Abstract

Purpose: International guidelines advocate intensive blood pressure (BP) lowering within 6 hours of acute intracerebral hemorrhage (ICH) to a target systolic BP of 130-140mmHg, though more intensive lowering may be associated with adverse outcome. Observational studies suggest impaired cerebral autoregulation (CA) following ICH. Transcranial Doppler ultrasonography (TCD), alongside continuous BP monitoring, provides a non-invasive bedside investigation that offers detailed perspectives on physiological perturbations post-acute ICH. This systematic review and meta-analysis focuses on all TCD studies of CA in ICH.

Methods: MEDLINE, EMBASE and CENTRAL were searched for studies of hemorrhagic stroke and blood flow measurement.

Results: Eight studies met inclusion criteria (293 ICH patients); CA was impaired up to 12-days post-acute ICH. Impaired CA was evidenced by reduced transfer function analysis phase and higher mean flow correlation (Mx) values: these were associated with worsened clinical parameters including ICH-volume and Glasgow Coma Scale. Meta-analysis of CBV demonstrated that, compared to controls, mean CBV was significantly lower in the ipsilateral (49.7 vs. 64.8cms^{-1}, Z=4.26, p<0.0001) and contralateral hemispheres following ICH (51.5 vs. 64.8cms^{-1}, Z=3.44, p=0.0006).

Conclusion: Lower mean CBV in combination with impaired CA may have implications for more intensive BP lowering and warrants further studies examining such strategies on cerebral blood flow and its regulatory mechanisms.

Keywords: cerebral blood velocity; hemorrhagic stroke; transcranial Doppler ultrasonography; meta-analysis; cerebral hemodynamics

Background and Purpose

Spontaneous acute intracerebral hemorrhage (ICH) is associated with devastating consequences, as evidenced by both high mortality and morbidity.[1] Blood pressure (BP) control remains the foremost approach to managing acute ICH.[2] However, controversy exists as to whether intensive BP lowering in acute ICH risks cerebral ischemia.[3] This is particularly the case if cerebral blood velocity (CBV) control mechanisms are altered by chronic hypertension or brain injury. Cerebral autoregulation (CA) provides a protective mechanism for the brain parenchyma from extremes of CBV change, with the risk of hyper- or hypoperfusion in response to systemic BP changes.[4] A key limitation of large-scale randomized controlled trials has been the ability to provide mechanistic insight into CBV during the acute phase of hemorrhagic stroke.

Importantly, focused metabolic studies examining BP reduction and risk of perihematomal hypoperfusion have not supported the hypothesis that BP reduction is associated with perihematomal ischemia, confirming the safety of early intensive BP treatment in acute ICH.[5] These findings concur with the intensive BP reduction in acute cerebral hemorrhage trial (INTERACT-2), which did not associate rapid BP reduction with worse clinical outcomes.[6] The INTERACT-2 study randomized patients to intensive- (target systolic BP<140mmHg) or guideline-based (systolic BP<180mmHg) BP management. The antihypertensive treatment of acute cerebral hemorrhage II (ATACH-II) trial used intravenous nicardipine to test the superiority of very intensive reduction (target systolic BP 100 to 130mmHg) versus standard treatment (target systolic BP 140mmHg to 179mmHg).[7] The key difference in the BP targets achieved between the two studies is demonstrated by the early profile of systolic BP in the standard-treatment group in ATACH-II being similar to values observed in the intensive-treatment group in INTERACT-2.[6,7] Primary outcome measures of death and disability showed no reduction with BP lowering for both studies, but ATACH-II did not confirm the improved functional outcome found in INTERACT-2.[6,7] However, an important limitation with both studies was the lack of inclusion of individuals with low Glasgow Coma Score and large intraparenchymal hematomas, thus providing little data on safety of intensive lowering of systolic BP in individuals with the highest intracranial pressures where CA is likely to be further impaired.[6,7]

Transcranial Doppler ultrasonography (TCD) offers repeatable non-invasive bedside investigation with high temporal resolution of the steady-state (static) and dynamic components of CA.[4] Dynamic CA (dCA) responds to instantaneous (over seconds) BP and associated cerebral perfusion pressure changes, and prior studies have demonstrated impairment in acute ischemic stroke.[8,9] dCA is often described using transfer function analysis

(TFA) parameters;[10] including phase (reflecting speed of autoregulatory response) and gain (associated with damping characteristics of dCA). Furthermore, TCD can provide information regarding the time-course of autoregulation parameters in acute ICH. Unfortunately, despite several TCD studies to date, there remains a lack of consensus as to whether CA is impaired in ICH and whether such impairment relates directly to clinical outcomes. Furthermore, there has been no amalgamation of the evidence of the relationship of CA impairment with time post ICH.

TCD studies are highlighted in this review as they offer the advantage of understanding beat-to-beat dynamics of the relationship between cerebral pressure-flow with attention to fast and slow responses, thus providing mechanistic insights beyond comparable alternative imaging methods. Therefore, this review will focus on TCD studies of CA in the setting of documented acute ICH, and will report impairments in CA and the natural history of CBV changes following acute ICH.

Material and Methods

Study identification

Cochrane Collaboration methodology for meta-analysis reviews modified for observational studies (www.equator-network.org) was used.

Search Strategy

Studies were identified with a search strategy across three English language databases (MEDLINE, EMBASE and CENTRAL) between 1966 and December 2017 accommodating different MeSH terms or subcategories available on each database (Supplemental Material Table 1). Bibliographies of selected articles were screened for additional relevant articles.

Inclusion and Exclusion Criteria

TCD studies of human CA after ICH were included. Eligibility was assessed by reading abstracts, and, if necessary, whole articles. The effects of impaired CA and CBV changes on neurological outcome were assessed. Excluded were case reports, non-English language articles, posterior territory stroke studies, and studies with ultrasound contrast agent injection, as well as other perfusion-based studies with CT or MRI.

Data Extraction

The following data were extracted: (1) number of patients and controls; (2) sex; (3) age; (4) acute (<72 hours) vs. chronic phase assessment (>72 hours); (5) method of data analysis; (6) neurological outcome; (7) cerebral blood velocity (CBV); (8) partial pressure of carbon dioxide ($PaCO_2$); (9) BP; (10) hematoma assessment method and size; and (11) main conclusions.

Study quality was assessed using a checklist proposed previously for authors, editors, and reviewers of meta-analyses of observational studies modified for specific use in TCD autoregulation observational studies (Supplemental Material Tables 2 and 3)[8] and based on the meta-analysis of observational studies in epidemiology: a proposal for reporting (MOOSE) guidelines.[11] Two independent reviewers (JSM, GG) undertook the methodological quality screening and data extraction of the included studies.

For the meta-analyses, the variables were compared in acute ICH patients versus control subjects. The software used was Review Manager 5.3 (RevMan 5) provided by the Cochrane Library. The analysis was performed using the fixed effects model; weighted mean difference was used for measurement data and 95% confidence intervals (CI) were used as the effect indicator for dichotomous variables. The heterogeneity assumption was checked by the χ^2-based Q test.

Results

General characteristics

Eight-hundred and thirteen publications met the search criteria and were evaluated (Figure 1). The commonest reasons for exclusion were alternative imaging modality used (e.g. CT, MRI, NIRS), animal studies, subarachnoid hemorrhage patients, and neonatal hemorrhage. Two further studies were excluded after initially meeting the eligibility criteria, as it was noted that PET and brain tissue oxygenation measurement, rather than TCD, were used.[5,12] Overall, the eligibility criteria were met by seven controlled and one observational study (Table 1). Two studies used the same dataset,[13,14] but both were included due to the different methods adopted for assessment of CA. Median score on the quality checklist was 10, range 9-11 (Supplemental Material Table 3). This demonstrated areas of consistent incomplete reporting of previously published minimum acceptable methodological criteria for observational studies.[8]

Patient numbers ranged from 12 to 114. All studies included patients in the 'acute' (<72 hours) range, though five studies[13-17] also had measurements beyond 72 hours (chronic phase). Three studies provided measurements beyond five days,[14,16,17] with the longest measurement interval from index to follow-up being 30 days.[16] In all studies, except two, neurological outcome data were provided using the National Institute Health Stroke Scale (NIHSS), with scores ranging from 5 to 17. All studies included an ABC/2 assessment of hematoma volume with a range from 14.7 to 51.7 cm^3. Two studies reported radiological outcome measures with correlation of blood flow with CT data and assessment of vasospasm.[15,18] Four studies detailed end-tidal carbon dioxide ($EtCO_2$) values for acute ICH patients. These ranged from 34.3 to 34.9mmHg in the acute phase (<72 hours)[13,14,16] and 34.7 to 35.2mmHg in the chronic (>72 hours) phase.[13,14,16,17] Studies provided varying detail for BP recordings, with three providing no data, three providing mean arterial pressure (MAP), and one providing systolic readings only.

Cerebral hemodynamic parameters

Six of the seven studies provided CBV for each hemisphere separately,[13,14,16-19] with three providing comparable healthy control CBV values.[16-18] All eight studies assessed[13-20] cerebral hemodynamic measurements at rest. In one study, providing CBV data up to 30 days following ICH onset, it was reported that CBV in both the affected and unaffected hemispheres failed to return to control subject values at all assessed time-points until day 30.[16]

dCA assessed by TFA and mean flow correlation index (Mx), was impaired in the acute (<72 hours) period in most,[13,16,18,20] but not all studies.[14] However, this latter study reported that a 'secondary decline' in dCA more than five days post-ICH onset was associated with clinical features likely to be associated with poor prognosis, including hematoma volume and GCS.[14] A further study found an increase in Pulsatility Index (PI) was associated with larger hematoma volumes, possibly reflecting increased mass effect.[19]

Meta-analysis of CBV data

There was significant heterogeneity in study design and presentation of basic physiological measurements. Therefore, a quantitative meta-analysis was only possible for two acute studies (<72 hours) of CBV data only,[16,18] which, compared to controls, demonstrated significantly lower mean CBV in the ipsilateral (49.7 vs. 64.8 cms^{-1}, Z=4.26, p <0.0001) and contralateral hemispheres following ICH (51.5 vs. 64.8 cms^{-1}, Z=3.44, p=0.0006) (Figure 2a and 2b). Unfortunately, the studies did not provide data on hand dominance. A more recent 2017 study my Ma et al. was excluded from meta-analysis as the cohort were of chronic ICH patients assessed at 4-6 days post stroke.[17] However, this study demonstrated lower CBV values and EtCO2 in ICH patients compared to controls.

Discussion

This systematic review of cerebral hemodynamics following acute ICH demonstrates impaired dCA, as assessed by TFA and Mx parameters, in both ipsilateral and contralateral hemispheres compared to control subjects. This impairment seems to persist for up to 12 days following ICH onset, though this conclusion is limited by the fact that only two studies investigated changes in the 'chronic' phase beyond 72 hours. Importantly, worsening CA parameters was associated with clinical features likely to be associated with poor prognosis, including hematoma volume and GCS score. The hypothesized relationship between autoregulation, cerebral blood flow and clinical outcome is summarised in Figure 3. This concurs with similar findings in ischemic stroke, where worsening CA is associated with adverse prognostic features, such as hemorrhagic transformation and cerebral edema.[21]

There are several limitations with the studies included in this systematic review. First, studies were mainly limited to patients with mild-to-moderate stroke severity, as evidenced by neurological impairment (NIHSS 5-12) and GCS >8. Secondly, these studies used BP instead of cerebral perfusion pressure to calculate dCA parameters, thus neglecting the potential contribution of intra-cranial pressure. Thirdly, no study formally assessed the effects of BP lowering therapy on dCA, so there are limited data on the impact of intensive BP lowering on cerebral

hemodynamics. Fourthly, the review is limited to data reported in the selected articles and does not examine individual patient data in the quantitative or qualitative analyses. Lastly, this review is limited to TCD studies (as opposed to CT, MRI or NIRS) as they provide a robust assessment of beat-to-beat, dynamic central and peripheral hemodynamic changes associated with the physiological perturbations precipitated by acute ICH. This limits generalizability of the findings to other modalities though does provide important mechanistic insights nonetheless. Therefore, a mechanistic understanding from a cerebral hemodynamic perspective of different targets for intensive BP lowering is lacking. Finally, the included studies generally suffer from methodological heterogeneity, lack of control subjects, and relatively small numbers. Nonetheless, the homogeneity of the evaluated pathology (supratentorial hemorrhage of similar stroke severity) should be regarded as a strength. Overall, the methodological quality of each study was good and assessed using objective criteria. Therefore, there are important findings with respect to key hemodynamic measures.

CBV

A limited meta-analysis demonstrated lower CBV values in ICH patients in both the ipsilateral and contralateral hemispheres compared to control subjects, though overall little data exist for CBV changes following acute ICH. By contrast, studies in acute ischemic stroke have shown similar lower CBV values for ipsilateral (43.5 cms^{-1}) and contralateral (41.1 cms^{-1}) hemispheres compared to control subjects (49.6 cms^{-1}).[22] Previous TCD work comparing flow velocities in small (<25mL) vs large (>25mL) ICH volumes measured using computer tomography (CT), demonstrated large ICH has consistently depressed ipsilateral mean velocities (35±13cm/s).[23]

Pulsatility Index

Previous studies have shown increased intracranial pressure and decreased cerebral perfusion pressure lead to characteristic changes in TCD waveforms – decrease in diastolic velocity and increase in PI.[19] Importantly, Marti-Fabregas et al[19] confirmed that PI values obtained using TCD correlated well with CT signs associated with mass effect, volume of hematoma and volume of surrounding edema, total volume, midline shift and intraventricular extension. This correlation was particularly evident when PI values were significantly raised. Interestingly, these findings highlight a role for TCD as an indirect assessment method of intracranial hypertension and mass effect.

Mean flow correlation index (Mx)

As well as dynamic indices of autoregulation, the time correlation index known as the mean flow correlation index (Mx), which is based on correlation coefficients between BP and CBV, was also studied. Two studies assessed Mx in acute ICH.[14,20] Interestingly, the first of the two studies provided negative findings in the acute phase of ICH (<72 hours), demonstrating no difference between Mx values in patients and controls up to Day 5. However, higher Mx values (i.e. poorer autoregulation) were associated with a lower GCS, ventricular extension and lower cerebral perfusion pressure, ultimately leading to a poorer clinical picture at 90 days. These findings suggest some preservation of CA in acute ICH, and certainly conflict with findings of studies with transfer function analysis and PI outcome measures. The second more recent study assessed variability of CBV using non-linear entropy analyses.[20] Ultimately, the authors drew comparisons between Mx and non-linear entropy analyses to assess sensitivity to CA changes. The data suggested that acute ICH does impair CA and increased CBV variability exists within the ipsilateral hemisphere.[20]

Transfer Function Analysis

Nakagawa et al[18] assessed patients with lobar or basal ganglia hemorrhage early (<72 hours) post ICH and compared to controls. The patients had higher gains across a wide range of frequency ranges compared to controls. This suggested that dCA is impaired in the early days after ICH. However, data presented by Oeinck et al[13] (same dataset as Reinhard et al[14] showed that phase was not altered in acute ICH but (similar to Mx) there were prognostic associations. This included poorer phase being associated with larger ICH volume, lower BP and worsened outcome. Interestingly, gain was generally higher in acute ICH but not associated with clinical factors for which phase has shown an association. The largest TFA based study in patients with supratentorial ICH included a robust set of serial measurements (days 1 to 2, 4 to 6, 10 to 12, and day 30).[16] Phase difference was lower bilaterally and therefore possibly impaired up to days 10 to 12 with a significant recovery by day 30.[16] Importantly, phase difference values were associated with clinical status in the acute stage, and impaired phase difference at 4 to 6 days post-ICH onset was an independent predictor for clinical outcome.[16] More recently, the bilateral disturbance of dCA was confirmed at the 4-6 day period post ICH with larger hematoma volume being independently predictive of poorer CA status ipsilateral to the hematoma.

Impaired Autoregulation

This review highlights the complex interplay that exists between different markers of autoregulatory impairment. Crucially, there exists a variation of approaches to assessment of autoregulatory impairment leading to difficulties

in interpreting the overall picture due to inherent heterogeneity. However, we can summarize that higher gain, higher Mx, and lower phase difference are all suggestive of poorer CA (Figure 3), and provide a platform for future work examining CA impairment and consideration for potential interventions targeting CA improvement.

Future studies

Future mechanistic work on blood flow is necessary to examine the nature of the lower CBV values in acute ICH. A dual modality approach of TCD and arterial spin labelling may provide more information. Significant heterogeneity in outcome measures prevented any further meta-analyses on CA measures or other physiological parameters. Hence basic physiological data is required in future TCD work to ensure that more robust intra-study comparisons can be made, particularly baseline $EtCO_2$ values, CBV values for all time points including any controls used. Above all, future studies should include assessment of dCA and its time course following interventions to reduce BP.

Conclusion

There is limited evidence to suggest that dCA is impaired up to 12 days post ICH. There is evidence for an association between reduced TFA phase and Mx values, and worsened clinical features, including hematoma volume and Glasgow Coma Scale values. Furthermore, lower bilateral CBV values as compared to controls provide a rationale for further studies examining the impact of intensive BP lowering strategies on cerebral blood flow and its regulatory mechanisms.

Abbreviations

ARI: Autoregulation index; BP: Blood pressure; CA: Cerebral autoregulation; CBV: Cerebral blood velocity; CO_2: Carbon dioxide; CrCP: Critical closing pressure; CVMR: Cerebral vasomotor reactivity; dCA: Dynamic cerebral autoregulation; ECG: Electrocardiogram; $EtCO_2$: End-tidal CO_2; HR: Heart rate; ICH: Intracerebral hemorrhage; MABP: Mean arterial blood pressure; MCA: Middle cerebral artery; Mx: mean flow correlation index; $PaCO_2$: Partial pressure carbon dioxide; PI: Pulsatility Index; RAP: Resistance-area product; SD: Standard deviation; TCD: Transcranial Doppler; TFA: Transfer function analysis.

Ethics approval and consent to participate

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

JSM, RBP and TGR designed the whole study and gave suggestions on revising the article. JSM, GG and PD searched and selected the studies. JSM analyzed the data, drafted and revised the article. JSM prepared the figures. All authors read and approved the final manuscript.

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Figure Legend

FIGURE 1. CONSORT diagram detailing search results

FIGURE 2. Meta-analysis of CBV (cms^{-1}) in acute ICH (<72 hours). Figure 2a demonstrates mean ipsilateral transcranial Doppler ultrasonographic measurements (cms^{-1}) compared to mean control measurements, Figure 2b demonstrates mean contralateral measurements (cms^{-1}) compared to mean control measurements. Control values are average values (cms^{-1}) from ipsilateral and contralateral measurements.

FIGURE 3. Hypothesized influences of cerebral autoregulation and cerebral blood flow on the outcome of acute intracerebral hemorrhage.