Neurocritical care for intracranial haemorrhage: a systematic review of recent studies

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Abstract

Intracerebral haemorrhage (ICH) is associated with significant early mortality (up to 50% at 30 days) and long-term morbidity (with permanent neurological deficits in 75–80% of patients) and represents a serious health issue worldwide. The past decade has seen a dramatic increase in clinical research on ICH diagnosis and treatment that has led to revision of the guidelines for the diagnosis and management of ICH from the American Heart Association and American Stroke Association in 2013. This systematic review reports recent clinical evidence (original studies published between September 2013 and July 2015) related to neurocritical care and intensive care unit management of patients with ICH. All but one publication included in this review report original studies related to management of patients with intracerebral or subarachnoid haemorrhage. These include insights on risk stratification and neurocritical care or intensive care unit treatment, management of haemodynamic variables and mechanical ventilation (goal-directed fluid therapy, advanced haemodynamic monitoring, and avoidance of hyperoxia and hyperventilation), and pharmacological neuroprotection.

Key words: intracranial haemorrhage; neurocritical care; stroke

Editor’s key points

- Intracerebral haemorrhage (ICH) is a common and devastating type of stroke and is a leading cause of disability among adults.¹ ² Occurrence of ICH is the result of a number of pathophysiological processes that lead to bleeding within the cranial vault as a result of blood vessel rupture and result in a localized haematoma in the brain parenchyma and associated compression of brain tissue.³ ⁴ Outcomes after spontaneous ICH remain bleak, with mortality up to 50% at 30 days and complications of permanent neurological deficits and disability present in 75–80% of survivors.⁵–⁸ Although ICH has traditionally lagged behind acute ischaemic stroke (AIS) and subarachnoid haemorrhage (SAH) in terms of evidence from clinical trials to guide management, the past decade has seen a dramatic increase in the clinical research on ICH diagnosis and treatment.⁹ The American Heart Association/American Society of Anesthesiologists guidelines for management of patients with ICH, published in July 2015, includes a formal literature search updated to August
Table 1 Class I recommendations from AHA/ASA guidelines for optimal clinical management of patients with ICH relevant for neurocritical care. BP, blood pressure; DVT, deep vein thrombosis; ICH, intracerebral haemorrhage; ICU, intensive care unit; INR, international normalized ratio; SAP, systolic arterial pressure; VKA, vitamin K antagonist

<table>
<thead>
<tr>
<th>Class I Recommendation</th>
<th>Monitoring and clinical management should take place in an ICU or dedicated stroke unit run by physician neuroscience acute care expertise</th>
</tr>
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<tbody>
<tr>
<td>General monitoring</td>
<td>For ICH patients presenting with SAP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SAP to 140 mm Hg is safe and can be effective for improving functional outcome</td>
</tr>
<tr>
<td>Arterial blood pressure management</td>
<td>(i) Coagulation factors or platelet replacement, or both when needed (ii) If INR is elevated because of VKA, withhold VKA therapy, replace vitamin K-dependent factors, and give vitamin K i.v. to correct INR (iii) Intermittent pneumatic leg compression beginning on hospital admission to prevent venous thromboembolism</td>
</tr>
<tr>
<td>Haemostasis and coagulopathy, antiplatelet agents, and DVT prophylaxis</td>
<td></td>
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<tr>
<td>Glucose management</td>
<td>Glucose should be monitored. Both hyperglycaemia and hypoglycaemia should be avoided</td>
</tr>
<tr>
<td>Seizures and antiseizure drugs</td>
<td>Clinical seizures should be treated with antiseizure drugs. Patients with a change in mental status who are found to have electrographic seizures should be treated with antiseizure drugs</td>
</tr>
<tr>
<td>Management of medical complications</td>
<td>A formal screening procedure for dysphagia should be performed in all patients before initiation of oral intake to reduce the risk of pneumonia</td>
</tr>
<tr>
<td>Prevention of recurrent ICH</td>
<td>BP should be controlled in all ICH patients. Measures to control BP should begin immediately after ICH</td>
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</table>

2013. Class 1 recommendations for neurocritical care (NCC) and intensive care unit (ICU) management are listed (Table 1).10

The purpose of this systematic review is to report recent clinical evidence, including original studies published between September 2013 and July 2015, related to NCC and ICU management of patients with ICH (spontaneous and post-traumatic) and SAH.

Methods

A systematic literature search of PubMed, Medline, Current Controlled Trials, and EMBASE was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement recommendations.11 Clinical literature (prospective randomized clinical trials, observational studies, and case series that have enrolled more than five patients) were searched using the PubMed database. The following search terms were used: ‘brain injury’ AND ‘intracranial haemorrhage’ (spontaneous and post-traumatic). The following filters were used: clinical studies; published between September 2013 and July 2015; full-length articles (no abstracts); and English language. After hand searching and revision of the full text, duplicates were eliminated.12 Details of the studies were recorded using a dedicated data-extraction form. Titles, abstracts, or both, of studies retrieved using the search strategy and those from additional sources were screened independently, and the full text of potentially eligible studies was retrieved and assessed independently for eligibility. Disagreement over eligibility was resolved through open discussion.

Results

A total of 51 articles were retrieved using the listed keywords. After screening for eligibility, 37 articles were excluded and 14 articles were selected (Fig. 1) and categorized into the following four subcategories: risk stratification and NCC or ICU treatment,13–16 haemodynamic management,17–22 mechanical ventilation,23 24 and pharmacological neuroprotection25 26 (Table 2).

Risk stratification and neurocritical care or intensive care unit treatment

Recent literature provides insights on risk stratification of ICH in patients receiving non-vitamin K-antagonist anticoagulants [new oral anticoagulants (NOACs)] and in patients presenting with seizures, co-morbidity and complications associated with ICU treatment, and on limited benefit of ICU treatment in low-risk patients presenting with post-traumatic ICH.13–16

Clinical characteristics and the relationship with arterial blood pressure of ICH associated with chronic use of NOACs is reported in a retrospective cohort study in six patients (five receiving rivaroxaban and one apixaban).15 In these patients, the mean time to onset was 146 (SD 112) days after starting NOACs, and mean systolic arterial pressure (SAP; recorded 1 month before ICH) was 138 (16) mm Hg. Although none of the therapies traditionally used to counteract coagulation abnormalities (infusion of fresh frozen plasma, activated prothrombin complex concentrate, recombinant activated factor VIIa, or haemodialysis) was used, ICH was not associated with haematoma expansion within the 24 h after onset of symptoms. The authors highlight how ICH occurred relatively soon after the start of NOAC therapy, and haematoma volume was small. These findings suggest that even stricter arterial pressure lowering and control within an acceptable range may be advisable to prevent ICH during NOAC therapy.

The relevance of seizures at presentation and relationship with in-hospital mortality was evaluated in a retrospective cohort study that recruited 247 patients presenting with seizures to the emergency department and admitted to the ICU for treatment.14 In this subgroup of patients, ICH was detected as a possible underlying cause of the seizures in 36 of 247 patients (14.5%). Overall, in-hospital death occurred in 7.7%. The authors concluded that rates of death and discharge to hospice were relatively low in this patient population.

Associated complications (cardiac and ventilatory), intensity of treatment (with mechanical ventilation), and the relationship
with short-term outcome, were evaluated in a retrospective cohort study in 347 patients with AIS or ICH in a series of 4958 patients admitted to a stroke unit.15 Besides stroke-related disturbances of consciousness that complicated 47.1%, the most commonly reported reasons for ICU treatment were as follows: cardiac (23.4%), respiratory (12.1%), or complications of interventional procedures requiring mechanical ventilation (11%). Mechanical ventilation was needed in 231 of 347 patients (66.6%) for a mean of 84 h. Overall in-hospital mortality (143 of 347; 41.2%) was associated with older age, poor National Institute of Health Stroke Scale (NIHSS) score at admission, and the need for mechanical ventilation ($P<0.001$). In patients $\geq 80$ yr old with ICH, the need for mechanical ventilation was strongly associated with an unfavourable outcome. Overall post-rehabilitation outcome did not differ between patients with ICH and AIS. The authors conclude that ICU admission is associated with a lifesaving outcome even among the elderly. However, functional outcome was poor in older patients, thus limiting the benefits of ICU treatment.

Use of the ICU or regular ward admission to treat ‘low-risk’ patients presenting with minor traumatic ICH was investigated in a retrospective cohort study to compare long-term neurological outcomes, measured with the extended Glasgow Outcome Scale (GOS) score at admission, and the need for mechanical ventilation ($P<0.001$). In patients $\geq 80$ yr old with ICH, the need for mechanical ventilation was strongly associated with an unfavourable outcome. Overall post-rehabilitation outcome did not differ between patients with ICH and AIS. The authors conclude that ICU admission is associated with a lifesaving outcome even among the elderly. However, functional outcome was poor in older patients, thus limiting the benefits of ICU treatment.

Haemodynamic management

Several aspects of the haemodynamic management of patients with ICH have been investigated. These include the relationship between lowering SAP, use of early goal-directed fluid therapy (EGDFT), and positive net fluid balance with functional follow-up and delayed cerebral ischaemia (DCI) after ICH or SAH.17–20 A secondary analysis of INTERACT1 and 2 provided information about the association between intraventricular haemorrhage (IVH) and early perihematomal oedema with outcome.21 22

In a retrospective cohort study, the impact of lowering SAP during the first week of stroke and the relationship with functional status and long-term mortality were assessed in 150 elderly patients (mean age at admission 83.6±5.5 yr) with AIS (82.7%) or ICH (10%).17 Outcome was measured with modified Rankin Scale (mRS) after 1 week and mortality at long-term follow-up (mean follow-up 7.5 yr). Within 7 days after admission, SAP was effectively lowered (using one or more of the following: calcium antagonists, $\beta$-blockers, diuretics, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and $\alpha$-blockers)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>n</th>
<th>Primary end point</th>
<th>Mortality (%)</th>
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<tr>
<td>Mutoh and colleagues</td>
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<td>EGDFT can reduce the incidence of DCI and improve functional outcome at 3 months</td>
</tr>
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<td>Prostacyclin did not increase the net perfusion of the brain</td>
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Table 2: Characteristics of studies included in this systematic review. BV, blood volume; DHEAS, dehydroepiandrosterone sulfate; EGDFT, early goal-directed fluid therapy; HV, hypervolaemia; ICH, intracranial haemorrhage; ICU, intensive care unit; IVH, intraventricular haemorrhage; NA, not available; NOAC, novel oral anticoagulant; NV, normovolaemia; PHE, early perihaematoma oedema; SAP, systolic arterial pressure.
from 147 (21) to 140 (20) mm Hg; *P*<0.001. Mean admission SAP predicted short-term functional status and long-term mortality, but there was no association between the change in SAP attained during the first week after stroke and short-term functional status (mRS at 1 week after admission) and long-term mortality in this group of stroke patients.

In patients with SAH, the use of EGDT effectively reduces DCI after SAH for patients with poor clinical grade. In a multicentre, prospective, randomized, non-blinded study, 160 SAH patients treated within 24 h were randomized to receive either EGDT guided by preload volume and invasive cardiac output monitoring or standard fluid therapy guided by fluid balance or central venous pressure. Functional outcome was determined by DCI (based on the clinical and imaging criteria) and mRS at 3 months.

There were no significant differences between the two groups in the incidence of DCI (33 vs 42%) and mRS score at 3 months (grade 0–3 in 67 vs 57%), but among patients with poor neurological status on admission, those assigned to EGDT had a significantly lower rate of DCI (5 vs 14%; *P*=0.036) and poor mRS score at 3 months (grade 0–3 in 32 vs 36%; *P*=0.026), and shorter length of ICU stay (mean stay: 14 vs 17 days; *P*=0.043) than those who received standard therapy. These results suggest that in patients with SAH and poor clinical status at admission, EGDT is beneficial to reduce DCI and to improve functional outcome.

To test whether positive fluid balance might adversely affect clinical outcomes in SAH, a retrospective cohort of 288 patients with SAH was studied. Fluid balance during NCC stay, clinical and radiographic evidence of vasospasm, cardiopulmonary complications, and functional outcomes by mRS on follow-up (mean 8 months) were collected. Poor functional outcome was defined as an mRS score of 3–6. Average net fluid balance during NCC was greater in patients with poor functional outcome (3.5 (5.5) vs –0.02 (5.3) litres in patients with good outcome; *P*<0.001). On multivariate analysis, positive fluid balance (*P*=0.002) was independently associated with poor functional outcome. They concluded that positive fluid balance is independently associated with poorer functional outcome in patients with SAH.

In a prospective cohort study of patients recruited in the Intensive Management of Pressure and Volume Expansion in Patients With SAH (IMPROVES) trial, 39 SAH patients receiving crystalloid fluid administration targeting normovolaemia (NV) or hypervolaemia (HV) were enrolled to evaluate effects on outcome. The primary outcome was 3 month GOS. Hypocapnia was common (92% of patients had one or more arterial partial pressure of carbon dioxide (aCO2) measurements <4.7 kPa), with 68% of these measurements determined or standard fluid therapy guided by fluid balance or central venous pressure. Functional outcome was determined by DCI (based on the clinical and imaging criteria) and mRS at 3 months.

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The relationship between ICH and outcome was evaluated with a post hoc analysis of the intensive arterial pressure reduction in acute cerebral haemorrhage (INTERACT2) trial. This was an open-blinded end-point, randomized controlled trial in 2839 patients with acute ICH (<6 h of onset) with elevated SAP randomly assigned to intensive (target SAP<140 mm Hg) or guideline-based (SAP<180 mm Hg) arterial pressure management. Associations of baseline IVH volume in 740 of 2613 (28%) patients and poor outcomes (death and major disability defined on the mRS) at 90 days were determined by linear and logistic regression models. Death or major disability occurred in 66% with IVH volume vs 49% in ICH-alone patients (adjusted odds ratio, 1.68 (95% confidence interval 1.38–2.06); *P*<0.01). Associations of IVH volume and clinical outcomes were strong and near continuous. The authors concluded that there is a strong association between IVH volume and poor outcome in ICH.

The association between perihaematomal oedema and clinical outcome after ICH was evaluated with a post hoc analysis of the INTERACT1 and 2 trials. Substudy participants (n=1310; 346 in INTERACT1 and 964 in INTERACT2) had blinded central analyses of digital images from standardized baseline and 24 h CT. Predictors of death or dependency (mRS scores ≥3) at 90 days were assessed in logistic regression models and reported with odds ratios and 95% confidence intervals. Of 1138 (87%) patients with two CTs available for oedema analysis and outcome information, time from ICH onset to baseline CT, baseline haematoma volume, 24 h haematoma growth, and intraventricular extension were independent predictors of 24 h perihaematomal oedema growth. Absolute growth in perihaematomal oedema volume was significantly associated with death or dependency at 90 days, and thus was an independent prognostic factor in ICH.

**Mechanical ventilation**

The goal of mechanical ventilation in patients with ICH is to prevent secondary cerebral ischaemia and improve neurological outcome. Both hyperoxia and hypocapnia are associated with increased mortality and worse neurological outcome. The relationship between hyperoxia and mortality in patients with stroke admitted to the ICU mechanically ventilated was evaluated in a retrospective study of 2894 patients. Patients were divided into the following three groups: hyperoxic (arterial partial pressure of O2 (PaO2) ≥40 kPa), hypoxic (PaO2 <8 kPa or PaO2 (in mm Hg)/PaCO2 <300), or normoxic (defined as being neither hyperoxic or hypoxic). Primary outcome was inhospital mortality. Out of the 2894 patients, 554 had AIS (19%), 936 SAH (32%), and 1404 ICH (49%). Of these, 450 (16%) were hyperoxic, 1346 (46%) were hypoxic, and 1084 (38%) were normoxic. Mortality was higher in the hyperoxic group compared with normoxic [crude odds ratio 1.7 (95% confidence interval 1.3–2.1); *P*<0.0001] or hypoxic group [crude odds ratio 1.3 (95% confidence interval 1.1–1.7); *P*<0.01]. For patients with stroke admitted to the ICU and needing mechanical ventilation, hyperoxia was independently associated with increased inhospital death.

The relationship between hypocapnia and neurological outcome was evaluated in a retrospective cohort study of 102 patients with aneurysmal SAH treated with mechanical ventilation. The primary outcome was 3 month GOS. Hypocapnia was common (92% of patients had one or more arterial partial pressure of carbon dioxide (PaCO2) measurements <4.7 kPa), with 68% of these measurements occurring while breathing spontaneously with minimal ventilator support. The median duration of hypocapnia was 4 days. Of all PaCO2 measurements on a given day, 48% were <4 kPa. An unfavourable neurological outcome (GOS<4) occurred in 52 of 89 patients (58%). The duration of hypocapnia was associated with an unfavourable outcome (adjusted odds ratio 1.33 for each additional day of hypocapnia). These results suggest that hypocapnia is common in patients with aneurysmal SAH who need mechanical ventilation and is associated with a worse neurological outcome. Furthermore, the duration of hypocapnia is independently associated with a poor functional outcome.
Pharmacological neuroprotection

Pharmacological neuroprotection has had mixed results in the past. Recent clinical studies have tested dehydroepiandrosterone sulfate (DHEAS) and prostacyclin in patients with SAH. The potential neuroprotective effects of DHEAS were evaluated in a prospective observational study where the relationship between interleukin-6, DHEAS serum concentrations, and functional outcome was reported. Complete data sets (measured values for days 0–14) for outcome according to mRS 6 months after SAH were available for 41 patients. Patients with follow-up mRS = 2 were considered to have a favourable outcome. At 6 month follow-up assessment, DHEAS concentrations were considerably higher in patients with a favourable outcome compared with those who had poor neurological status (P = 0.001), and lower interleukin-6 concentrations were observed in the patients with favourable outcome (P < 0.001). This suggests a functional link between the anti-inflammatory properties of DHEAS and reduced interleukin-6 expression after SAH.

The safety and efficacy of prostacyclin as a single bolus were tested in 90 patients with SAH in a single-centre randomized, blinded, pilot trial to investigate effects on cerebral perfusion. The primary outcome was the difference from baseline in global cerebral blood flow, and the secondary outcome measures were the occurrence of delayed ischaemic neurological deficits, angiographic vasospasm, and clinical outcome at 3 months. No statistically significant differences in the change of global cerebral blood flow or clinical outcome were found. In patients with SAH, a single bolus dose of prostacyclin was not effective in increasing global cerebral blood flow or preventing delayed ischaemic neurological deficits or vasospasm.

Discussion

This systematic review of clinical literature published between September 2013 and July 2015 reports evidence related to NCC/ICU treatment of patients with ICH. Recent AHA/ASA guidelines have been implemented based on clinical evidence published up to August 2013; we report an update on risk stratification and NCC/ICU treatment, haemodynamic and mechanical ventilation management, and pharmacological neuroprotection. The multiple treatment challenges in patients with ICH lead to a significant increase in the rate of admission to NCC/ICU. Recent population-based studies demonstrate that patients presenting with small ICHs have improved survival when treated according to appropriate medical care guidelines. The growing number of patients with stroke admitted to the ICU parallels advances in ICU management and a trend towards more aggressive and invasive treatments that are associated with an increased survival rate. This benefit does not extend to low-risk patients with post-traumatic ICH, suggesting the need for selective ICU admission based on the severity of the acute illness and underlying clinical conditions. Given that the elderly are the largest proportion of people cared for in ICUs worldwide, there is increasing awareness that clinical status is important to defining prognosis.

The occurrence of ICH associated with use of NOACs is an increasingly frequent challenge for NICU/ICU physicians. Evidence suggests that, in these patients, ICH occurs relatively soon after the start of NOAC therapy, haematoma volume is generally small, and there is no indication to treat coagulation abnormalities. Seizures represent 1% of visits to emergency departments in the USA; a small proportion of these patients need immediate ICU management. The mortality rate of patients presenting with seizures is relatively low even when the underlying cause is ICH when immediately treated in the ICU. In elderly ICH patients, a better outcome is associated with normal arterial pressure compared with those having high SAP, whereas in low-risk patients presenting with ICH after head trauma there is no difference after ICU or ward admission.

The need to optimize cerebral and systemic perfusion makes advanced haemodynamic monitoring necessary for patients with acute brain injury, and recent evidence provides insights on optimal fluid therapy. After aneurysmal SAH, ECDFT is associated with a lower incidence of DCI and better prognosis. In SAH patients treated in an NCC, the risk of symptomatic vasospasm is higher, positive fluid balance is strongly associated with poor functional outcomes, and fluid administration targeted to HV does not increase CBV or ensure avoidance of hypovolaemia. Most NCC patients are mechanically ventilated, and recent evidence shows that hyperoxia is common and associated with a lower likelihood of survival after hospital admission. Hyperventilation with hypocapnia is also frequently observed, and intubation of hypocapnia is associated with poor functional outcome at 3 months and symptomatic vasospasm. This provides important information in the management of mechanical ventilation in patients with ICH.

Given the severity, long-term consequences, and costs of brain damage from ICH, pharmacological strategies for neuroprotection are of great importance. Although disappointing results have been obtained with pharmacological neuroprotection, recent evidence shows that DHEAS has protective properties, probably via its anti-inflammatory effects, whereas prostacyclin was without positive effects. Decompressive craniectomy and intracranial pressure monitoring might be beneficial in the treatment of ICH patients, although there is still not conclusive evidence.

In conclusion, recent studies related to NCC/ICU treatment of patients with ICH provide new information on risk stratification (related to NOACs, patients presenting with seizures, and co-morbidities), haemodynamic and mechanical ventilation management (use of goal-directed fluid therapy and avoidance of hyperoxia and hypocapnia), and pharmacological neuroprotection (use of DHEAS).

Authors’ contributions

Study design, data analysis, and manuscript writing: R.B., F.B.

Declaration of interest

None declared.

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