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Early Carotid Endarterectomy After Acute Stroke Yields Excellent Outcomes: An Analysis of The Procedure-Targeted ACS-NSQIP

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Abstract

OBJECTIVES: Recurrent ischemic events have been associated with delayed carotid endarterectomy (CEA) for patients who present with acute strokes. As such earlier intervention has been advocated in order to preserve cerebral function and expedient rehabilitation. We sought to determine the differences in 30-day postoperative major adverse clinical events (MACEs) for patients who undergo early (< 7 days) and delayed (>7 days) CEA following acute stroke

METHODS: Our sample consisted of patients captured in the CEA-targeted ACS NSQIP dataset between 2011 and 2015. The primary outcome was 30-day postoperative MACEs (death, stroke or myocardial infarction (MI)). Differences in postoperative MACEs were determined between early and delayed CEA treatment. In addition, multivariable analyses were done to determine the association between various patient factors and postoperative complications after CEA for patients who presented with acute strokes.

RESULTS: A total of 3427 patients were identified who underwent CEA for acute stroke in the CEA-targeted files between 2011 and 2015. Overall, perioperative rates of 30-day death, stroke or MI were 1.30% (n=43), 2.74% (n=94) and 0.96% (n=33) respectively. There were no differences in 30-day postoperative death, stroke or MI for early or delayed CEA after acute strokes. On multivariable analysis, independent predictors for postoperative MACEs in acute stroke patients were age ≥ 80 [OR 2.41; 95% CI [1.15-5.06], preoperative beta blocker use [OR 2.11; 95% CI (1.13-3.93)] and operative time > 150 minutes [OR 2.39; 95% CI (0.82-4.98)].

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CONCLUSIONS: There are no differences in postoperative 30-day death, stroke or MI in early and delayed CEA following an acute stroke. These results substantiate the recommendation for early (< 7 days) CEA after acute strokes.

INTRODUCTION

Carotid endarterectomy (CEA) is a well-established treatment for subsequent ischemic stroke reduction among patients with symptomatic extra-cranial carotid artery disease [1, 2]. While current guidelines denote the association between the severity of stenosis and the risk reduction after CEA among symptomatic patients with carotid disease and that early CEA is recommended among patients with transient ischemic attacks (TIA), what remains controversial is the timing of CEA after an acute cerebral infarction. In addition, there is a dearth of information on potential prognostic factors associated with CEA outcomes using non-administrative databases. Most of the risk factor analyses include data from clinical trials or administrative databases that are known to have validity issues [3]. Using data outside of clinical trials or non-administrative databases may prove informative and add more to the knowledge accrued for CEA outcomes [4].

Original reports indicated the increased risk of intracerebral hemorrhage and mortality after early intervention.^{5,6} It had been traditional dogma that CEA be deferred for 4 to 6 weeks after the index presentation of symptomatic carotid artery disease in order to mitigate this risk of intracerebral hemorrhagic conversion and mortality [5, 6]. However, contemporary data has demonstrated that this approach increases the risk to the patient of a subsequent cerebral infarction and/or carotid occlusion [7].

Using the nationally validated risk-adjusted American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) procedure-targeted dataset, we sought to (1) determine the predictors of 30-day postoperative major adverse clinical events (MACEs) for patients who presented with acute stroke in a large cohort and (2) identify the clinical consequence of early (< 7 days) and delayed (>7 days) among patients with acute neurologic symptoms and extra-cranial carotid stenosis.

METHODS

The CEA-targeted ACS NSQIP dataset from 2011 to 2015 was used for this study. The patients included in this study had acute ischemic strokes, were admitted and subsequently underwent CEA during the same admission. The Northwestern University Institutional Review Board office approved the use of de-identified data for this study and required no informed consent.

The primary outcome of the study was 30-day postoperative major adverse clinical events (MACEs). MACE was defined as death, stroke or myocardial infarction (MI). Per the participant use data file user guide provided by NSQIP, stroke was defined as development of “an embolic, thrombotic or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) that persists for 24 or more hours.” Myocardial infarction was defined as an acute

MI occurring intraoperatively or within 30 days with typical documented electrocardiogram changes for MI or by physician diagnosis [8].

Potential predictors for MACEs in our analysis included history of a bleeding disorder. NSQIP defines a bleeding disorder as an “active condition that places the patient at risk for excessive bleeding (e.g. vitamin K deficiency, hemophilia, thrombocytopenia, chronic anticoagulation therapy (other than NSAIDs) that has not been discontinued prior to surgery” [8]. Other predictors examined were gender, race, age, smoking status, diabetes, American Society of Anesthesiologists (ASA) class, chronic obstructive pulmonary disorder (COPD), anatomic location of stenosis (ipsilateral or contralateral), hypertension, preoperative beta blocker use, preoperative aspirin use and preoperative statin use. In NSQIP, Hispanic is considered an ethnicity and not race. Procedural factors available in NSQIP such as operative time and type of anesthesia used were also included in the model.

As a secondary analysis, overall 30-day incidence of MACEs between patients treated within 7 days (early CEA) and those treated after 7 days (delayed CEA) was determined using chi-square tests for patients who presented with acute stroke. We note that there is no clear consensus on what ‘early’ or ‘delayed’ CEA is and as such the use of these terms was to dichotomize the patients into two groups for analysis. The association between 30-day postoperative MACEs and various predictors as outlined in the foregoing paragraphs, was modeled using multivariable logistic regression. These potential confounders of postoperative MACEs after CEA for patients who present with acute strokes to be included in the model were chosen *a priori*. Using the standard, death/stroke endpoint, instead of MACEs, we sought to determine if the results of the two models would differ qualitatively. Statistical significance was set at p values less than 0.05. Odd ratios as well as 95% confidence intervals are also reported. Stata 13 (StataCorp LP, College Station, TX) was used for all analyses.

RESULTS

Demographics

The 2011 to 2015 CEA-targeted ACS NSQIP Participant Use Data Files contained 3427 patients that underwent CEA for carotid artery stenosis after an acute presentation of stroke. A majority of the patients were male (p=0.36), less than 70 years of age (p=0.52), white (p=0.75, had ASA class of 0 to 3 (p=0.39), had ipsilateral carotid stenosis of 80%-100% (p=0.12) and contralateral carotid stenosis of less than 80% (p=0.30) [Table 1].

30-day outcomes

In terms of outcomes, there were no statistically significant differences in terms of the frequency of MACEs for early CEA or delayed CEA for patients who presented with acute stroke. [Table 2]. In the 3427 patients studied, perioperative rates of death, stroke or MI were 1.30% (n=43), 2.74% (n=94) and 0.96 (n=33) respectively. The peri-operative rate of death, stroke or MI for intervention for early CEA and delayed CEA were as follows: [(1.17% vs 2.78%; p= 0.06), (2.65% vs 2.78%; p=0.92) and (0.99% vs 0.56%; p=0.57) respectively].

Multivariable analysis—Multivariable analysis showing the association between patient-level factors and 30-day MACEs is shown in Table 3. For patients who presented with symptoms of stroke at the index hospitalization, age ≥ 80 was significantly associated with increased odds of postoperative MACE (OR 2.41, p=0.02). Additionally, other race (Asian Native, Pacific Islander, American Indian) (OR 2.34, p=0.02), preoperative beta-blocker use (OR 2.11, p=0.02) and operative time over 150 minutes (OR 2.39, p=0.04) were also associated with increased odds of postoperative MACE for patients who initially presented with an acute stroke.

The logistic regression model for the standard 30-day death/stroke did not produce results qualitatively different from the MACE model and is included in supplemental materials (Appendix 1)

DISCUSSION

In this study of cumulative multicenter CEA, our analysis shows that for patients that present with symptomatic extra-cranial carotid artery disease, there is no difference in death, stroke and myocardial infarction between patients who were operated on within 7 days or 7 days after their neurologic event.

Currently, it is generally accepted that CEA should be performed within 14 days particularly among patients who are neurologically stable [1, 9, 10]. A recent meta-analysis has shown that the pooled risk of stroke is 3.2% if the procedure is performed within 7 days and 3.4% if performed within 15 days [11]. Another recent multi-center, retrospective analysis of vascular registry data has shown that CEAs performed within 2-5 days after neurological symptoms have similar complication outcomes compared to those performed after 6 days [12]. Most of the studies guiding the recommendation of performing CEA within two weeks are from clinical trials or use generic claims-based data sources. To further increase our knowledge on the best practices for symptomatic carotid artery disease treatment, the use of data from a “real-world” setting is needed.

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) procedure-targeted dataset allows for the examination of specific procedures such as CEA in a real-world setting. The risk-adjusted surgical outcome measures provided in the dataset allows for performance improvement to decrease surgical morbidity and mortality. The CEA-targeted dataset captures patient demographic variables, in addition to specific variables of CEA interest such as laterality of carotid artery stenosis. The variables found in these datasets are abstracted by surgical clinical reviewers and collected preoperatively and up to 30 days postoperatively [13].

Based on results of randomized clinical trials, professional society guidelines and/or consensus statements, the anticipated risk of post-CEA death or stroke among symptomatic patients undergoing CEA is less than 6%, which supports the findings of our study [14]. A recent analysis of early CEA in a prospectively maintained vascular registry showed that the rate of postoperative MI was 1.9% and 2.1% for CEA performed within 2 to 5 days and 6 days after admission respectively [12]. In this same study, the rate of stroke for CEA

performed within 2 to 5 days and 6 days was 4% and 2.1% respectively while the rate of postoperative death was 1.9% and 1.1% respectively. These results are consistent with the findings of our study and reinforces the recommendation of early CEA following an acute stroke after proper risk stratification. While our results show that delayed CEA does not necessarily affect postoperative outcomes, early CEA could potentially lead to cost savings and avoidance of unintended post-operative, iatrogenic complications.

The risk of immediate and recurrent strokes due to delayed CEA has been well-established. Pooled studies from the North American and European CEA trials have shown that CEA performed within 2 weeks of the cerebral ischemic event leads to a decreased incidence of stroke [15]. In fact, operating within 2 weeks of the index event may be considered a benchmark for secondary stroke prevention [16]. However, the actual interval within the two-week time frame that is considered safe for CEA is up for debate. For example, the United Kingdom and other European CEA guidelines recommend carotid endarterectomy within 48 hours [17, 18, 19, 20]. Although there are concerns for hemorrhagic conversion of the acute cerebral infarct, instability of the carotid artery plaque in the acute phase of stroke and increased susceptibility of the ischemic penumbra to further ischemia, these concerns have not been well-validated [21]. Hemorrhagic conversion of a cerebral infarct after carotid endarterectomy is a rare event that has been attributed to cerebral hyperperfusion syndrome usually after repair of a severely stenotic carotid artery [22, 23, 24, 25]. Intensive care monitoring and management of blood pressure have led to a decrease in these events [26]. Furthermore, advances in magnetic resonance imaging technology has led to increased sensitivity in detection of cerebral microhemorrhages which may preclude early CEA. Diffusion-weighted imaging, the most sensitive MRI sequence, aids in the early detection of cerebral ischemic changes in acute stroke patients and may guide the timing of surgery [27]. Certainly, the advantages of early CEA include reduction of a subsequent ischemic event and/or carotid occlusion. Additionally, it would also facilitate a more expedient recovery and rehabilitation from the initial event.

There remains controversy on whether octogenarians (patients with age 80) represent a high-risk group for CEA. Many of the large carotid trials placed the upper limit of age at 80 as an inclusion criterion [27, 28, 29, 30]. Previous studies have shown that periprocedural complications are increased in octogenarians who undergo CEA [31]. In contrast, Reichmann et al have shown through a systematic review that 30-day MACEs after CEA in octogenarians in recent large, randomized trials is consistent with complication rates seen in younger patients thus suggesting that CEA should be offered to octogenarians if clinically indicated [32]. Meanwhile, the results of our study show that there is an association between being an octogenarian and 30-day postoperative MACEs. It is possible that most of the patients included in the NSQIP dataset had their beta blocker stopped in the 48-hour perioperative period, which is known to be associated with increased cardiac events [33]. Taken together, our results suggest that special attention needs to be paid to this age group with consideration of other well-known risk factors during preoperative workup.

A recent study showed that longer duration of carotid endarterectomy can may lead to increased mortality [34]. The duration of a CEA is a complex interplay between patient-level and/or surgeon-level factors. One could argue that vascular surgery patients, in general, have

advanced atherosclerosis, requiring meticulous dissection, adequate exposure and identification of anatomical landmarks which may necessitate longer operative times. Conversely, an argument could be made for that shorter operative times are mostly due to experience of the operating surgeon and thus, better outcomes. While the reason for increased postoperative MACEs remains to be fully determined, the increased risk of MACEs may be due to the overall reduced physiological reserve of acute stroke patients and may not necessarily be due to the length of the operation.

The impact of race and/or ethnicity on poor postoperative outcomes after CEA has been described though the results are conflicting. Previous studies have shown that there is an association between Black patients and poor post-CEA outcomes [35, 36]. A population-based study of Medicare patients in New York undergoing CEA has also shown that when compared to White patients, Black and Hispanic patients have increased 30-day stroke and death outcomes [37]. However, other studies have shown no differences between Black and White patients when confounders such patient or procedure-related characteristics are accounted for. Our study shows that other racial groups (Asian Native, Pacific Islander or American Indian) had increased odds of postoperative 30-day MACEs compared to White patients. Whether these race-based disparities are due to disproportionate selection into hospitals with low-volume surgeons or due to increased cerebrovascular burden in these patients warrants further investigation [35, 36].

This study has a few limitations that need to be acknowledged. First, the ACS NSQIP participant data use file does not have hospital or surgeon identifiers precluding clustering of cases. Because we are unable to account for the non-independence of patients within hospitals (and higher levels of clustering), it is possible that our standard errors may be underestimated, reported confidence intervals may be narrower than they otherwise would be, and statistical significance may be overstated. That said, the covariate of interest, 30-day MACEs which includes an aggregate death, stroke or MI, is measured at the individual level, not at the aggregate hospital or surgeon level. Thus, unless there is marked sorting of patients across hospitals or surgeons based on death, MI and stroke (and we do not expect there to be such sorting), we cautiously suggest that the qualitative conclusions of our logistic regression modeling may not change even if we were able to account for the hierarchical nature of the data in our model. Second, the outcomes and risk factors of our study may not be generalizable to non-NSQIP hospitals. Lastly, it is impossible to determine the reasoning behind the timing of surgery. A surgeon could have myriad of reasons for performing the CEA at a particular time point. For example, some variables not accounted for may impact the timing of CEA including the need for cardiac stratification or lack of available hospital personnel to help perform the procedure at a particular time.

CONCLUSIONS

In this study of outcomes and risk factors after CEA using a prospectively maintained risk-adjusted procedure-specific data source, there is no difference in 30-day death, stroke, or myocardial infarction between patients who received CEA within 7 days and those who received CEA after 7 days following an acute neurologic event. Our study substantiates the

recommendation of early CEA following acute strokes with important consideration given to risk stratification in octogenarians.

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Appendix 1.: Association between Patient/Procedural Factors and 30-day postoperative Death/Stroke after Carotid Endarterectomy

	Stroke OR [95% CI]	p Value
Gender		
Female	REF	
Male	0.65 [0.36-1.17]	0.15
Age		
<70	REF	
70-79	1.08 [0.53-2.23]	0.83
80	2.30 [1.04-5.09]	0.04
Race		
White	REF	
Black	2.08 [0.75-5.71]	0.16
Other	2.11 [0.97-4.59]	0.06
ASA class		
0-3	REF	
4-5	0.59 [0.29-1.19]	0.14
Ipsilateral Stenosis		
<80%	REF	
80%-100%	1.29 [0.68-2.48]	0.44
Contralateral Stenosis		
<80%	REF	
80%-100%	1.22 [0.66-2.26]	0.52
Smoker		
No	REF	
Yes	1.71 [0.66-2.26]	0.12
Diabetes		
No	REF	
Yes	0.90 [0.47-1.73]	0.76
COPD		
No	REF	
Yes	1.49 [0.59-3.76]	0.40
Bleeding Disorder		
No	REF	
Yes	0.90 [0.46-1.74]	0.75
Hypertension		
No	REF	

	Stroke OR [95% CI]	p Value
Yes	1.02 [0.42-2.48]	0.05
Preoperative Beta Blocker		
No	REF	
Yes	2.00 [1.04-3.86]	0.04
Preoperative Aspirin		
No	REF	
Yes	0.66 [0.28-1.57]	0.35
Preoperative Statin		
No	REF	
Yes	1.21 [0.53-2.76]	0.66
General Anesthesia		
No	REF	
Yes	3.37 [0.80-14.27]	0.10
Operative Time, minutes		
<90	REF	
90-150	1.36 [0.59-3.15]	0.47
>150	2.02 [0.82-4.98]	0.13

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; Other Race, Asian Native, Pacific Islander or American Indian

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Table 1.

Characteristics of 3427 Patients Undergoing Carotid Endarterectomy after presentation with Acute Stroke

	Stroke N	No (%) with major adverse event	P Value
Gender			
Male	2181	71 (3.3)	0.36
Female	1246	48 (3.9)	
Age			
<70	1719	60 (3.5)	0.52
70-79	992	30 (3.0)	
80	716	29 (4.1)	
Race			
White	2755	94 (3.4)	0.75
Black	204	9 (4.4)	
Other	468	16 (3.4)	
ASA class			
0-3	2592	87 (3.4)	0.39
4-5	826	31 (3.8)	
Missing	9	1 (11.1)	
Ipsilateral Stenosis			
<80%	1310	81 (3.9)	0.12
80%-100%	2068	38 (2.9)	
Contralateral Stenosis			
<80%	374	19 (5.1)	0.30
80%-100%	871	33 (3.8)	
Smoker			
No	2352	82 (3.5)	0.95
Yes	1075	37 (3.4)	
Diabetes			
No	2378	79 (3.3)	0.07
Yes	1049	40 (3.8)	
COPD			
No	3126	103 (3.3)	
Yes	301	16 (5.3)	
Bleeding Disorder			
No	2502	79 (3.2)	0.10

	Stroke N	No (%) with major adverse event	P Value
Yes	925	40 (4.3)	
Hypertension			
No	732	17 (2.3)	0.06
Yes	2695	102 (3.8)	
Preoperative Beta Blocker			
No	1726	49 (2.8)	0.07
Yes	1677	68 (4.1)	
Preoperative Aspirin			
No	427	16 (3.8)	0.01
Yes	2981	100 (3.4)	
Preoperative Statin			
No	634	26 (4.1)	<0.01
Yes	2779	90 (3.2)	
General Anesthesia			
No	447	10 (2.2)	0.13
Yes	2980	109 (3.7)	
Operative Time, minutes			
<90	770	21 (2.7)	0.41
90-150	1736	59 (3.4)	
>150	897	38 (4.2)	
Missing	24	1 (4.2)	

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; Other Race, Asian Native, Pacific Islander or American Indian

Table 2.

Thirty-Day Outcomes by Timing of Carotid Endarterectomy after Index Hospital Presentation for Acute Stroke

	Stroke (N=3427)		
	7days N (%)	>7 days N (%)	p Value
Mortality	38/3247(1.17)	5/180 (2.78)	0.06
Stroke	86/3247(2.65)	5/180 (2.78)	0.92
MI	32/3247(0.99)	1/180 (0.56)	0.57

Table 3.

Association between Patient/Procedural Factors and 30-day postoperative major adverse clinical events (MACE) after Carotid Endarterectomy for Stroke

	Stroke OR [95% CI]	p Value
Gender		
Female	REF	
Male	0.66 [0.38-1.16]	0.15
Age		
<70	REF	
70-79	1.10 [0.51-2.02]	0.98
80	2.41 [1.15-5.06]	0.02
Race		
White	REF	
Black	1.88 [0.69-5.13]	0.22
Other	2.34 [1.14-4.82]	0.02
ASA class		
0-3	REF	
4-5	0.68 [0.36-1.28]	0.23
Ipsilateral Stenosis		
<80%	REF	
80%-100%	1.49 [0.80-2.781]	0.21
Contralateral Stenosis		
<80%	REF	
80%-100%	1.06 [0.59-1.911]	0.85
Smoker		
No	REF	
Yes	1.62 [0.85-3.071]	0.14
Diabetes		
No	REF	
Yes	0.99 [0.54-1.81]	0.97
COPD		
No	REF	
Yes	1.83 [0.80-4.20]	0.15

	Stroke OR [95% CI]	p Value
Bleeding Disorder		
No	REF	
Yes	0.88 [0.47-1.64]	0.68
Hypertension		
No	REF	
Yes	0.94 [0.41-2.17]	0.89
Preoperative Beta Blocker		
No	REF	
Yes	2.11 [1.13-3.93]	0.02
Preoperative Aspirin		
No	REF	
Yes	0.80 [0.34-1.90]	0.62
Preoperative Statin		
No	REF	
Yes	0.87 [0.42-1.81]	0.72
General Anesthesia		
No	REF	
Yes	3.90 [0.93-16.46]	0.06
Operative Time, minutes		
<90	REF	
90-150	1.27 [0.57-2.82]	0.56
>150	2.39 [1.03-5.53]	0.04

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