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ORIGINAL ARTICLE

Comparison of anticoagulation and antiplatelet therapy for treatment of blunt cerebrovascular injury in children <10 years of age: a multicenter retrospective cohort study

Vijay M. Ravindra[1,2] · Robert J. Bollo[1,2] · Michael C. Dewan[3,4] · Jay K. Riva-Cambrin[5] · Daniel Tonetti[6] · Al-Wala Awad[1,2] · S. Hassan Akbari[7,8] · Stephen Gannon[3,4] · Chevis Shannon[3,4] · Yekaterina Birkas[1,2] · David Limbrick[7,8] · Andrew Jea[9,10] · Robert P. Naftel[3,4] · John R. Kestle[1,2] · Ramesh Grandhi[1,2]

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Abstract

Purpose Blunt cerebrovascular injury (BCVI) is uncommon in the pediatric population. Among the management options is medical management consisting of antithrombotic therapy with either antiplatelets or anticoagulation. There is no consensus on whether administration of antiplatelets or anticoagulation is more appropriate for BCVI in children < 10 years of age. Our goal was to compare radiographic and clinical outcomes based on medical treatment modality for BCVI in children < 10 years.

Methods Clinical and radiographic data were collected retrospectively for children screened for BCVI with computed tomography angiography at 5 academic pediatric trauma centers.

Results Among 651 patients evaluated with computed tomography angiography to screen for BCVI, 17 patients aged less than 10 years were diagnosed with BCVI (7 grade I, 5 grade II, 1 grade III, 4 grade IV) and received anticoagulation or antiplatelet therapy for 18 total injuries: 11 intracranial carotid artery, 4 extracranial carotid artery, and 3 extracranial vertebral artery injuries. Eleven patients were treated with antiplatelets (10 aspirin, 1 clopidogrel) and 6 with anticoagulation (4 unfractionated heparin, 2 low-molecular-weight heparin, 1 transitioned from the former to the latter). There were no complications secondary to treatment. One patient who received anticoagulation died as a result of the traumatic injuries. In aggregate, children treated with antiplatelet therapy demonstrated healing on 52% of follow-up imaging studies versus 25% in the anticoagulation cohort.

Conclusion There were no observed differences in the rate of hemorrhagic complications between anticoagulation and antiplatelet therapy for BCVI in children < 10 years, with a nonsignificantly better rate of healing on follow-up imaging in children who underwent antiplatelet therapy; however, the study cohort was small despite including patients from 5 hospitals.

Keywords Blunt · Cerebrovascular · Injury · Trauma · Anticoagulation · Antiplatelet · Pediatrics

✉ Ramesh Grandhi
neuropub@hsc.utah.edu

[1] Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, 175 N. Medical Drive East, Salt Lake City, UT 84132, USA

[2] Division of Pediatric Neurosurgery, Primary Children's Hospital, Salt Lake City, UT, USA

[3] Department of Neurosurgery, Vanderbilt University, Nashville, TN, USA

[4] Division of Pediatric Neurosurgery, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA

[5] Department of Clinical Neurosciences, Division of Pediatric Neurosurgery, University of Calgary, Calgary, Alberta, Canada

[6] Department of Neurosurgery, Division of Pediatric Neurosurgery, University of Pittsburgh, Pittsburgh, PA, USA

[7] Department of Neurosurgery, Washington University in St. Louis, St. Louis, MO, USA

[8] Division of Pediatric Neurosurgery, St. Louis Children's Hospital, St. Louis, MO, USA

[9] Department of Neurosurgery, Indiana University, Bloomington, IN, USA

[10] Division of Pediatric Neurosurgery, Riley Children's Hospital, Indianapolis, IN, USA

Introduction

Blunt cerebrovascular injury (BCVI) is a rare occurrence in children [1] but can have a wide variety of neurological consequences [2–5]. Blood vessel injury can lead to stroke and immediate neurological damage; in addition, there is a risk for delayed cerebral infarction from thromboembolic events after the initial injury.

Prevention of secondary thromboembolic complications from the initial arterial injury remains a primary concern for practitioners. Treatment options include observation, medical management, and open surgical/endovascular management. Medical management may include either antiplatelet or anticoagulation therapy. There are well-established treatment guidelines for BCVI in adults, which are also generally applied in children over the age of 10 years [6], but substantial evidence is lacking about treatment in children younger than 10 years. Dewan et al. [1] reported outcomes on 57 pediatric patients diagnosed with BCVI and concluded that treatment of BCVI is safe with either antiplatelet or anticoagulant therapy. The risks of antiplatelet therapy in young children include bleeding, gastrointestinal upset, and Reye syndrome, which can lead to fatal hepatic fatty degeneration and encephalopathy [7]. Anticoagulation also carries a risk of bleeding and may necessitate blood testing and other frequent monitoring. Thus, there is no consensus on which particular antithrombotic agent should be used for treatment of BCVI in children under 10 years of age.

In the current investigation, we compared radiographic and clinical outcomes based on medical treatment modality for BCVI in children < 10 years of age. We hypothesized that there is no difference between treatment methods based on vascular injury complication profile, radiographic response, and medication adverse effects.

Methods

Study population

This was a retrospective cohort study of patients from 5 level one pediatric trauma centers across the USA. We identified all children < 10 years of age who underwent computed tomography angiography (CTA) of the head or neck for suspected traumatic cerebrovascular injury during a 15-year period (January 1, 2003–December 31, 2017); this age cutoff was chosen because these children are considered "at risk" for antiplatelet agent complications. The decision to obtain a CTA was at the discretion of the multidisciplinary teams of treating physicians. From this initial cohort, we identified children in whom BCVI was confirmed and treated to comprise our study group. The Institutional Review Board and Privacy Board approval were obtained at each center with a waiver of patient consent. The Strengthening Reporting of Observational Studies in Epidemiology checklist was used in preparing this paper.

Data collection

The methodology for data collection has been described in previous publications [8, 9]. Briefly, trauma and radiology databases were queried to identify patients, and data were abstracted from the medical and radiology records. Demographic information included treatment center and patient age, sex, and race. The mechanism of injury (motor vehicle accident, pedestrian vs. vehicle, fall > 1 or < 1 story, nonaccidental trauma, other blunt injury, penetrating, hanging), initial Glasgow coma scale (GCS) score at neurosurgical evaluation, presence of focal neurological deficits on initial examination, and method of treatment for traumatic brain injury (TBI) (medical vs. surgical) were recorded. Radiological factors included the presence of concomitant intracranial injury, the presence of hypodensity on noncontrast head CT consistent with stroke, and Rotterdam score [10] (a validated 6-point score based on initial noncontrast CT that predicts 6-month mortality in moderate and severe TBI). If cervical spine imaging was performed, we recorded the modality, injury type (none, fracture, ligamentous injury, fracture dislocation), level, and, specifically, fracture involving the foramen transversarium.

For the current investigation, we limited the search to children under the age of 10 years (120 months). Treatment modalities were limited to medical therapy, either antiplatelet therapy or anticoagulation. The dosage of antiplatelet therapy was either 81 or 325 mg of aspirin. In the one instance that clopidogrel was used, a standard dose of 75 mg was administered. With respect to anticoagulation, weight-based dosing was used for administration of low-molecular-weight heparin, and intravenous heparin dosing was based on partial thromboplastin time nomogram.

The primary outcome of interest was the presence of an adverse event from treatment: hemorrhage, need for blood transfusion, or Reye syndrome. Secondary outcomes included radiographic progression, improvement, or no change. Each injury was classified according to the BCVI scale [6]. Radiographic progression was defined as worsening of the vascular injury (either by grade or severity) on follow-up neurovascular imaging.

Statistical analysis

Data from all centers were managed using Research Electronic Data Capture (REDCap) tools [11]. Data were descriptively reported as means with standard deviations for continuous variables and with counts and frequencies for categorical data. A Fisher exact test was performed to compare

the treatment cohorts for the primary and secondary outcomes. Statistical significance was placed at a p value of < 0.05. Statistical analysis was performed using SPSS (IBM, Armonk, NY).

Results

Patient characteristics

Six hundred and fifty-one pediatric patients were evaluated for traumatic cerebrovascular injury with CTA of the head or neck. Of these, 362 children were < 10 years of age at the time of evaluation. A total of 17 (4.7%) patients (82.4% male; mean age 64 ± 35.8 months, median 72 months) were included in the analysis. A majority of the children were white (12, 70.6%). There were 3 Hispanic children (17.6%), 1 black child (5.9%), and 1 characterized as other (Pacific Islander, American Indian, Alaskan Native, or Native Hawaiian) (5.9%) (Table 1).

Mechanism of injury

The most common mechanism of injury was other blunt, low energy (struck with object, fell from horse) in 6 (35.3%) patients, followed by ground-level fall (< 1 story) and pedestrian vs. vehicle in 4 (23.5%) each. Motor vehicle accident, a fall from height (> 1 story), and non-accidental trauma each occurred in 1 patient (Table 1). Ten injuries were classified as low energy (58.8%) and 7 were high energy (41.2%).

Table 1 Summary of demographic information

Category	*n (%) or mean (range)*
Age (months)	65 (14–119)
Male sex	14 (82%)
Mechanism of injury	
Motor vehicle accident	1 (5.9%)
Pedestrian vs. vehicle	4 (23.5%)
Fall (> 1 story)	1 (5.9%)
Non-accidental trauma	1 (5.9%)
Other blunt (struck with object, fall from horse)	6 (35.3%)
Ground-level fall (< 1 story)	4 (23.5%)
Total patients	17
Total vessel injuries	18
Evidence of intracranial injury	8
Management of TBI during hospitalization	
Medical only	13 (76.4%)
Surgical + medical	4 (23.5%)

Clinical and radiographic findings

The median initial GCS was 12 (range 3–15). Nine children (52.9%) had a focal neurological examination on initial evaluation. Eight children had evidence of a stroke on the initial CT scan, 5 of which were symptomatic with a neurological deficit. Eight (47.1%) children had associated intracranial injuries, including multiple injuries in some children: 4 epidural hematomas, 2 subdural hematomas, 1 subarachnoid hemorrhage, and 6 intracranial contusions. Four (23.5%) children (multiple treatments in some) were also managed surgically: 1 underwent craniotomy, 3 had external ventricular drain (EVD) placement, and 3 had intracranial pressure (ICP) monitor placement. Six patients had a temporal bone fracture (1 squamosal and 5 petrous) and 3 had linear fractures through the carotid canal. Four (23.5%) patients had associated facial fractures. The mean radiation dose for CTA imaging was 610.14 mGy/cm^2. Three children had additional vascular pathology: 1 with a traumatic cerebral aneurysm, 1 with traumatic venous thrombosis, and 1 with moyamoya disease.

Fourteen of the 17 patients had dedicated cervical spine imaging performed (more than one imaging type in some children): 11 underwent CT, 7 had magnetic resonance imaging (MRI), and 2 required flexion/extension X-ray imaging. One (5.9%) child experienced a cervical spine injury requiring long-term external fixation/orthosis; this child also had a fracture through the foramen transversarium at the level of C2–3 with an associated ligamentous injury.

Management/imaging follow-up

There were 11 intracranial carotid artery injuries, 4 extracranial carotid artery injuries, and 3 extracranial vertebral artery injuries (1 patient experienced both extra- and intracranial carotid artery injury). The most common injuries were grade I (7/17: 41.2%); there were also 5 grade II, 1 grade III, and 4 grade IV (Table 2). Eleven patients were treated with antiplatelet therapy (10 aspirin and 1 clopidogrel) and 6 with anticoagulation (4 unfractionated heparin, 2 low-molecular weight heparin, including 1 patient who transferred from unfractionated to low-molecular-weight heparin) (Table 3). Sixty-six percent of those treated with anticoagulation harbored high-grade lesions (grade II–V), whereas 55% of those treated with antiplatelet medication had high-grade lesions. There were no complications secondary to treatment. One patient (anticoagulation group) died as a result of the burden of traumatic injuries.

Initial follow-up imaging was performed in 14/17 children, 6 with CTA and 8 with MRA. Overall, 8 patients (57.1%) demonstrated improvement, 4 patients demonstrated no change (28.6%), and 2 had progression (14.3%) (Table 4). The mean time to first follow-up imaging study was 78 ± 120.9 days (antiplatelet group 97.1 ± 137.6 days vs.

Table 2 Summary of vessel injury and location

Location	*n*	Grade of vascular injury				
		I	II	III	IV	V
Intracranial carotid artery injury	11	7 (64%)	2 (18%)	1 (9%)	1 (9%)	0 (0%)
Extracranial carotid artery injury	4	0 (0%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)
Intracranial vertebral artery injury	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Extracranial vertebral artery injury	3	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)

Grade I—dissection/intramural hematoma with < 25% luminal stenosis; grade II—dissection/intramural hematoma with ≥ 25% narrowing; grade III—pseudoaneurysm; grade IV—vessel occlusion; grade V—vessel transection

anticoagulation group 31.25 ± 27 days). The mean duration of initial treatment was 187 ± 301 days with a median of 105 days. Nine children had secondary follow-up imaging: CTA in 3, MRA in 5, and digital subtraction angiography in 1. Three children demonstrated improvement, 5 with no change, and 1 with progression. The mean time to second follow-up imaging study was 414 ± 582.5 days (antiplatelet 514 ± 625.6 days vs. anticoagulation 65 ± 22 days).

Five (29%) patients had a change of medication during the course of treatment in their antithrombotic medication regimen. Four of the 5 patients who were initially started on anticoagulation were switched to antiplatelet therapy because of vessel healing (2 cases), progression of injury (1 case), and no change (1 case) on the initial follow-up imaging (Table 5); the other was started on clopidogrel and transitioned to aspirin after follow-up imaging demonstrated healing. The mean duration of the secondary treatment was 931 ± 1364 days, with a median of 300 days. There were no complications from the secondary treatment. No children required a treatment modality change after that point.

Six children had a third follow-up image: CTA in 2, angiogram in 1, and MRA in 3. The mean time to third follow-up imaging study was 471 ± 482.8 days (antiplatelet 609.75 ± 590 days vs. anticoagulation 193.5 ± 10.5 days). Two demonstrated improvement and 4 demonstrated no change. There was no statistical difference in the radiographic outcomes between the treatment groups. By assessing aggregate imaging studies, we found that children treated with antiplatelet therapy demonstrated healing on 52% of follow-up imaging studies versus 25% in the anticoagulation cohort.

Clinical outcomes

With respect to the primary clinical outcome, there were no adverse events from either treatment method or thromboembolic complications. There was 1 death among the 17 patients, an 8.1-year-old boy who was struck by a vehicle and had intracranial contusions and underwent ICP monitor and EVD placement. He sustained a grade II injury of the intracranial internal carotid artery and was found to have a large vessel distribution infarct. He was treated with systemic anticoagulation (heparin) for 48 h and then transitioned to aspirin monotherapy following documentation of stability of the BCVI. Given his poor neurologic examination and extensive intracranial injuries, his family elected to transition to comfort care. Over half (52.9%) of the children were discharged home and 7 (41.2%) required inpatient rehabilitation stay before going home.

Table 3 Summary of treatment based on vessel injury type

Grade of vascular injury	Antiplatelet		Anticoagulation		
	Aspirin	Clopidogrel	Unfractionated heparin	Low-molecular-weight heparin	Warfarin
I	4	1	2	0	0
II	3	0	1	1	0
III	1	0	0	0	0
IV	2	0	1	2	0
V	0	0	0	0	0

Grade I—dissection/intramural hematoma with < 25% luminal stenosis; grade II—dissection/intramural hematoma with ≥ 25% narrowing; grade III—pseudoaneurysm; grade IV—vessel occlusion; grade V—vessel transection

Table 4 Summary of complications and radiographic outcomes based on treatment type

Primary outcomes		Antiplatelet (n = 11)	Anticoagulation (n = 6)	P value
Complications		0	1 (16%)	
Intracranial hemorrhage		0	0	
Body cavity or solid organ hemorrhage		0	0	
Drug reaction/allergy		0	0	
Death		0	1 (16%)	
Radiographic				
First follow-up (n = 14)	Improved	6 (60%)	2 (50%)	1
	Stable	3 (30%)	1 (25%)	1
	Worsened	1 (10%)	1 (25%)	.51
	Total	10	4	
Second follow-up (n = 9)	Improved	3 (43%)	0 (0%)	.50
	Stable	3 (43%)	2 (100%)	.44
	Worsened	1 (14%)	0 (0%)	1
	Total	7	2	
Third follow-up (n = 6)	Improved	2 (50%)	0 (0%)	.47
	Stable	2 (50%)	2 (100%)	.47
	Worsened	0	0 (0%)	
	Total	4	2	

Discussion

Epidemiology and diagnosis

Cerebrovascular injury resulting from trauma is relatively uncommon in the pediatric population. Using a administrative database, Harris et al. [12] determined a 0.33% incidence of BCVI in children. Children above the age of 10 years are treated similar to adults, for whom treatment algorithms are well established [13], because there is a paucity of data regarding medical management in children, especially for those < 10 years of age.

The current study is underpowered to make a determination on which treatment method is superior, but there were no complications in our study cohort from either therapy, suggesting they may be safe for use in this population. In this study, 8 patients (57.1%) demonstrated improvement on their initial follow-up imaging while on anticoagulation or antiplatelet therapy, and there was no difference in the proportion that improved between the two groups. There was no statistical difference in the radiographic outcomes between the treatment groups. Overall, the outcomes were on par for children who experience significant traumatic injury, with over half able to go home but a significant percentage requiring an inpatient rehabilitation stay. Notably, there were no reported ischemic or hemorrhagic complications as a result of treatment of the BCVI. An additional interesting finding is that the mean time to first follow-up imaging study was 78 ± 120.9 days, but differed between the two cohorts (antiplatelet group 97.1 ± 137.6 days vs. anticoagulation group 31.25 ± 27 days). This may allude to the fact that clinicians were more aggressive with early follow-up imaging among children in the anticoagulation group for purposes of demonstrating vessel "healing" and, in turn, consideration of transitioning the antithrombotic medication regimen to an antiplatelet. Given the lack of difference in the outcomes observed between the groups of patients, perhaps the use of antiplatelets as a "first-line" treatment could lead to more streamlined, efficient care.

Because there were no adverse events or thromboembolic complications, we draw a simple conclusion that treating

Table 5 Treatment changes from first-line therapy

Patient	Injury grade	Initial treatment	First follow-up imaging	Secondary treatment
1	IV	Anticoagulation	Healing/improvement	Aspirin
2	I	Clopidogrel	Healing/improvement	Aspirin
3	II	Anticoagulation	No change	Aspirin
4	IV	Anticoagulation	Healing/improvement	Aspirin
5	II	Anticoagulation	Progression	Aspirin

BCVI in children < 10 years is feasible with either anticoagulation or antiplatelet therapy. We did find that children treated with antiplatelet therapy demonstrated better rates of healing on follow-up imaging studies as compared with the anticoagulation cohort; however, a higher proportion of patients with high-grade injuries were treated initially with anticoagulation. This may reflect inherent bias among clinicians for treatment of higher risk lesions with anticoagulants and also account for the better rate of healing seen among those treated with antiplatelet medications. Although both treatments appear to be safe from the current cohort study, we highlight the low number of events and difficulty drawing a conclusion in this light. In the CADISS trial, which investigated the efficacy of antiplatelet and anticoagulant drugs at preventing stroke and death in 250 adults with nontraumatic symptomatic carotid and vertebral artery dissection, the authors concluded that nearly 10,000 participants would be needed for an appropriate power calculation [14]. Although the current study highlights the use of both agents, we acknowledge that each patient must be evaluated on an individual basis and consideration must be given to concomitant injuries; in addition, a multidiscipinary approach to managing children with BCVI is critical (Fig. 1).

Antiplatelet side effects

Low rates of hemorrhagic complications have previously been reported in pediatric patients [5, 15, 16]. Based on this limited cohort, we suggest that antithrombotic medication can be used for pediatric patients < 10 years of age with BCVI. Specifically, no hemorrhagic complications were encountered in this series; of note, 8 children had concomitant intracranial injuries but did not require further intervention secondary to hemorrhagic complications or worsening from BCVI treatment. There is some support for the use of anticoagulation initially and supplementation with antiplatelet therapy if there is development of thromboembolic complications [17]. No patients in the current report experienced thromboembolic complications; rather, 4 out of 5 patients who had a change in their initial treatment started on anticoagulation and were switched to antiplatelet therapy, likely because of vessel healing, progression of injury, or no change (Table 5).

Although the use of aspirin can be associated with a lower risk of bleeding, no need for monitoring levels, and ease of administration (oral tablet vs. subcutaneous injection with low-molecular-weight heparin), the use of aspirin in young children has been associated with Reye syndrome. Reye syndrome has not been reported during aspirin use for childhood acute ischemic stroke [18], and in this cohort study there were no reported immediate or delayed cases of Reye syndrome. Nevertheless, the theoretical concern for subsequent development of Reye syndrome may influence the clinician's decision of which particular antithrombotic medication to use for young children with BCVI.

The most common side effect of both anticoagulation and antiplatelet therapy is bleeding. A large case crossover study performed in French children ranging from 2 months to 16 years who had received one dose of aspirin or a nonsteroidal anti-inflammatory drug determined the adjusted odds ratio of drug exposure in upper gastrointestinal bleeding was 7.3 for

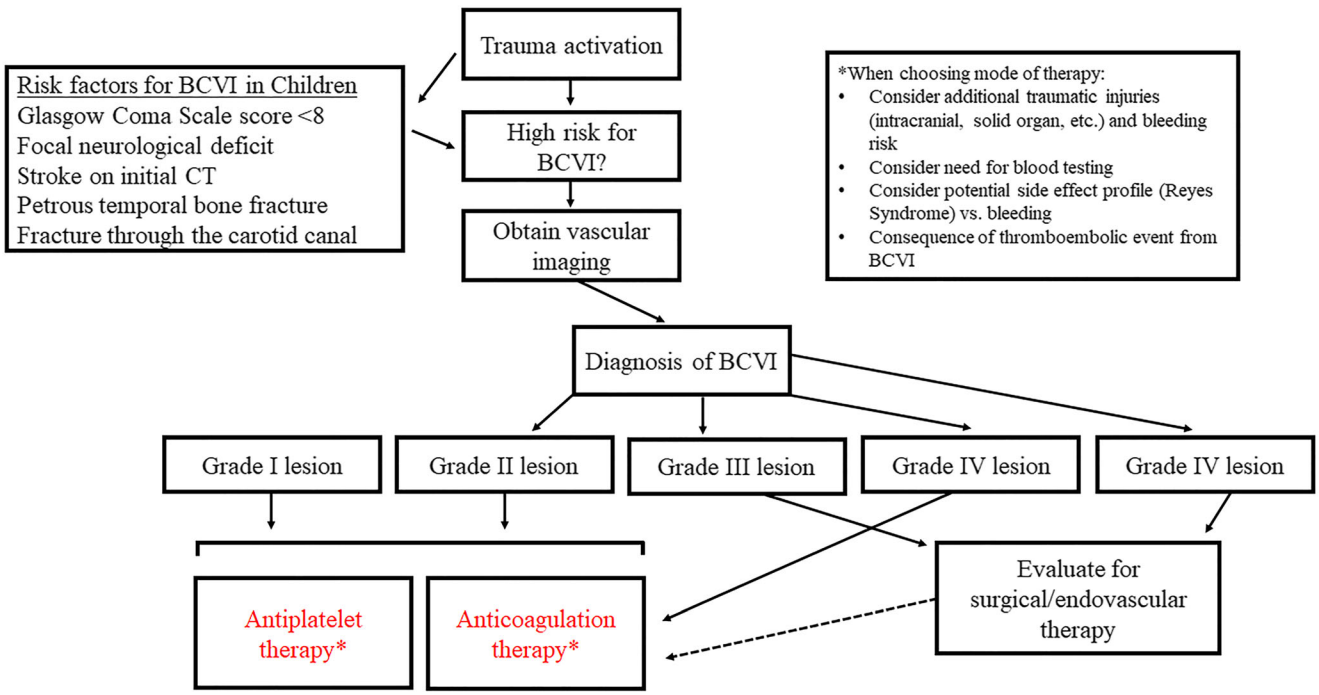

Fig. 1 Flow diagram outlining potential management of BCVI in children < 10

aspirin and 10 for ibuprofen [19]. In our cohort, there were no instances of increased bleeding among patients treated with either antithrombotic agent.

Limitations

The retrospective design of the study inherently limits the information available. For example, functional outcome scales were not reliably reported in the existing medical record. Although this represents the experience and practice among 5 large, metropolitan tertiary referral centers, treatment and practice patterns are not standardized, and treatment decisions were made on a case-by-case basis [1]. Although this was multi-institutional study, more sites and patients would be needed to analyze efficacy for different treatment modalities and provide conclusive recommendations. Furthermore, the small sample size meant that matching the groups for injury severity was not possible. Only patients screened with CTA were included, which may have selected toward lower grade, less life-threatening injuries, as higher grade injuries and higher acuity patients may have been taken directly to surgery or underwent urgent endovascular intervention. An additional limitation lies in the heterogeneity of follow-up length and time, which is often of concern in trauma-based studies.

Although this investigation suffers from a small sample size collected over 5 centers, we believe the findings are helpful as a "stepping stone" towards answering the question of whether there is a preferred treatment method for pediatric BCVI.

Conclusions

This is a relatively large series of children < 10 years of age treated for BCVI with either anticoagulation or antiplatelet therapy. Overall, both treatment strategies appear safe and may be efficacious in children. Relative to those on anticoagulation, patients on antiplatelet therapy were more likely to demonstrate improvement in vessel injury on follow-up imaging, although the difference was not statistically significant. Antiplatelet and anticoagulation therapy can be considered in the setting of BCVI in children < 10 years of age. Future prospective, head-to-head study of both treatment methods across multiple centers may elucidate specific treatment recommendations.

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Compliance with ethical standards

Conflict of interest Dr. Limbrick reports research funding for an unrelated project through Medtronic and educational funds and research funding through Storz. Dr. Grandhi is a consultant for Medtronic Neurovascular, Cerenovus, and BALT Neurovascular. The other authors have no disclosures.

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