Traumatic brain injury and intracranial hemorrhage–induced cerebral vasospasm: a systematic review

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OBJECTIVE Little is known regarding the natural history of posttraumatic vasospasm. The authors review the pathophysiology of posttraumatic vasospasm (PTV), its associated risk factors, the efficacy of the technologies used to detect PTV, and the management/treatment options available today.

METHODS The authors performed a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the following databases: PubMed, Google Scholar, and CENTRAL (the Cochrane Central Register of Controlled Trials). Outcome variables extracted from each study included epidemiology, pathophysiology, time course, predictors of PTV and delayed cerebral ischemia (DCI), optimal means of surveillance and evaluation of PTV, application of multimodality monitoring, modern management and treatment options, and patient outcomes after PTV. Study types were limited to retrospective chart reviews, database reviews, and prospective studies.

RESULTS A total of 40 articles were included in the systematic review. In many cases of mild or moderate traumatic brain injury (TBI), imaging or ultrasonographic studies are not performed. The lack of widespread assessment makes finding the true overall incidence of PTV a difficult endeavor. The clinical consequences of PTV are important, given the morbidity that can result from it. DCI manifests as new-onset neurological deterioration that occurs beyond the timeframe of initial brain injury. While there are many techniques that attempt to diagnose cerebral vasospasm, digital subtraction angiography is the gold standard. Some predictors of PTV include SAH, intraventricular hemorrhage, low admission Glasgow Coma Scale (GCS) score (< 9), and young age (< 30 years).

CONCLUSIONS Given these results, clinicians should suspect PTV in young patients presenting with intracranial hemorrhage (ICH), especially SAH and/or intraventricular hemorrhage, who present with a GCS score less than 9. Monitoring and regulation of CNS metabolism following TBI/ICH-induced vasospasm may play an important adjunct role to the primary prevention of vasospasm.

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KEY WORDS traumatic intracranial hemorrhage; posttraumatic vasospasm; traumatic brain injury

THE incidence and impact of traumatic brain injury (TBI) within the general population have increased over the past few years.[6] Although the primary injury associated with TBI may be debilitating, secondary injury associated with posttraumatic arterial vasospasm is an important and dangerous consequence of TBI. The incidence of vasospasm in aneurysmal subarachnoid hemorrhage (aSAH) has been extensively studied; less is known regarding the epidemiology of posttraumatic vasospasm (PTV), with the largest study examining only 299 patients.[25] Because of limited studies and small numbers of enrolled patients, PTV continues to be poorly characterized. Current literature suggests that PTV portends a more severe neurological injury, but its magnitude is un-

known. Oftentimes, surveillance for PTV is not routinely performed during management of TBI. This is in sharp contrast to the management of aSAH, where signs and symptoms of neurological deterioration are frequently uncovered due to surveillance (such as transcranial Doppler [TCD] ultrasonography and repeat CT angiography [CTA]/ CT), and the well-established correlation between aSAH and vasospasm. In this review, we examined the natural history of PTV and review the pathophysiology and efficacy of detection technologies, as well as management and treatment options.

Methods

Search Strategy and Study Eligibility

An electronic search of literature published between 1989 and 2016 was performed using PubMed, Google Scholar, and CENTRAL (Cochrane Central Register of Controlled Trials) in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement. Search terms used in various combinations included "vasospasm," "subarachnoid hemorrhage," "post-traumatic vasospasm," "traumatic brain injury," "epidemiology," "pathophysiology," "treatment," "management," "predictors," "incidence," "risk factors," "digital subtraction angiography," "computed tomography angiography," "computed tomography perfusion," "electroencephalography," "transcranial Doppler ultrasonography," "brain tissue oxygenation," "microdialysis," "thermal diffusion flowmetry," and "jugular bulb oximetry." Eligibility for this review was restricted to articles in the English-language literature. Selected study designs were limited to retrospective chart reviews, database reviews, and prospective studies. No restrictions were made based on publication date. All studies used were peer reviewed, published, and conducted in humans. One reviewer (A.C.) conducted the search, which was verified by 3 other reviewers (M.L., E.W., N.P.). The focus was on the pathophysiology of PTV, associated risk factors, and the efficacy of modern detection/treatment approaches. Studies not pertinent to the scope and intent of this review were excluded.

Data Extraction

Data on epidemiology, pathophysiology, time course, predictors of PTV and delayed cerebral ischemia (DCI), optimal means of surveillance/evaluation of PTV, applications of multimodality monitoring (such as brain tissue oxygenation, microdialysis, thermal diffusion flowmetry, and jugular bulb oximetry), modern management and treatment options, and patient outcomes after PTV were collected. Other variables included country of origin, study type, and year of publication.

Quality Evaluation

The first author (F.A.) independently evaluated all included studies for quality using the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence (http:// www.cebm.net/ocebm-levels-of-evidence/). In this schema, the highest level of evidence for a study is a systematic review of randomized controlled trials (Level 1), followed by random trials or observational studies with dramatic

effect (Level 2), and nonrandomized controlled cohort/ follow-up studies (Level 3). Lower levels of evidence are given to case series, case-control studies or historically controlled studies (Level 4), and mechanism-based reasoning studies (Level 5). Due to the paucity of information regarding the subject of vasospasm following TBI, this review includes only studies of Levels 3, 4, and 5. Risk of bias assessment was not performed because of significant variability in study methodologies used in this review.

Results

Search Results

The number of articles retained at each stage of data acquisition is shown in Fig. 1. Our initial search identified 6230 studies from collective databases, with the majority being found using the key word combination "traumatic brain injury vasospasm;" 5748 articles remained after duplicates were removed, and 961 articles remained after the aforementioned eligibility exclusion criteria were applied. Based on a survey of titles and abstracts, 40 articles were pertinent and ultimately used in the analyses.

The breakdown of the 40 articles was as follows: epidemiology (3), pathophysiology (9), time course (5), predictors (5), digital subtraction angiography (DSA; 4), CTA (3), CT perfusion (3), 3 electroencephalography (3), TCD ultrasonography (3), brain tissue oxygenation (1), microdialysis (2), thermal diffusion flowmetry (2), jugular bulb oximetry (2), and treatment (7) studies. The main findings are compiled in Table 1.

Epidemiology

PTV is not routinely assessed unless there are signs or symptoms suggesting its presence, which makes determining its true incidence a difficult endeavor. Investigating the inherent risk of PTV requires clinical vigilance because SAH, thought to be a major contributing factor in the development of PTV, is present in up to 60% of patients who have sustained a TBI.[3]

Angiographic studies originally reported vasospasm incidence rates between 5% and 18.6%.[20] As neurosonography and imaging technologies have become more accessible, rates of PTV detection have increased, now ranging from 27% to 63%, with a rate of 36.3% in the pediatric population.[24] Although technologies such as neurosonography have allowed for increased detection of vasospasm, increasing the sensitivity of these modalities results in an increased rate of false positives.[34]

Pathophysiology

Many theories have been proposed concerning the pathophysiology of PTV; however, the exact mechanism remains unknown. Wilkins and Odom asserted in 1970 that PTV was mechanistically similar to vasospasm in aSAH, in which the subarachnoid blood irritates the cerebral vessels.[37] However, clinical evidence shows that PTV can occur without the presence of blood in the subarachnoid space.[14,25] Mechanical factors have been implicated in the pathogenesis of PTV, with in vitro studies showing that vasospasm can occur from mechanical manipulation or irritation, although experimentally it is sustained for a
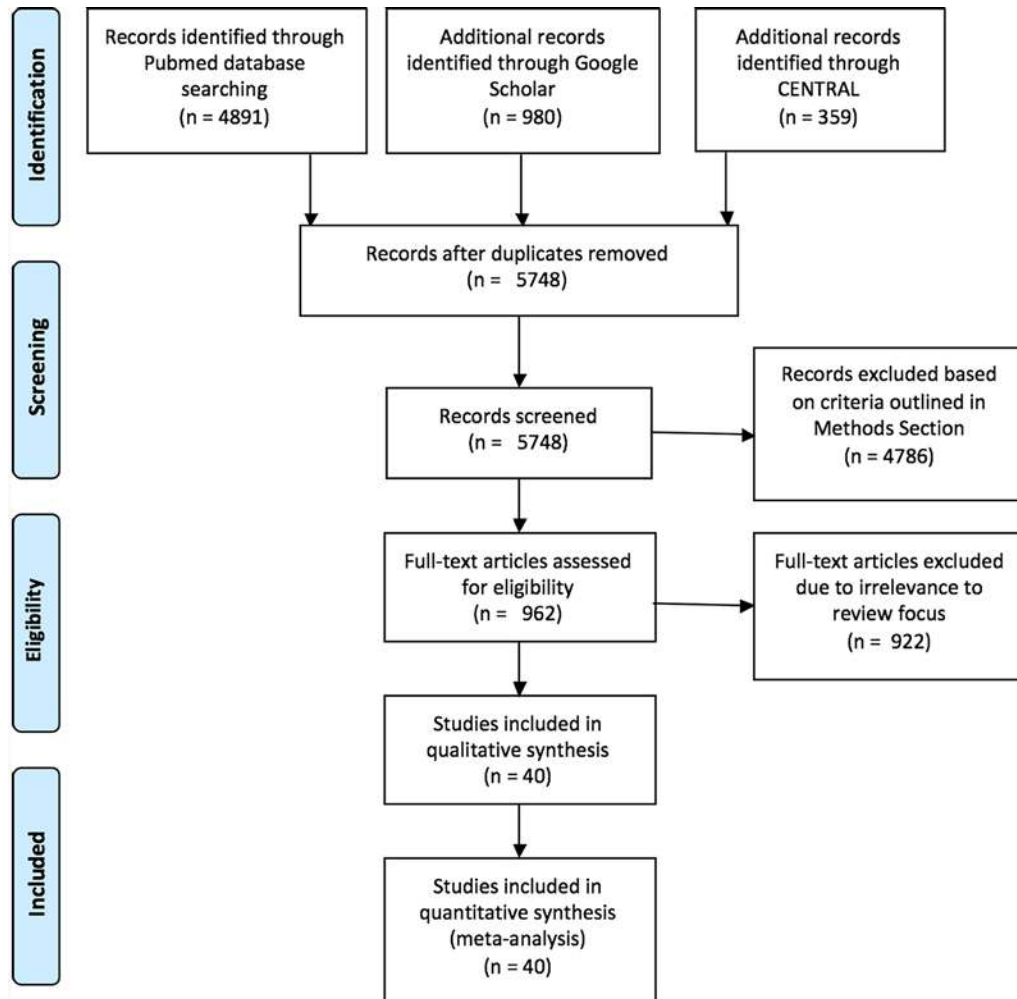
FIG. 1. PRISMA study flow diagram demonstrating the number of articles retained at each stage of data acquisition. Data added to the PRISMA template (from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group [2009]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6[7]:e1000097) under the terms of the Creative Commons Attribution License.

shorter time than is seen clinically.[5,42] Stretching of cerebral vessels during blast injuries has also been proposed as a cause of PTV without cisternal or subarachnoid blood.[14]

Although the pathophysiology of cerebral vasospasm continues to be a topic of debate, there is a general consensus that spasmogenic and neuroinflammatory substances generated from lysis of subarachnoid blood propagate the process.[27] Molecular models focus around endothelin-1 protein and its effect on endothelin receptor A. CSF and serum obtained in patients who have sustained a TBI show increased levels of endothelin-1, supporting its involvement in TBI and subsequent vasospasm in these patients.[8]

PTV results in diminished blood flow to areas of the brain, producing DCI and manifesting in new-onset neurological deterioration occurring after initial brain injury.[21] Westermaier et al. found neurological evaluation to be the most accurate method for discovering vasospasm or infarction following aSAH. Unfortunately, symptoms develop much later, when intervention may not alleviate neurological dysfunction.[36] It remains to be seen wheth-

er these evaluation techniques are directly applicable to discovering PTV or whether different techniques may be more efficacious.

Time Course

Understanding the specific chronology of PTV relative to TBI may provide valuable information regarding optimal surveillance. Current literature shows that PTV typically occurs earlier [after TBI] than does aneurysmal vasospasm (2–3 days posttrauma vs 3–5 days post–aneurysmal vasospasm).[12,14] Rarely does PTV occur as late as 6 days posttrauma. The range of PTV onset times makes it difficult for clinicians to effectively assess a patient for PTV. The duration of of PTV has been reported to last longer than 5 days in less than 50% of patients.[24,25] Martin et al. distinguished traumatic SAH-related PTV from non-SAH PTV, and showed that non-SAH PTV has a shorter duration than SAH-related PTV.[20] In the same study, the authors found the time course of vasospasm in traumatic SAH to be similar to that in aSAH.

TABLE 1. Summary of PTV risk factors

Authors & Year	Study Type (no. of patients)	Patient Age in Yrs	Correlations, Conclusions, & Effects of Risk Factors on PTV
Zubkov et al., 2000	Prospective (90)	Range 14–67	Presence of epidural hematomas on CT: statistically significant increase in risk of PTV development; presence of subdural hematomas on CT: statistically significant increase in risk of PTV development; GCS score: inverse relationship btwn score & incidence of PTV
Oertel et al., 2005	Prospective (299)	Mean 35 (range 16–87)	Younger age in population: statistically significant increase in risk of PTV development; lower GCS score: statistically significant increase in risk of PTV development; presence of SAH on CT: statistically significant increase in risk of PTV development
Armonda et al., 2006	Retrospective chart review (57)	Adults	No. of lobes injured: statistically significant increase in risk of PTV development; presence of pseudoaneurysm: statistically significant increase in risk of PTV development; presence of non-SAH hemorrhage: statistically significant increase in risk of PTV development (grouped study of epidural, subdural, intraventricular, or mixed hemorrhage)
Shahlaie et al., 2011	Database review (46)	Mean 33.4 (range 2–92)	Fever on admission: statistically significant increase in risk of PTV development; presence of small contusions (<1 cm) on CT: statistically significant increase in risk of PTV development; cisternal/cortical/sulcal SAH on CT: statistically significant increase in risk of PTV development (NS on multivariate analysis); elevated WBC count on admission: statistically significant increase in risk of PTV development (NS on multivariate analysis)
O'Brien et al., 2015	Prospective (69)	Children	MVA as mechanism of injury: statistically significant increase in risk of PTV development; GCS score ≤8: statistically significant increase in risk of PTV development; ISS: statistically significant increase in risk of PTV development; fever on admission of ≥38°C: statistically significant increase in risk of PTV development

ISS = Injury Severity Score; MVA = motor vehicle accident; NS = not significant; WBC = white blood cell.

Predictors of PTV

PTV risk factors stem from studies that have shown a correlation between imaging findings and the incidence of vasospasm linked to each finding (Table 1). Severe SAH has consistently been linked to a high incidence of PTV,[25,42] with some studies showing an increased predilection for developing PTV in cases of intracerebral hematoma.[25] An increased incidence of PTV has also been reported in some cases of epidural and subdural hematomas.[42]

Certain clinical presentations have also been shown to correlate with an increased risk of developing PTV. Shahlaie et al. showed that fever was independently associated with PTV.[30] The Injury Severity Score has been found to positively correlate with the incidence of vasospasm in children, although this finding was not significant in adults.[23] In pediatric and adult populations, the Glasgow Coma Scale (GCS) score was more likely to determine the risk of vasospasm.[4,23,42] Armonda et al. examined blast-related TBI associated with Operation Iraqi Freedom and similarly showed that as the number of cerebral lobes affected by the traumatic injury increases, the incidence of vasospasm increases, especially when 3 or more lobes are involved (p = 0.012).[4] In addition, the presence of an associated pseudoaneurysm or hemorrhage at presentation was significantly correlated (p = 0.05 and 0.03, respectively) with the development of PTV. Clinical outcomes were worse for patients who experienced cerebral vasospasm.

Surveillance and Evaluation of PTV

Neuroimaging
Digital Subtraction Angiography

DSA was one of the first imaging modalities used to diagnose vasospasm in head trauma (Fig. 2).[38] Over time,

cerebral DSA has been performed more selectively due to its invasiveness, risk of complications, and the advancements in safer imaging technology.[15] DSA remains the gold standard in vasospasm diagnosis following aSAH and may provide an option for endovascular therapeutic intervention when indicated.[19] Limitations of DSA include a total complication rate of approximately 5% and a 0.5%–1% risk of stroke.[1]

CTA and CT Perfusion

Extensive meta-analyses have shown that CTA scans are adept at determining the presence of severe vasospasm,[10] with less efficacy in determining mild or moderate vasospasm.[1] CT perfusion (CTP) imaging is very effective in diagnosing vasospasm when DCI is suspected. CTP imaging demonstrates sensitivities and specificities near 90%, positive predictive values of approximately 71%, and negative predictive values as high as 99%.[39] Differences in certain parameters are useful in determining the presence of vasospasm; the mean transit time can be used as a screening tool due to its high sensitivity, and cerebral blood flow (CBF) can be used as a confirmatory parameter due to its high specificity.[35] Zhang et al. showed that quantitative data from CTP imaging can be used to prospectively determine if the vasospasm is severe enough to cause symptomatic changes in the patient.[40] Early CTP imaging can also efficaciously stratify patients at risk for developing DCI.[18]

Electroencephalography

Electroencephalography (EEG) studies have shown corresponding signs of change in electrical activity after TBI, even prior to the development of neurological symptoms.[22] Vespa et al. showed that 100% of the patients in
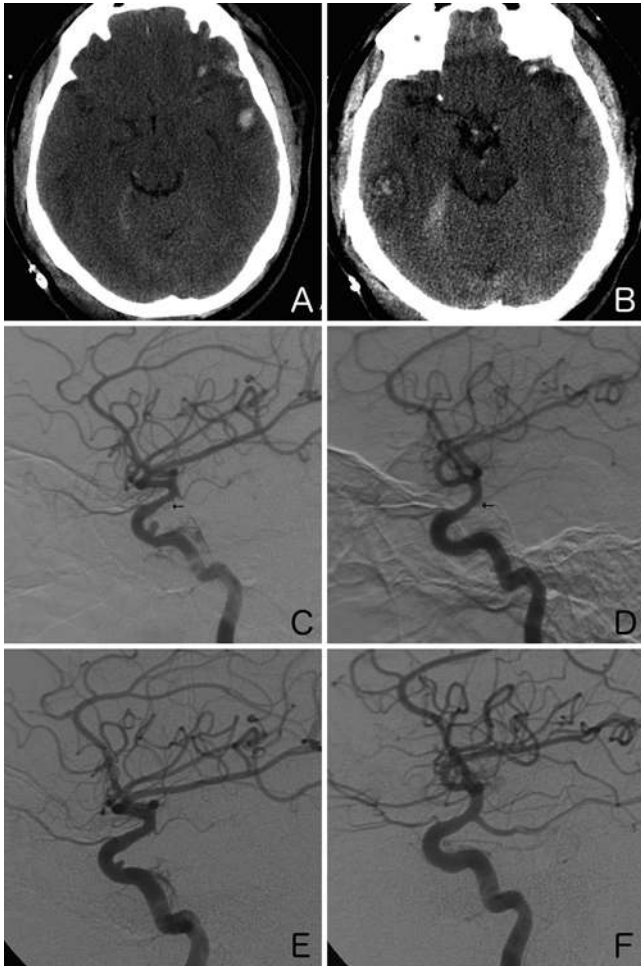
FIG. 2. Illustrative case. This 25-year-old man presented to our emergency department after an assault to the head. **A:** Axial noncontrast CT scan of the head showing a left temporal parenchymal hematoma with adjacent subarachnoid hemorrhage. **B:** Additional contrecoup right temporal parenchymal hematoma and subdural hemorrhage along the tentorium cerebelli. **C and D:** Right (C) and left (D) internal carotid artery (ICA) DS angiograms (lateral view) obtained on posttrauma Day 10 showing moderate vasospasm of the supraclinoid segments of both ICAs. Note the traumatic pseudoaneurysm of the cavernous right ICA as well as a traumatic right carotid-cavernous fistula. **E and F:** Follow-up right (E) and left (F) ICA DS angiograms (lateral views) showing resolution of vasospasm. The pseudoaneurysm was eventually treated with coil embolization.

their study with vasospasm due to aSAH had EEG findings of decreased relative alpha variability, a sign sometimes seen days prior to vasospasm diagnosed via TCD ultrasonography.[33] While continuous EEG has potential as a screening tool for detecting reversible ischemia in patients susceptible to PTV, treating physicians must be aware that many confounding neurological conditions may also cause decreased relative alpha variability, i.e., increased intracranial pressure, herniation, and hemorrhage.[33]

Importantly, continuous EEG monitoring can detect DCI from vasospasm before irreversible infarction of cerebral tissue occurs.[7] To our knowledge, no study has examined EEG correlates of PTV to date. Although mecha-

nistic differences may exist between aSAH and trauma-related vasospasm, it is possible that EEG might have some role in the detection of PTV in patients with TBI.

TCD Ultrasonography

TCD ultrasonography has been vital in guiding early management of TBI patients by monitoring the mean blood velocity and acting as a surrogate for measuring cerebral perfusion pressure.[28] Currently, the overall sensitivity of TCD ultrasonography in determining vasospasm in the context of SAH ranges between 50% and 60%, with both specificity and positive predictive values at 100%. TCD ultrasonography has been especially successful in determining the occurrence of vasospasm in the middle cerebral artery (MCA), with sensitivity and specificity rates as high as 84% and 89%, respectively.[31] Sensitivity of detecting vasospasm increases as the value of the mean blood flow velocity on TCD ultrasonography increases and should be highly suspected with velocities above 200 cm/sec.[16]

Multimodality Monitoring

Brain Tissue Oxygen Monitoring

Brain tissue oxygen (PbtO$_2$) monitoring involves implantation of a probe in a brain region that is at risk for vasospasm. This method provides information on oxygenation of tissue proximal to the probe at repeated time intervals. Studies have reported that lower oxygenation levels conferred a greater risk for vasospasm. This technique is rather invasive and of questionable reliability, as it is only able to monitor a limited region, thus possibly missing other brain areas at risk for DCI.[26]

Cerebral Microdialysis

Cerebral microdialysis uses artificial CSF dialysate exposed by a microdialysis catheter with a semipermeable membrane to allow molecules to equilibrate down a concentration gradient. The dialysate is collected, and local levels of interstitial cerebral metabolic markers, such as glutamate, lactate, pyruvate, and glucose, are measured.[12] Cerebral microdialysis provides data on levels of these markers and may detect ischemia presymptomatically with 89% specificity by examining changing levels of glutamate, glucose, and lactate. Elevated levels of taurine, lactate, and nitrate on microdialysis have been associated with poor neurological outcomes. Despite its predictive value, microdialysis is invasive and regionally limited (like PbtO$_2$ monitoring), which may result in overlooking other brain areas afflicted with DCI.[26]

Continuous Regional Cerebral Blood Flow Monitoring Using Thermal Diffusion Flowmetry

This method involves inserting one heat-transmitting probe into the brain and measuring the spread of heat to another area of the brain. Heat dissipation provides insight into the tissue's ability to transport heat, which is heavily influenced by local CBF.[29] Although this technique yields useful real-time data on the area of brain at risk for ischemia, like PbtO$_2$ monitoring and microdialysis, it is limited by the relatively small region of brain it

is able to monitor. Studies have shown this technique to be more reliable than TCD ultrasonography in detecting symptomatic cerebral vasospasm in patients with high-grade SAH, with increasing sensitivity and specificity as CBF increases.[26]

Jugular Bulb Oximetry

In this technique, an oxygen saturation probe is inserted into the jugular vein above the facial vein, providing oxygenation data for the intracranial circulation and allowing for a more global view of cerebral perfusion compared with microdialysis and $PbtO_2$.[13] When hemoglobin concentration, arterial oxygen saturation, and cerebral metabolic demand are maintained, jugular venous oxygenation saturation is proportional to cerebral perfusion. This technique, while somewhat invasive, is relatively safe and has been associated with negligible infection rates. One complication, however, is the risk of internal jugular vein thrombosis with prolonged use.[26]

Contemporary Paradigms in Management and Treatment

The goal in treating vasospasm is to prevent secondary ischemic injury to the central nervous system. Although "triple-H" (hypertension, hypervolemia, and hemodilution) therapy was previously used in managing vasospasm due to aSAH as well as PTV, this management modality has fallen out of favor.[41] Triple-H therapy can cause or worsen cerebral edema, which may be more severe in trauma than in aneurysmal rupture and may worsen neurological function.[14]

Currently, nimodipine is the most efficacious and widely used medication in the setting of PTV .[11] Nimodipine works as a calcium channel blocker by antagonizing the effect of dihydropyridine channels in smooth muscle cells. This decreases calcium influx into cells, which then decreases smooth muscle cell contractility, ultimately preventing vasospasm from occurring.[2] Although some moderately sized studies have shown that nimodipine has some benefit in reducing the incidence of vasospasm, large-scale meta-analyses have shown that differences in mortality rates were not statistically significant with the addition of nimodipine.[11] Stein and Le Roux proposed that there might be a role for nimodipine usage in a smaller subset of PTV cases as evidenced by a decreased incidence of vasospasm; however, this requires further investigation.[31] Patients receiving calcium channel blocker therapy must be monitored for hypotension, which may cause hypoperfusion and resultant cerebral ischemia.[41]

Papaverine, a phosphodiesterase-III inhibitor, has shown some efficacy in reducing vasospasm. Nevertheless, the effect is short lived and vasospasm often recurs, requiring multiple intraarterial doses. Currently, less is known about the usage of papaverine than that of nimodipine; further study is required.[2] Lastly, endothelin receptor blockers at high doses, such as clazosentan at 15 mg/hr, displayed a reduction in vasospasm-related morbidity and all-cause mortality in the context of aSAH but did not show improved long-term functional outcomes.[17] This could be due to other confounding factors, such as side effects or study design, causing apparent persistent ischemia.[9] Given their novelty, further studies are required to delineate the role of endothelin receptor blockers in PTV. However, results from recent animal models show promise.

The management of vasospasm is undergoing a paradigm shift in which treating the sequelae of vasospasm rather than vasospasm itself is favored.[26] Inconsistent efficacies of pharmacological agents have pushed forward monitoring and regulating CNS metabolism itself using techniques such as cerebral microdialysis and tissue oxygen monitoring rather than attempting to stop the occurrence of vasospasm.[32] The results are still in their infancy but seem encouraging.

Patient Outcomes

Twelve studies provided analyses based on patient outcomes. The duration of MCA spasms lasted an average of 3–5 days.[1,4] The duration of vasospasm was shorter if the anterior circulation was involved, resolving in 2.5 days.[1] In pediatric patients, good neurological outcome (defined as a GCS score of ≥ 4 1 month after TBI) after moderately severe brain injury was seen in 76% of patients without vasospasm but in only 40% of those with vasospasm.[15] Rates of good neurological outcome for severely injured patients also demonstrated worsening for those with vasospasm compared with those without (15% vs 29%). Regarding therapy, some medical management and interventional options have been found to provide vasospasm relief and improve outcomes. Interventionally, microballoon angioplasty in adult patients was found to significantly lower MCA and basilar artery flow velocities.[16] Medically, patients treated with nimodipine had significantly lower incidences of death, vegetative survival, or severe disability at 6 months posttrauma compared with placebo.[34] Patients treated with clazosentan instead had nearly equal rates of poor neurological outcome (defined as GCS score of ≤ 4) and mortality rates at 12 weeks when compared with placebo.[37] Clazosentan was additionally found to have higher rates of pulmonary complications, anemia, and hypotension in those patients.

Conclusions

We reviewed the current literature available on cerebral vasospasm in posttraumatic injury, focusing on the etiology of vasospasm, risk factors, surveillance and evaluation of PTV, and management options. While there are many different techniques for evaluating PTV, the gold standard for diagnosis remains DSA. We found an overwhelming majority of the literature showing an increased incidence of PTV in patients with SAH, an admission GCS score less than 9, and patient age younger than 30 years. There also seems to be an association with intraventricular hemorrhage and PTV, although to a lesser extent than with SAH. Patients copresenting with a pseudoaneurysm may also be at an increased risk for PTV. Given the results of this review, clinicians should suspect PTV in young patients presenting with intracranial hemorrhage (ICH), especially SAH and/or intraventricular hemorrhage, who present with a GCS score less than 9. Due to the inconsistent efficacies of pharmacological agents, it is suggested that monitoring and regulation of CNS metabolism following TBI/ICH-induced vasospasm may play an important adjunct role to the primary prevention of vasospasm.

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Disclosures

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Author Contributions

Conception and design: Al-Mufti, Al-Marsoummi, Alzubaidi. Acquisition of data: all authors. Analysis and interpretation of data: Al-Mufti, Amuluru, Changa, Lander, Patel, Wajswol, Alzubaidi, Singh, Nuoman, Gandhi. Drafting the article: Al-Mufti, Amuluru, Changa, Lander, Patel, Wajswol, Al-Marsoummi, Singh, Nuoman, Gandhi. Critically revising the article: all authors. Reviewed submitted version of manuscript: Al-Mufti, Al-Marsoummi, Alzubaidi, Singh, Nuoman, Gandhi. Approved the final version of the manuscript on behalf of all authors: Al-Mufti. Administrative/technical/material support: Al-Mufti. Study supervision: Al-Mufti, Singh, Nuoman, Gandhi.

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