Impact of cerebral complications in acute infective endocarditis: a retrospective single-center study

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Research Article

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Abstract

BACKGROUND

The treatment of patients with infective endocarditis (IE) who have cerebral complications remains less understood. Therefore, this study aimed to retrospectively evaluate the clinical outcomes of patients with acute IE based on preoperative intracranial findings.

METHODS

Of 32 patients with acute IE treated at our hospital between August 2015 and March 2022, 31 patients of whom preoperative intracranial imaging evaluation was available were included in our analysis and compared with those with and without intracranial findings. The preoperative background, intraoperative findings, cardiopulmonary bypass (CPB) data, and postoperative courses were reviewed.

RESULTS

Among the 31 patients, 20 (65%) had preoperative imaging findings. The group with intracranial findings was significantly older, with more embolisms in other organs and positive intraoperative pathology findings. Patients with intracranial findings had significantly longer CPB times. A new cerebral hemorrhage developed postoperatively in one patient without intracranial findings. There were no early deaths; two patients had recurrent infections in each group, and one died as a result of sepsis in the late phase in the group with intracranial findings.

CONCLUSIONS

Positive intracranial findings indicated significantly active infectious conditions preoperatively but did not affect the postoperative course. Patients without cerebral complications can develop serious cerebral hemorrhage. Although meticulous examination of cerebral complications in all patients with IE is essential, a strategy should be adopted to prevent cerebral hemorrhage, even in patients without lesions.

BACKGROUND

Cerebral complications occur in 20–40% of patients during the active course of infective endocarditis (IE) and can be associated with poor clinical outcomes [1, 2]. Particularly, cerebral hemorrhage may worsen the degree of brain injury due to the use of anticoagulants during cardiopulmonary bypass (CPB), which can cause devastating brain damage with poor prognosis [3]. The appropriate timing of surgery for patients with IE who have cerebral complications remains controversial [4]. Guidelines from the Society of Thoracic Surgeons recommend delaying surgery for at least 4 weeks when patients have experienced major ischemic strokes or intracranial hemorrhage [5, 6]. In addition, several recent studies have reported

that the risk of neurological impairment is lower than that estimated in patients with IE who have cerebral infarctions and have undergone early surgery [7, 8]. However, it may be more difficult to determine the optimal timing of surgery in patients with intracranial hemorrhage [9–11].

Moreover, cerebral hemorrhage can occur even without obvious preoperative cerebral lesions. Intracranial hemorrhage of undetermined etiology can also result from septic arteritis, with erosion of the vessel wall caused by “microemboli” but without a well-delineated aneurysm [12, 13]. It is also important to note that mycotic aneurysms are frequently located in the peripheral arteries, as they are too small to be detected using computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) [14, 15]. Recently, silent intracranial findings have been detected because of the advances in neuroimaging technology, and their incidence is significantly higher than expected, at approximately 80% [16].

Furthermore, the relationship between intracranial hemorrhage and anticoagulation therapy is not well established. Ota et al. [17] successfully managed CPB by continuous administration of nafamostat mesylate. To decrease the tendency toward hemorrhage, some researchers have suggested that reduced heparinization combined with a heparin-coated pump system would be useful during cardiac surgery [14]. However, the relative importance of blood pressure and pump flow in patients with intracranial hemorrhage as determinants of cerebral perfusion during CPB remains unclear.

Here, we retrospectively evaluated the clinical outcomes of patients with acute IE by categorizing them into those with and without intracranial findings based on preoperative imaging evaluation. Notably, at our institute, heparin dosage is adjusted to avoid over extension of activated clotting time (ACT), and ACT is strictly controlled with a target of approximately 500 s. In addition, steps are taken to prevent abnormally high perfusion pressures during CPB.

METHODS

Study design

We retrospectively reviewed 32 cases of acute IE treated at our hospital from August 2015 to March 2022. In the 31 cases in which preoperative cerebral examinations were performed, we examined preoperative patient background, intraoperative CPB management, and postoperative course based on with or without preoperative intracranial findings. Preoperative intracranial findings were defined as those with or without positive findings from brain magnetic resonance imaging (MRI), MRA, or computed tomography angiography (CTA). All patients had been diagnosed with acute IE according to modified Duke criteria [18, 19]. The exclusion criteria included IE that healed in the chronic phase and right-sided IE that did not involve the left-side valves. In addition, one patient who did not undergo preoperative brain MRI because of cardiogenic shock was excluded. Thirty-one patients were categorized into those with (n = 20) and without (n = 11) preoperative intracranial findings.

The following patient demographics and comorbidities were recorded: age, sex, diabetes mellitus, chronic renal disease requiring hemodialysis, immunosuppressive drug administration, history of cardiac surgery,

history of coronary artery disease, history of cerebrovascular disease, and whether it was an emergency case. The following preoperative data related to IE and cardiac function were also collected: duration from onset to diagnosis, duration from diagnosis to surgery, causative microorganisms, particularly *Staphylococcus* and *Streptococcus*, thrombi in other organs, and preoperative echocardiographic data. Other organ embolisms were excluded from CT. All patients had undergone transthoracic echocardiography. The echocardiographic data included IE-related valve regurgitation and perivalvular lesions, which were defined as the presence of an abscess, pseudoaneurysm, or fistula. Vegetation was determined based on whether the maximum vegetation length was > 1 cm. Based on blood culture results, antibiotics were administered according to the recommendations of the infection control team at our institute. Our patients received intravenous antibiotics for at least 4 weeks preoperatively and 4–6 weeks postoperatively. Postoperative antibiotics were administered for either 6 weeks if the intraoperative culture was positive or 4 weeks if it was negative. Based on intraoperative pathological findings, a case was classified as pathologically “active” if either of the following was observed in the excised valve: (1) an acute inflammatory reaction microscopically or (2) organisms found microscopically [20]. Major adverse cardiac and cardiovascular events (MACCE) were the primary endpoints. MACCE were defined as the composite of all-cause mortality, hospitalization due to heart failure, repeat cardiac surgery, and brain-related events, including cerebral hemorrhage or stroke. Secondary endpoints were IE-related postoperative events related to IE, recurrence, and adverse events related to recurrent IE.

An intracranial mycotic aneurysm was diagnosed based on the CTA or MRA results. Preoperative intracranial findings were defined as fresh lesions from a cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or intracranial mycotic aneurysms. In addition, pre-and postoperative symptoms related to neurological deficiency included deep coma, disturbances in consciousness, hemiplegia, and speech impediments. Deficits that persisted until hospital discharge were designated as permanent neurological deficits. Delayed awakening, transient loss of orientation, slurred language, poor response to commands, and transient hemiparesis that resolved by hospital discharge were designated as temporary neurological deficits. In the case of intracranial mycotic aneurysms, catheter-based cerebral angiography was performed if required. Although intracranial aneurysms with a maximum diameter > 5 mm were considered for endovascular treatment, the decision to clip or resect the aneurysms depended on the neurosurgeon. Therefore, in patients with ruptured mycotic aneurysms, neurosurgery or endovascular surgery should be initially performed when necessary, and cardiac surgery should be postponed for at least 4 weeks with adequate antibiotic therapy [5, 6].

CPB and anticoagulation procedure

Indications for valve surgery included heart failure unresponsive to medical therapy, persistent infection, repeat embolization, high embolic risk, and perivalvular extension of the IE. All surgeries were performed using routine procedures except for CPB anticoagulation and perfusion flow management. Anticoagulation during CPB was managed as follows: before connecting to the extracorporeal circuit, 100 IU/kg of heparin (our normal dosage for CPB:300 IU/kg) was administered to obtain an ACT 300 s. The ACT was targeted at approximately 500 s during CPB (our standard range was 400 s or longer, with no

upper limit). The target mean arterial blood pressure during cardiopulmonary bypass was approximately 50 mmHg. The maximum intraoperative ACT and mean arterial blood pressure during CPB were measured. Continuous bilateral cerebral regional oxygen saturation values were monitored using the INVOS™ Cerebral/Somatic Oximetry Adult Sensors (Medtronic, Minneapolis, MN, USA) were also recorded and assessed.

Statistical procedures

Continuous and categorical variables are expressed as mean ± standard deviation or median (range) and number (%) of patients, respectively. Categorical variables were analyzed using Fisher's exact test, continuous variables were compared using Student's t-test, and non-parametric variables were analyzed using the Mann–Whitney U test. All data analyses were performed using the JMP 17.1 software (SAS Institute, Cary, NC, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 summarizes the preoperative clinical characteristics of the 31 patients. Of the 31 patients, 16 (52%) were male. The median age of the patients was 67 years (range, 32–82 years). Four patients (13%) had prosthetic valve infections, eight (26%) had aortic valve infections alone, 17 (55%) had mitral valve infections, 5 (16%) had combined valve infections, and 2 (6%) had ventricular septal defect infections. Blood cultures were positive in 30 (97%) patients, with *Streptococcus* in 23 (74%) and *Staphylococci* in 7 (23%). Surgical indications were heart failure unresponsive to medical therapy in 18 (58%) patients, high embolic risk in 9 (29%), persistent infection in 2 (6%), and perivalvular extension of the IE in 2 (6%). Overall, eight (26%) patients required emergency surgery: four cases of severe heart failure, including two cases requiring intra-aortic balloon pumping after intracranial examinations, two cases for high embolic risk, and two cases for the presence of perivalvular extension of the IE.

Table 1
Characteristics of patients

	with cerebral complications n = 20	without cerebral complications n = 11	p value
Age	71 (42–82)	54 (32–73)	0.0053
Sex (male, %)	10 (50)	6 (55)	0.81
Previous cardiac surgery (%)	4 (20)	0	0.051
Prosthetic valve endocarditis (%)	4 (20)	0	0.051
Diabetes mellitus (%)	2 (10)	2 (18)	0.52
Use of immunosuppressive drugs (%)	3 (15)	1 (9)	0.63
Hemodialysis (%)	1 (5)	0	0.34
Preoperative ejection fraction	65 (25–80)	65 (55–75)	0.88
Embolism to other organs	11 (55)	2 (18)	0.040
Blood culture (%)	19 (95)	11 (100)	0.34
Staphylococci (%)	4 (20)	3 (27)	0.56
Streptococcus (%)	15 (75)	8 (73)	
Duration from onset of symptoms to diagnosis (days)	16 (1-213)	19 (1-150)	0.70
Duration from diagnosis to surgery (days)	22 (0-157)	28 (1-143)	0.24

No significant differences were observed between the two groups in sex, duration from symptoms to diagnosis or from diagnosis to surgery, causative organisms, diabetes mellitus, hemodialysis, use of immunosuppressive drugs, previous cardiac surgery, history of ischemic heart disease, history of cerebral infarction, emergency cases, or preoperative cardiac function. However, the group with preoperative intracranial findings was significantly older ($p = 0.0053$) and had embolisms in other organs ($p = 0.040$). Furthermore, heart failure was significantly more common in the group without intracranial findings, whereas those with intracranial findings had various surgical indications ($p = 0.025$). Including duplicates, of the 20 (65%) patients with preoperative intracranial findings, 19 had fresh infarcts, 6 had cerebral hemorrhages, including 3 subarachnoid hemorrhages, and 6 had intracranial mycotic aneurysms. Four (20%) of the patients in this group had neurological symptoms: two experienced disturbances in consciousness, one had paralysis of the extremities, and one had a speech impediment. Patients in this group were referred for neurosurgery preoperatively; however, none of them required preoperative neurosurgical intervention.

Table 2 summarizes the operative procedures, intraoperative CPB data, and postoperative outcomes. Nineteen (61%) patients underwent minimally invasive cardiac surgery, and two (6%) required complicated surgical manipulation, including annular repair, due to extensive infection spread to the valve annulus. All patients were uneventfully weaned from CPB and no assistance device was required. Intraoperative pathology specimens revealed active IE in 24 patients (77%). No early postoperative deaths were observed; however, one patient (3%) in the group without preoperative intracranial findings (Fig. 1a, 1b) developed extensive cerebral bleeding (Fig. 1c), requiring tracheostomy. The patient recovered to almost normal neurological status after meticulous rehabilitation. The median follow-up period was 421 days (range, 20–2030 days). During the follow-up, MACCE occurred in four (13%) cases, of which one patient with preoperative intracranial findings died in the late period because of sepsis, one without preoperative intracranial findings developed a transient ischemic attack, and two in each group needed redo open-heart surgery. These patients underwent mitral valve replacement for the recurrence of severe mitral valve regurgitation but not for IE recurrence. Considering IE-related postoperative events in five (16%) cases, during follow-up, sepsis caused by recurrent IE developed in three patients: one with preoperative intracranial findings and two without preoperative intracranial findings. One patient with preoperative intracranial findings developed a ruptured mycotic splenic artery aneurysm, which was treated with interventional radiology.

Table 2
Operative procedures and outcomes

		with cerebral complications n = 20	without cerebral complications n = 11	p value
Operative indication	Heart failure unresponsive to medical therapy	8 (40)	10 (91)	0.025
	High embolic risk	8 (40)	1 (9)	
	Persistent infection	2 (10)	0	
	Perivalvular extension	2 (10)	0	
Emergency surgery (%)		7 (35)	1 (9)	0.086
Minimally invasive cardiac surgery (%)		11 (55)	8 (73)	0.33
Operation time (minutes)		372 (210–792)	247 (219–452)	0.085
CPB (minutes)		198 (101–410)	177 (82–248)	0.046
ACC (minutes)		115 (58–213)	94 (46–136)	0.071
Maximum ACT (seconds)		502 (388–628)	485 (405–569)	0.96
Maximum mean arterial blood pressure (mmHg)		63 (49–78)	70 (50–87)	0.0011
ICU stay (days)		3 (1–28)	2 (2–15)	0.84
Hospitalization (days)		29 (14–43)	15 (8–84)	0.23
Neurological outcomes (%)		1 (5)	1 (9)	0.66
Tracheostomy (%)		1 (5)	1 (9)	0.66
Pacemaker implantation		2 (10)	0	0.18
Renal complication (%)		0	0	
Pathological results (%)		19 (95)	5 (45)	0.0026
Early mortality (%)		0	0	
Late mortality (%)		1 (5)	0	0.34
MACCE (%)		2 (10)	2 (18)	0.52
Events related to infection (%)		2 (10)	3 (27)	0.22

ACC, aortic cross-clamp; ACT, activated clotting time; CPB, cardiopulmonary bypass time; ICU, intensive care unit; MACCE, major adverse cardiac or cerebrovascular events

No significant differences were observed in the minimally invasive cardiac surgery cases, operation time, aortic cross-clamp time, maximum ACT, length of intensive care unit stay, length of hospital stay, early postoperative death, postoperative neurological complications, postoperative cardiac-related complications, late postoperative death, recurrent infection, and MACCE. However, significant differences were observed in CPB time ($p = 0.046$), maximal mean arterial blood pressure ($p = 0.0011$), and pathological results ($p = 0.0026$) between the two groups. The Kaplan–Meier curves showed no significant difference in MACCE between the two groups ($p = 1.0$; Fig. 2a). The Kaplan–Meier curves showed no significant difference in events related to IE between the two groups ($p = 0.56$; Fig. 2b).

DISCUSSION

In this study, no early postoperative death or new cerebrovascular complications occurred in the group with preoperative intracranial findings. In contrast, a new cerebral hemorrhage developed in one patient whose preoperative MRI showed neither infarction nor hemorrhage.

Recently, silent intracranial findings have been detected because of advances in neuroimaging technology, and their incidence is much higher than expected, at approximately 80% [16]. Despite the improved accuracy of head MRI, detection of microscopic emboli, vascular injuries, and disruptions remains difficult. Therefore, it would be beneficial if more detailed tests were developed, although. in any case, suspecting a microembolism is crucial.

In this study, the group with intracranial findings was significantly older, had more positive intraoperative pathological findings, and had more organ embolisms. Cerebral complications occur during the active course of IE [1, 2]. The risk of embolism is reportedly greatest within 14 days of initial IE diagnosis [5]. Therefore, prompt initiation of antibiotic therapy is the most effective strategy to reduce the rate of septic embolism [2]. Furthermore, patients with intracranial hemorrhage reportedly have higher rates of other symptomatic systemic embolisms and mycotic aneurysms [21]. In this study, no significant differences were observed in most CPB data and postoperative courses, although the group with intracranial findings showed more active infection compared with those without.

To decrease the tendency toward hemorrhage, reduced heparinization combined with a heparin-coated pump system would be useful during cardiac surgery [14, 17]. Okada et al. reported successful mitral repair with the addition of low-dose heparin and nafamostat mesylate in a young female patient with a recent extensive cerebral infarction due to septic embolization [22]. Ota et al. successfully managed CPB with the continuous use of nafamostat mesylate in patients with acute IE with recent intracranial hemorrhage [17]. However, nafamostat mesylate is difficult to adjust, and its use requires informed consent as well as approval by an ethics committee. In addition, the ACT value fluctuates relative to the increase or decrease in the sustained amount of nafamostat mesylate during CPB; consequently, it cannot be used as an absolute measure, which raises safety concerns. Therefore, our strategy of strict ACT control after heparin administration may be acceptable and feasible for preventing intracranial

hemorrhage. In general, the use of anticoagulant therapy and appropriate flow pressure in patients with intracranial hemorrhage remains controversial. Further studies are required to address these issues.

Study limitations

This study had some limitations. First, relatively few patients were included because of the rarity of the condition. Second, this was a retrospective single-center experience lacking any form of randomization. Third, cases in which MRI could not be performed were excluded from this study, and true severe cases were excluded. Fourth, current literature does not provide any recommendations on mean arterial blood pressure in patients with intracranial hemorrhage during CPB. Therefore, further studies on the effects of perfusion pressure on cerebral hemorrhage are warranted.

CONCLUSION

Patients with positive intracranial findings were in a significantly active infectious condition preoperatively; however, this did not affect their postoperative course. As serious postoperative cerebral complications can develop even in the absence of preoperative intracranial imaging findings, it is extremely important to take precautions against postoperative cerebral complications in all IE cases. We expect that our strategy of maintaining a low intraoperative ACT may be an effective measure; however, further studies related to appropriate mean systemic flow pressure are warranted.

Declarations

Ethics approval and consent to participate

All procedures were performed in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Aichi Medical University Hospital approved the study on July 28th, 2022 (approval number 2022-051). All patients provided written informed consent for the use of their clinical data in scientific presentations or publications.

Consent for publication

The patient provided permission to publish the features of survey. The identity of the patient has been protected.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Competing interests

Kayo Sugiyama, Hirotaka Watanuki, Masato Tochii, Takayuki Kai, Daisuke Koiwa, and Katsuhiko Matsuyama have no conflicts of interest. The authors did not receive any financial support for this study.

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Authors' contributions

Study conception: KS; Data collection: KS; Analysis: KS, KM; Investigation: KS; Writing: KS; Funding acquisition: KS; Critical review and revision: all authors; Final approval of the article: all authors; Accountability for all aspects of the work: all authors. All authors read and approved the final manuscript.

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Figures

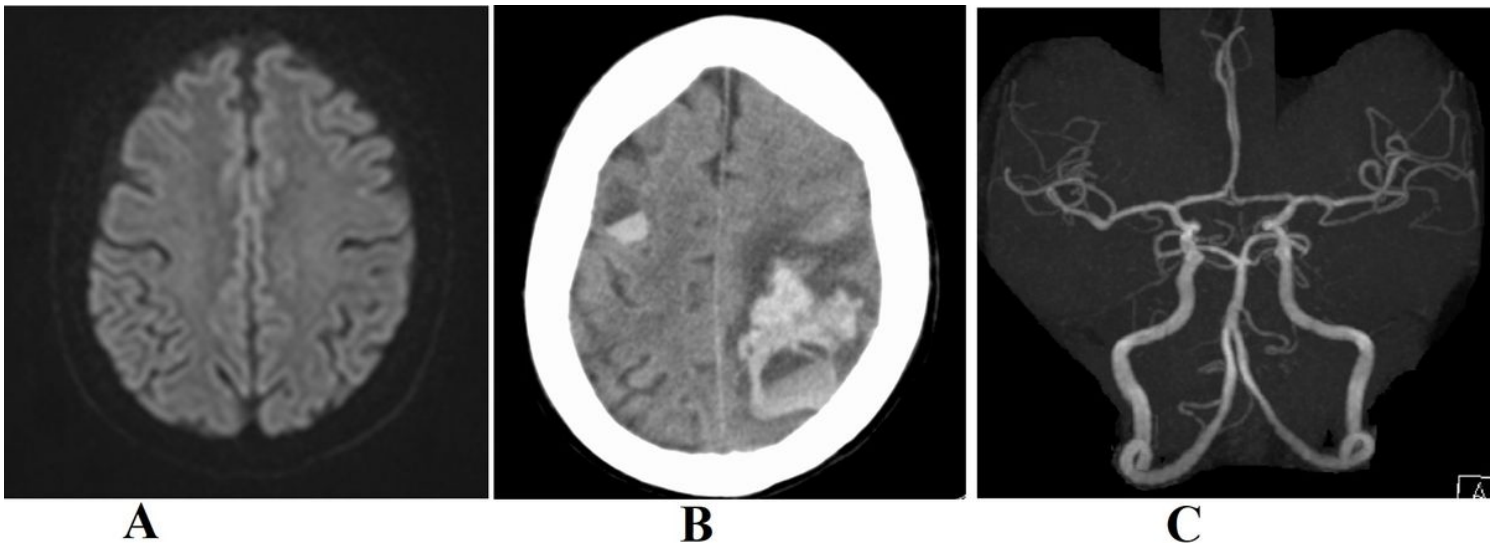

Figure 1

a Preoperative head magnetic resonance imaging of a patient showing almost normal

b Preoperative head magnetic resonance angiography of a patient showing no mycotic aneurysm

c Postoperative head computed tomography image of a patient showing broad cerebral hemorrhage

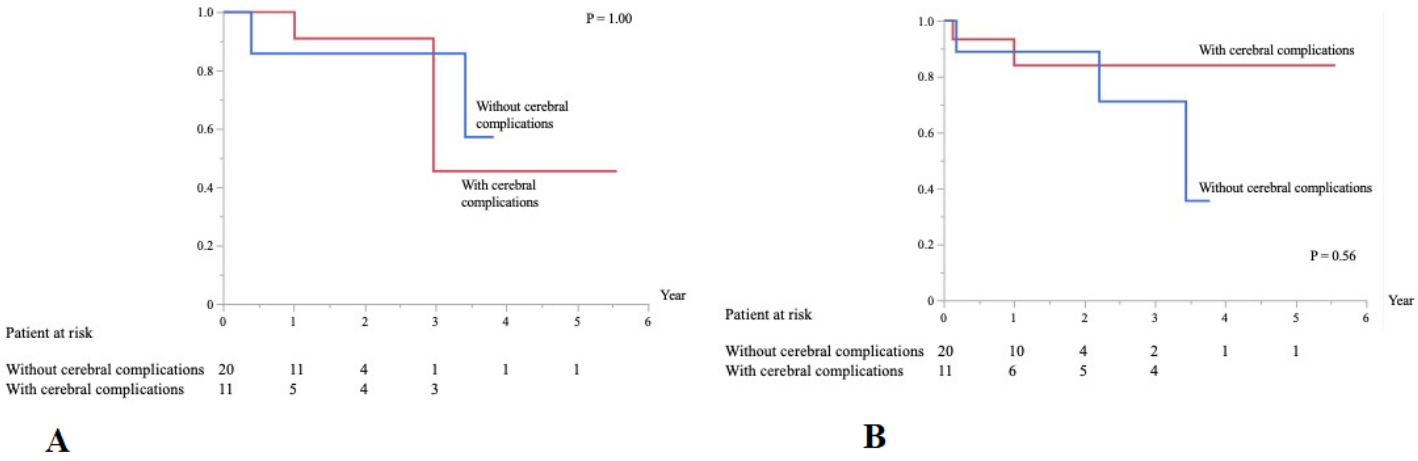

Figure 2

a Freedom from MACCE in patients with and without cerebral complications

b Freedom from events related to IE in patients with and without cerebral complications