Treatment for Blunt Cerebrovascular Injuries

Equivalence of Anticoagulation and Antiplatelet Agents

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Hypothesis: We hypothesize that the 2 antithrombotic treatment regimens, systemic heparin sodium vs antiplatelet agents, are equivalent for the treatment of blunt cerebrovascular injuries (BCVIs) to prevent devastating injury-related strokes.

Design: Retrospective review of a prospective database.

Setting: Level I trauma center.


Main Outcome Measures: Incidence of cerebrovascular accident (CVA), stratified by treatment.

Results: During the study period, 422 BCVIs were identified in 301 patients (64.8% men; mean [SEM] age, 37.0[0.8] years; mean [SEM] injury severity score, 27.0[0.9]). A total of 22 patients presented with neurologic ischemia, and 5 patients sustained CVAs after embolization and/or stenting of an injury. Treatment was initiated for 282 asymptomatic BCVIs (heparin, 192; aspirin, 67; aspirin and/or clopidogrel, 23); 1 patient had a CVA (0.5%). Of 107 patients with untreated, asymptomatic BCVIs, 23 (21.5%) had a CVA. For untreated patients sustaining BCVI-related CVAs, the mean (SEM) time to diagnosis was 58(10) hours. For those who did not exhibit symptoms within 2 hours of injury, mean time to diagnosis of CVA was 75(11) hours. Injury healing rates (heparin, 39%; aspirin, 43%; aspirin/clopidogrel, 46%) and injury progression rates (12%; 10%; 15%) were equivalent between therapeutic regimens.

Conclusions: With an overall CVA risk of 21% and a documented latent period, comprehensive screening, early diagnosis, and institution of antithrombotic therapy for BCVI are clearly warranted. The type of treatment, heparin vs antiplatelet agents, does not appear to affect either stroke risk or injury healing rates.

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Abbreviations: BCVI, blunt cerebrovascular injury; CT, computed tomographic; GCS, Glasgow Coma Scale.

Table 2. Denver Grading Scale for Blunt Cerebrovascular Injury

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Irregularity of the vessel wall or a dissection/intramural hematoma with less than 25% luminal stenosis</td>
</tr>
<tr>
<td>II</td>
<td>Intraluminal thrombus or raised intimal flap is visualized or dissection/intramural hematoma with 25% or more luminal narrowing</td>
</tr>
<tr>
<td>III</td>
<td>Pseudoaneurysm</td>
</tr>
<tr>
<td>IV</td>
<td>Vessel occlusion</td>
</tr>
<tr>
<td>V</td>
<td>Vessel transection</td>
</tr>
</tbody>
</table>

Table 3. BCVI Classified by Location and Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>CAI</th>
<th>VAI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>125</td>
<td>97</td>
<td>222</td>
</tr>
<tr>
<td>II</td>
<td>37</td>
<td>33</td>
<td>70</td>
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<tr>
<td>III</td>
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<tr>
<td>IV</td>
<td>0</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>V</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: BCVI, blunt cerebrovascular injury; CAI, carotid artery injury; VAI, vertebral artery injury.

RESULTS

PATIENT DEMOGRAPHICS

From January 1, 1997, to January 1, 2007, there were 18,431 admissions to our state-designated level I urban trauma center for blunt trauma, and 422 BCVIs were identified in 301 patients (1.6%). Most patients were men (64.8%) with a mean (SEM) age of 37.0 (0.8) years, and a mean injury severity score of 27.0 (0.9). The BCVI included 222 grade I injuries, 70 grade II injuries, 63 grade III injuries, 52 grade IV injuries, and 15 grade V injuries (Table 3). Mechanism of injury included motor vehicle collisions (179 patients), falls (35 patients), automobile/pedestrian accidents (26 patients), motorcycle/snowmobile collisions (18 patients), snowboard accidents (11 patients), bike accidents (5 patients), hangings (4 patients), assaults (4 patients), and other (19 patients). Associated injuries included intracranial hemorrhage/diffuse axonal injury (156 patients [51.8%]), midface/mandible fractures (72
patients [23.9%]), cervical spine injuries (166 patients [39.1%]), thoracic injuries (120 patients [39.9%]), abdominal injuries (59 patients [19.6%]), pelvic fractures (43 patients [14.3%]), and extremity fractures (46 patients [15.3%]). Mean (SEM) intensive care unit and hospital lengths of stay were 14(1) and 18(1) days, respectively. Overall mortality was 9%, and the mortality for patients who did not have a BCVI-related stroke was 3%.

TREATMENT FOR BCVI

Treatment was initiated for 282 asymptomatic BCVIs: heparin for 192 (68.1%), aspirin for 67 (23.8%), and aspirin and clopidogrel for 23 (8.2%) (Table 4). One patient (0.5%) with a grade II VAI who was appropriately treated with systemic heparin had a stroke. Of 107 asymptomatic BCVIs that did not receive adequate treatment, 23 (22%) resulted in stroke (13 CAIs and 10 VAIs). There were bleeding complications in 8 patients (patient 1); in an asymptomatic patient, systemic heparin was started using a 5000-U bolus followed by a continuous infusion. Ten hours later, the patient had an acute decrease in mental status; a computed tomographic scan of the head showed an epidural hematoma with shift, and the patient was taken to the operating room for evacuation. On transfer to the rehabilitation unit on hospital day 10, the patient had normal findings on motor neurologic examination (patient 2). In an asymptomatic patient, 10 days after heparin therapy was started, the patient had recurrent epistaxis with a PTT of 51 seconds; he underwent nasal packing and was given 2 U of RBCs to attain a hematocrit level of 28% (patient 3). An aspirin/clopidogrel regimen was started (without the input of an attending neurosurgeon) for an asymptomatic patient with a subdural hemorrhage following a recent craniotomy. The patient required a second craniotomy because of bleeding (patient 4). An asymptomatic patient being given a heparin infusion developed a hepatic hematoma requiring 4 U of RBCs; PTT at the time of bleeding was 120 seconds (patient 5). Seven days after beginning treatment with heparin, an asymptomatic patient with a known grade I renal laceration had a slow drift in hematocrit level for 48 hours. Computed tomographic imaging showed a retroperitoneal hematoma; the patient required a 5-U transfusion of RBCs, and PTT at the time of bleeding was 56 seconds (patient 6). A heparin drip was started for a patient with a combined aortic thrombus (goal PTT was higher than the normal BCVI anticoagulation protocol) and grade I VAI; 72 hours later, the patient’s hematocrit dropped to 12%, and he received a transfusion of 4 U of RBCs; PTT at this time was 60 seconds. Findings from angiography were normal, and the heparin drip was restarted 24 hours later (patient 7). Following heparinization for a BCVI-related middle cerebral artery stroke, a patient developed retroperitoneal bleeding; he was given a transfusion of 2 U to attain a hematocrit level of 28%. The PTT at the time of bleeding was 50 seconds (patient 8). Following a carotid stent-related stroke, heparin therapy was started. Several days later, the patient had an intracranial hemorrhage requiring craniotomy for evacuation.

Of 422 patients with injuries, 292 (69.2%) had imaging again a mean (SEM) of 10(0.9) days after initial angiography to document injury healing, progression, or stability. The BCVI outcome, stratified by treatment regimen, is reported in Table 5. In patients who underwent imaging again, several comparisons are noted. For the 210 patients with CAIs, there was no change in the grade of injury on the second angiogram for 92 (34%) grade I injuries, 24 (33%) grade II injuries, and 32 (88%) grade III injuries. For the 212 patients with VAIs, there was no change in the grade of injury on the second angiogram for 68 (40%) grade I injuries, 20 (30%) grade II injuries, 23 (78%) grade III injuries, and 27 (78%) grade IV injuries. For BCVI overall, there was stability in injury grade on the second angiogram in 160 (36%) grade I injuries, 44 (32%) grade II injuries, and 55 (83%) grade III injuries. On 10-day follow-up imaging for those patients undergoing therapeutic treatment, injury healing rates for all BCVIs were 46% for aspirin and/or clopidogrel, 43% for aspirin, and 39% for heparin. Conversely, injury progression rates for all treated BCVIs were 10% for aspirin, 12% for heparin, and 15% for aspirin and/or clopi-
BCVI-RELATED NEUROLOGIC EVENTS

A total of 50 patients who were not treated with antithrombotic agents sustained a stroke related to their BCVI, and 6 patients had bilateral strokes because of bilateral injuries; 22 patients (44%) presented to the hospital with signs or symptoms of neurologic ischemia; and 5 patients had a stroke after primary embolization or stenting (3 patients with unilateral CAI, 1 patient with bilateral CAI, and 1 patient with a unilateral VAI). Of 107 asymptomatic BCVI that did not receive adequate treatment, 23 (21%) resulted in stroke (13 CAI and 10 VAI). Of 50 patients sustaining BCVI-related stroke, 45 had a stroke unrelated to catheter-based interventions. Mean (SEM) time to diagnosis of stroke in these 45 patients was 58 (10) hours after injury. For the 34 patients who did not have symptoms within 2 hours of injury, the mean (SEM) time to diagnosis of stroke was 75 (11) hours. Grade of injury for the 45 patients with stroke unrelated to catheter-based intervention was I for 23 injuries, II for 19, III for 20, and IV for 5. Diagnosis of a BCVI-related stroke in these 45 patients was based on symptoms in 28 patients and imaging alone in 17 patients; the 17 patients were intubated, unevaluable patients who had an indication for a computed tomographic scan (routine follow-up for head injury in 14 patients and a change in neurologic status in 3 patients). To our knowledge, no patient had a stroke related to BCVI after discharge, but long-term follow-up in this trauma population is limited. The stroke-related mortality was 30% (15 of 50 patients).

COMMENT

During the past decade, a wealth of studies has provided the scientific rationale to promote the early screening and treatment of BCVI. If untreated, CAIs have a stroke rate of up to 50%, and increasing stroke rates correlate with increasing grades of injury; VAIs have a stroke rate of 20% to 25%. If the injury occurs in a surgically accessible area, particularly the common carotid artery, operative management is warranted. The vast majority of BCVI lesions, however, occur in surgically challenging or inaccessible areas, either high within the carotid canal at the base of the skull or within the foramen transversarium. Such a location makes the standard open vascular approaches for reconstruction or thrombectomy difficult, if not impossible. Consequently, antithrombotic therapy was initiated as treatment for these injuries.

To date, multiple studies suggest that early antithrombotic therapy in asymptomatic patients with BCVI reduces or nearly eliminates BCVI-related strokes. Miller et al found a reduction in stroke rate for CAIs from 64% in untreated patients to 6.8% in patients treated with antithrombotic therapy (either anticoagulation or antiplatelet agents), and, for VAIs, a reduction from 54% to 2.6% in treated patients. Cothren et al demonstrated a stroke rate of 0.5% in 187 BCVIs treated with antithrombotic agents, whereas untreated patients had an overall stroke rate of 21%. To date, several nonrandomized studies with relatively small numbers of patients suggest equivalence for anticoagulation and antiplatelet agents with regard to stroke rate.

The present study, including 422 BCVIs, corroborates these findings. Patients treated with antithrombotic agents had a stroke rate of 0.5%. Of interest, both types of treatment, anticoagulation and antiplatelet agents, were effective in preventing stroke, and only 1 patient had a stroke while receiving systemic heparin. However, there is a difference in the number of patients treated with each modality; almost twice as many BCVIs were treated with antiplatelet therapy compared with antiplatelet agents. This difference is likely for 2 reasons. First, intravenous heparin had been our treatment of choice based on early reports of neurologic improvement in patients sustaining BCVI-related ischemic neurologic events, as well as reports of reduced stroke rates for asymptomatic patients with BCVI. It was assumed that systemic heparin promoted clot stabilization, if present, and clot resolution through intrinsic fibrinolytic mechanisms and prevented further thrombosis. Second, following the bleeding complication related to antiplatelet agents requiring craniotomy, hospital neurosurgeons have been reluctant to embrace the early use of antiplatelet agents in patients with intracranial hemorrhage.

In our study, patients with BCVI not treated with either anticoagulation or antiplatelet agents had a stroke rate of 21%. Some authors have argued that BCVI-related stroke is inevitable and unpreventable; hence, screening for these injuries, in their opinion, should not be pursued. Although our group responded to this concern, and continued to advocate aggressive screening, there may still be some question of utility in this approach. Unfortunately, there is a group of patients who will exhibit neurologic symptoms within 1 to 2 hours of admission; these patients cannot be effectively screened and treated because of the early onset of neurologic sequelae. Fortunately, however, this group of patients represents the few patients with BCVI. Most patients have a latent period that permits timely diagnosis and intervention. In our study, patients who did not have symptoms within 2 hours had a mean delay to stroke of 75 hours. Moreover, BCVI-related mortality is significant; in this series, the stroke-related mortality was 30%, whereas the overall mortality for patients not suffering stroke was only 5% in this group of patients with multiple injuries. Therefore, our results indicate screening in the at-risk population should be aggressively pursued and treatment appropriately initiated based on associated injuries and physiologic indices.

With an apparent equivalence of therapies for the primary end point, namely, BCVI-related stroke, an analysis of injury healing or progression as well as complications is an important variable in choosing antithrombotic treatment for an individual patient. Most of our patients had repeated imaging during the acute phase of injury, approximately 10 days after the initial diagnosis. Ap-
proximately one-third of treated grade I and grade II injuries were unchanged on a second angiogram. For treated grade I injuries, 53% healed, whereas 10% progressed. For treated grade II injuries, fewer healed (27%) and more progressed (35%). Unlike grade I and grade II injuries, grade III and grade IV injuries were predominantly unchanged on the second angiogram (83% and 78%, respectively), with rare cases of complete healing or resolution with treatment. Comparing antithrombotic treatment groups, there does not appear to be a significant difference in healing or progression rates, but this analysis is limited by small sample size.

In patients with multiple injuries, institution of antithrombotic therapy should always be carefully considered because of the risk of bleeding complications. In this study population, several patients had bleeding that required intervention. In reviewing these complications individually, several points may be learned. First, early modification of our heparin protocol has undoubtedly reduced bleeding complications. Several of the reported complications occurred after a heparin bolus was administered or with a PTT above our current goal of 40 and 50 seconds. Second, 2 patients with reported bleeding complications underwent a transfusion of RBCs to attain a hematocrit level of 28%. According to currently used transfusion triggers in the surgical intensive care unit, these patients would not have received RBCs by today’s standards. Finally, as previously mentioned, use of antiplatelet agents in patients with intracranial hemorrhage, particularly following craniotomy, has been markedly reduced in our institution following a bleeding complication. Despite a better understanding of the scenarios that can lead to bleeding, each patient must be individually analyzed for therapeutic intervention, with the input of consulting physicians, particularly neurosurgeons. Only after carefully weighing the stroke risk vs the bleeding risk should the type of antithrombotic therapy be chosen and initiated. Currently, we tend to use systemic heparin during hospitalization with transition to aspirin as an outpatient.

There are several limitations of this study. This was not a randomized, controlled trial. As such, the choice of antithrombotic treatment as well as timing of initiation of such treatment was individualized, which could affect the complication rates noted. For example, because of the isolated bleeding complication of the patient treated with antiplatelet agents requiring another craniotomy, it is the determination of our neurosurgical colleagues that any patient with traumatic brain injury cannot receive antiplatelet agents for treatment in the acute phase. This, understandably, introduces bias into the treatment groups evaluated. In addition, there are few long-term results because few patients were compliant with outpatient follow-up. Comprehensive follow-up beyond the acute hospitalization has not been extensively reported in the literature, as is true in most trauma population studies. Edwards et al reported the longest follow-up of patients with CAIs, but their study sample appears to be a selected group. Therefore, whether these injuries heal or persist during the lifetime of the patient is unknown.

Diagnosis and treatment of BCVI has evolved during the past 3 decades. Originally thought to be a rare occurrence, BCVIs are now diagnosed in more than 1% of patients experiencing blunt trauma. The recognition of a clinically silent period allows for screening for BCVI in asymptomatic patients based on the mechanism of trauma and the patient’s constellation of injuries. The early diagnosis of BCVI allows prompt initiation of treatment, with apparent equal efficacy of anticoagulation and antiplatelet agents in preventing stroke. The choice of therapy should be individualized based on the patient’s associated injuries and risk of bleeding.

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Analysis and interpretation of data: Cothren and Biffl.
Critical revision of the manuscript for important intellectual content: Moore, Kashuk, and Johnson.
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REFERENCES

Mark Williams, MD, Youngstown, Ohio: The report presented today is another analysis and update from this group's prospectively collected clinical database on BCVI. Since they began collecting and publishing this data 12 years ago, they have provided the grading of these injuries, defined the criteria to use for cost-effective screening, and shown that anticoagulation is the gold standard for treatment, as there is an asymptomatic latent period, thus, devastating strokes can be prevented.

Over 10 years, among 18 431 blunt trauma admissions, there were 422 BCVI in 301 patients (1.6%); 389 injuries were initially asymptomatic, 107 did not get adequate antithrombotic treatment, and the stroke rate was 21%. Two hundred eighty-two received adequate antithrombotic treatment, and only 1 stroke occurred, a stroke rate of 0.3%. This reduction in strokes, presumably because of the antithrombotic therapy, was at a cost of bleeding complications that resulted in 3 craniotomies, 17 U of packed RBCs transfused, and a nasal packing procedure. Because 90 patients got aspirin and/or clopidogrel instead of heparin and did not have strokes, the authors suggest that antiplatelet therapy is as effective as heparin in preventing strokes caused by BCVI.

Some patients got antiplatelet therapy because heparin was contraindicated. Many of these patients also have intracranial hemorrhage. Our neurosurgeons are horrified by even the thought of giving them aspirin or clopidogrel. What exactly is a contraindication to heparin that is not also a contraindication to aspirin or clopidogrel?

How do you know that patients treated with aspirin and clopidogrel are adequately treated? Based on platelet aggregometry, 23% of people are nonresponders to aspirin. There is also a wide variability in the effect of clopidogrel on coagulation. Aspirin and clopidogrel do keep atherosclerotic coronary arteries and coronary stents open, but yet is preventing thrombosis in atheromatous arteries where the blood stream is acutely exposed to subendothelial collagen, the most thrombogenic substance in the body?

There has been available for years a simple test for the evaluation of platelet function and the aspirin effect on that function, the platelet function analyzer, PFA-100. We use it to determine if there is an aspirin-induced coagulopathy in trauma patients. Soon, there will be a cartridge available for that machine that will evaluate clopidogrel's effect. Another analysis, thromboelastography, has been used for years to monitor the coagulopathy of cardiac bypass. It can detect the anticoagulant effect of clopidogrel and aspirin. With our cardiac perfusionist's assistance, we routinely use this examination. Not only can patients be subtherapeutic on heparin but some can be subtherapeutic on aspirin and/or clopidogrel. Why are you not using anything to monitor the anticoagulant effect of your aspirin/clopidogrel therapy?

Dr. Cothren: Dr. Williams questioned what contraindications of heparin would not also be contraindications to aspirin or clopidogrel. In our phrasing of “contraindications,” perhaps we should say that this is, in fact, surgeon or team preference, meaning they felt that it was contraindicated or not warranted to give a patient systemic heparin, although they did feel comfortable giving the patient an antiplatelet agent. Of interest, the subsequent bleeding complications in our patient population, which are obviously the downside to antithrombotic therapy, have shifted our relative contraindication scale. For example, after one patient had an intracranial hemorrhage from aspirin/clopidogrel therapy and required a craniotomy for evacuation, our neurosurgeons have been much more hesitant in allowing us to use antiplatelet agents in these patients; that was definitely a change in our practice management that persists and impacts our treatment options in these patients.

Regarding the issue of either platelet function analysis or thromboelastography, I think you bring up the excellent point of measuring inherent hypercoagulability in these patients. We actually have begun using point-of-care thromboelastography to help determine how to manage these patients, ie, to evaluate whether it is an enzymatic vs a platelet function problem. I think the broader issue, however, emphasized with a recent hemorrhagic complication in a patient who we treated with antiplatelet agents based on thromboelastography results, is whether this testing should be done in the acute phase. In other words, if both heparin and antiplatelet agents prevent stroke in the acute phase, and the correction of heparin-related hemorrhagic complications is easier, then perhaps heparin should be used in the acute phase. At the time of discharge, however, thromboelastography might determine the appropriate long-term treatment for these patients. Therefore, I agree that figuring out which side of the coagulation cascade causes their hypercoagulability is important. The question is, in the acute phase, which series of treatment-related bleeding complications or the ability to reverse those agents would you rather undertake?

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