ORIGINAL RESEARCH

Referral facility CT perfusion prior to inter-facility transfer in patients undergoing mechanical thrombectomy

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ABSTRACT

Background and purpose The use of CT perfusion (CTP) imaging at a referring hospital is feasible and may shorten the door to puncture time for patients with acute ischemic stroke.

Methods We conducted a single center retrospective review of a prospectively maintained database of consecutive ischemic stroke patients transferred to our center for consideration of endovascular therapy. Patients were divided into two groups. Group 1 consisted of patients transferred from facilities where CTP (using automated RAPID software) was routinely performed and group 2 consisted of patients transferred from facilities that did not perform perfusion imaging.

Results We identified a total of 132 patients, all of whom were transferred to our center, from April 2014 to April 2017. There were no differences in baseline characteristics between the two groups. A total of 34 patients were transferred from a facility after CTP (group 1) and 98 were transferred from a facility with no CTP (group 2). Door to puncture time was significantly shorter for patients in group 1 compared with those in group 2 (median 12 (IQR 8–16) min and 48.5 (32.8–71.8) min, respectively; P<0.001). Despite obtaining additional pre-transfer imaging in group 1, there was no difference in door in and door out times at the referring facilities compared with group 2.

Conclusions We found that triaging from a primary stroke center after CTP RAPID was feasible and significantly reduced the door to puncture time without any significant delay in the transfer process.

INTRODUCTION

A critical aspect of acute ischemic stroke therapy is optimization of workflow and reduction of times to treatment. Both intravenous tissue plasminogen activator (IV tPA) and intra-arterial therapy are now the gold standard management for select patients. Both of these treatments, however, are most effective if they are delivered rapidly.[1 2] Despite five randomized clinical trials (MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, and REVASCAT) showing the benefit of endovascular therapy in selected patients, the role of advanced imaging to select patients remains uncertain.[1 3–6] CT perfusion (CTP) is an option to estimate the core and penumbra, and to select patients for endovascular therapy.[7] However, the challenge is to obtain an accurate interpretation, as results are not typically quantitative, and to factor in the additional time it takes to acquire CTP. The RAPID software (iSchemaView, Menlo Park, California, USA) allows for faster interpretation of CTP results and also provides quantitative information. RAPID has been demonstrated to provide accurate software to determine the core and penumbra.[8]

One other challenge of acute stroke therapy is inter-facility transfer, which may add significant delay to treatment. Identifying who would benefit from being transferred to a comprehensive stroke center can also be difficult. When patients are selected based solely on non-contrast CT (NCCT) and the National Institutes of Health Stroke Scale (NIHSS) score, the levels of diagnostic error for large vessel occlusion (LVO) increase.[9]

The combination of CTP RAPID, NCCT, and CT angiography (CTA) could assist in the selection of the appropriate patient for transfer and could reduce the door to puncture time when done at the referral facility. To test this hypothesis, we installed CTP with RAPID software ability in addition to NCCT and CTA at five of our referral facilities. Here we describe our workflow process in addition to comparing the difference in time to treatment between acute ischemic stroke patients transferred to the Baptist Medical Center (BMC, hub hospital) for possible endovascular therapy using CTP and those transferred without CTP at the spoke hospitals.

MATERIALS AND METHODS

We conducted a retrospective review of a prospectively maintained database to identify ischemic stroke patients transferred from primary centers to BMC for consideration of endovascular therapy from April 2014 to April 2017. The study was approved by the BMC institutional review board. Consent was waived because this was a retrospective medical record review and no additional intervention was performed. Demographics and baseline characteristics, as well as CTP imaging and procedural data, were collected.

Workflow process

In our system, we have a spoke to hub model composed by 11 referral facilities. Patients are transferred to the hub, a comprehensive stroke center, for the possibility of endovascular therapy. Of these 11 spoke hospitals, five have CTP ability in

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addition to NCCT and CTA since 2015, which has been used to triage patients. The remaining six facilities rely mostly on NCCT and clinical examination and, on rare occasions, CTA for triage.

Our transfer patients were divided into two groups: group 1 consisted of patients triaged using CTP at a spoke hospital using RAPID software, and group 2 consisted of transfer patients who did not undergo CTP imaging at the spoke hospital prior to transfer.

Group 1. We have protocolized a stroke code process where, on arrival of any suspected stroke patient, a code stroke is called to the telemedicine physician who is a vascular trained neurologist. We have also added a pre-notification process to alert the emergency department and the telemedicine neurologist prior to the patient's arrival when possible. The stroke patient undergoes NCCT on arrival and receives IV tPA if eligible. Based on our protocol, if a patient has a NIHSS score ≥6 and no hemorrhage on NCCT, CTA/CTP is obtained. However, it is the telemedicine neurologist who ultimately decides on obtaining CTA/CTP, and every effort is made so that there is no delay in IV tPA administration. The result of CTP RAPID is sent automatically to the stroke team, including the endovascular physician, telemedicine physicians, and neuro ICU team via email. NCCT and CTA are available to all of the team members mentioned above through a joint server. The decision to transfer is then made by both the endovascular physician on call and the telemedicine physician. If there is a high suspicion of an LVO based on NIHSS and favorable NCCT (NIHSS ≥6 and Alberta Stroke Program Early CT Score (ASPECT) ≥6), the treating physician will alert the endovascular team prior to having the CTA/CTP results. The transfer process is canceled if CTA/CTP fails to show the patient as an appropriate transfer candidate. If the patient arrives to the hub without a prolonged delay and has a favorable profile, the patient will be taken directly to the angiosuite for thrombectomy. Some images may be repeated in the event of a prolonged delay.

Group 2. The stroke patient is evaluated by a local neurologist and undergoes NCCT and, in some cases, CTA. The patient receives IV tPA if eligible. The patient is transferred based on the clinical presentation and the result of NCCT, including CTA when available. CTA and CTP are done to determine if the patient is a candidate for thrombectomy if the patient arrives at the hub and no CTA was performed. CTA imaging is not typically repeated if it was done at the referring facility. Once the imaging is completed, the decision is made to proceed with thrombectomy if the patient is deemed a candidate.

All CTP imaging data in group 1 were postprocessed in real time using the fully automated RAPID software. Ischemic core was identified by the RAPID software as tissue with >70% reduction in cerebral blood flow compared with the corresponding normally perfused tissue. The hypoperfused volume was defined as tissue with a Tmax >6 s. An example of RAPID outputs is shown in figure 1.

General indications for endovascular therapy in our center were as follows: acute stroke with disabling neurological deficits, occlusion of a targeted large vessel, absence of significant early ischemic infarct (ASPECT score ≥6), and perfusion imaging indicating a target mismatch either with or without intravenous thrombolysis. Target mismatch was derived from DEFUSE 2 and defined as core ischemic volume <70 mL, mismatch volume ≥15 mL, and mismatch ratio ≥1.80.[10] The time window is no longer an absolute contraindication for endovascular therapy at our institution. If CTP cannot be obtained, endovascular therapy may also be offered due to a high NIHSS score and a favorable ASPECT score without advanced imaging at the discretion of the treating physician. Successful endovascular recanalization was defined as achieving a modified Thrombolysis in Cerebral Infarction (TICI) reperfusion score of 2b or 3. NIHSS score and the modified Rankin Scale (mRS) score were assessed at patient admission and discharge by a vascular neurologist. Symptomatic hemorrhagic transformation was classified based on the European Cooperative Acute Stroke Study (ECASS) as parenchymal hematoma type 2.[11 12]

The primary endpoint was to evaluate the feasibility of having CTP at a referral facility and to compare the workflow process of the door (hub arrival time) to puncture time between groups. Secondary endpoints were door in and door out (DIDO) times at the spoke hospital and rates of good clinical outcome, as defined by an mRS score of 0–2 at discharge.

Statistical analysis

Descriptive data are presented as mean (SD) or median (IQR) for continuous variables, as appropriate, and absolute values and percentages for categorical variables. The data distribution was analyzed using histograms, boxplots, and the Shapiro–Wilk

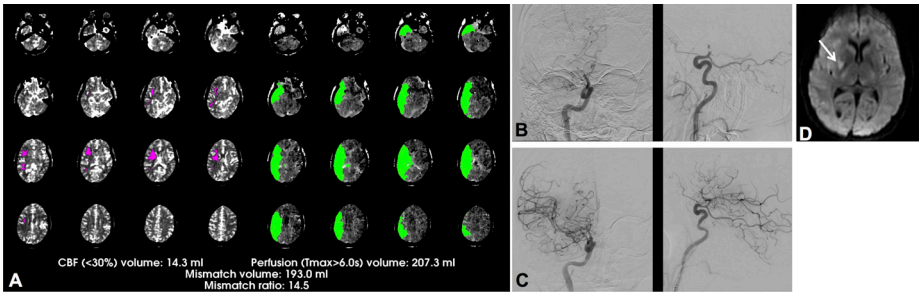

Figure 1 Illustrative case. A patient in the fifth decade of life presented to a spoke hospital with left sided weakness and an initial National Institutes of Health Stroke Scale (NIHSS) score of 20. The patient's last known well was at 9:15 am. Initial non-contrast head CT was negative for hemorrhage. CT angiography demonstrated occlusion at the terminus of the right internal carotid artery (ICA). (A) RAPID CT perfusion at the spoke hospital demonstrated an ischemic core volume of 14.4 mL and hypoperfused tissue (Tmax >6 s) of 207.3 mL, compatible with a target mismatch profile. Intravenous tissue plasminogen activator was administered at 10:14 am. The patient was transferred by helicopter directly to the angiosuite of the hub hospital. Hub arrival time was at 11:03 am. The time of groin puncture was 11:17 am. (B) Initial catheter based angiography demonstrated a right ICA terminus occlusion. (C) After mechanical thrombectomy (one pass), the ICA terminus and middle cerebaral artery branches filled without any filling defect, indicating complete revascularization (Thrombolysis in Cerebral Infarction 3). (D) MRI on day 2 showed a small infarct volume (white arrow) comparable with the core infarct on the initial RAPID CT perfusion. The patient was discharged 72 hours after the intervention and improved to an NIHSS score of 0. At the 90 day clinical follow-up, the patient had no neurological deficits. CBF, cerebral blood flow.

test. Continuous variables were analyzed using the independent samples t test or the Mann–Whitney U test, based on data distribution. The χ^2 or Fisher's exact tests were used for comparisons between categorical variables, as appropriate. Statistical significance was set at $P<0.05$, and all p values were reported as two sided. Statistical analysis was performed using Stata software, V.14 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 132 were included in the analysis, of whom 34 patients (26%) were transferred to BMC for endovascular therapy using CTP and 98 patients (74%) were transferred without CTP imaging. Fifty-seven (58.2%) of 98 patients that were transferred from hospitals with no perfusion imaging underwent CTP at the hub hospital. The demographic and clinical characteristics of the two groups at baseline are summarized in table 1. Sixty patients (45.5%) received IV tPA (all of them at the spoke hospitals), 10 patients (7.6%) with unknown time of symptom onset were transferred, and 35.2% (43/122) underwent cerebral angiogram after 6 hours of symptom onset. Of the 132 patients, 15 patients (11.4%) presented as acute stroke and underwent cerebral angiogram but no thrombectomy was performed as no proximal intracranial occlusion was found either due to spontaneous recanalization after non-invasive imaging or clinical improvement. From these 15 patients, 3 had no LVO and belonged to group 2. Among the 117 patients who underwent endovascular

Table 1 Demographics and baseline characteristics

	All cases (n=132)	CTP at spoke hospital (n=34)	No CTP at spoke hospital (n=98)	P value
Age (years) (mean (SD))	68.2 (15.4)	70.5 (15.9)	67.4 (15.3)	0.31
Men (n/N (%))	61/132 (46.2)	15/34 (44.1)	46/98 (46.9)	0.78
Baseline NIHSS (median (IQR))	15 (10–19)	13.4 (8.5–18)	15 (11–19)	0.3
IV tPA (n/N (%))	60/132 (45.5)	22/34 (64.7)	38/98 (38.8)	0.009
Pre-stroke mRS (n/N (%))				
0–2	103/109 (94.5)	28/30 (93.3)	75/79 (94.9)	0.67
Comorbidity (n/N (%))				
Hypertension	92/132 (69.7)	22/34 (64.7)	70/98 (71.4)	0.46
Dyslipidemia	70/132 (53)	19/34 (55.9)	51/98 (52)	0.7
Diabetes	24/132 (18.2)	5/34 (14.7)	19/98 (19.4)	0.54
Afib	37/132 (28)	10/34 (29.4)	27/98 (27.6)	0.84
TIA/stroke	27/132 (20.6)	7/34 (20.6)	20/98 (20.4)	0.98
Myocardial Infarction	8/132 (6.1)	3/34 (8.8)	5/98 (5.1)	0.42
Current or past tobacco use	49/130 (37.7)	10/33 (30.3)	39/97 (40.2)	0.311
Site of occlusion (n/N (%))				
No LVO	3/132 (2.3)	0	3/98 (3.1)	0.56
Tandem	9/132 (6.8)	2/34 (5.9)	7/98 (7.1)	1
ICA terminus	21/132 (15.9)	4/34 (11.8)	17/98 (17.3)	0.44
MCA-M1	63/132 (47.7)	13/34 (38.2)	50/98 (51)	0.2
MCA-M2	16/132 (12.1)	7/34 (20.6)	9/98 (9.2)	0.12
Vertebral/basilar	15/132 (11.4)	6/34 (17.6)	9/98 (9.2)	0.21
Other*	5/132 (3.8)	2/34 (5.9)	3/98 (3.1)	0.6
Imaging characteristics				
NCT performed at spoke (n/N (%))	131/131 (100)	34/34 (100)	97/97 (100)	–
CTA performed at spoke (n/N (%))	75/129 (58.1)	33/34 (97.1)	42/95 (44.2)	<0.001
CTP/RAPID performed at spoke (n/N (%))	34/132 (25.8)	34/34 (100)	0/98	–
NCT performed at hub (n/N (%))	74/132 (56.1)	4/34 (11.8)	70/98 (71.4)	<0.001
CTA performed at hub (n/N (%))	62/132 (47)	1/34 (2.9)	61/98 (62.2)	<0.001
CTP/RAPID performed at hub (n/N (%))	60/132 (45.5)	3/34 (8.8)	57/98 (58.2)	<0.001

	All cases (n=94)	CTP at spoke hospital (n=34)	CTP at hub hospital (n=60)	P value
Baseline RAPID imaging results				
Core (median (IQR))	2.9 (1–14.7)	1.5 (1–7.32)	4.6 (1–17.9)	0.7
Tmax >6 s (median (IQR))	108.9 (58.9–175.3)	84.8 (41.1–194.4)	112.8 (67.3–172)	0.83
Target mismatch profile (%)	92/94 (97.9)	33 (97.1)	59 (98.3)	1

*Other includes anterior and posterior cerebral arteries.

Afib, atrial fibrillation; CTA, CT angiography; CTP, CT perfusion; ICA, internal carotid artery; IV tPA, intravenous tissue plasminogen activator; LVO, large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin Scale; NCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table 2 Procedure characteristics

	All cases	RAPID at spoke hospital	No RAPID at spoke hospital	P value
Conscious sedation (n/N (%))	112/132 (84.8)	30/34 (88.2)	82/98 (83.7)	0.52
General anesthesia (n/N (%))	20/132 (15.2)	4/34 (11.8)	16/98 (16.3)	0.52
Final TICI 2B/3 (n/N (%))	105/117 (89.7)	25/27 (92.6)	80/90 (88.9)	0.73
LKW to puncture time (min) (median (IQR))	292.5 (203.5–441)	205 (166–304)	322 (236–504.5)	<0.001
Parenchymal hematoma type 2 (ECASS) (n/N (%))	3/132 (2.3)	0	3/98 (3.1)	0.57
Mortality at discharge (n/N (%))	9/132	1/34 (2.9)	8/98 (8.2)	0.45

ECASS, European Cooperative Acute Stroke Study; LKW, last known well; TICI, Thrombolysis in Cerebral Infarction.

therapy, complete reperfusion (TICI 2B or 3) was achieved in 105 (89.7%). Detailed procedure characteristics, including type of anesthesia, device used, number of passes, and final TICI, are presented in table 2.

Primary endpoint

Patients who were transferred to the hub using CTP RAPID at the spoke hospital had significantly faster door to puncture time than patients transferred without CTP at the spoke hospital (median 12 (IQR 8–16) min and 48.5 (32.8–71.8) min, respectively; P<0.001) (table 3).

Secondary endpoints

There was no difference in DIDO time between groups (median 96 (IQR 59.5–133) min and 94 (65.5–164) min, P=0.57). Rate of good clinical outcome (mRS 0–2) at discharge was nominally higher in patients triaged using CTP at the spoke hospital compared with patients without CTP (55.9% and 44.9%, P=0.26) although this was not statistically significant (table 3).

DISCUSSION

Our study demonstrates that inter-facility transfers using CTP with RAPID software is feasible and is associated with significantly reduced door to puncture time. Despite additional time needed for obtaining advance imaging, we did not find any difference in DIDO time at the referring facility. Patients who are triaged based on a favorable RAPID profile at a spoke hospital, on arrival at the hub, are usually taken directly from ambulance or helicopter to the angiosuite without any repeat imaging. In addition, once patients are selected based on CTP results, the endovascular team is already mobilized and ready to receive the patient on arrival. On the other hand, patients who arrive from a facility without advance imaging typically undergo further imaging with CTA/CTP and then are taken to the angiosuite for possible thrombectomy. In addition, due to the uncertainty of the presence of a target mismatch, the endovascular team may not be ready on patient arrival, further delaying the puncture time.

Results from the recent HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials) patient level pooled meta-analysis of five randomized phase III trials, including ESCAPE, SWIFT PRIME, REVASCAT, MR CLEAN, and EXTEND-IA, have demonstrated a strong relationship between inhospital treatment speed and functional independence (mRS 0–2) at 3 months.[2] For every 4 min delay in emergency department arrival to reperfusion time, 1 of every 100 treated patients had a worse disability outcome. In addition, initial randomized controlled trials failed to show the benefit of intra-arterial therapy over medical therapy alone. Newer trials, on the other hand, have shown significant benefit by placing emphasis on better patient selection, better recanalization techniques, and faster treatment times and workflow.[13] Therefore, it is essential to establish a workflow, where eligible patients can be identified quickly and rapid successful thrombectomy can be performed.

Although there is currently not enough evidence to make treatment decisions based on CTP, except for patients outside the 6 hour time window, we have demonstrated that the installation of CTP RAPID at a spoke hospital is feasible and can improve the workflow process. A common criticism against advanced imaging is possible delay to revascularization. For instance, adding CTP to the workflow may add up to 30 min from door to puncture time.[14] However, as shown in this study, the DIDO time in patients who had CTP was not significantly different from patients who did not have CTP at the referring hospital. This perhaps may be due to a more efficient workflow that is in place in CTP capable hospitals. There is typically a delay between transfer decision to the actual transfer time and if an efficient workflow is in place at the spoke hospital, obtaining advance imaging may not significantly affect the DIDO times.

Another advantage of CTP with RAPID software is that there is no need for manual postprocessing, and therefore there is minimal delay in receiving RAPID results which are usually available via email in 3 min from when the time scan is completed. In addition, CTP at the referring facility can also help physicians select patients who would likely benefit from endovascular therapy while avoiding transfer of patients who are unlikely to benefit. This can help prevent overcrowding the hub hospital with unnecessary transfers while at the same time the CTP RAPID email generates a generalized awareness among the physicians about a potential candidate and lessens the likelihood of missing an LVO at a referral facility. It should be noted that we did not have enough information to account for the number of patients who underwent CTP RAPID and were not transferred, and therefore we cannot make any conclusions regarding this. Furthermore, CTP RAPID can select patients with a low NIHSS

Table 3 Primary and secondary endpoints

	CTP at spoke hospital (n=34)	No CTP at spoke hospital (n=98)	P value
Primary endpoint			
Door to puncture time (min) (median (IQR))	12 (8–16.8)	48.5 (32.8–71.8)	<0.001
Secondary endpoint			
Door in and door out time from spoke hospital (min) (median (IQR))	96 (59.5–133)	94 (65.5–164)	0.57
mRS 0–2 at discharge (n/N (%))	19/34 (55.9)	44/98 (44.9)	0.26

CTP, CT perfusion; mRS, modified Rankin Scale.

Table 4 Inter-facility transfer workflow challenges and solutions

Challenge	Action plan
Data collection	One of the important parts of this project was to create a formal process where workflow data were collected and reviewed on a regular basis by a multidisciplinary team, including different ,departments to recognize areas for improvement.
Delays in stroke recognition, neuroimaging, and neurology contact	Emergency department and emergency medical services staff were educated on multiple occasions, and code stroke process was optimized to include a pre-notification to identify patients who have a likelihood of LVO or potential IV tPA candidates, with prompt and direct triage of these patients to CT scanner with simultaneous notification of the neurologist. Emphasis was placed on limiting non-essential interventions, such as ECG, chest x-ray, and additional venous access in favor of rapid neuroimaging. Telemedicine has also greatly contributed to a faster and more efficient way for the neurologist on call to evaluate a code stroke patient when an on site neurologist was not present.
Delay in recognition of a patient with LVO	Installation of RAPID software in referral facility in addition to CTA allowed for easier recognition of a potential patient with LVO with significant penumbra. RAPID results are available via email to all of the team members, further increasing the awareness of potential transfer patients.
Delay in transportation and delay in endovascular team contact	A single telephone number was created to reach the stroke or endovascular team and transfer center. As part of the code stroke protocol, we have started activating the transfer center and alerting the endovascular team earlier, prior to having all of the information available (ie, results of CTP and CTA). The transfer center is canceled if CTA/CTP are unfavorable. We have also emphasized the importance of reviewing CTA as it becomes available and not waiting for the official report to make the transfer decision.
Rapid triage at the hub	We have optimized the hub workflow process to allow for rapid triage and rapid endovascular therapy. We try to avoid repeating any images in patients with proven or a high likelihood of LVO and have the team ready to receive such patients directly to the angiosuite in cases of short inter-facility transfer times.

CTA, CT angiography ; CTP, CT perfusion; IV tPA, intravenous tissue plasminogen activator; LVO, large vessel occlusion.

score who have LVO, perhaps due to good collaterals who may further deteriorate and may benefit from rapid tertiary center transfer where they can undergo endovascular therapy should they have any clinical worsening. Moreover, CTP can also select patients in extended time windows who may benefit from endovascular therapy. It is also important to highlight that we used both CTP and CTA results in our decision making. CTA at a referring facility can be a helpful tool to assess for intracranial LVO, significant extracranial disease and collaterals, as well as to estimate significant infarct progression which is associated with poor collaterals.[15]

Our results showed a trend towards better outcome in discharge mRS in patients who were transferred from a spoke hospital with CTP compared with a spoke hospital with no CTP, although this difference was not statistically significant, most likely due to the small sample size. Discharge mRS may not accurately predict the 90 day mRS but it is most likely correct in 80% of cases.[16] Additionally, it is important to highlight that the purpose of this paper was not to assess clinical outcome, as prior trials have already demonstrated better clinical outcomes with faster door to puncture times.[13]

Many challenges were faced in this study with regard to creating an efficient workflow process for transferring patients in group 1. Table 4 highlights some of these challenges and proposed solutions in reference to our transfer patients from the spoke hospitals.

Our study has several limitations. The design was observational with retrospectively collected data and a small sample size. Additionally, our results reflect a single center experience and may not be generalizable to other facilities. Another limitation is that we did not address infarct growth for the transfer patients after they had CTP. However, considering our clinical outcome, we do not believe infarct growth is significant, most likely because our referring facilities are mostly within an hour from the hub. Repeat imaging may be necessary for referring patients with significant transportation delay. In addition, we did not include all of the patients who were transferred but not taken to the angiosuite for thrombectomy or all of the patients who underwent advance imaging but were not transferred, and therefore further studies are needed to determine if CTP RAPID at the spoke hospitals can improve transfer decision accuracy. Further randomized trials are needed to identify the best imaging modality to select patients for endovascular therapy.

CONCLUSIONS

We found that transferring from a primary stroke center with CTP RAPID ability was both feasible and significantly reduced door to puncture time, without any significant delay in the transfer process, when compared with patients transferred with no perfusion imaging.

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Contributors AA and PA-S were responsible for the study concept and design. PA-S, GC, and RS contributed to acquisition of the data. All authors were responsible for analysis and interpretation of the data. All authors contributed to drafting of the manuscript. AA, ES, and RH contributed to critical revision of the manuscript for important intellectual content. All authors were responsible for administrative, technical, and material support. AA, ES, and RH contributed to study supervision.

Competing interests RH is a consultant for Covidien, Stryker, Codman, and MicroVention.

Ethics approval Institutional review board approval (institutional review board of Baptist Health, #16-58) and HIPAA waiver were obtained because of the retrospective nature of the study.

Provenance and peer review Not commissioned; externally peer reviewed.

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Notes