Strokes in the ICU

Subjects: Neurosciences

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The mortality and neurological sequelae are worse in patients with in-hospital stroke than in those with community-onset stroke. The leading cause of this tragic situation is the delay in emergent treatment.

Keywords: in-hospital stroke ; intensive care unit (ICU) ; perioperative stroke

1. Introduction

In this decade, treatments for acute ischemic stroke (AIS) are developing radically. Intravenous (IV) thrombolysis is an effective treatment for AIS, and it is highly beneficial for patients with AIS up to 4.5 h after symptom onset [1][2]. Furthermore, Guidelines for the Early Management of Patients With Acute Ischemic Stroke recommended that even when the time of symptom onset is unclear or already over 4.5 h from the last known well, patients with AIS could receive IV thrombolysis if they showed diffusion-positive fluid-attenuated inversion recovery-negative lesions on magnetic resonance imaging (MRI) testing or perfusion mismatch on computed tomography (CT) or MRI perfusion [3]. In addition, randomized, controlled trials have proven the utility of endovascular thrombectomy (EVT) for AIS. Within 6 h from symptom onset, patients with AIS due to anterior large vessel occlusion have an opportunity to receive a beneficial effect from EVT. In addition, when a sufficient clinical-core mismatch is detected by computed tomography or MRI, and the patient fulfills the eligibility criteria of the DAWN trial or the DEFUSE-3 trial, the patients could be rescued by acute therapy even up to 24 h after onset [4][5].

Recently, the Recovery by Endovascular Salvage for Cerebral Ultra Acute Embolism Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT), a randomized, multicenter study in Japan, showed that patients with a large ischemic core could enjoy better functional outcomes with EVT than with medical treatment alone [6]. Owing to those recent guidelines and studies, patients have a better chance of recovering from severe symptoms of AIS.

Despite the progress in treatment, in-hospital stroke is still tragic. Unlike community-onset stroke, the incidence of in-hospital stroke has not been investigated in detail. More than 30,000 patients are estimated to have an in-hospital stroke every year in the United States, and approximately 7% of all stroke events occur in the hospital [7][8]. More than 90% of all stroke events in the hospital were ischemic strokes [8]. Patients with in-hospital stroke have more severe disabilities than those with community-onset stroke due to their comorbidities [9][10]. In addition, they have fewer opportunities to receive acute therapy, especially IV thrombolysis [8][11][12]. One reasonable explanation is that patients with in-hospital stroke are often ineligible for IV thrombolysis due to their various situations: they have undergone surgery or a procedure, have received complicated antithrombotic therapy, or have fatal comorbidities, such as intracranial hemorrhage, trauma, and gastric bleeding. However, unfortunately, delayed recognition of in-hospital stroke may be crucial.

2. Causes of Stroke in the ICU

2.1. Cardiovascular Diseases and Cardiac Surgery/Procedures

- Among the patients in the ICU, 9–25% would suffer from new-onset atrial fibrillation (AF) due to various situations.
- Stroke is a common thromboembolic complication due to infective endocarditis (IE). IV thrombolysis is not applicable, so EVT is expected to be beneficial.
- Perioperative stroke after coronary artery bypass graft (CABG) is caused by arrhythmias and hemodynamic instability.
- In thoracic endovascular aneurysm repair (TEVAR), more proximal stent landing and stent covering the left subclavian artery are the risks for perioperative stroke.
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After transcatheter aortic valve implantation (TAVI), silent infarction could be detected in 70% of the patients, and 1.1–6.7% would suffer from symptomatic stroke.

An observational, retrospective study in Korea demonstrated that 60% of in-hospital strokes were associated with surgery or procedures, and the most common cause of in-hospital stroke was cardiac surgery [13]. Commonly, patients with cardiovascular disease undergoing surgery or critical illness are at increased risk of stroke and are often admitted to the ICU. Only a few reports have described in-hospital stroke patients' characteristics in detail. Approximately 0.2% of patients who underwent cardiac surgery developed ischemic stroke during their hospitalization, and patients in cardiology-related departments were at 10-fold higher risk for stroke than those in other departments [13]. Another study showed that approximately 40% of patients with in-hospital stroke were hospitalized due to cardiovascular diseases [14]. Naturally, cardiovascular diseases and cardiac surgery or procedures are strongly related to in-hospital stroke; therefore, it is imperative to pay close attention to patients with cardiovascular diseases during hospitalization.

AF is a well-known etiology of stroke. Patients sometimes develop new-onset AF during their hospitalization and may have worse outcomes if they develop a stroke than patients without AF [15]. In particular, 9–25% of patients who were admitted to an ICU presented with new-onset AF triggered by clinical illness, such as surgery and sepsis [16][17]. Cardiac surgery is the most responsible, but 10–20% of patients who underwent noncardiac surgery experienced perioperative AF [18][19]. Inflammation, sympathetic response, and cardiac hypoperfusion induced by surgery may synergistically contribute to AF [19]. Similarly, AF is triggered in sepsis by bacterial infection, oxidative stress, electrolyte imbalance, and vasopressor agents [20][21]. A systematic review reported that 13.5% of patients with sepsis had new-onset AF, and increased mortality in the ICU was found on multivariable metaregression (RR: 2.12, 95% CI: 1.86–2.43) [20]. However, the stroke risk of new-onset AF due to critical illness may vary for each patient, and routine anticoagulant agent use is still debated because of the lack of sufficient evidence [22]. Therefore, stroke risk should be assessed individually.

IE is a devastating infectious disease. *Staphylococcus aureus* is the most common cause of IE, and nearly half of IE cases are associated with surgery [23]. This fatal bloodstream infection is strongly associated with systemic embolism by vegetation formed on the mitral valve. Ischemic stroke associated with IE accounts for over 60% of all embolic events of IE, and the most affected artery is the middle cerebral artery [23][24]. *Staphylococcus aureus*, *Candida*, *Haemophilus species*, *Aggregatibacter species*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella species* are regarded as the main causes of ischemic stroke induced by IE [23]. Regrettably, even though large vessel occlusion occurs with IE, IV thrombolysis is typically not applicable for patients with ischemic stroke induced by IE since the presence of IE itself and an abnormal coagulation profile are listed in the exclusion criteria for IV thrombolysis [25], whereas the efficiency of EVT has been reported recently [26][27]. A systematic review of the literature showed that 37% of the patients had better outcomes 90 days after EVT [27]. In fact, 13.3% of all cases experienced intracranial hemorrhage after EVT in the study, but researchers should not give up thinking about how to rescue IE patients from ischemic stroke.

Generally, cardiac surgical procedures, such as graft interposition of the ascending aorta, CABG, percutaneous coronary intervention (PCI), and implantation or removal of external pacemakers, contribute to perioperative stroke. CABG is one of the most common cardiac surgeries. The incidence of stroke after CABG is about 1%, and the incidence is gradually decreasing over the decades [28][29]. Stroke commonly occurs two days after the surgery due to arrhythmias and hemodynamic instability [28][30]. Age and several comorbidities, including severe kidney disease, severe chronic lung disease, carotid artery disease, and other heart diseases, are regarded as crucial risk factors for stroke after CABG [28][31][32][33]. Off-pump coronary artery bypass (OPCAB), which is performed without cardiopulmonary bypass, is associated with a reduced risk of neurological complications compared to on-pump CABG [34][35]. Compared to CABG, PCI is associated with a relatively lower risk of procedural stroke [36], less than 0.5% [37]. Stroke after PCI occurs commonly within 48 h [28][38]. Proper anticoagulation and operator experience are the keys to preventing stroke after PCI [28].

TEVAR is one of the common vascular surgeries. Approximately 70% of thromboembolic events result from aortic manipulation and scraping atheromatous plaque; the rest are associated with hypoperfusion during surgery [39]. The stroke rate after TEVAR is 2.9–11.5% [40][41][42], and age, body mass index, diabetes mellitus, chronic obstructive pulmonary disease, urgency of repair, and type of anesthesia are recognized as significant contributors [41]. In addition, more proximal stent landing and stent covering the left subclavian artery are considered to be associated with stroke [40][43].

TAVI is an alternative procedure to surgical aortic valve replacement or severe aortic valve stenosis and has emerged worldwide in recent years. By a catheter procedure, the bioprosthetic valve is delivered and placed on the aortic valve, and TAVI now prevails worldwide because of its less invasiveness. On the other hand, embolic stroke after TAVI is an important problem. During the aortic valve replacement procedure, embolic debris from the valve and aorta can scatter

and cause ischemic stroke [44][45]. Regardless of whether the transfemoral approach or transapical approach is used, new silent cerebral infarctions detected by MRI were found in approximately 70% of patients after TAVI [46][47][48]. Further, several studies showed that 1.1–6.7% of patients who underwent TAVI experienced a symptomatic ischemic stroke or transient ischemic attack within 30 days after the procedure [49][50]. Cerebral embolic protection devices (CEPDs) are expected to reduce debris and embolic complication. In the procedure, CEPD is delivered by catheter and deployed in the aortic arch. CEPD may capture the debris or deflect the debris away from cerebral arteries. Although CEPD use seems to be reasonable, the efficiency has not been proven, and further study is needed [51].

2.2. Extracorporeal Circulation and Left Ventricular Assist Devices (LVADs)

- Of the patients maintained with extracorporeal membrane oxygenation (VA-ECMO), 1.4% experience stroke. EVT is expected to be an effective treatment for AIS during ECMO.
- Approximately 4% of the patients who were supported by Impella would experience a stroke.
- Among the patients who were implanted with left ventricular assist devices (LVADs), 14% would suffer from stroke within a year after the implantation.

In a case with cardiogenic shock, the use of extracorporeal circulation, including intra-aortic balloon pumping (IABP), VA-ECMO, and Impella (Abiomed Inc., Danvers, MA, USA), an intravascular heart pump device, are crucial for providing life support. IABP is used worldwide in the ICU to support left ventricular function. According to the Intra-aortic Balloon Pump in Cardiogenic Shock (IABP-SHOCK) II trial, a multicenter, open-label, randomized study, there was no significant relationship between IABP and stroke [52][53].

VA-ECMO is another life-supporting device used in cases with refractory lung and heart failure, and its use has increased in this decade [54]. Neurological complications are strongly associated with death or long-term disability, but their frequency has not been described in detail [55]. Cho et al. investigated 15,872 patients who were supported by VA-ECMO. Of these patients, 215 (1.4%) experienced an ischemic stroke, and they found that acidemia, hypoxemia, and abnormal coagulation status were independent predictors of acute brain injury [56]. In addition, microemboli in cannulae and pulseless flow are regarded as other risk factors [57]. Cardiac arrest or global ischemia may lead to loss of cerebral autoregulation [58], and the patients become more vulnerable to the up/downregulation of cerebral circulation.

The Impella is a new percutaneous left ventricular assist device for cardiogenic shock. It is located at the left ventricle and pumps blood to the aorta to reduce the workload on the left ventricle [59]. The incidence of ischemic stroke associated with its use is unknown. One previous single-center study in the United States showed that 3 of 79 patients (3.8%) in whom the Impella was used developed ischemic stroke. Of them, two patients were maintained with inadequate anticoagulation [59]. The Impella and IABP are often combined with ECMO, making it difficult to assess the risk of stroke accurately. However, proper management during extracorporeal circulation, including appropriate anticoagulation, monitoring of cannulae, and optimizing oxygenation, is crucial to prevent stroke.

LVADs are mechanical pumps that support the circulatory system. They are implanted in patients waiting for a heart transplant. It has been reported that the rate of ischemic stroke events within 30 days after the implantation of LVADs was 0.06–0.62 per patient-year [60][61][62][63][64]. Ischemic stroke during the peri-implantation period might be associated with hypercoagulation, AF, and infection due to surgery [65][66][67]. After that period, continuous abnormal coagulation, inflammation, and shear stress caused by LAVDs are responsible for ischemic stroke. In addition, patients with LVADs must be maintained on anticoagulant agents [68][69][70]. However, adequate management is sometimes challenging to control hemorrhagic or thromboembolic event risks. One multicenter observational study showed that 14% of patients with LVADs experienced stroke one year after implantation [70]. Stroke is a fatal complication for patients with LVADs, who may lose their chance to undergo heart transplantation. Therefore, researchers should pay close attention to patients with LVADs.

It is difficult for patients maintained by extracorporeal circulation devices to receive acute therapy for AIS, and they are on anticoagulant agents, so IV thrombolysis is not applicable. Though EVT may be theoretically possible, it is also quite challenging because of the choice of vascular access. However, there are some case series of patients treated with EVT during ECMO [71]. In addition, successful EVT for patients with LVADs has been reported [64]. Further study is needed to determine the efficacy of EVT for patients with extracorporeal circulation devices.

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