

Advances in the management of intracerebral hemorrhage

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Abstract Intracerebral hemorrhage (ICH) is one of the most detrimental sub-types of stroke and accounts for 10–15 % of all strokes Qureshi et al. (Lancet 373(9675):1632–1644, 2009). ICH has an incidence of 10–30 cases per 100,000 people/year which is increasing and expected to double by the year 2050 Qureshi et al. (N Engl J Med 344 (19):1450–1460, 2001). Mortality rates still remain poor (30–50 %) and functional dependency after ICH is high (~75 %) van Asch et al. (Lancet Neurol 9 (2):167–176, 2010). Up to now, all randomized controlled trials investigating treatment approaches in ICH have failed to document improvements on clinical endpoints Mayer et al. (N Engl J Med 358 (20):2127–2137, 2008); Brouwers and Goldstein (Neurotherapeutics 9 (1):87–98, 2012). Only a specialized treatment of severely injured patients at dedicated neuro intensive care units [NICU] has been shown to be beneficial Qureshi et al. (Lancet 373(9675):1632–1644, 2009); Suarez et al. (Crit Care Med 32 (11):2311–2317, 2004). Currently, ongoing trials are investigating aggressive blood pressure lowering, hemostatic therapies, different operative strategies, intraventricular thrombolysis as well as neuroprotective approaches, and brain edema therapies. This review will summarize advanced treatment strategies and novel approaches which are currently under investigation.

Keywords Intracerebral hemorrhage · Brain edema treatment · Intraventricular fibrinolysis · Hypothermia

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Introduction

Etiologically, intracerebral hemorrhage (ICH) can be grouped into primary spontaneous ICH which is mainly associated with hypertension (~70 %) and amyloid angiopathy (~30 %) or into secondary causes such as oral anticoagulant therapy, neoplasms, vascular malformations, or aneurysms (Qureshi et al. 2001). Several risk factors have been identified over the last decades consisting mainly of genetic aspects, pre-existing medical conditions, and life style factors. Two different apolipoprotein E alleles ($\epsilon 2/4$) have been related to an increased risk and a greater recurrence of ICH, further genetic associations relate to ethnic differences (O'Donnell et al. 2000; van Asch et al. 2010). The most relevant prior medical history is the diagnosis of arterial hypertension which—if treated—may lead to a risk reduction of ICH in patients with cerebrovascular disease (Arima et al. 2010). Moreover, ICH-associated life style factors include a history of smoking, drug abuse, or heavy alcohol intake (O'Donnell et al. 2010). Predictive factors of poor outcome may be divided into non-modifiable or modifiable (potentially treatable). Initial hematoma volume, age, neuro status on admission, and ICH location are non-modifiable; whereas potentially treatable factors are avoiding hematoma growth, treat acute hydrocephalus and resolve intraventricular hemorrhage, reduce brain edema evolution, as well as general critical care management of these patients (O'Donnell et al. 2010).

General critical care management

Most patients with ICH are cared for in general critical care units, but numbers of dedicated neuro-critical care units are

increasing. Treatment in the latter is promising and has been proven to influence clinical endpoints. Recently, Kurtz et al. (2011) published a “snap-shot” of 69 intensive care units of the Greater New York Area comparing the management of brain injured patients among specialized versus general ICUs Rincon and Mayer (2007). Their observations highlight possible differences with an increased use of hemodynamic and intracranial monitoring as well as more frequent tracheostomies, nutritional support, and decreased doses of intravenous sedating agents for NICUs (Kurtz et al. 2011). A major theme in the treatment of brain injured patients is always the avoidance of secondary brain injury, and temperature management plays a crucial role (Schwarz et al. 2000). It has been shown that increased body temperatures were associated with a poorer prognosis in ICH patients (Schwarz et al. 2000). For this purpose, different conservative medical approaches as well as cooling devices are being investigated to achieve normo- or hypothermia in ICH patients (NCT01530880, NCT01607151).

The NICE-SUGAR trial has greatly improved our understanding of glucose control, yet brain injured patients may represent a special cohort in which cerebral glucose utilization is even more critical and further investigated (NCT01137773) (Finfer et al. 2012; Kimura et al. 2007). Mechanical ventilation strategies have not gained as much interest in neuro-critical care, though ventilator liberation may be diverging (Navalesi et al. 2008). For the general ICU population, early tracheostomy does not seem to be of benefit neither regarding outcome nor pneumonia rates; whereas in stroke patients, this is heavily debated and contrary to the above and expert opinions considering early tracheostomy to be beneficial (Navalesi et al. 2008; Wang et al. 2011; Freeman and Morris 2012). Unfortunately, large RCTs in general ICU patients have excluded brain injuries (Navalesi et al. 2008; Wang et al. 2011). The need for tracheostomy in mechanically ventilated ICH patients is fairly high with 31 % (Huttner et al. 2006a). Hence, two German RCTs are currently enrolling to investigate the associations of early (<3 days) versus late tracheostomy in supratentorial ICH and stroke patients (NCT01176214, NCT01261091). Endpoints of these studies are length of stay and ventilation, sedative use, as well as its associated complications and influence on functional outcome. Moreover, limited information exist regarding risks and benefit of thrombosis prophylaxis in ICH which has led to a phase 3 and another phase 4 study (NCT01573169, NCT00699465) (Broderick et al. 2007a). Based on retrospective data, the use of low molecular weight heparins after 24 h and concomitantly present evidence of suspended ICH may seem safe (Broderick et al. 2007a; Kip-huth et al. 2009). There are two studies investigating this issue, one compares low dose enoxaparin—started after

24 h—versus placebo—changed to enoxaparin after 72 h—in combination with pneumatic compression stockings in both arms (NCT00699465). The second study that started recently in 2012 will compare standard compression stockings and early mobilization versus enoxaparin after 72 h (NCT01573169).

Hematoma growth [HG]

Hematoma growth reflects an important and well-established predictor of poor outcome in ICH (Brott et al. 1997; Davis et al. 2006). Though large interventional RCTs investigating possible effects of hemostatic treatment with a recombinant activated factor VII showed a reduction of HG, those studies failed to influence a clinical endpoint (FAST trial) which has led to great disillusionment amongst neuro-critical-care physicians (Mayer et al. 2008). Generally, it is accepted that hematoma growth occurs in up to 26–40 %, especially in the acute phase or “hyper-acute” phase after spontaneous ICH (Davis et al. 2006; Brott et al. 1997; Mayer 2003). Therefore, most currently enrolling RCTs, focussing on hematoma growth, are using a time window from symptom onset until presentation of 0–6 h as inclusion criterion (Anderson et al. 2008; Qureshi 2007). Nevertheless, a large proportion of patients (especially those who are on oral anticoagulant therapy) may experience HG at later times or with unknown time windows necessitating different means of detecting a potential high-risk patient (Davis et al. 2006). Recently, the more frequent use of contrast CT in ICH has led to the establishment of a radiologic predictor of HG (Goldstein et al. 2007). The so-called “spot-sign”, which reflects contrast extravasation into the hematoma, has increasingly gained attention and many studies have included this parameter to promote recognition of a potential target population in HG prevention (Wada et al. 2007). All of these phase 2 studies, STOP-IT (NCT00810888), SPOTLIGHT (NCT01359202), and STOP-AUST (NCT01702636), corroborate invasive treatment approaches using either recombinant factor VII or tranexamic acid to assess its influence on the primary endpoint of HG. It will be awaited whether the anticipated results may also be powerful enough to impact secondary endpoints such as functional outcome in these high-risk patients.

Another ancillary study of the ATACH II trial will investigate the spot-sign as criterion, the so-called SCORE-IT study which will potentially clarify its associations with HG and blood pressure management (Goldstein et al. 2012). Very high blood pressures (BP > 200 mmHg) have been recognized to increase HG, though precise data on the risks and benefits of acute BP lowering remain limited (Kazui et al. 1997; Broderick et al. 2007a; Morgenstern

et al. 2010; Anderson et al. 2010). This lack of data is reflected in AHA and ESA guidelines which determine rather vague and unspecific BP goals (Morgenstern et al. 2010; Broderick et al. 2007a). The pilot studies (INTERACT I; ATACH I) revealed the safety profile and lower risks of HG when aggressive BP lowering to systolic BP between 110–140 mmHg was achieved (Anderson et al. 2010; Qureshi and Palesch 2011). The subsequent larger trials (ATACH II and INTRACT II) are currently ongoing or recruiting patients primarily focussing on intensive blood pressure reductions to influence HG rates, functional outcome, and edema progression (NCT01176565; NCT00716079). It has to be mentioned that the increasing use of MRI imaging in smaller prospective investigations has improved recognition of acute ischemic lesions (DWI-lesions) beyond the peri-hemorrhagic zone which may be associated with aggressive BP lowering and might hypothetically impair functional outcome (Menon et al. 2012). Another approach currently being investigated in a selective sub-group of ICH patients with previous intake of antiplatelet medications or an assessed reduced platelet activity is the efficacy analysis of platelet infusions or desmopressin injections to prevent HG (NCT00699621, NCT00961532) (Naidech et al. 2009).

Surgical approaches

The results of the STICH trial have shaken neurosurgical grounds and led to widespread discussions amongst the society of neuro-critical-care physicians (Mendelow et al. 2005). After including more than 1,000 patients at 83 participating centres based on the principle of uncertainty, the results were published in 2005 and revealed no overall benefit of early surgical hemorrhage evacuation in supratentorial ICH as compared to conservative treatment (Mendelow et al. 2005). It remains fairly undisputed that larger (diameter >3 cm) cerebellar ICH patients with or without hydrocephalus or brainstem compression benefit from evacuation and trepanation (Morgenstern et al. 2010; Mendelow et al. 2005; Broderick et al. 2007b). Furthermore, the most recently completed STICH II trial ($n = 601$) will clarify the ongoing discussions of a possible benefit of surgery in lobar ICH patients with a cortical adjacency of the hematoma of <1 cm and ICH volumes of 10–100 cm³ (ISRCTN22153967) (Gregson et al. 2012; Mendelow et al. 2011). No evidence-based statement can be made for basal ganglia or thalamic ICH that may promote conventional surgery (Broderick et al. 2007a).

In recent years, minimally invasive techniques have emerged that allow smaller craniotomies and less damaging procedures which hypothetically may allow less traumatizing evacuations. An additional innovative approach

was realized by the MISTIE II trial representing a minimally invasive access with a sequential parenchymal clot lysis using rtPA versus conservative management (Morgan et al. 2008b). This randomized study has included 96 supratentorial ICH patients with ICH confined to a deep location in more than 60 % (Morgan et al. 2008b). The results of the study were presented at the International Stroke Conference this year and demonstrated an increased rate (14 %) of functional independency at 1 year for treated patients, which, however, did not reach significance because of small patient numbers. Furthermore, a recent non-randomized study was published that investigated solely thalamic ICH patients by a stereotactic and clot lysis (Urokinase) approach and showed significantly improved 90-day outcome (Chen et al. 2012). Despite the potential bias in the non-randomized analysis and non-significant clinical endpoints of the MISTIE II trial, these findings strongly support the need for a larger trial.

Peri-hemorrhagic edema [PHE]

PHE develops in most patients with ICH and has been linked to early neurological deterioration and moreover, was shown to be a negative predictor of poor functional outcome (Mayer et al. 1994; Gebel et al. 2002b). The time course of edema evolution may be separated into an acute phase (0–48 h) and a delayed phase with maximal edema formation at the end of week two (Gebel et al. 2002a; Mayer et al. 1994; Inaji et al. 2003). Therefore, mainly two responsible mechanisms have been postulated within the literature. Acutely pro-osmotic substances (protein, electrolytes) leak from the clot into the perihematomal area and lead to an early vasogenic edema (Xi et al. 2006; Butcher et al. 2004). Second, delayed processes start a few days after ictus with an activation of the coagulation cascade, thrombin production, and erythrocyte/hemolysis products inciting inflammation resembling a mixed picture of cytotoxic and vasogenic edema (Wagner et al. 2003; Butcher et al. 2004; Lee et al. 1997; Xi et al. 2006). The underlying injurious action is an increase of mass lesion and intracranial pressure which consecutively leads to a decrease in cerebral perfusion in turn may result into secondary brain damage (Zazulia et al. 1999; Xi et al. 2006; Rincon and Mayer 2004). A whole myriad of different agents have been used and are investigated in the management of PHE though none could proof efficacy. Very few evidence exists and therefore recommendations cannot be made (Broderick et al. 2007b; Morgenstern et al. 2010).

Potentially promising treatment approaches consist of continuous hypertonic saline infusions or mild prolonged hypothermia (Kollmar et al. 2010; Staykov et al. 2012; Hauer et al. 2011; Wagner et al. 2011). Experimental

models attribute combined effects to hypothermia such as blood–brain barrier stabilization and reduction of inflammatory processes which may engage on both mechanisms of edema development (Kawanishi et al. 2008; Fingas et al. 2007). A small pilot study could document significant effects on PHE size as well as potential effects on functional outcome (Kollmar et al. 2010; Staykov et al. 2012). Hence, this approach is most recently investigated in two randomized controlled (ISRCTN28699995; NCT01607151). Moreover, similar to decompressive hemicraniotomy studies in malignant middle cerebral artery infarctions (Vahedi et al. 2007), attempts are made to investigate the influence of this procedure in ICH patients (NCT01113645).

Intraventricular hemorrhage and acute hydrocephalus

Intraventricular hemorrhage (IVH) complicates ICH in almost half of the patients and has been established as important negative prognostic factor for mortality and functional outcome (Tuhrim et al. 1999; Mayer et al. 2005; Hanley 2009; Steiner et al. 2006). IVH represents a potentially lethal threat in ICH patients due to casting of CSF outflow structures (3rd/4th Ventricle) leading to intracranial pressure increase, development of acute occlusive hydrocephalus with a decrease in cerebral perfusion, or even consequent herniation (Hanley 2009; Bhattathiri et al. 2006; Staykov and Schwab 2013). Other potential mechanisms of brain injury may relate to the mass effects of IVH itself damaging ependymal/sub-ependymal and brainstem-structures directly, or possibly with concomitant autonomic dysregulation; as well many blood breakdown products aggravate inflammatory processes which may lead to chronic hydrocephalus necessitating consecutive permanent shunt surgery (Wasserman et al. 2007; Staykov et al. 2011; Simard et al. 2011; Hanley 2009; Bhattathiri et al. 2006).

Available treatment options consist of the acute placement of an external ventricular drainage (EVD) to alleviate imminent herniation (Bhattathiri et al. 2006; Broderick et al. 2007a). There is evidence that rapid IVH clot removal by means of intraventricular fibrinolysis (IVF), minimally invasive neuroendoscopy, or adjunct placement of lumbar drainages may decrease associated complications and further may positively influence outcome (Webb et al. 2012; Huttner et al. 2007; Hanley 2009; Staykov et al. 2009; Longatti et al. 2004). Based on available data, the current treatment concept should consist of ipsilateral EVD placement and IVF after suspended ICH with doses of 1 mg of rtPA every 8–12 h until 3rd and 4th ventricle have cleared and possibly overlapping lumbar drainage placement to accelerate bloody CSF resolution (Huttner et al.

2007; Webb et al. 2012; Ziai et al. 2012; Hanley 2009; Morgan et al. 2008a; Staykov et al. 2010). These promising therapies have been investigated in pilot trials or well-designed prospective studies, but sound evidence is urgently awaited. Therefore, 2010 AHA guidelines have considered EVD placement as reasonable and IVF as investigational treatment (Morgenstern et al. 2010). The CLEAR-IVH program has started in 2003 to investigate these strategies for safety, dose finding, and efficacy, including patients presenting with IVH, acute hydrocephalus, and ICH volumes equal or less to 30 cc to randomize these patients to treatment (IVF) versus placebo (Naff et al. 2011). Emanating the placebo-controlled CLEAR-III study will include 500 patients to determine the influence of this strategy on clinical endpoints such as functional outcome and mortality (NCT00784134). These results are strongly awaited and justified hope exists that it may be completed this year.

Moreover, treatment with early lumbar drainages may have synergistic effects with IVF to reduce the rate of shunt dependency after ICH (Huttner et al. 2006b; Staykov et al. 2009; Huttner et al. 2007). In a smaller prospective study, only one patient out of 32 treated with early LD, importantly after clearance of the 3rd and 4th ventricle due to herniation risk, required permanent ventricular-peritoneal shunting (Staykov et al. 2009). This approach is currently investigated in a randomized controlled trial with functional outcome at 3 and 6 months as secondary clinical endpoints and hopefully will be completed this year as well (NCT01041950). Another attractive operative approach, probably the fastest for intraventricular clot evacuation, is minimally invasive neuroendoscopy (Longatti et al. 2004). Different accesses, endoscopes, irrigation solutions, with or without the use of fibrinolytics have been described (Chen et al. 2011; Zhang et al. 2007; Staykov and Schwab 2013; Basaldella et al. 2012). A recent study reported no difference regarding surgical complications and mortality, but a decreased length of ICU stay and dramatically reduced rates of shunt dependency (Chen et al. 2011). Nevertheless, those results are promising, yet further research is needed to establish this operative technique.

Summary

ICH remains a dramatic disease with high morbidity and mortality, mainly because the strongest predictive factors for outcome are those who are not modifiable, such as age, initial hemorrhage volume, and corresponding clinical status. Despite all efforts to treat and minimize complications such as hematoma growth, edema formation, or intraventricular clot resolution, there are up to now no valid data from randomized controlled trials addressing efficacy

of emerging innovative strategies—such as hypothermia or intraventricular fibrinolysis—for treatment of acute and long-term sequelae.

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