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Neurologic Complications of Extracorporeal Membrane Oxygenation

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Background and Purpose The rate and outcomes of neurologic complications of patients receiving extracorporeal membrane oxygenation (ECMO) are poorly understood. The purpose of this study was to identify these parameters in ECMO patients.

Methods All patients receiving ECMO were selected from the Nationwide Inpatient Sample between 2001–2011. The rate and outcomes of neurologic complications [acute ischemic stroke, intracranial hemorrhage (ICH), and seizures] among these patients was determined. Discharge status, mortality, length of stay, and hospitalization costs were compared between patients with and without neurologic complications using chi-squared tests for categorical variables and Student's *t*-test for continuous variables.

Results In total, 23,951 patients were included in this study, of which 2,604 (10.9%) suffered neurologic complications of seizure (4.1%), stroke (4.1%), or ICH (3.6%). When compared to patients without neurologic complications, acute ischemic stroke patients had significantly higher rates of discharge to a long-term facility (12.2% vs. 6.8%, $p<0.0001$) and a significantly longer mean length of stay (41.6 days vs. 31.9 days, $p<0.0001$). ICH patients had significantly higher rates of discharge to a long-term facility (9.5% vs. 6.8%, $p=0.007$), significantly higher mortality rates (59.7% vs. 50.0%, $p<0.0001$), and a significantly longer mean length of stay (41.8 days vs. 31.9 days) compared to patients without neurologic complications. These outcomes did not differ significantly between seizure patients and patients without neurologic complications.

Conclusions Given the increasing utilization of ECMO and the high costs and poor outcomes associated with neurologic complications, more research is needed to help determine the best way to prevent these sequelae in this patient population.

Key Words extracorporeal membrane oxygenation, stroke, neurology/neurologic (deficits, disease, injury).

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an increasingly used technique providing cardiopulmonary support to patients with severe refractory cardiac and respiratory failure. Standard ECMO involves venous drainage from the femoral vein or left atrium with artificial extracirculatory oxygen exchange and return of the blood to the body through the same veins (venovenous) or to the arterial system through the femoral artery or ascending aorta (venoarterial).[1] ECMO is commonly used in neonates and infants with congenital heart defects or respiratory distress syndrome, and it is also increasingly being used as a transplant bridge in adults who survive cardiopulmonary resuscitation, and in patients with cardiogenic shock and severe respiratory failure.[2,3]

Some studies have demonstrated that neurologic complications are rather common

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among patients receiving ECMO.[4] These complications are generally related to thrombosis with infarction, or hemorrhage.[5] Intracranial hemorrhage (ICH) in particular has been associated with higher rates of mortality.[4,6] However, much of the evidence regarding the incidence and outcomes of neurologic complications among ECMO patients is limited to small case series.[7]

A large, multihospital database, the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality, was studied between 2001–2011. We sought to characterize the rate and outcomes of neurologic complications among patients receiving ECMO.

METHODS

Patient population

The NIS hospital discharge database for the period 2001–2011 was obtained from the HCUP of the Agency for Healthcare Research and Quality. This database represents 20% of all inpatient discharges from nonfederal hospitals in the United States. Patients included in this study were selected using the International Classification of Diseases 9th Revision (ICD-9) procedure code for extracorporeal membranous oxygenation, 3965.

Demographic characteristics, indications, and comorbidities

The demographic information analyzed included age and gender. Age was categorized into neonates (<1 month), infants (1 month to 1 year), children (1–17 years), adults (18–64 years), and seniors (≥65 years). These age groups were similar to those in the Extracorporeal Life Support Organization (ELSO) registry, with the exception that adults were defined as aged ≥18 years in the present study and a separate group of patients aged ≥65 years was also included.[8]

Comorbidities and complications included in this study were congenital heart disease [clinical classification software code (CCS): 213], sepsis (CCS: 2), cardiac arrest (CCS: 107), shock (CCS: 249), respiratory distress syndrome (CCS: 221), and respiratory failure, insufficiency, arrest (CCS: 131). The prevalence of these comorbidities among ECMO patients in each age group was studied. The Charlson Comorbidity Index was calculated for each patient.[9]

Outcomes

The primary endpoints of this study were the following neurologic complications: ICH (ICD-9: 430, 431, 4320, 4321, 4329), acute ischemic stroke (ICD-9: 433.X1, 434.X1, 436, 437.0, 437.1, 437.4, 437.5, 437.7, 437.8, and 437.9), and seizure (CCS: 83). The discharge status (discharge to home or

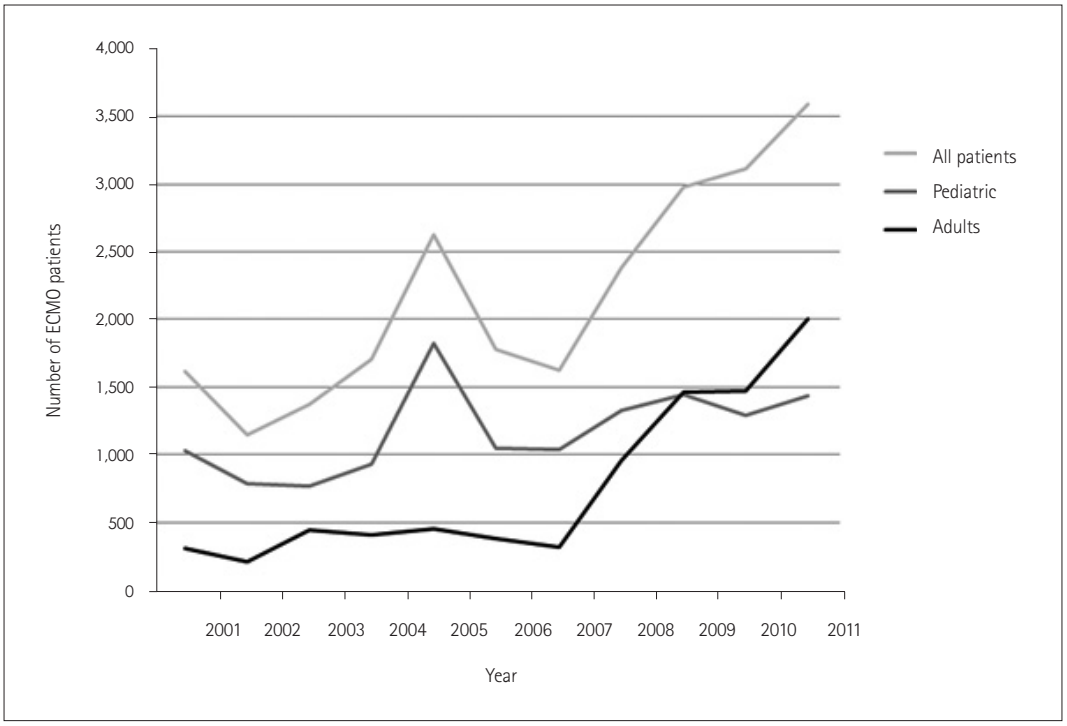

Fig. 1. Number of patients treated with extracorporeal membrane oxygenation (ECMO) during the period 2001–2011. Graphical representation of ECMO utilization in the United States Nationwide Inpatient Sample from the period 2001–2011. ECMO utilization increased from 1,613 patients in 2001 to 3,597 patients in 2011. Utilization in adults increased from 309 patients in 2001 to 2004 patients in 2011; these data for the pediatric population are 1,027 and 1,434 patients, respectively.

Table 1. Demographics and outcomes

Variable	*n* (%) or mean±SD
Age (years)	18.5±56.3
Female	10,128 (42.2)
Age group	
<1 month	7,741 (36.3)
1 month to 1 year	1,854 (8.7)
1–17 years	3,311 (15.5)
18–64 years	6,622 (31.1)
≥65 years	1,775 (8.3)
Indication/comorbidity*	
Congenital heart disease	11,712 (48.9)
Cardiac arrest	4,769 (19.9)
Sepsis	6,377 (26.6)
Shock	7,369 (30.8)
Respiratory distress syndrome	1,218 (5.1)
Respiratory failure (adult)	11,407 (47.6)
Neurologic outcome	
ICH	862 (3.6)
Ischemic stroke	980 (4.1)
Seizure	986 (4.1)

*Indications for extracorporeal membrane oxygenation (ECMO) do not add up to 100% since many of the patients suffered multiple comorbidities.
ICH: intracerebral hemorrhage.

discharge to long-term facility), in-hospital mortality, length of stay, and 2011-adjusted hospitalization costs of patients with neurologic complications with patients who did not suffer neurologic complications were compared. Rates of neurologic complications were also compared across age groups and comorbidities/indications. A separate analysis of the rate of neurologic complications was also performed by age group, and trends in the utilization of ECMO during the period 2001–2011 were examined.

Statistical analysis

Chi-squared tests were used to compare categorical variables, and the Student's *t*-test was used to compare continuous variables, assuming a cutoff for statistical significance of $p<0.05$. Probability values for outcomes were obtained using the no-neurologic-complications group as a reference group. Discharge weights were applied to make the data nationally representative. Two multivariate analyses were performed; one was designed to determine the comorbidities and demographic characteristics associated with neurologic complications (stroke, ICH, or seizure) and in-hospital mortality; all comorbidities, indications, and demographic factors were forced into this model. Except where stated otherwise, the data are presented as mean±SD values. All statistical analyses were performed using the SAS-based statistical package JMP (www.jmp.com).

RESULTS

Patient population

In total, 23,951 patients were included in this study. The number of patients receiving ECMO increased from 1,613 patients in 2001 to 3597 patients in 2011 (Fig. 1). The number of pediatric patients receiving ECMO increased from 1,027 to 1,434 during the same time period, while the number of adult ECMO patients increased from 309 to 2004 (Fig. 1). Age data were available for 21,304 patients; these patients were 18.5±56.3 years old, and 7,741 patients (36.3%) were younger than 1 month and 8,398 patients (39.4%) were ≥18 years old. The most common indication/comorbidity was congenital heart disease (*n*=11,712, 48.9%) followed by adult respiratory failure (*n*=11,407, 47.6%) and shock (*n*=7,369, 30.8%). These data are summarized in Table 1. The most common indications/comorbidities by age group were congenital heart disease for patients aged <1 month (86.8%) and aged between 1 month and 1 year (71.0%). Respiratory failure was the most common indication in patients aged 1–17 years (70.5%), 18–64 years (77.0%), and ≥65 years (66.6%). These data are summarized in Supplementary Table 1 (in the online-only Data Supplement).

Neurologic complications and outcomes

A total of 2,604 patients (10.9%) suffered neurologic complications of seizure (*n*=986, 4.1%), stroke (*n*=980, 4.1%), or ICH (*n*=862, 3.6%). When compared to patients without neurologic complications, acute ischemic stroke patients had a significantly higher rate of discharge to a long-term facility (12.2% vs. 6.8%, $p<0.0001$), a significantly longer mean length of stay (41.6 days vs. 31.9 days, $p<0.0001$), and significantly higher costs (US$ 639,528 vs. US$ 501,184, $p<0.0001$). When compared to patients without neurologic complications, ICH patients had a significantly higher rate of discharge to a long-term facility (9.5% vs. 6.8%, $p=0.007$), a significantly higher mortality rate (59.7% vs. 50.0%, $p<0.0001$), a significantly longer mean length of stay (41.8 days vs. 31.9 days, $p=0.01$), and significantly higher hospitalization costs (US$ 641,636 vs. US$ 501,184, $p=0.002$). The outcomes did not differ significantly between seizure patients and patients without neurologic complications. These data are summarized in Table 2.

The results of univariate analyses of variables associated with neurologic complications are presented in Table 3. Patients aged <1 month had the lowest rate of acute ischemic stroke (2.5%), while patients aged between 1 month and 1 year had the highest rate (6.4%, $p<0.0001$). Patients with shock had the highest rate of acute ischemic stroke (6.0% vs.

Table 2. Outcomes of ECMO-associated neurologic complications

Outcome	No neurologic complication	Ischemic stroke	*p*	ICH	*p*	Seizure	*p*
Home, *n* (%)	5,266 (24.7)	394 (21.4)	0.001	174 (20.2)	0.002	304 (30.8)	<0.0001
Long term, *n* (%)	1,452 (6.8)	225 (12.2)	<0.0001	82 (9.5)	0.007	57 (5.8)	0.08
Death, *n* (%)	10,671 (50.0)	949 (51.5)	0.18	515 (59.7)	<0.0001	455 (46.2)	0.01
LOS (days), mean±SD	31.9±82.6	41.6±106.6	<0.0001	41.8±112.8	0.01	29.5±67.5	0.16
Costs, US$ mean±SD	501,184±923,942	639,528±1,202,380	<0.0001	641,636±1,188,231	0.002	474,168±887,208	0.22

ECMO: extracorporeal membrane oxygenation, LOS: length of stay.

Table 3. Rate of neurologic complications by demographic, comorbidity, and indication characteristics

Baseline characteristics	Acute ischemic stroke	*p*	ICH	*p*	Seizure	*p*
Gender		0.44		<0.0001		0.06
Male	554 (4.0)		422 (3.1)		540 (3.9)	
Female	426 (4.2)		440 (4.4)		446 (4.4)	
Age group		<0.0001		<0.0001		<0.0001
<1 month	190 (2.5)		139 (1.8)		131 (1.7)	
1 month to 1 year	119 (6.4)		184 (9.9)		258 (13.9)	
1–17 years	188 (5.7)		202 (6.1)		300 (9.1)	
18–64 years	343 (5.2)		196 (3.0)		167 (2.5)	
≥65 years	62 (3.5)		43 (2.5)		<10 (0.3)	
Indication/comorbidity						
Congenital heart disease		<0.0001		<0.0001		0.38
Yes	404 (3.5)		363 (3.1)		496 (4.2)	
No	576 (4.7)		499 (4.1)		491 (4.0)	
Cardiac arrest		<0.0001		<0.0001		<0.0001
Yes	246 (5.2)		221 (4.6)		398 (8.3)	
No	734 (3.8)		642 (3.4)		588 (3.1)	
Sepsis		0.64		<0.0001		0.003
Yes	267 (4.2)		331 (5.2)		222 (3.5)	
No	713 (4.1)		531 (3.0)		764 (4.4)	
Shock		<0.0001		<0.0001		0.02
Yes	445 (6.0)		322 (4.4)		270 (3.7)	
No	535 (3.2)		541 (3.3)		716 (4.3)	
Respiratory distress syndrome		0.003		<0.0001		<0.0001
Yes	30 (2.5)		15 (1.2)		24 (2.0)	
No	950 (4.2)		847 (3.7)		962 (4.2)	
Respiratory failure (adult)		<0.0001		<0.0001		0.002
Yes	561 (4.9)		591 (5.2)		518 (4.5)	
No	419 (3.3)		271 (2.2)		468 (3.7)	

Data are *n* (%) values.
ICH: intracerebral hemorrhage.

3.2%, $p<0.0001$), while those with respiratory distress syndrome had the lowest rate (2.5% vs. 4.2%, $p<0.0001$). Patients aged <1 month also had the lowest rate of ICH (1.8%), while those aged between 1 month and 1 year had the highest rate (9.9%, $p<0.0001$). Respiratory distress syndrome was associated with the lowest rate of ICH (1.2% vs. 3.7%, $p<0.0001$). Patients aged <1 month had the lowest rate of seizure (1.7%), while those aged between 1 month and 1 year had the highest (13.9%, $p<0.0001$). Cardiac arrest was the comorbidity associated with the highest rate of seizure (8.3% vs. 3.1%, $p<0.0001$), and respiratory distress syndrome was associated with the lowest rate (2.0% vs. 4.2%, $p<0.0001$). The results of analyses of variables associated with neurologic complications by age are summarized in Supplemental Table 2–6 (in the online-only Data Supplement).

Multivariate analysis

Variables predictive of neurologic complications (stroke,

Table 4. Multivariate predictors of mortality

Variable	Death OR (95%CI)	*p*	Neurologic complications OR (95%CI)	*p*
Female gender	1.12 (1.02–1.22)	0.01	1.12 (1.02–1.22)	0.01
Age group				
<1 month	Reference	Reference	Reference	Reference
1 month to 1 year	0.87 (0.77–0.97)	0.01	4.83 (4.10–5.68)	<0.0001
1–17 years	1.05 (0.94–1.17)	0.36	2.27 (2.02–2.56)	<0.0001
18–64 years	1.88 (1.69–2.09)	<0.0001	1.44 (1.21–1.72)	<0.0001
≥65 years	2.34 (2.04–2.68)	<0.0001	0.93 (0.72–1.19)	0.55
Indication/comorbidity				
Congenital heart disease	0.97 (0.89–1.05)	0.46	0.99 (0.87–1.12)	0.86
Cardiac arrest	1.49 (1.38–1.60)	<0.0001	1.30 (1.17–1.45)	<0.0001
Sepsis	1.12 (1.05–1.20)	0.0009	1.12 (1.01–1.24)	0.03
Shock	1.20 (1.13–1.29)	<0.0001	1.24 (1.12–1.37)	<0.0001
Respiratory distress syndrome	0.59 (0.51–0.68)	<0.0001	0.94 (0.69–1.27)	0.71
Respiratory failure (adult)	1.16 (1.08–1.25)	<0.0001	1.03 (0.92–1.15)	0.59
Neurologic complication				
Ischemic stroke	0.73 (0.63–0.83)	<0.0001	NA	NA
ICH	2.31 (1.89–2.84)	<0.0001	NA	NA
Seizure	0.84 (0.73–0.87)	0.02	NA	NA

CI: confidence interval, ICH: intracerebral hemorrhage, OR: odds ratio.

ICH, or seizure) on multivariate analysis included cardiac arrest [odds ratio (OR)=1.30, 95% confidence interval (CI)=1.17–1.45, $p<0.0001$], sepsis (OR=1.12, 95%CI=1.01–1.24, $p=0.03$), and shock (OR=1.24, 95%CI=1.12–1.37, $p<0.0001$). Compared to neonates, all age groups had significantly lower odds of neurologic complications on multivariate analysis, with the risk being highest for infants aged between 1 month and 1 year. These data are summarized in Table 4.

Variables predictive of mortality on multivariate analysis included cardiac arrest (OR=1.49, 95%CI=1.38–1.60, $p<0.0001$), sepsis (OR=1.12, 95%CI=1.05–1.20, $p=0.0009$), shock (OR=1.20, 95%CI=1.13–1.29, $p<0.0001$), and respiratory failure (OR=1.16, 95%CI=1.08–1.25, $p<0.0001$). ICH was the only neurologic complication associated with higher odds of mortality (OR=2.31, 95%CI=1.89–2.84, $p<0.0001$). Adult patients (aged 18–64 years) had significantly higher odds of mortality compared with the pediatric cohort (OR=1.88, 95%CI=1.69–2.09, $p<0.0001$), as did seniors (aged ≥65 years; OR=2.34, 95%CI=2.04–2.68, $p<0.0001$). These data are summarized in Table 4.

DISCUSSION

The findings of this study show that the rates of ICH, acute ischemic stroke, and seizure among patients receiving ECMO were each approximately 4%, but nearly 11% of patients treated with ECMO had one of these neurologic complications. Compared to patients without neurologic complications, those suffering neurologic complications of acute ischemic stroke and ICH had higher rates of discharge to a long-term facility, and ICH patients had higher rates of mortality. Lengths of stay and hospitalization costs were also significantly higher among acute ischemic stroke and ICH patients. It was also found that the rate of neurologic complications was lower among neonates than in the other age groups. Furthermore, patients with cardiac arrest and shock had significantly higher rates of neurologic morbidity and mortality than those without these conditions.

The present findings also demonstrated that the number of patients receiving ECMO in the United States is increasing rapidly, especially among adults. There was a 40% increase in the number of pediatric patients receiving ECMO during the period 2001–2011, and an impressive 650% increase in the number of adult patients receiving ECMO. Given these rapid increases in the number of patients receiving ECMO, it is important to have a comprehensive understanding of the incidence of neurologic complications among them. Several studies have shown that patients suffering neurologic complications while on ECMO have higher rates of long-term disability and suffer significantly higher morbidity and mortality rates.[10,11] The present study confirms this finding, albeit on a much larger scale, and also shows that hospitalization costs are more than US$ 100,000 higher among patients with neurologic complications than among those without such

complications. Given the higher rates of morbidity and mortality and the high costs associated with neurologic complications, future studies should investigate the development of methods for preventing neurologic complications such as ischemic stroke and ICH.

Several studies have highlighted the high rates of mortality among adult ECMO patients.[12-14] In a series of 87 adult patients, Matteen et al.[4] found a stroke rate of 8%, an ICH rate of 10%, and a seizure rate of 0%. Overall, 50% of patients in their series suffered neurologic complications defined as stroke, ICH, seizure, encephalopathy, brain death, or coma. Similar to the present study, Matteen et al.[4] found that increasing age was associated with higher rates of death and neurologic morbidity. In a series of 607 adult patients, Lan et al.[10] found that ischemic and hemorrhagic stroke affected 7% of the patients and was associated with significantly higher odds of death. In a meta-analysis of 1,866 adult patients with cardiogenic shock, Cheng et al.[15] found that stroke occurred in approximately 6% of patients, which is a similar rate to rate of approximately 5% reported herein.

The neurologic outcomes of pediatric patients receiving ECMO have been studied previously,[16] and several risk factors for central nervous system complications have been identified, including the use of vasopressor/inotropic medications, infection, serum bicarbonate, pulmonary failure, acidosis, elevated creatinine, and myocardial stunning.[17] In a retrospective review of approximately 5,000 pediatric patients (aged 1 month to 18 years) from the ELSO database receiving ECMO, Cengiz et al.[17] found that approximately 13% of patients developed acute severe central nervous system complications, with the rate of neurologic complications and mortality increasing with age. Other studies from the ELSO registry have found rates of ischemic stroke of 7.4% and 4% in neonates and children, respectively, and ICH rates of 7% and 6%. Clinical seizures were reported in 9.4% of neonates and 5.9% of children.[18] Similar rates of neurologic complications are reported herein; however, neonates had significantly lower rates of neurologic complications than other pediatric patients in the present study.

Limitations

This study was subject to certain limitations. First, it was not possible to distinguish between patients receiving venoarterial and venovenous ECMO. It is possible that complication rates differ according to the type of ECMO received by patients. However, many studies comparing venoarterial to venovenous ECMO have found no difference in complication rates.[19-21] Second, it was also not possible to determine whether the duration of ECMO support was associated with neurologic complications, since this information was not available in the NIS database. Neurologic complications were instead identified using discharge data in the form of ICD-9 codes; therefore, the data are potentially subject to coding errors. Third, long-term outcomes among patients included in this database could not be studied, and it was not possible to determine whether any particular neurologic complication seen in this study resulted from the original insult that triggered the use of ECMO or if it was a complication of the ECMO procedure itself. Whether ECMO is a risk factor for neurologic complications per se, or if patients with these specific neurologic conditions are just more likely to require ECMO has yet to be ascertained. Fourth, it is possible that many of these patients were not examined with neuroimaging; thus, the incidence of stroke or ICH could be underestimated. One neuroimaging and neuropathologic study of 74 children receiving ECMO found that more than 20% of patients had ischemic infarctions,[22] and another study using T2-weighted MRI among ECMO patients found that nearly all imaging patients had microhemorrhages on MRI.[11] Finally, no adjustment for multiple comparisons was made in the present analyses, and so it is possible that some of the findings were due to chance. For example, multivariate analysis of mortality predictors revealed that stroke and seizure patients had lower odds of death than those who did not suffer these complications; this is almost certainly a chance finding.

The utilization of ECMO is increasing exponentially in the United States, especially among adult patients. Neurologic complications such as ICH, acute ischemic stroke, and seizures affect approximately 11% of patients. ICH is an independent predictor of mortality, while stroke is associated with a higher rate of discharge to a long-term facility. Given the increasing utilization of ECMO and the high costs and poor outcomes associated with neurologic complications, more research is needed to determine the best way to prevent neurologic complications in this patient population.

Supplementary Materials

The online-only Data Supplement is available with this article at http://dx.doi.org/10.3988/jcn.2015.11.4.383.

Conflicts of Interest

The authors have no financial conflicts of interest.

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