Outcomes after early or late timing of surgery for infective endocarditis with ischaemic stroke: a retrospective cohort study

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Abstract

OBJECTIVES: The timing of cardiac surgery for infective endocarditis with ischaemic stroke remains controversial.

METHODS: Using a nationwide inpatient database in Japan, we conducted a retrospective observational study. We identified patients aged 20 years or older with ischaemic stroke on admission who were diagnosed with infective endocarditis and underwent cardiac surgery during the initial hospitalization between July 2010 and March 2013. In-hospital mortality and perioperative complications were compared between the early (≤7 days) and late (>7 days) surgery groups using logistic regression analyses with adjustment for propensity scores and inverse probability of treatment weighting.

RESULTS: We identified 253 patients who underwent cardiac valve surgery for infective endocarditis with ischaemic stroke on admission. In-hospital mortality rates were 8.6 and 9.5% in the early (n = 105) and late (n = 148) surgery groups, respectively. There were no significant differences in the in-hospital mortality between the early and late surgery groups in the propensity score-adjusted model (odds ratio (OR), 0.95; 95% confidence interval (CI), 0.35–2.54) and inverse probability-weighted model (risk difference, −0.82%; 95% CI, −6.43 to 4.84%). The perioperative complication rates were 42.9 and 37.8% in the early and late surgery groups, respectively, and showed no significant differences in the propensity score-adjusted model (OR, 1.11; 95% CI, 0.63–1.97) and inverse probability-weighted model (risk difference, 1.54%; 95% CI, −7.13 to 10.2%).

CONCLUSIONS: Early timing of surgery for infective endocarditis patients with ischaemic stroke was not associated with higher in-hospital mortality or complications after admission. Early timing of surgery may not be contraindicated for infective endocarditis patients with ischaemic stroke.

Keywords: Endocarditis (all infectious agents) • Stroke • Surgery • Complications

INTRODUCTION

Neurological complications are some of the most common and serious complications associated with infective endocarditis (IE). Stroke is the most frequent complication, occurring in 10–40% of patients with IE [1–5], and is associated with poor outcomes [1, 2, 6–9].

Several studies have suggested that the risk of postoperative neurological complications related to cardiac surgery in patients with preoperative ischaemic stroke may be lower than previously assumed [10–12]. However, the timing of surgery for IE patients with ischaemic stroke remains controversial [7, 8, 10–16], and it is challenging for physicians to decide the optimal timing of such surgery.

Current guidelines provide inconsistent recommendations for the optimal timing of surgery for IE patients complicated with ischaemic stroke. The European Society of Cardiology guidelines [17] recommend that surgery for IE patients with ischaemic stroke should not be delayed unless contraindicated. The guidelines show that surgical indications include heart failure, uncontrolled infection, abscess or persistent high embolic risk, whereas delayed surgery is recommended for patients with intracranial haemorrhage, severe neurological damage or severe comorbidities. In particular, the guidelines show that surgery must be delayed for at least 1 month when intracranial haemorrhage exists. In contrast, the Society of Thoracic Surgeons guideline [18] recommends that surgery should be delayed for at least 2–4 weeks after most occurrences of ischaemic stroke, if possible. However, these recommendations were only based on limited studies with small cohort numbers and case series.

A recent study that evaluated the timing of surgery for IE patients with stroke indicated that delayed surgery was not significantly associated with better outcomes in terms of in-hospital mortality and 1-year mortality [19]. However, the study lacked preoperative information on stroke severity and did not assess perioperative complications.

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In the present study, we compared the occurrence of perioperative complications as well as the in-hospital mortality between early and delayed surgeries for IE patients with ischaemic stroke, using a large national inpatient database in Japan.

MATERIALS AND METHODS

Data source

The Japanese Diagnosis Procedure Combination (DPC) database is a nationwide inpatient administrative claims database that covers ~50% of all acute care inpatient hospitalization in Japan. All 82 academic hospitals in Japan are obliged to participate in the database, whereas community hospitals participate voluntarily.

The database contains the following information: patient age and sex; main diagnoses and comorbidities on admission and complications after admission encoded with International Classification of Diseases, Tenth Revision (ICD-10) codes and text data in Japanese; surgical procedures encoded with original Japanese codes; drugs and devices used; dates of admission, discharge and surgery; type of admission; discharge status; consciousness levels at admission and discharge classified according to the Japan Coma Scale (JCS) [20]; and type of hospital (academic or non-academic). Attending doctors are required to record all data for diagnoses and comorbidities for individual patients, because the database is linked with a lump-sum payment system.

Because of the anonymous nature of the data, informed consent for this study was waived. Study approval was obtained from the Institutional Review Board of The University of Tokyo.

Patient selection and data

Using the DPC database, we selected patients aged 20 years or older who were diagnosed with ischaemic stroke (ICD-10 code, I63) on admission, and also were diagnosed with endocarditis (ICD-10 code, I13) and underwent cardiac surgery during the initial hospitalization between July 2010 and March 2013. We excluded patients with other neurological complications on admission, including central nervous system haemorrhage [subarachnoid haemorrhage (ICD-10 code, I60), intracerebral haemorrhage (I61) or other non-traumatic intracranial haemorrhage (I62)], intracranial abscess and granuloma (G06.0), encephalitis (G04 and G05), meningitis (G00–G03) and transient ischaemic attack (G45).

Cardiac surgery was defined as repair or replacement of the affected valves with IE. We defined the early surgery group as those who underwent cardiac surgery within 7 days of admission, and the late cardiac surgery group as those who underwent surgery thereafter.

We collected data on referral from other hospitals, ambulance service use, preoperative stay in the intensive care unit, preoperative mechanical ventilation, receipt of transoesophageal echocardiography on admission, active or treated endocarditis, JCS at admission and discharge, Charlson comorbidity index (CCI) and hospital volume.

Active endocarditis was defined as currently being treated for endocarditis at the time of surgery, while treated endocarditis was defined as being not given antibiotic medication (other than prophylactic medication) at the time of surgery [21].

The JCS is an assessment tool for the consciousness level. The classification details are as follows: JCS 0, completely awake and alert; JCS one-digit codes (1–3), drowsy but awake without stimuli; JCS two-digit codes (10–30), drowsy but temporarily awake with some stimuli and JCS three-digit codes (100–300), coma. The CCI was calculated as a weighted score of specific co-morbid diseases based on the ICD-10 codes [22]. Hospital volume was defined as the average annual caseload of surgery for IE at each hospital.

Outcomes

The primary outcomes were in-hospital mortality and at least one complication after admission. Complications after admission included: neurological complications [ischaemic stroke; central nervous system haemorrhage (subarachnoid haemorrhage, intracerebral haemorrhage or other non-traumatic intracranial haemorrhage); intracranial abscess and granuloma; encephalitis; meningitis; transient ischaemic attack]; cardiac complications [myocardial infarction (ICD-10 code, I21–I22); heart failure, I50]; systemic embolization except for cerebral arteries (pulmonary embolism, I26; infarction of spleen, D73.5; ischaemia and infarction of the kidney, N28.0; infarction of the liver, K76.3; acute vascular disorders of the intestine, K55.0; arterial embolism and thrombosis, I74) and infection (sepsis, A40–A41; disseminated intravascular coagulation, D65; infection of cardiac valve prosthesis, T826; pneumonia, J15–J18; infection following a procedure, T814).

Statistical analyses

We performed univariate comparisons of the baseline characteristics in the two groups using the Wilcoxon rank sum test for continuous variables, and the χ² test or Fisher’s exact test for categorical variables, as appropriate. Median age was compared between the groups using the Wilcoxon rank sum test. For comparisons of categorical variables, we used Fisher’s exact test when the expected number of observations under the null hypothesis in any cell of the 2 × 2 table was less than 5. Otherwise, we used the χ² test.

We performed propensity score analyses to minimize confounding by surgical procedure indications. To calculate propensity scores for the patients with early surgery, we used a non-parsimonious multivariate logistic regression model. Baseline variables and interaction terms used to predict the propensity scores included age, sex, CCI >2, active or treated endocarditis, JCS score on admission (0, one-digit, two-digit and three-digit), cardiogenic shock on admission, acute heart failure on admission, sepsis on admission, infection of cardiac valve prosthesis on admission, systemic embolization on admission, receipt of transoesophageal echocardiography on admission, type of hospital, hospital volume, referral from other hospitals, ambulance transport, ICU stay before surgery, ventilation before surgery and interaction terms (referral from other facilities × ambulance transfer; JCS score × ambulance transfer; receipt of transoesophageal echocardiography on admission × ambulance transfer). The C-statistic was calculated to evaluate the goodness of fit.

We conducted two statistical analyses using the propensity scores. First, a logistic regression analysis was performed to examine the associations of in-hospital mortality or complications after admission with timing of surgery with adjustment for the propensity scores. Secondly, the propensity scores were used with inverse probability of treatment weighting (IPTW). In this method,
patients who underwent early surgery were weighted for the reciprocal of the propensity score, and those who underwent late surgery were weighted for the reciprocal of 1 minus propensity score [23].

We used IBM SPSS Statistics version 22.0 (IBM SPSS, Armonk, NY, USA) to conduct all statistical analyses.

RESULTS

We identified patients aged 20 years or older with ischaemic stroke on admission. Among them, 268 patients were diagnosed as IE and underwent cardiac surgery during the initial hospitalization. Fifteen patients were excluded because they met the exclusion criteria (6 with central nervous system haemorrhage, 1 with encephalitis and 8 with meningitis). Finally, 253 patients were included in the analyses. Of these, 105 (41.5%) patients underwent early surgery and 148 (58.5%) underwent late surgery.

Table 1 summarizes the baseline characteristics in the early and late surgery groups, and the adjusted baseline characteristics by IPTW. The C-statistic for goodness of fit was 0.77 [95% confidence interval (CI), 0.72–0.83] in the propensity score model. Regarding the unadjusted baseline characteristics, the early surgery group was significantly younger, more likely to be transferred by ambulance and more likely to be preoperatively managed in the intensive care unit compared with the late surgery group. After adjustment by IPTW, the baseline characteristics were well balanced between the two groups.

The overall in-hospital mortality rate was 9.1% (23/253). The unadjusted in-hospital mortality rate was 8.6 and 9.5% in the early and late surgery groups, respectively (Table 2). There were no significant differences in the in-hospital mortality between the unadjusted groups (risk difference, −0.89%; 95% CI, −8.03 to 7.01%) and the inverse probability-weighted groups (risk difference, −0.82%; 95% CI, −6.43 to 4.84%).

Among the 253 patients, 101 (39.9%) had at least one complication after admission. The proportion of patients with at least one complication was 42.9 and 37.8% in the early and late surgery groups, respectively. The proportions of patients with at least one complication did not significantly differ between the early and late surgery groups in the unadjusted groups (risk difference, 5.02%; 95% CI, −7.16 to 17.25%) and the inverse probability-weighted groups (risk difference, 1.54%; 95% CI, −7.13 to 10.2%).

<table>
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<tr>
<th>Table 1: Patient characteristics</th>
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<tr>
<td>Unadjusted groups</td>
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<tr>
<td>Early surgery (N = 105)</td>
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<tr>
<td>Age (year), median (IQR)</td>
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<tr>
<td>Male sex, n (%)</td>
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<tr>
<td>Comorbidities at admission, n (%)</td>
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<tr>
<td>Shock</td>
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<td>Cardiac failure</td>
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<td>Sepsis</td>
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<td>Infection of cardiac valve prosthesis</td>
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<td>Arterial embolism, n (%)</td>
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<td>Pulmonary embolism</td>
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<td>Splenic artery</td>
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<td>Hepatic artery</td>
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<td>Renal artery</td>
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<td>Abdominal or upper or lower extremities</td>
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<td>Charlson comorbidity index &gt;2, n (%)</td>
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<td>Active endocarditis, n (%)</td>
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<td>Japan Coma Scale at admission, n (%)</td>
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<tr>
<td>Alertness</td>
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<td>Dizziness</td>
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<td>Somnolence</td>
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<td>Coma</td>
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<td>Type of hospital, n (%)</td>
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<td>Non-academic</td>
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<td>Academic</td>
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<td>Referral from other hospitals, n (%)</td>
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<td>Ambulance use, n (%)</td>
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<td>Preoperative ICU stay, n (%)</td>
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<td>Preoperative mechanical ventilation, n (%)</td>
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<td>Transoesophageal echocardiography on admission, n (%)</td>
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<td>Type of surgery, n (%)</td>
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<td>Valve plasty</td>
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<td>Valve replacement</td>
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IQR: interquartile range; ICU: intensive care unit. 
*Inverse probability-weighted groups reported as %.
bWilcoxon rank sum test.
cFisher’s exact test.
The detailed data about complications after admission and the JCS at discharge are presented in Table 3. Fourteen (5.5%) patients had neurological complications, 44 (17.4%) had cardiac complications, 4 (1.6%) had systemic embolization and 53 (21%) had infection. There were no significant differences between the groups for neurological complications, cardiac complications, systemic embolization and infection.

Perioperative ischaemic stroke occurred in 1 patient in the late surgery group. Perioperative subarachnoid haemorrhage occurred in 3 patients in the early surgery group and 1 patient in the late surgery group. Perioperative other non-traumatic intracranial haemorrhage occurred in 1 patient in the early surgery group and 1 patient in the late surgery group.

The total number of central nervous system haemorrhagic complication occurrences was 7 in the early surgery group and 3 in the late surgery group ($P = 0.098$). Of these, 2 patients died among the 7 patients in the early surgery group, and 1 patient died among the 3 patients in the late surgery group. In the IPTW
approach, the rates of central nervous system haemorrhagic complications were 6.3% in the early surgery group and 4.3% in the late surgery group ($P = 0.318$).

The univariate logistic regression model showed that timing of surgery was not significantly associated with in-hospital mortality (odds ratio (OR), 0.90; 95% CI, 0.37–2.16) or at least one complication after admission (OR, 1.23; 95% CI, 0.74–2.05). In the logistic regression model with the propensity score adjustment approach, timing of surgery was not significantly associated with in-hospital mortality (OR, 0.95; 95% CI, 0.35–2.54) or at least one complication after admission (OR, 1.11; 95% CI, 0.63–1.97).

DISCUSSION

Using a nationwide administrative database, our results indicated that early timing of surgery for IE patients with ischaemic stroke was not associated with higher in-hospital mortality or complications, compared with late timing of surgery, even after adjustment for propensity scores and IPTW.

In previous studies, the in-hospital mortality rate after surgery for IE patients with preoperative stroke varied widely from 6 to 21%, owing to the small sample sizes ($n = 5$–198), different study populations and years [3, 7, 15, 16, 19, 24]. In the present study, the overall mortality rate was 9.1% in a relatively large sample size ($n = 253$).

The results of the present study are compatible with those in a previous study [19], in that early timing of surgery was not significantly associated with increased in-hospital mortality.

To the best of our knowledge, the present study is the first to compare perioperative complications between early and late surgery for IE patients with ischaemic stroke at admission with adjustment for patient background characteristics using propensity scores and IPTW.

The safety of using cardiopulmonary bypass in patients with acute ischaemic stroke is controversial [10–12, 15]. The use of cardiopulmonary bypass in the acute phase of ischaemic stroke might cause severe deterioration of neurological injuries in terms of secondary cerebral haemorrhage and extension of the ischaemic lesion, because of hypotension and anticoagulation during cardiac valve surgery. However, several previous studies have suggested that the risk of postoperative neurological deterioration after early surgery may be lower than previously assumed or expected in patients with cerebral haemorrhage [7, 10, 11, 25].

A total of 14 (5.5%) neurological complications occurred, even though we excluded patients with central nervous system haemorrhage on admission. Gaca et al. [21] reported that the incidence of postoperative stroke was low (4.3%) in IE patients with preoperative stroke who underwent surgery, and suggested that preoperative cerebrovascular disease was not a risk factor for postoperative complications in patients with IE. Our results for the proportion of perioperative neurological complications were consistent with this previous study.

In the present study, the proportion of perioperative central nervous system haemorrhage was slightly higher in the early surgery group than in the late surgery group (7/105 vs 3/148, $P = 0.098$), but the IPTW analysis showed no significant difference in perioperative haemorrhage between the two groups. Further studies on the associations between timing of surgery and perioperative complications are needed using larger sample sizes. Furthermore, our results for perioperative complications remain inconclusive because our analysis did not fully take into account the possible benefit or harm of late timing of cardiac surgery.

Several limitations of this study should be acknowledged. First, this study was based on a retrospective observational design, and the treatment assignment was not random. Measured confounders were adjusted by the propensity score analyses, but the results may still be biased by unmeasured confounders. Secondly, we used an administrative claims database, in which recorded diagnoses may be less well-validated than those in planned prospective studies. In particular, it was not clear whether the diagnosis of IE was based on the modified Duke criteria. Thirdly, the DPC database lacks some types of clinical data about past history; microbial aetiology (blood culture findings); artificial prosthesis or devices implanted; presence, location and size of vegetation; cardiac function and findings on clinical imaging. For example, we could not obtain the findings on clinical imaging such as extent of stroke. However, surgical indications, such as shock, cardiac failure, sepsis and infection of cardiac valve prosthesis at admission, were well balanced between two groups, and the JCS at admission was classified as 0 status (completely awake and alert) for nearly 70% of each group. Moreover, we excluded patients with other neurological complications, including central nervous system haemorrhage, on admission because of the risk of postoperative neurological deterioration, and recommendations of the timing of surgery were different from IE patients with stroke on admission. Fourthly, the database does not provide any information after discharge, and therefore long-term mortality could not be assessed. Finally, although our sample size was larger than those in previous studies, our study may have been underpowered.

In conclusion, our study suggests that early timing of surgery for IE patients with ischaemic stroke was not associated with in-hospital mortality or complications after admission. These findings may imply that there is no definite reason for delaying surgery in IE patients with preoperative ischaemic stroke.

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