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Vasospasm in traumatic brain injury

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Summary

Given the large societal burden from morbidity and mortality associated with traumatic brain injury (TBI), this disease entity has been the focus of extensive research over the past decades. Since primary injury in TBI is *preventable* whereas secondary injury is *treatable*, most of the research effort has been targeted at identifying factors that contribute to secondary injury and ways to minimize their deleterious effects. Whether post-traumatic vasospasm is one such factor is open for debate. Although radiological or anatomical vasospasm following head injury has been repeatedly demonstrated using various diagnostic techniques, its clinical significance is still under investigation. At the present time, no proven treatment regimen aimed specifically at decreasing the potential detrimental effects of post-traumatic vasospasm exists. Although calcium channel blockers have shown some promise in decreasing death or severe disability in those with traumatic subarachnoid haemorrhage, whether their mechanism is by minimizing vasospasm is open to speculation. Therefore, currently, vigilant diagnostic surveillance, including serial head CT's and the prevention of secondary brain damage due to hypotension, hypoxia, and intracranial hypertension, may be more cost effective than attempting to minimize post-traumatic vasospasm.

Keywords

Traumatic subarachnoid haemorrhage; cerebral vasospasm

Introduction

Cerebral vasospasm following spontaneous subarachnoid haemorrhage (SAH) due to aneurysmal rupture has been one of the most extensively studied areas in neurosurgery [22]. With the advancement of neuro-diagnostic techniques, radiological or anatomical vasospasm via angiography [10,28,30,32,47] and doppler ultrasonography [8,12,20,32,33,36,38,40,42, 46,53] has similarly been demonstrated following moderate and severe traumatic brain injury (TBI). Furthermore, Zubkov *et al*. has shown that more clinically mild, post-traumatic vasospasm resembles the morphological features of aneurysmal vasospasm in histopathological studies [54]. Post-traumatic vasospasm may occur earlier than post-aneurysmal rupture vasospasm following the ictus, but the duration of the former for 10–12 days is similar to that of the latter [12,20,30,32,38,40,46,53]. Although vasospasm has been shown to occur following traumatic SAH (tSAH), it can be detected in 2–41% of patients with head injury by angiography [30,53] and as high as 60% by TCD [12,20,30,32,38,40,46,53] even in the absence of tSAH [36]. Post-traumatic vasospasm can be seen in patients with tSAH, intraventricular haemorrhage, subdural hematoma and contusions, but not in those with normal CT's, cerebral edema, or epidural hematoma alone [32].

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Approximately 150,000 deaths occur per year as a result of trauma in the U.S. [7] and nearly half of these are due to TBI [2,3,13]. The primary injury in TBI is irreversible but preventable, whereas secondary injury due to hypotension, hypoxia, intracranial hypertension, seizure, infection, and the ensuing inflammatory cascades is treatable [4,37]. Thus, a reduction in morbidity and mortality is best achieved by minimizing secondary injury [19], including potential brain ischemia from vasospasm. The large societal burden from morbidity and mortality associated with head injury [2,3,13] warrants a clear understanding of its pathophysiology. However, despite decades of basic and clinical research, TBI remains poorly understood [4].

Considerable controversy exists about the precise relationship between TBI, tSAH, and post-traumatic vasospasm [4]. The challenge in learning about the underlying mechanisms of head injury in part stems from the heterogeneity of the TBI patient population, presence of multi-system injuries and multiple confounding variables, thus making the analysis of individual variables difficult [37]. Similarly studying head injury in the laboratory can be as difficult as in the clinical setting. For example, the Thomas *et al*. model for tSAH [51,52] (i.e. modified weight drop model of Marmarou [31]), the only animal model specifically designed to study tSAH, can experimentally produce tSAH only by concurrently also causing diffuse brain injury, thereby not allowing for studying tSAH in isolation.

tSAH occurs in as high as 60% of patients with TBI, is associated with a two-fold increase in risk of death [15], and is considered as one of the most important negative prognostic risk factors in head injury [15,23]. Whether tSAH is an independent causative factor for worse clinical outcome following TBI by deleterious processes such as vasospasm [12,16,27,32,49, 53], or merely a marker of more severely incurred head injury [9,34,43] still remains highly debated [4]. Furthermore, assuming tSAH is an independent causative factor for worse clinical outcome, whether its deleterious effects are through ischemic mechanisms secondary to vasospasm as thought to occur in aSAH is still open to speculation [4]. Having found that half of those with radiographic vasospasm showed hypodense areas on follow-up CT's in his TBI series, Harders *et al*. concluded that tSAH related ischemia secondary to vasospasm was responsible for the hypodensities [21]. Similarly, an association of anatomic vasospasm with subsequent neurological deficits is suggested by postmortem evidence of strokes in those with radiological post-traumatic vasospasm [30]. On the other hand, some investigators emphasize the frequent association of tSAH with other cerebral lesions such as subdural hematomas and contusions, reflecting the more severe nature of the head injury [15,24,44]. Similarly, studies have shown that the subsequent hypodensities on CT's in tSAH tend to occur at sites of earlier contusions, rather than in vascular territories as would occur if vasospasm were involved [9, 17].

Although the risk of developing vasospasm following aneurysmal SAH (aSAH) is considered to be related to blood clot burden [16], the fact that post-traumatic vasospasm can occur in the absence of demonstrable SAH questions whether aneurysmal vasospasm and post-traumatic vasospasm even share similar pathophysiology. In fact, in one series, patients with lower Glasgow Coma Scores (GCS) at admission were more likely to develop hemodynamically significant vasospasm, regardless of the presence of tSAH ($p < 0.001$) [36]. Nonetheless, other studies have found that the amount and location of subarachnoid blood plays a role in TBI prognosis [18,34,35]. Direct stretching or mechanical irritation of cerebral arteries are among the other factors thought to lead to the development of post-traumatic vasospasm [5,48,49].

Moreover, although post-traumatic vasospasm morphologically resembles aneurysmal vasospasm [54], whether the former entails similar clinical significance as the latter is still under investigation [4]. Proton magnetic resonance spectroscopy of patients with TBI and SAH has not revealed any evidence of ongoing anaerobic metabolism as would be expected if

ischemia secondary to post-traumatic vasospasm played a major deleterious role in TBI and tSAH [29]. Additionally, even in the extensively investigated aSAH, the precise relationship between the widely feared entity of aneurysmal vasospasm and delayed ischemic neurological deficit is still not clear [4]. Only a portion of aSAH patients with radiological vasospasm develop symptomatic vasospasm; 30–70% of aSAH patients show radiological vasospasm on angiography on day 7 post ictus while only 20–30% of aSAH patients develop symptomatic vasospasm[25], and anatomic vasospasm occurs frequently without any signs of ischemia.

Nonetheless, Oertel *et al*. has shown through cerebral blood flow studies combined with transcranial doppler ultrasonography that hemodynamically significant vasospasm does occur frequently in TBI [36]. However, despite this finding, he was not able to further clarify the relationship between radiological vasospasm and the more clinically relevant symptomatic vasospasm (i.e. neurological deterioration). As he notes, neurological deficit can not be readily identified in patients with severe TBI who are in a comatose state. Nevertheless, an earlier study by his group, found the 6-month outcome, based on the Glasgow Outcome Score, to be significantly related to hemodynamically significant vasospasm, independent of the subjects' age and admission GCS; patients with hemodynamic compromise had worse outcomes [27].

In the midst of conflicting data regarding the pathophysiology of TBI and its relationship with tSAH and post-traumatic vasospasm, six randomized controlled trials [1,11,21,26,39,45,50] have been conducted, investigating the use of calcium channel blockers (CCBs) in TBI and specifically tSAH [4]. A recent Cochrane review and meta-analysis of the data has found no significant beneficial effects of CCBs in TBI overall, but showed a statistically significant, although relatively small, beneficial effect in the tSAH subgroup in terms of the reduction of unfavorable outcome (death or severe disability) as reflected in Table 1. However, the review concluded that the possible benefits of CCB use in this setting may be outweighed by increased adverse events (e.g. hypotension) from its use [26]. Additionally, whether the small benefit in the tSAH subgroup is even related to its minimizing the risk of post-traumatic vasospasm development is open for debate. Many investigators now believe that even in the setting of aSAH, CCBs exert their modest benefits through mechanisms other than the prevention of vasospasm [4], including neuro-protection via limiting the entry of calcium into ischemic cells [41], antiplatelet aggregation [14], and dilation of collateral leptomeningeal arteries [6]. It should be noted that the comparability of the results from these randomized controlled trials is limited due to differences in study parameters and reported outcome measures [37] as shown in Table 2. It is clear that larger randomized control trials are necessary to study the effects of CCBs in TBI and specifically the tSAH subgroup, where the reported outcomes are not only death and severe disability, but also quality of life and economic utility of the medications [4].

Based on the discussion above, it is evident that the exact role and significance of post-traumatic vasospasm in TBI pathophysiology and prognosis still remains under investigation. Therefore, vigilant diagnostic surveillance, including serial CT's and prevention of secondary injury due to hypotension, hypoxia and intracranial hypertension, may be more cost-effective than attempting to treat vasospasm associated with TBI as currently no effective proven treatment is available to counteract any potential clinically detrimental effects of post-traumatic vasospasm. Future studies including positron emission tomography and advanced magnetic resonance imaging studies are clearly needed to determine the extent to which posttraumatic vasospasm causes cerebral ischemia and infarction, and whether its development is directly affected by tSAH.

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Table 1

Meta-analysis results of randomized controlled trials on the role of calcium channel blockers in TBI [4]

Outcome variables (pooled odds ratios)	Results (treatment vs. placebo) (95% confidence interval)
Unfavorable outcome (mortality, severe disability, persistent vegetative state) in TBI	0.85 (0.68–1.07)
Death in TBI	0.91 (0.70–1.17)
Unfavorable outcome (mortality, severe disability, persistent vegetative state) in tSAH subgroup	0.67 (0.46–0.98)
Death in tSAH subgroup	0.59 (0.37–0.94)

Table 2

Characteristics of randomized controlled trials on the role of calcium channel blockers in TBI [4]

Study	**Compton[11]**	**HIT I[50]**	**HIT II[1]**	**HIT III[21]**	**HIT IV[45]**	**Sahuquillo[39]**
Setting	Britain	Europe	Europe	Germany	International (13 countries)	Spain
Sample						
Total (n)	31	351	852	123	592	22
Treatment (n)	20	176	423	63	290	11
Placebo (n)	11	175	429	60	287	11
Inclusion	severe TBI vasospasm on TCD	moderate, severe TBI	Moderate TBI	tSAH	tSAH	moderate, severe TBI
tSAH subgroup included	no	yes	yes	yes	yes	no
Intervention	nicardipine	nimodipine	nimodipine	nimodipine	nimodipine	nicardipine
Reported risks:						
• Unfavorable Outcome (mortality, severe disability, persistent vegetative state)	no	yes (yes – tSAH group)	yes (yes – tSAH group)	yes (yes – tSAH group)	yes	yes
• Death	yes	yes	yes (yes – tSAH group)	yes (yes – tSAH group)	no	yes
• Side effects (hypotension, increase in pancreatic/liver enzymes)	no	yes	yes	yes	no	no

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