

Among the nine published studies, surgery was beneficial in six studies [5–9,12], neutral in two studies [10,13] and without benefit in one study [11]. How can we conciliate these different results? Can we conclude that surgery is beneficial in IE? In 2008, Tleyjeh et al. published a systematic review of the first six papers [21]. Among these six studies, only one adjusted for survivor bias [11]. This time-dependent bias occurs because patients who live longer are more likely to undergo surgery than those who die early [22,23]. A correlation of longer survival with surgery may be wrongly interpreted as evidence that treatment improves survival because of this bias. In order to control for this bias, Tleyjeh et al. used time-dependent covariates [11]. A time-

dependent covariate is a variable whose value is allowed to change with time [22–24].

In most cases, similar results are observed whether the adjustment for confounding uses traditional regression or whether propensity scores are used [25–27]. However, many studies do not use propensity scores correctly. One weakness of propensity score analysis that was seen in the six studies was the lack of guidelines and model diagnostics for selecting variables with which to construct propensity scores. This results in ad hoc variable selection that is partially driven by the availability of data on relevant variables and may diminish study comparability.

Some studies included NVE only [7,12] and one study included PVE only [13]. Studies should group NVE and PVE, and use PVE as a variable in the propensity score or for subgroup analysis. Tleyjeh et al. concluded that well designed, prospective studies, addressing the previously analysed limitations, are needed to further define the role of surgery in IE, and that until then, careful scrutiny is warranted when making management decisions in complicated, left-sided IE. A well designed, cohort study should be prospective, multicentric (representative of the general IE population), of sufficient size and with a comprehensive list of variables. The timing of the different events should be recorded. Transoesophageal echocardiography in all patients would be preferable. The statistical analysis should include valid propensity score analysis and instrumental variable analysis. The team that conducted the reported AEPEI study [6] undertook a similar study during 2008. This study complied with all the criteria specified by Tleyjeh. We thus hope that
The authors obtained results consistent with those of the five previous reports (Fig. 2). The concordance of the results in the previous studies and the results in the study by Bannay et al. [6] when applying the same statistical technique as in each study is impressive. When they used a binary coding for the surgery variable, they observed a protective effect of surgery on mortality, significant at 6 months (as Vikram et al. [12]) and 5 years (as Aksoy et al. [5]) and non-significant during hospitalization (as Wang et al. [13] and Cabell et al. [7]). However, when using a partitioned time-dependent coding for surgery variable, they showed a non-significant relationship between surgery and 6-month mortality after adjustment for short-term mortality (as Tleyjeh et al.). The negative impact of surgery on mortality observed by Tleyjeh et al. could be explained by an insufficient follow-up duration of only 6 months [11], as Bannay et al. [6] showed that the benefit of surgery appears later, because of early postoperative mortality [6]. This is even more obvious in the Wang et al. [13] and Cabell et al. [7] studies.

Thus, previous conflicting results appear to be related to differences in statistical methods. When using appropriate models, Bannay et al. [6] found that surgery was significantly associated with reduced long-term mortality.

Conclusions

Results from these observational studies suggest that current surgical practices in IE are beneficial in terms of long-term survival. However, we cannot conclude from the results that surgery is beneficial and must be performed in all patients with IE. Surgery was associated with a favourable outcome in those patients in whom IE presentation and patient characteristics led the physicians to perform surgery. Patients who seem to benefit most from surgery are those who fulfill management guidelines (embolic event, CHF and/or intracardiac abscess) [3,4].

As it is difficult to draw definitive conclusions from observational studies, even with the use of statistical techniques aimed at controlling for different sources of bias, randomized trials are needed. Fortunately, two groups of investigators have recently launched randomized trials of surgery vs medical treatment alone in the care of patients with IE [28,29].

Conflict of interest statement

The author has no conflict of interest.

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References


